Event-Based Modelling and Simulation of Hospital Acquired Infection Propagation Dynamics by Contact Transmission in Hospital Wards

Department of Civil, Environmental, Land, Building Engineering and Chemistry

RISK AND ENVIRONMENTAL, TERRITORIAL AND BUILDING DEVELOPMENT

Ph.D. Course

SSD: ICAR/20 – Urban and Regional Planning

Final Dissertation

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Course n°30, 01/11/2014-31/10/2017

Dipartimento di Ingegneria Civile, Ambientale, Territoriale,
Edile e Chimica

Corso di Dottorato in
RISCHIO, SVILUPPO AMBIENTALE, TERRITORIALE ED EDILIZIO

SSD: ICAR/20 – Tecnica e Pianificazione Urbanistica

Tesi di Dottorato

Modellazione e simulazione Event-Based della dinamica di propagazione delle infezioni nosocomiali trasmesse per contatto nei reparti ospedalieri

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A Giulio, passato e futuro.

EXTENDED ABSTRACT

The research aims presented in this study form part of a development of decision support systems for Land Engineering, particularly within the field of space knowledge management in risk conditions.

The aim of decision-making in this context is characterised by its being part of a complex system composed of different, equally complex sub-systems. Indeed, this complexity is a feature of all systems which include living elements and in any land planning scenario, a human or natural agent is ubiquitous.

In order to develop the research study, a problematic sector was chosen; the spread of infection in hospital wards. In particular, it was decided to concentrate specifically on transmission by contact.

This topic has proved to be of particular global importance, not only from an economic point of view but more importantly due to its direct risk to human health.

The first part of the thesis deals with an investigation of the topic's principal characteristics as well as the control and prevention measures which are available to experts in the field and which are used to contrast this phenomenon.

As statistics demonstrate, current strategies are insufficient in preventing the occurrence of the phenomenon, much less eliminating it altogether, even if there are counter-measures which are relatively efficient in dealing with the problem once it has been officially declared, with all its ensuing ominous consequences.

It is thus beneficial to present a research study which provides a more detailed description of the problem, proposing improved intervention strategies and supporting the decision-making required to prevent or control outbreaks of the phenomenon.

Although the subject has long been widely researched, above all in the field of epidemiology, the development of new software based on multi-agent paradigms can, in our opinion, play an important contributing role.

Thus, it was decided to use a modelling and Event-Based simulation approach, a development of the agent-based system. It proved capable of realistically representing complex human activity and use of space scenarios by integrating the classic bottom up approach with a high-level architecture to plan agent behaviour.

The structured knowledge generated during the system problem analysis phase have been attributed to elements of the completed logical model. Moreover, the characteristics that the agents were able to display were fitted with the pre-selected topic and extended.

During the development of the model, our aim was to stress the potential of the approach as a means to yielding interesting and detailed considerations. The framework was extended to include other features, for example agent perception of the situation or the influence of environmental conditions on his behaviour.

The underlying aim was to increase the descriptive capacity of the framework (and thus the expressive level of the simulation) to achieve a higher degree of complexity, so rendering the model more geared toward the reality of the phenomenon.

Compared with other examples in literature, our model was built to overcome a number of conceptual and instrumental limits, above all regarding the spatial spread of contamination. Even if current available data in literature is not detailed enough to allow for an accurate quantification of the weight of interrelations between the variables under study.

A further innovative feature is that of interpreting the phenomenon with regard to its relationship with built spaces, both in a physical sense as well as that perceived by agents. It was chosen to analyse this aspect in collaboration with

Prof. Yehuda E. Kalay's research group at the Faculty of Architecture of Technion (Israel).

The behaviour of system agents with regard to their conditions and contamination capacity was formulated by the use of a discrete equation. The model and equation were then implemented within a virtual simulation environment, Unity 3D, and the logical functions coded in c#.

The simulation of a hypothetical case study and scenarios with initial varied settings helped to verify the efficacy of the modelling and formalisation thanks to the possibility of dynamic visualisation provided by the tool software.

It is true that the model requires further calibration, which could also be through data collection to retrieve all the information necessary to feed the system. However, the modelled scenarios and an initial sensitivity analysis provide us with a certain degree of confidence about the validity of the output results.

We can thus state that the developed system may be used as decision-making support for this particular modelled phenomenon, thus justifying our choice of agent methodology in the modelling of complex phenomena in the field of urban planning.

As research continues, so improvements will be made in the definition of the discrete formula adopted, continuously extending it to reflect real life. A further aim is the application of the system to a real-life case study, providing us with a database in line with the proposed model.

key words

Decision Support System, Event-Based Modelling, Agent-Based Simulation, Hospital Acquired Infection, Infection Prevention and Control, Hand Hygiene.

EXTENDED ABSTRACT

Il percorso di ricerca presentato in questo lavoro si inserisce nell'ambito dello sviluppo dei sistemi di supporto alla decisione nel campo dell'Ingegneria del Territorio, nel caso particolare della gestione della conoscenza spaziale in condizioni di rischio.

L'oggetto di decisione in questo ambito è caratterizzato per essere un sistema complesso, composto di svariati sotto sistemi anch'essi complessi. La complessità è infatti una caratteristica propria di tutti i sistemi che comprendono elementi viventi e nella pianificazione territoriale l'agente umano o naturale è ubiquo.

Per poter sviluppare la ricerca si è scelto un settore problema che è quello della diffusione delle infezioni nei reparti ospedalieri. In particolare si è scelto di concentrarsi sulla trasmissione tramite contatto.

Questo tema è stato dimostrato essere una questione di rilevanza planetaria, da un punto di vista economico e ancor più per il rischio diretto alla salute umana.

Nella prima parte della tesi il tema è indagato, sia rispetto alle sue precipue caratteristiche, sia rispetto alle misure di controllo e prevenzione che esperti del settore hanno a disposizione ed attuano per contrastare il fenomeno.

Come le statistiche dimostrano le attuali strategie non sono sufficienti a evitare il verificarsi del fenomeno, né tantomeno potrebbero eliminarlo, quanto piuttosto sono delle contromisure più o meno efficaci ed intraprese quando il problema è conclamato, con tutte le nefaste conseguenze.

La ricerca di un più raffinata descrizione del problema, così da suggerire migliori strategie di intervento e supportare la presa di decisioni atte a prevenire l'insorgenza del fenomeno o a controllarlo, è auspicabile.

Per quanto la questione sia stata ampiamente indagata nei secoli soprattutto nel settore della epidemiologia, lo sviluppo di nuovi strumenti software basati sul paradigma del sistema multi agente può a nostro parere dare un contributo rilevante.

Si è quindi scelto di utilizzare un approccio di modellazione e simulazione Event-Based, che è un'evoluzione del sistema ad agenti puro. Esso si è dimostrato capace di rappresentare realisticamente complessi scenari di attività umane e d'uso di spazi tramite l'integrazione del classico approccio bottom-up con una architettura di alto livello per la pianificazione dei comportamenti degli agenti.

La conoscenza strutturata che si è generata nella fase di analisi del sistema problema è stata attribuita agli elementi del modello logico realizzato. Le caratteristiche che gli agenti erano in grado di esprimere sono state accordate al tema prescelto ed ampliate.

Inoltre nello sviluppo del modello si è voluto stressare le potenzialità dell'approccio scelto al fine di poter introitare interessanti considerazione di dettaglio. Il framework è stato esteso per rappresentare aspetti quali ad esempio la percezione del contesto da parte degli agenti e l'influenza delle condizioni ambientali sui loro comportamenti.

Il fine sotteso è stato quello di aumentare le capacità descrittive del l'approccio e di conseguenza l'espressività della simulazione verso una complessificazione che rendesse il modello più calzante alla realtà del fenomeno.

Rispetto ai modelli di letteratura quello qui presentato è stato costruito per superarne alcune limitazioni concettuali e strumentali soprattutto riguardanti l'inclusione dell'aspetto di diffusione spaziale della contaminazione, ancorché i dati attualmente disponibili in letteratura non sono sufficientemente fini per poter correttamente quantificare il peso delle interrelazioni fra le variabili considerate.

L'interpretazione del fenomeno rispetto alla sua relazione con gli spazi costruiti, sia fisici sia considerati nella comprensione di essi da parte degli agenti, è un aspetto innovativo che si è scelto di analizzare in collaborazione con il gruppo di ricerca del Prof. Yehuda E. Kalay presso la facoltà di architettura del Technion, (IL).

Dunque il comportamento degli agenti del sistema rispetto alla loro condizione e capacità di contaminazione è stato formulato attraverso una equazione discreta. Il modello e la equazione sono stati poi implementati in un ambiente di simulazione virtuale, Unity 3D e le funzioni logiche codificate in C#.

La simulazione di un caso di studio ipotetico e di scenari iniziali variamente settati è servita a verificare la bontà della modellazione e della formalizzazione, grazie alla possibilità di visualizzazione dinamica che offre lo strumento software.

Per quanto il modello necessiti di ulteriori passaggi di calibrazione, anche attraverso una campagna di data-collection mirata a raccogliere in maniera contestuale tutti i dati necessari come input per il sistema, gli scenari modellati e una prima analisi di sensitività ci offrono un certo grado di confidenza sulla bontà degli output.

Possiamo quindi affermare che il modello sviluppato può fungere da supporto alle decisioni per lo specifico fenomeno modellato ed ancor più conforta la nostra scelta della metodologia ad agenti per la modellazione di fenomeni complessi nel campo della pianificazione territoriale.

Come proseguo della ricerca ci si propone di migliorare la definizione della formulazione discreta adottata, estendendola al continuo così da rispecchiare la realtà ed è inoltre auspicabile l'applicazione del sistema ad un caso di studio reale che ci offra una base dati coerente con il modello proposto.

key words

Decision Support System, Event-Based Modelling, Agent-Based Simulation, Hospital Acquired Infection, Infection Prevention and Control, Hand Hygiene.

INDEX/INDICE

1 INTRODUCTION

This chapter starts by giving a presentation of the research in order to provide an initial understanding of the scientific reference areas and of the essential steps taken to tackle the core topic, followed by a description of how the thesis is organized.

It continues by outlining a scientific and pragmatic overview of the background problems encountered in carrying out the study.

Subsequently, the case study is presented together with the principal reasons behind the research, a hypothesis drawn up to respond to questions brought up by the study and a description of requirements and constraints.

A summary of estimated results and potential applications concludes the chapter.

1,1 PREFACE

The healthcare environment is a complex system of several agents: physical (environment), biological (pathogens) and cognitive (humans).

Every element and its relations exhibit typically structured behaviour which follows readable patterns, as well as emerging dynamic ones that are usually unpredictable, through mathematical modelling approaches (R. Axelrod, 1997). Consequently, it is difficult to find an optimal plan to manage hospital resources as regards the effects of organizational intervention and the impact of built space. Models and simulations are frequently employed to support decision-making in two areas of health care management: optimization of the use of hospital resources and control of the spread of HAIs, hospital-acquired infections, i.e. infections contracted during the hospitalization (Ferrer, Salmon and Temime, 2013).

The spread of infections is recognized worldwide as a major hazard affecting hospital security. (World Health Organization, 2002). HAIs, if not always deadly, can be severely detrimental to patient well-being and contribute to a significant burden for both the patient and public health resources. In these circumstances, HAI prevention and control becomes absolutely vital (World Health Organisation, 2004). Moreover, the failure to assess HAI risks properly in the earlier stage of hospitals construction can subsequently lead to expensive re-design and renovation. An unwanted consequence of this is the exposure of patients and healthcare workers to infectious diseases caused by dust and fungal spores that are released during demolition and re-construction (Department of Heallth Estates & Facilities, 2013).

Nowadays, healthcare managers rely on the expertise of practitioners to assess and improve on this issue, e.g. reconfiguring the hospital staffing organization and rearranging operational units both physically and through regulations. Nevertheless, to guarantee an effective infection prevention and control program it is essential to improve the current limited understanding of the dynamics of infection spread and to foresee the effects of intervention policies, environmental organization and spatial design against HAIs. Likely adapting this knowledge domain to features (type of operational unit, architecture of environment, workflow organization and more) of the specific context of interest.

In this study, we present the modelling and simulation of Hospital Acquired Infection (HAI) propagation dynamics through exogenous cross-infection by a contact transmission route in a hospital ward.

The contamination propagation phenomenon has multi-factor roots and proceeds through a dynamic transmission mechanism which often leads to outbreaks. It overlaps hospital processes, events and workflows at the top level of the system. This, in turn, affects lower levels through infection prevention and control procedures. Finally, at the bottom level, it influences and is influenced by spatial design related aspects.

The processes of analysing, modelling and simulating such multi-level relations through interaction among these agents are both challenging and intriguing for our research study. Due to its inherent complexity, it is a crucial yet still unresolved issue.

To tackle this subject, our study develops a “what-if” analysis that focuses on the modelling of a mechanism for contamination transmission. Our major concern is to assess how infectious diseases will progress under different environmental conditions and parameter settings. To this end, computer simulation is a valuable approach in investigating “what-if” scenarios, providing evidence in support of decision-making processes. Simulation has been recognised by international literature as an efficient method for evaluating the performance of designed systems when the relationships among decision variables are too difficult to be established analytically (Kalay, 2004).

The present study develops a model and simulation framework that is meant to deal with a wide range of pathogen types and scenarios of their spread within a hospital environment, i.e. a system adaptable to various hospital units which is easily modifiable and can be extended to integrate relevant emerging factors in the dynamic evolution of HAIs.

Our approach relies on the Event Based Modelling and Simulation (EBMS) technique and is a flexible system that can be calibrated with a high degree of sensitivity for the behaviour and interaction of agents (Schaumann et al., 2015) Its application to the specific domain of HAI has never been attempted previously. Therefore, the EBMS was expanded with the aim of simulating both HAI transmission via a contact route in a spatially explicit, heterogeneously mixed environment and its propagation dynamics within a hospital ward, modelling the profile and behaviour of individuals, the characteristics of pathogens and the role of inanimate objects and spaces.

References, guidelines and sessions with experienced medical practitioners led us to understand the features of HAIs and the established protocols and best practices to manage them. This step helped us to verify our hypotheses and build a model that aimed to accurately manage and represent the complex inter-relations between all the major features which up to now have only been investigated singly.

Thus, we developed the model and its architecture and demonstrated its potential applications through the simulation of a hypothetical case study built in a Unity 3D environment. It was then tested with different virtual scenarios, allowing for the real-time visualization of contamination transmission and understanding the effect of different control measures, architectural design and spatial distribution on pathogen propagation.

It proved useful to study the dynamics of pathogen circulation (e.g. to visualize clusters of infected patients and patterns of occurrence), as this demonstrated how these may vary depending on initial causes and conditions, the heterogeneity of agents' features and spatially related configurations.

The developed framework can be used as a decision support system (DSS) for practitioners and policymakers when employed as forecasting tool for the evaluation of policies idea. In fact, a system user can generate new input conditions and after system parameter tuning (e.g. actors' profiles and behaviour and re-configuration of settings), by simulating scenarios she/he may figure out the possible state patterns in the development of a situation (Jit and Brisson, 2011).

A comparison of the experiment's qualitative results is valuable in assessing the effectiveness of the implementation of control strategies, namely practices and procedures (e.g. agent hygiene behaviour and contact precautions), as well as shedding light on possible control protocol breaches in infection outbreak management (Fatah, 2012).

Finally, this study attempts to test the potential of the EBMS framework in modelling human spatial behaviour, envisioning how social interaction and spatial influences can affect the spread of HAIs.

Currently, we are applying this method to a hospital that has already been built in order to gather information and data and compare simulated functions with real-life circumstances, thus validating the modelling structure and its results.

1,2 OUTLINE OF THE DISSERTATION

The thesis is divided into five principal chapters as follows:

In the introduction, we present the scope of the thesis, highlighting the problem domain that forms the core of this study and the role of the model dealing with complex systems. The motivation, aims and objectives of the thesis are then presented and the research requirements included. The questions posed by the research are discussed through the definition of a hypothesis and aims for the chosen subject. Possible results and their relevance are then outlined.

Subsequently, the second chapter of the thesis focuses on the problem domain. We define in detail the case study characteristics, discussing prevention and control guidelines and features related to a healthcare environment.

The second part of the thesis sets out the solution domain and describes our proposal.
In the third chapter, we present a literature review of theoretical approaches and formal approaches to model and simulate HAIs, namely the major mathematical, compartmental and agent-based approaches applied to HAIs. In the same chapter, there is a detailed description of the framework selected, the Event Based Modelling and Simulation approach.

After this, our framework for infection propagation is defined in detail.
In the fourth chapter, we describe the conceptualization, methodology and architecture and formulation created for the model. The model is then tested by means of a simple case study simulated in a Unity 3D environment, comparing different scenarios; simulation assessments with an outline of experiment outcome analysis close the chapter.

A final chapter concludes the thesis, with a discussion and possible areas for future work and applications.

0.3 DECISION SUPPORT SYSTEM

This research study focuses on decision-making support for the management of complex systems under conditions of risk.

Decision-making support involves the analysis of a system through methods and models and consideration of the context and its variables. The analysis aims to understand the system more clearly; moreover, its objective is to use this knowledge to facilitate decision-making. Conversely, the aims of decision-making influence the way in which its support should be defined (Fig 1).

Research in the field of Decision Support Systems (DSS) applied to planning aims towards improving decision-making processes in public administrations and aiding professionals in the field of infrastructural and service development within cities. DSS approaches help managers in estimating the implications and consequences of possible decisions before their actual execution, allowing them to make better decisions (Furtado, 2015).

Decision-making, on the other hand, involves identifying the various possibilities of actions and choosing one or more of these through an evaluation process; the choice must be sensible and rational, based on evidence. The objective of the decision is to plan policies and measures that oversee the development of the system under study (Fig. 1).

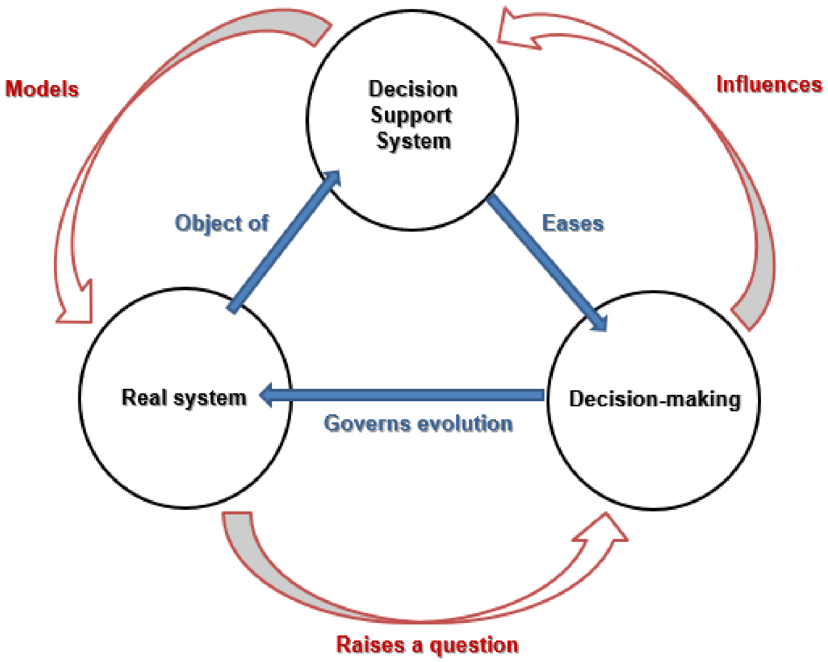


Fig. 1 – Model of relationships in a Decision Support System.

Decisions in the field of Land Engineering have long-term implications which directly affect its development. They involve the creation of public spaces and infrastructures to develop socialising and activities through the realisation of urban projects in selected areas. This in turn affects people's experience of cities and life, since built environments support the living and safety needs of their inhabitants (McLoughlin, 1969).

The design of public infrastructures is increasingly significant in a context which sees numerous economic interests, user needs and interrelated functions expressed through built space.

This complex reality makes the proposals of designers, together with the choices made by contractors such as public administrations, a complex process (Bertuglia, Bianchi and Mela, 1998). In such a context, envisioning the various

consequences of implementing specific solutions is of the utmost importance for the process to succeed (Borri et al., 2015).
This issue becomes considerably more difficult when the objects of interest are complex infrastructures such as hospitals, where performances are related to a large number of functional, typological and organizational requirements. It is also where, among other factors, human considerations such as satisfaction with the quality of care and patient and staff safety are major concerns.
A badly-designed, inefficient building, failing to support the activities of the people that occupy it (e.g. a waste of space) will not only hinder the users' quality of life, but could sometimes be potentially dangerous. It could lead to delays in job task accomplishment, dissatisfaction and stress and user safety hazards (health risks such as fall injuries or diseases) (Schaumann, Pilosof, et al., 2016).
In this respect, when designing settings architects should meet the requirements and expectations expressed by their intended users. This is a task inherently oriented to account for human factors as they should be able to assess to what extent the future design will support activities and needs.

Nowadays, practitioners and policymakers have at their disposal several computational tools which follow established mathematical models. These can help predict and evaluate a plethora of quantitative building performances and characteristics such as costs, energy consumption, material features, structural stability, temperature, acoustic and light impact and so on (Schaumann, Pilosof, et al., 2016)
Nevertheless, in addition to such measurable issues, contemporary sustainable design should likewise consider social dimensions as a fundamental part of it. Analytical approaches in evaluating most qualitative aspects (e.g. buildings-use, human spatial behaviour, human satisfaction and safety issues) suffer from severe limitations and neither can a real-size prototype be built and tested before construction itself. Furthermore, this aspect has become a critical issue in the

challenge to translate it into effective guidelines, moving from general thematic goals to applicable suggestions and rules.
Hence, human-related decisions are normally based on partial knowledge, such as designers' intuition, imagination or know-how based on similar cases and their successes and failures. The best cases are based on a set of average users' requirements and on the assumption that they will fulfil the needs of most them. A more truthful evaluation on whether a design fits the needs of users can be performed solely post-construction through Post Occupancy Evaluation (POE) (Zimring, 2002). Yet this is a risky method, especially for complex, expensive projects like healthcare facilities, as errors could cost millions. Problems may appear when it is too late, after building has been completed, leading to destructive and costly reconstruction without guarantee and whereby improvements frequently only relieve symptoms.
Decision makers must rely on (and at the same time respect) regulations, design rules and legislative factors. Nevertheless, their capacity to fully comprehend the complexity of human-building interaction has shown its limits, mirroring the increasing complexity of building design and variety of human behaviour with all its consequent requirements (Simeone et al., 2013).

Understanding the role which the environment plays in human performance early in the planning process phase poses a major difficulty, particularly given how different environments impact on human decisions, movement and socializing (Gehl, 2010) (Wei and Yehuda, 2007).
The system of human spatial behaviour depends on an individual's "decisions through actions" that are generally influenced by numerous factors linked in an unpredictable way. Indeed, human behaviour in space shows mixed mechanisms that give rise to emergent phenomena: from the natural tendency to stay at a distance (e.g. proxemics) to imitation effect, from competition for shared space and between different activities to co-operation (non-written social norms) to prevent stall situations (Hall, 1966) (Stokols, 1972).

More complications appear when considering human heterogeneity, the co-ordinated activities of multiple agents and the varieties of social interaction occurring simultaneously between individuals during their behaviour development. These factors frequently lead to unexpected conflicts, such as gathering and crowding, queueing or interruption of activity. These have been extensively investigated in literature, see for instance (Hoogendoorn, 2001) (Shelby, Vaske and Heberlein, 1989) (Pan, Han and Law, 2005) (Hajibabai et al., 2007)

On the other hand, there is an intrinsic limit to what extent decision makers can use their imagination and experience to forecast emerging phenomena in spatial complex systems. This is because the form (design options) following the function (processes and activities) of artefacts is given by the designer, who draws shapes and structures in order to address a need that he has identified. Nonetheless, the use of these artefacts could be different from what the designer previously intended, since this could be entirely different from the artefact's function and it changes as a response to context (cultural, environmental, psychological, and so on). Use dictates spatial behaviour in humans as well as reflecting emerging understanding and creativity. This is why it is more dynamic (varying from person to person and over a short time) than any functional considerations (Arecchi, 2007).

For these reasons, decision makers often fail to foresee the implications of their decisions. Human related aspects are too complex to be predicted accurately. However, while a gap exists between expected and actual agent behaviour (which may lead to unintended consequences), decisions cannot simply be ignored.

Therefore, decision makers constantly require innovative methods to assess the implications of decisions related to humans, as these are crucial in addressing issues appropriately and as early and thoroughly as possible.
This topic poses a huge challenge for multidisciplinary research studies since it requires a consideration of human factors, qualitative variables deriving from social and cognitive sciences and psychology and sociology, affecting the choices of each user and thus impacting upon their behaviour.

0,4 CASE STUDY

It is worth considering that in human related sciences such as architecture, social sciences and urban planning, proof is hard to come by due to an absence of predictive theories and mathematical representation of phenomena (Crooks, Patel and Wise, 2014). These sciences cannot produce general, context-independent theories and so ultimately have nothing else to offer other than concrete, context-dependent knowledge (Flyvbjerg, 2006).
Nevertheless, case study research excels at providing an understanding and explanation of a complex issue and can extend experience or add strength to what is already known through previous research. Case study research emphasizes detailed contextual analysis of specific evenst or conditions and their relationships. In such circumstances, the case study approach is especially well-suited to produce the kind of knowledge needed to support the decision-making process (Soy, 1997).
Although research observes methods and models, it can not develop a theoretical study methodology. Its aim is rather that of developing a model to support and improve the decision-making processes in a specific domain.

As stated previously, the area of interest in this study is a system under conditions of risk, specifically that of healthcare environment management and design.
Hospitals are particularly complex buildings, with a wide variety of users and functions that are carried out in the same location. At the same time, they are conceived as human-centred settings designed to cure patients, where a wide array of expertise is used and procedures are devised to maximize the number of patients to be treated in the most efficient ways. Even if they can be considered as highly specialized "machines", a balance to meet the different needs of patients, visitors and staff members within hospitals is constantly being researched (Schaumann, Pilosof, et al., 2016). Although all sub-systems, namely

environment, personnel and technology share a common objective (i.e. to guarantee that patients regain their health and are not harmed further during their stay in the hospital), there may be conflicts between the sub-systems themselves, for instance if they are competing for the same space to conduct different activities at the same time. (Jiménez, Lewis and Eubank, 2013)

Hospitals around the world deal with the perennial pressure of ensuring cost efficiency and so target areas include the optimization of processes and flow and the reduction of admission and waiting times and length of stay. However, these concerns do not always correspond to user satisfaction or safety.

Operational efficiency in hospitals is heavily influenced by the design of the built environment and by decisions taken to manage them.

Since every solution is created to address a problem, our chosen area related to a healthcare environment and the health risk of a Hospital Acquired Infection (HAI) with particular emphasis on the spatial spread of the risk. Safety and health risks often arise and must be managed through decision-making processes. They can be divided into "problem areas" by type and by location, such as specific patient care spaces, departmental areas (nursing units, diagnostic and treatment units) and public areas (corridors, lobbies, waiting rooms) (Yehuda, 2013). This feature of risk was of particular interest in the selection and interpretation of our case study.

Moreover, such a core domain exploits crucial safety requirement in healthcare environments. It guarantees that our research is of relevance, since HAIs are a major threat to hospital users all over the world and are cited as the third most common cause of death in the USA.

Furthermore, focusing on HAIs in a hospital ward setting allows us to reduce the overall complexity of human spatial behaviour to a fully expressive level, which is more manageable for our agent-based method. The Event Based modelling and simulation of the case study aims to demonstrate its potential in supporting decision-making for uncertain and risky situations, such as the spread of infections in hospitals.

This case study choice supports us in proving our hypothesis and testing our methodology. Moreover, it does not affect the general validity of the approach, since our model framework is designed in such a way that it can be easily modified and extended to make it applicable to other domains.

0,5 THE ROLE OF THE MODEL

In the writer's opinion, it would be useful to illustrate in a concise way how decision support systems (namely systems of inquiry and the elaboration of knowledge applied to complex systems) are formally useful in describing reality and its evolution, where possible. Moreover, it is interesting to see how, under certain conditions, they are able to determine it in a significant way, verifying the principle which states that "every action is knowledge and every knowledge is action" (Maturana and Varela, 1980).

Firstly, we must remember that complexity does not exist in nature as an entity in itself and there is no uniform, formal definition of it. Indeed, there are numerous cases in various scientific areas where the theme of complexity is investigated. On the other hand, we know how to recognize complexity when it is necessary, or rather when we have to deal with a system that displays such a condition. This means that its properties, albeit emerging, have been identified and are useful in describing the different features of systems that give rise to complexity (Lloyd, 2001).

These properties thus form a more precise definition of complexity that the scientific investigation then uses to explain the fundamental characteristics of the living systems that allow it to evolve. We can therefore state that the complexity of a system is not only an intrinsic property; as it always refers to its emerging description, it also depends on the method used for its own understanding, namely the model of representation and knowledge (Le Moigne, 1994).

Even if it may seem trivial, it is useful to focus on the fact that complexity is both a real and semantic feature of systems. Therefore, in order to understand complex reality it is necessary to broaden our background knowledge of it. In other words, it is essential to improve the methods of knowledge formation for complex systems, or rather to organize complex and disorganized knowledge in organized forms of complex knowledge (Weaver, 1948). This condition is of interest, since it shows the role of meaning in giving value to a real context in reorganization (Jacobs, 1961), when, for example, in linguistics one focuses on the precise opposite; "nothing has meaning without a context". There are examples throughout scientific research where even though a resource may be available (for example, oil), it cannot be used until the establishment of a context that has been influenced by new knowledge; in the case of oil this can be seen as the industrial revolution and the invention of the combustion engine.

Among the many properties of complex systems, it is useful to recall the principle of the adjacent possible proposed by S. Kauffman, according to whom at any given moment there are billions of potential configurations of future evolution of reality (a complex system) that are not, however, infinite since each stage must derive from what precedes it (Kauffman, 1995). What is achieved is therefore only one particular path traced along the constant succession of bifurcation moments and choices, where each bifurcation is an instability and potentially a crisis. Thanks to the concept of bifurcation, it is possible to analyse the historical dimension of the complex system, Fig. 2 (May, 1976).

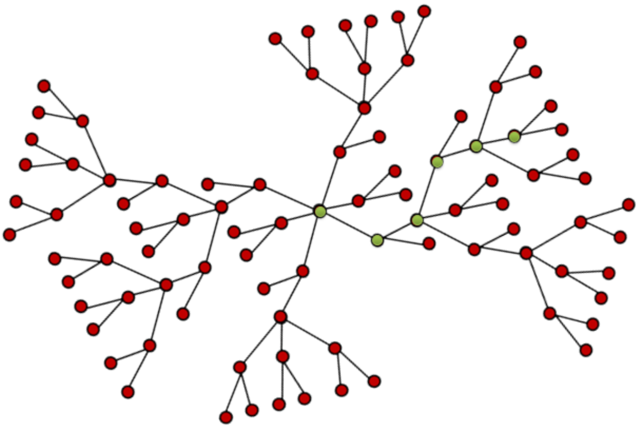


Fig. 2 – Tree shaped representation of a complex system development over time.

Fig. 2 represents the path towards the development of a complex system in an abstract way as a succession of green points. The figure can only be created by looking at the past from the point where it is observed. Indeed, the future is not a path that has already been traced and has numerous alternative scenarios. The evolution of the system is therefore unpredictable because at every point of bifurcation we cannot predict which branch will be followed by the system. Consequently, the intrinsically complex system has the quality of being dependent on a unique path that has been traced up to that instant and is therefore inherently unpredictable.

We can easily understand that the more we (hypothetically) direct our gaze to the future, the greater the number of possible branches reality can take. The margins of evolutionary possibilities expand and likewise our ability to predict accuracy decreases; in effect, “prédire n’est pas expliquer” (Thom, Noël and Chenciner, 2009).

A reaffirmation that every evolutionary path is unique can be seen in the principle of equifinality proposed by Von Bertalanffy. According to this theory, in open systems (complex real systems) the same results can have different origins. In

other words, the same final state ("final" since the study is due to end at that moment) can be achieved in several ways (paths), starting from different initial conditions. This principle was elaborated to demonstrate how deterministic explanations (causative mechanisms) were insufficient in the analysis of complex phenomena (Von Bertalanffy, 1968).
This argument adds to the fact that there are many probable scenarios for a future evolution of complex systems, while there are many likely past paths that have led to that particular state of the system. If we modify the representation accordingly, the image does not develop into a tree shape but to a semilattice, Fig. 3 (Alexander, 1966).

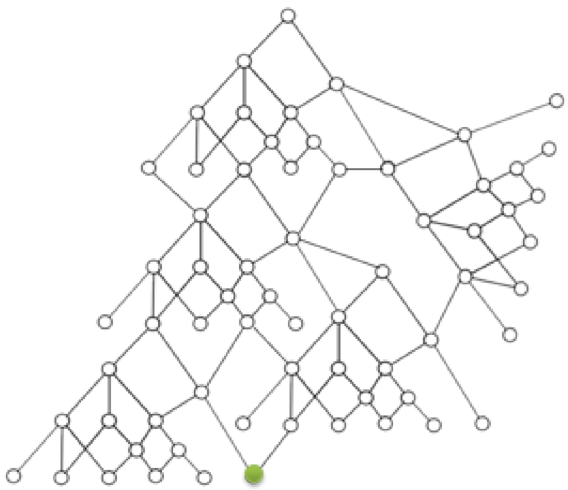


Fig. 3 – Semilattice-shaped representation of a complex system development over time up to the moment of observation.

Thus, to reach a certain point in the development path of a complex system (green point), different paths can be followed. For this same reason, the evolutionary path of a complex system is also irreversible, since from a certain point in time it cannot be traced back along exactly the same path that was being followed until that moment.

Whereas this is the case for the past, we can fractally extend the figure to consider the future of the complex system Fig 4, (Mandelbrot, 1983).

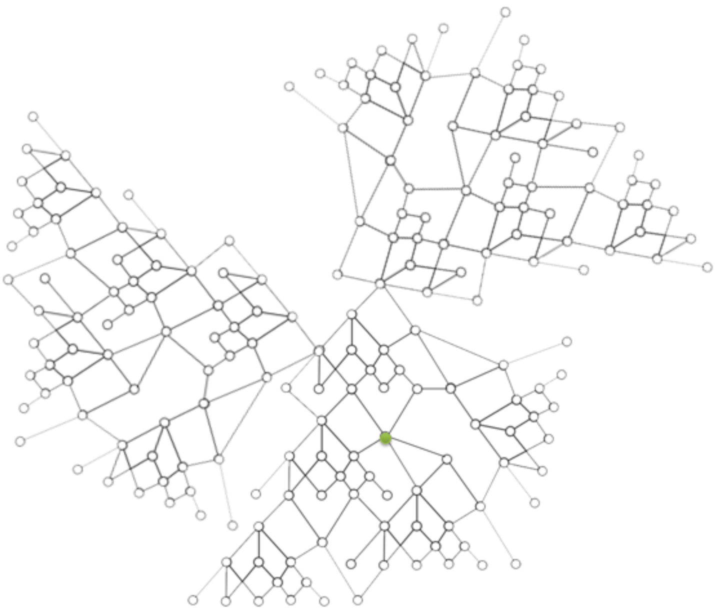


Fig. 4 – Semilattice-shaped representation of a complex system development over time towards the future.

We may now consider that nodes with greater connections are most likely along the evolutionary path and act as evolutionary attractors (Bertuglia and Vaio, 2011).

As regards this subject, the system developed in the thesis allows us to visualize temporal-space pathways of pathogens that work similarly on a semilattice shape with an agent or an event in each node. The system can be used to identify critical nodes during pathogen spread and suggest that the decision-maker acts on these so as to block propagation or channel it along controlled development paths. In the modelling of our case study, it was essential to allow for an imaginary description of these particular nodes.

Conversely, the line of reasoning adopted in the methodology has implications for the role of the model itself. As it cannot predict the evolution of a complex system, it can perhaps determine the evolution of the complex system of which it becomes part. This is because a model is created to understand the functioning of the complex system, which is characterized by the fact that it also uses knowledge models in order to evolve (Holland, 1995).

Above all, we believe that the model, operating as a synthesiser of knowledge and scenario-maker, generates ideas creatively. "Creativity is expressed in a context of strong intention: intention finalizes choices, recombines elements, and activates potentials in a given situation." (G. Rabino)
Perhaps we could also say that in essence, the concept behind the model is the idea that it produces, with a substantial overlap of causality and purpose.

At the time of its creation, the model gave rise to a concept of possibility that had not existed previously. This concept can act as an attractor for the future of the system which it refers to and which it is now part of. When such a concept blends into the form of ideas in the complex system, acting as a groundbreaking feature and establishing connections with real cases before its concrete space-time expression, it can influence its evolution.

It seems plausible, therefore, that this part-learned and part-imagined intangible knowledge can in fact guide the material evolution of the complex system. Only in this way can mankind attempt, like Alice, to strike the hedgehog with the flamingo (Carrol, 1865).

0,6 PURPOSE, REQUIREMENTS AND CONSTRAINTS

The developed model is a clear, formal description of a real-system problem.
The problem domain was interpreted in terms of a system process and in order to study it, we made a set of assumptions on how it operates. These assumptions are the basis of our model and use a number of different forms, from mathematical and logical relationships to behavioural rules.
Our model is the result of a conceptual abstract of reality. It is a process of grouping together data and information with its summary and interpretation, based on the knowledge that clarifies what its relevant aspects are. Consequently, it focuses on the principal features for the context in which the system was studied, excluding non-essential details.
We attempt to explain the mechanisms behind the phenomenon under study in an attempt to gain some understanding of how the corresponding system behaves.
If the relationships that compose models were sufficiently simple, it would have been possible to use mathematical methods, e.g. system equations, to obtain precise information for our areas of interest. This is referred to as an analytic solution (Kelton, Sadowski and Sturrock, 2010).
In our case, the real-world system is too complex to allow for a realistic model to be evaluated analytically; thus, analytical solution is not available or is computationally inefficient (Borshchev and Filippov, 2004).
Alternatively, such highly complex systems could be replicated and therefore studied by means of computer simulation. A simulation model is preferable to model complex systems as it is more appropriate for modelling dynamic and transient effects (Pidd, 2004).

We chose Event Based modelling and simulation (EBMS) techniques to represent the development of the model over time and in space. Where possible or available, data was collected in order to estimate the desired true characteristics of the model. We used a computer engine simulation to implement the model, investigating, more likely quantitatively or less likely qualitatively, how the inputs in question could affect the output measurements of performance (Law and Kelton, 1991)

Our purpose was to apply EBMS method to the management of Hospital Acquired Infections. One of the key functions of management is planning, which is directly related to decision-making. Therefore, the underlying aim of our method was to support decision-making processes.

We represent the building and its users in the situation of HAI risk in a coherent and dynamic system.

Our agent-based system works through the variation of one specific agent feature, which is his contamination condition and capacity. This constantly relates to the contamination condition and capacity of other agents through the agents' relation law, which we formalized.

Thus, we create a contamination spreading model, translating the knowledge of the problem into the semantic enrichment of the elements which compose it, allowing us to perform the subsequent simulation.

We developed the simulation by coding the script into the event-based simulator, a tool currently under development at the Kalay research group at Technion (Israel). The C# code is the link between the conceptual process of modelling the phenomenon and the simulation itself.

Thus, that we integrate the system elements in a virtual simulation of the use of space in the building, correlated with the contamination propagation through a contact transmission route.

Such a simulation allows for the visualization of contamination propagation due to human spatial behaviour and user activities in the built environment, with real-time results and a data-log.

The working proof of a "what-if" scenario concept demonstrated the value of the developed framework as a decision support system (DSS) in the field of hospital management.

Processes underlying human behaviour in space are considered up to a level of abstraction which becomes relevant from a decision-making point of view, visualizing their influence on spaces and places. To this end, in considering the 1st step (the problem domain knowledge which acts as research input) and the 3rd step (the research outputs), we need a brief initial explanation of the 3rd step used to modify the 2nd intermediate step (model breadth), i.e. showing how input data is elaborated by the modelled system to produce a coherent output. This does not mean that we need to have the answer to the stated problem in advance, but rather that we need to define what the significant features of it are, which can be useful in assembling the framework in a more effective way.

Our objective is to model and simulate the transmission dynamics of HAI related to human spatial behaviour and considerations about the use of built space. Thus, the foundation for our model is based on human factor studies, cognitive science, environmental psychology, artificial intelligence and more, see for instance (Fishbein and Ajzen, 2009) (Gibson, 1986) (Minsky, Kurzweil and Mann, 1991) (Simon, 1992) (Montello, 1997) (Langley, Choi and Shapiro, 2004) (Schmidt and Passau, 2005) (Laird, 2012) (Reynaud et al., 2013) (Vernon, 2014) (Esposito, Mastrodonato and Camarda, 2017)

The following table lists the key themes in the context of the research study, organized according to the level of enquiry. They form a significant role in the theoretical and methodological mainstream framework of the study (Table 1).

RESEARCH ENQUIRY LEVELS	LEVELS OF REPRESENTATION OF THE SUBJECT	RESEARCH APPROACHES TO STUDY THE SUBJECT
UNDERSTANDING AND DESCRIPTION OF WHY IT HAPPENS	HUMAN SPATIAL COGNITION AND PERCEPTION FUNCTIONS	COGNITIVE SYSTEM ARCHITECTURES
UNDERSTANDING AND DESCRIPTION OF HOW IT HAPPENS	PROCESSES OF HUMAN SPATIAL MOTIVATION AND BEHAVIOUR	HUMAN SPATIAL BAHAVIOUR AND DECISION-MAKING SYSTEMS
UNDERSTANDING AND DESCRIPTION OF WHAT HAPPENS	INTERACTION MECHANISMS ARISING AGENTS AND SPACE	EVENT-BASED MODEL AND SIMULATION OF THE PHENOMENA

Table 1 – Key themes in the context of the research study.

This wide-reaching representation shows that we are not (or, at least, not only) applying an established simulation approach such as event-based model and simulation (EBMS) to a new subject, as we need a new understanding to develop the EBMS approach further. Thus, we are using the selected HAI topic to do so, by interpreting the case study in the light of a number of interesting insights on spatial cognition and perception through the application of a modified and adapted EBMS framework.

Space, to our knowledge, is not only a physical entity. Due to the presence of cognitive agents through which it is interpreted, space can express qualities, features, potential and more. Our work focuses on properties of the environment as activated, perceived and cognized by humans. Therefore, the model includes aspects of perception of scenery, as well as knowledge of user activity in a hospital setting.

Human spatial behaviour both affects and is affected by the environment, in a feedback loop manner. This refers to agents capable of understanding their environment and acting accordingly, with particular regard to the individual and internal processes which lead to intentions and planning phases in developing specific behaviour (as well as to the consequences of such behaviour) in terms of learned experience.

Given this comprehensive perspective, for the purposes of the present study we focus on observable situations produced and driven by behavioural relationships between actors and spaces. Specifically, it could be the environment which affects an agent's internal status, but unless this implies a change in an agent's spatial behaviour it will not be taken into consideration, as this relates primarily to the post-evaluation phase of agent condition and not the real-time mechanism of interaction, which is what we want to simulate.

These considerations lead us to a definition of the main areas of the present study:

1. Investigation of the multiple features of HAIs;
2. Definition of the relationships and interaction among its key elements;
3. Development of the model framework;
4. Formalization of the conceptual model;
5. Implementation of the formal model in a Unity3D engine environment;
6. Analysis of the simulation experiment results;
7. Simulation assessment.

0,7 EXPECTED RESULTS

The development of the system, applied and tested with the outcomes of the simulation, is fundamental in verifying our hypothesis. This process aims to provide the following features:

- to support decision makers with choices that could impact on the safety of users in a healthcare environment;
- to test "what-if" scenarios in order to explore the effects of possible solutions for the HAI phenomenon and define a balanced, satisfactory trade-off with requirements;
- to estimate the effectiveness of a range of policies aimed at preventing and controlling the HAI of interest;
- to represent the impact of social and spatial factors on the performance of procedures in preventing the outbreak of infection;
- to evaluate to what extent an EBMS (agent-based approach) can be applied as a general framework for modelling and simulation to support decisions and management in the case of HAIs.

The present research was carried out in collaboration with Prof. Kalay's research group at the Architecture Faculty of Technion. The model, together with the EBMS technique built in a tool currently under development, will complement design systems for buildings and should eventually lead to the design of hospitals that are less prone to the outbreak of infection.

The joint evaluation and elaboration of the research has led to the broader purpose of improving understanding of the potential impact of physical and social settings in a built environment on human spatial behaviour. Moreover, it provides insights about human perception and cognition, as well as decision-making and actions to help policy makers and experts to interpret the relationship between the organization of places and human behaviour.

Therefore, the broader scope of the joint research is:

- to provide a visualization of how a building is used and experienced;
- to forecast and assess the building's capacity to support user activities and to satisfy users' functional needs, e.g. safety and satisfaction;
- to examine to what extent the virtual simulation of human behaviour can be suitable in estimating human-related building performances.
- to support designers while making decisions that could impact on the lives of the users of future buildings;
- to evaluate alternative building project proposals and designers' choices before moving onto the construction phase

Consequently, the principal value of the research is to build a model to improve the planning and design of a "human-centred" built environment, thus enabling a consideration of the use of built infrastructures by urban agents. Accordingly, an understanding of individual decisions in actions and behavioural processes in space can support professional knowledge and public administrations in their decision-making procedures in the field of urban infrastructures.

The ability to clarify these themes could have positive consequences for a more concrete way to understand and evaluate the impact of infrastructural design on the future of today's cities. This knowledge will provide strong support for government decision-making processes, allowing decision makers to envision more aware and effective spatial planning and design in the sustainable development of future cities.

2 CASE STUDY DESCRIPTION

2,1 HOSPITAL ACQUIRED INFECTION - PROPAGATION

2,1,1 INTRODUCTION

The first part of the thesis, systematically describe the problem domain and its boundaries.
After the brief discussion on the most urgent issues in hospital environment, the threat e of Hospital Acquired Infection is presented through key concepts. HAIs are defined in relation to the distinctive features of the phenomenon, i.e. pathogens, sources and transmission routes, in the light of human behaviours in hospital spaces and healthcare environment design. Description of well-known intervention policies to prevent and control HAI closes the chapter.

2,1,2 HEALTHCARE ENVIRONMENT CRITICAL ISSUES

Hospital environments are emergency site by definition, so often emerge critical situations to be addressed.
Aiming at addressing the question: “What is the most critical issue in healthcare environments?”. The research Critical Issue in Health Care Environment (HCE) developed and provide a survey through questionnaires. (Cohen, Allison and Witte, 2009)
It was structured in three streams to distinguish between three healthcare environments, i.e. hospital, ambulatory, and long-term care settings.
The objective of the project was to identify and describe critical issues and to associate them with the specific locations where problems occur. Therefore, the research focuses on issues and problems which have a bearing on and from the physical environment.

By highlighting critical problem areas and unresolved issues in need of intervention, the findings can also provide important research questions, setting the priorities of research agenda for healthcare environments.

Over 100 most critical issues in healthcare environments were identified. Top ranked problems included patient care and safety issues, such as hospital acquired infection (HAI), medication and treatments errors and falls, which were shared significantly among all care settings, Fig 5.

Patient care is provided in facilities which range from highly equipped clinics and technologically advanced university hospitals to front-line units with only basic facilities, therefore all over the world a primary charge for healthcare organizations and facilities is to optimize therapeutic outcomes and patient safety.

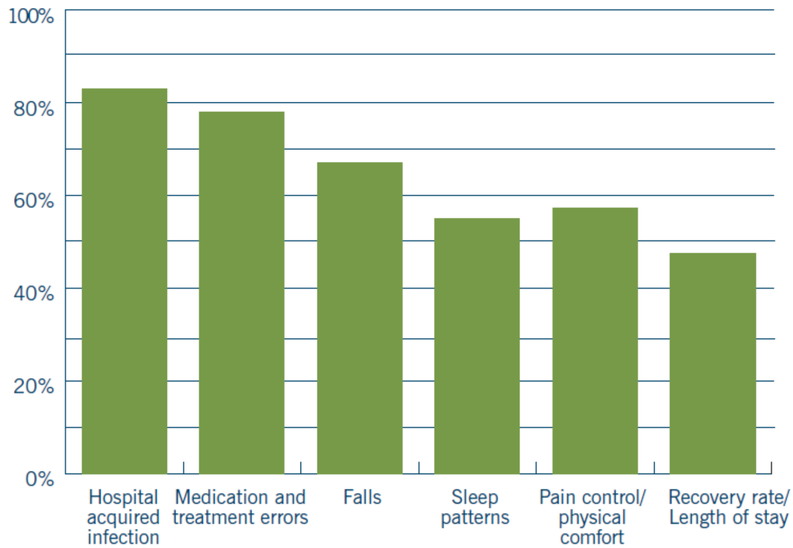


Fig. 5 - Hospital Setting: Percentage of respondents that define patient care problems as serious – ranked either 4 or 5 on scale where 1= “not a problem” and 5= “major problem” (Cohen, Allison and Witte, 2009).

The second part of the survey focuses to the question: “Which locations are associated with more significant and/or a greater number of problems?”, Fig. 6.

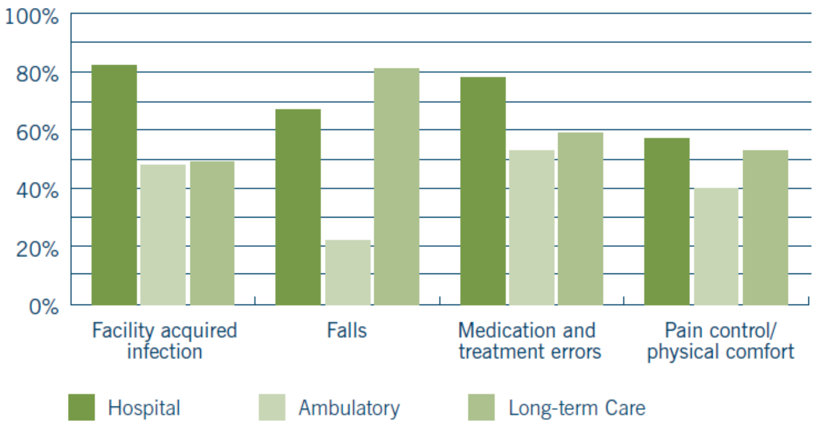


Fig. 6 - Comparison of Serious Patient Care Problems Across Settings – ranked either 4 or 5 on a scale where 1 = "not a problem" and 5 = "major problem" (Cohen, Allison and Witte, 2009)

The question in this subsequent part of the survey is important for two reasons. First, focusing on specific locations in the facility is one approach that can sharpen the focus when conducting built-environment research. Secondly, given the limited resources for conducting health environment research, it is critical to identify the places where research is most needed and significant. Research should be focused first on those places within healthcare settings where problems concentrate, are common, and have the potential for greatest adverse impact if not mitigated.

The results show that specific places associated with either more or greater problems in all facilities were generally spaces where the most significant patient care was delivered, such as patients' rooms, treatment and exam rooms, diagnostic and treatment spaces, preoperative and recovery spaces, and staff work areas.

Although some problems were facility-wide, many other problems converged in particular locations, or had more critical manifestation in those particular locations. For example, patients' rooms in hospitals were top ranked and were the locus for safety issues.

Table 2 below summarizes the findings for the most problematic locations in all three settings:

Table 13: Summary of Locations Identified as Most Problematic

	SPECIFIC PATIENT SPACES	DEPARTMENTS	PUBLIC SPACES
Hospital setting	Patients' rooms	Emergency rooms and departments Nursing units	Parking Waiting rooms
Ambulatory setting			
Facility Types:			
Ambulatory surgical facilities	Treatment and exam rooms		Waiting rooms
Urgent care centers	Pre operative and recovery spaces		
Long-term care environment			
Facility Types:			
Skilled nursing facilities	Resident's rooms Staff control and work areas		Outdoor activity areas

Table 2 - Locations identified as most problematic (Cohen, Allison and Witte, 2009).

Response to the question, "Most problematic location" for the hospital setting revealed the top-ranking problematic locations, Table 3:

	RANK	MEAN	HIGHLY[1] PROBLEMATIC	MOST OFTEN VERY PROBLEMATIC AS A MATTER OF...
Specific spaces or rooms				
Patient rooms**	1	3.45	52.7%	OE
Operating rooms	2	3.12	40.2%	OE / AE
Treatment and exam rooms	3	3.12	37.7%	PC / OE
Diagnostic imaging rooms	4	3.04	35.0%	AC
Departments or Units				
Emergency**	1	3.71	67.6%	PC / OE
Nursing units**	2	3.56	59.7%	PC / OE
Critical care units**	3	3.49	57.4%	PC
Surgery**	4	3.26	43.3%	OE
NICU's**	5	3.06	39.4%	PC
Imaging**	6	2.99	32.3%	AC
Birthing units**	7	2.88	26.1%	PC
Rehab services	8	2.69	20.1%	US
General or Public Areas				
Parking**	1	3.20	44.2%	US
Waiting rooms**	2	3.09	40.2%	US
Corridors**	3	2.87	30.5%	US / PC
Exterior site areas	4	2.61	19.8%	US
Entry and lobby sites	5	2.57	20.9%	US / OE

[1] Highly problematic – combined ranking of 4 and 5 on scale where 1 = "Not problematic" and 5 = "Very problematic"
PC = patient care, US = user satisfaction, OE = operational efficiency, AC = accommodating change
** $p < .01$. * $p < .05$

Table 3 – Ranking of most problematic locations (Cohen, Allison and Witte, 2009).

- Specific Spaces or Rooms: Patients' rooms topped the list, rated as highly problematic by 52.7% of the respondents.
- Departments or nursing units: Emergency rooms and departments topped the list, rated as highly problematic by 67.6% of the respondents, followed by nursing units at 59.7%.
- Public areas: Parking topped the list of problematic spaces and was rated as highly problematic by 44.2% of respondents, followed closely by waiting rooms at 40.2%.

The extreme ratings of hospital locations as very problematic has closely tied to issues of patient care, operational efficiency and user satisfaction.
Results demonstrate that in Hospital settings most frequently identified critical issues and problems concern the patient safety and security issues, such as hospital acquired infection, medical and treatment errors and falls, all those

patient care topics might be influenced by the decisions in regarding the built environment.

Ulrich quantified that and hospital-acquired infections is a leading cause of death in the United States, killing more Americans than AIDS, breast cancer, or automobile accidents. His research was direct on how improved design make hospitals less risky, improving safety. He also proves that a growing scientific literature (his research team identified more than 120 studies linking infection to the healthcare built environment) is confirming that the conventional ways that hospitals are designed contributes to stress and danger. Improved physical settings can be an important tool in making hospitals safer, more healing, and better places to work.
Among other topics, research literature shows that the physical environment strongly impacts hospital-acquired infection rates by affecting both airborne and contact transmission routes. A critical issue for planners is definitely to improves the hospital safety by reducing risk from hospital-acquired infections.
(Ulrich et al., 2004)
Nevertheless, according to Stiller, guidelines for design of healthcare facilities are often vague in their formulation of infrastructural characteristics due to limited evidence in this field of research, a detailed research to enlighten the correlation between hospital design and HAI is mandatory and can lead to the conclusion that hospital ward design could contribute to HAI control (Stiller et al., 2016)

2,1,3 HOSPITAL ACQUIRED INFECTION – DEFINITION

Nosocomial Infections, or Hospital Acquired Infections (HAIs) made their first appearance with the invention of hospitals, mostly associated with surgical operations carried out when germ theory and hand-hygiene were unheard of and post-surgical mortality could be as high as 90% (Coen, 2012).

Hospital Acquired Infections, can be defined as infections caused by microorganisms acquired within in a hospital or other health care facility by a patient who was admitted for a reason other than that infection (World Health Organization, 2002).
Therefore, there must be no evidence that the infection was present or incubating at the time of hospital admission, but develop during the stay in hospital (Emori, 1988).
The Hospital Infection Prevention and Control Guidelines sets in 48 hours the minor limit to define HAI, i.e. HAI are infections detected more than 48 hours after admission. Nevertheless, suggest also that it must be considered that different infections have different incubation periods, so that each occurrence must be evaluated individually to determine the relationship between its occurrence and hospitalization.
HAIs includes infections acquired in the hospital and become evident only after discharge as well as occupational infection among staff of the facility (World Health Organisation, 2004)

2,1,4 HOSPITAL ACQUIRED INFECTION – FREQUENCY

Despite progress in public health and hospital care, infections continue to develop in hospitalized patients, and may also affect hospital staff. HAIs infections occur worldwide and affect both developed and resource-poor countries, laying a serious public health problem.
A prevalence survey conducted under the auspices of World Health Organisation (WHO) in 55 hospitals of 14 countries representing 4 WHO Regions (Europe, Eastern Mediterranean, South-East Asia and Western Pacific) showed an average of 8.7% of hospital patients had nosocomial infections (World Health Organisation, 2004)
At any time, over 1.4 million people in the world suffer from infectious complications acquired in hospital. In line with the statistics in the UK about 9

percent of patients in the hospital have a HAI, making an estimated total of 100,000 patients a year (Meng et al., 2010).
The most frequent nosocomial infections are infections of surgical wounds, urinary tract infections and lower respiratory tract infections. Studies have also shown that the highest prevalence of nosocomial infections occurs in intensive care units and in acute surgical and orthopaedic wards. Infection rates are higher among patients with increased susceptibility because of old age, underlying disease, or chemotherapy (World Health Organization, 2002)

2,1,5 HOSPITAL ACQUIRED INFECTION – IMPACT

HAIs are one of the most common complications of health care environments and are among the major causes of death and increased morbidity among hospitalized patients. HAIs lead to longer length of stay for patients and increased costs associated with hospitalization and insurance companies (National Centre for Disease Control, no date)
HAIs if not fatal can severely detriment patient welfare, adding to functional disability and emotional stress of the patient and may, in some cases, lead to disabling conditions that reduce the quality of life (Meng et al., 2010).
What's more organisms causing HAIs can be transmitted to the community through discharged patients, HCWs and visitors, which may cause significant disease in the community.
HAIs are a significant burden both for the patient and for public health resources, for instance treatments are very costly and may not be effective.
It is estimated by the Committee to Reduce Infection Deaths (http://www.hospitalinfection.org) that infections acquired in U.S. hospitals lead to almost 2 million infection cases with over 100,000 deaths per year and an additional $30.5 billion in hospital costs (Barnes, 2011)
If only 10% of adult HAI infections could be prevented, £93 million could be saved in England and Wales alone (Coen, 2012). Each year in the UK, around 5,000

deaths might be primarily attributable to HAIs and in a further 15,000 cases HAIs might be a substantial contributor. In UK the cost of increased length of stay and treatment for patient affected by HAI is thought to be about £1,000 million a year. Increased length of stay accounts for most of the extra financial cost, with the average increase for surgical site infections to be 8.2 days (Meng et al., 2010).

The increased duration of hospitalization for infected patients has unintended consequences over costs. In fact, prolonged stay not only increases direct costs to patients or payers but also indirect costs due to lost workdays.
The increased use of drugs, the need for isolation, and the use of additional laboratory and other diagnostic studies also contribute to costs.
Hospital-acquired infections add to the imbalance between resource allocation by diverting scarce funds intended to cure newly admitted patients to the management of potentially preventable conditions arising in hospital (World Health Organization, 2002)

Further progress in reducing the burden of HAIs is hindered by uncertainty surrounding the role of asymptomatic carriers, environmental transmission and the recent emergence of bacteria other than MRSA and C. difficile, such as Enterobacteriaceae (van Kleef et al., 2013)
The more frequent impaired immunity (age, illness, treatments) of patients admitted to health care settings, the greater prevalence of chronic diseases among admitted patients and the increasing bacterial resistance to antibiotics will provide continuing pressure HAIs in the future (World Health Organization, 2002)

2,1,6 ANTIBIOTIC-RESISTANT BACTERIA

HAIs are generally correlated with, but not synonymous to, antibiotic resistant organisms. In effect, one of the main reasons for HAI worldwide progression is

that pathogens have become increasingly resistant to antimicrobial treatment. Their recursive correlation is exposed below.
The invention of antibiotics reduced mortality, but subsequently led to the emergence of infections adapted to survival in the antimicrobial-rich hospital environment. An arms race where the bacterium and the pharmacist are running to beat each other (Coen, 2012).
Nowadays antimicrobial resistance is a serious public health threats for people in every country in the world. Infections from resistant bacteria are now too common, and some pathogens have even become resistant to multiple types or classes of antibiotics (antimicrobials used to treat bacterial infections) (Frieden, 2013).
Many patients receive antimicrobial drugs. Through the bacteria selection and exchange of genetic resistance elements, antibiotics promote the emergence of antimicrobial resistant strains of bacteria; microorganisms in the normal human flora sensitive to the given drug are suppressed, while resistant strains persist and may become endemic in the hospital and spread inside and outside medical settings. Consequently, antimicrobial agents become less effective because on such developed resistant bacteria. As an antimicrobial agent becomes widely used, bacteria resistant to this drug eventually emerge and may spread in the health care setting. Some examples are Klebsiella and Pseudomonas prevalent in many hospitals. The widespread use of antimicrobials for therapy or prophylaxis is the major factor leading to antibiotic resistance. Antibiotics are among the most commonly prescribed drugs used in human medicine. However, up to 50% of all the antibiotics prescribed for people are not needed or are not optimally effective as prescribed (World Health Organization, 2002).

Firstly, the spread of infection in healthcare environment causes the augment of the number of patient which need the cure with antimicrobial drugs and subsequently this condition rises the probability of development of antimicrobial resistance bacteria. Therefore, preventing infections from spreading reduces the

total amount of antibiotics used, this, in turn, slows the pace of antibiotic resistance development.
Furthermore, directly preventing infections propagation also prevents the spread of antimicrobial resistant bacteria which are cause of such kind of infection.
At lastly, the spread of infection caused from antimicrobial resistance bacteria increases the probability of death. Especially for patients contracting an antibiotic-resistant infection in healthcare settings is dangerous because they are already vulnerable due to weak immune systems and underlying illness. This problem can affect anyone since almost all people will receive care in a medical setting at some point of their life.

The loss of effective antibiotics will undermine our ability to fight infection spread and manage the infectious complications common in vulnerable patients undergoing chemotherapy, dialysis, and surgery, especially organ transplantation, for which the ability to treat secondary infections is crucial.
In addition, when first-line and then second-line antibiotic treatment options are limited by resistance or are unavailable, healthcare providers are forced to use antibiotics that may be more toxic to the patient and frequently more expensive and less effective (Frieden, 2013)
Even when alternative treatments exist, research has shown that patients with resistant infections are often much more likely to die, and survivors have significantly longer hospital stays, delayed recuperation, and long-term disability. By preventing infection spread from antibiotic resistance in healthcare settings, patients' health can be better preserved. In addition, healthcare facilities, systems, insurers and patients can save dollars that otherwise would have been spent on more complex care and medications needed to manage antibiotic-resistant infections.

Each year in the United States, more than two million people acquire serious infections with bacteria that are resistant to one or more of the antibiotics designed to treat those infections, At least 23,000 people die each year as a direct result of these antibiotic-resistant infections. The estimates are based on conservative assumptions. They are the best approximations that can be derived from currently available data.

In addition, almost 250,000 people each year require hospital care for Clostridium difficile (C. difficile) infections. In most of these infections, the use of antibiotics was a major contributing factor leading to the illness. At least 14,000 people die each year in the United States from C. difficile infections. Many of these infections could have been prevented.

Antibiotic-resistant infections add considerable and avoidable costs to the U.S. healthcare system. In most cases, antibiotic-resistant infections require prolonged and/or costlier treatments, extend hospital stays, necessitate additional doctor visits and healthcare use, and result in greater disability and death compared with infections that are easily treatable with antibiotics. The total economic cost of antibiotic resistance to the U.S. economy has been difficult to calculate. Estimates vary but have ranged as high as $20 billion in excess direct healthcare costs, with additional costs to society for lost productivity as high as $35 billion a year (2008 dollars) (Frieden, 2013)

Additional efforts to fight the spread of antibiotic resistance include

- preventing infections from occurring and preventing resistant bacteria from spreading;
- tracking resistant bacteria;
- improving the use of antibiotics;
- promoting the development of new antibiotics and new diagnostic tests for resistant bacteria.

Immunization, infection control and reducing person-to-person spread are for the explained reasons and for our research of great interest. The first major factor in the growth of antibiotic resistance is the spread of the resistant strains of bacteria from person to person, or to the environment.

2,1,7 THE CHAIN OF INFECTION

The general idea about HAI is that (susceptible) patients spend time on a ward, they have physical contacts with health-care workers (HCWs), visitors, other patients and with contaminants in the environment. Such exposure can lead to colonization with infectious organisms that may sooner or later cause debilitating clinical infection (Coen, 2012).

Transmissible HAIs are caused by contagious pathogens, and in most cases the pathogens are in the form of bacteria although viruses and fungi are often involved. Our simulation is meant to visualize the mechanism of diffusion of HAIs. We must consider the chain of infection which represent the transmission path of an infectious pathogen, Fig. 7. In fact, despite the variety of pathogens, germs spread from person to person through a common series of events, which we meant to simulate. There are six points at which the chain of the infection can be broken and a germ can be stopped from infecting one more person, or from the other hand that are needed to close the transmission chain. The simulation helps to visualize the diffusion of the pathogen, suggesting where to operate to break the chain.

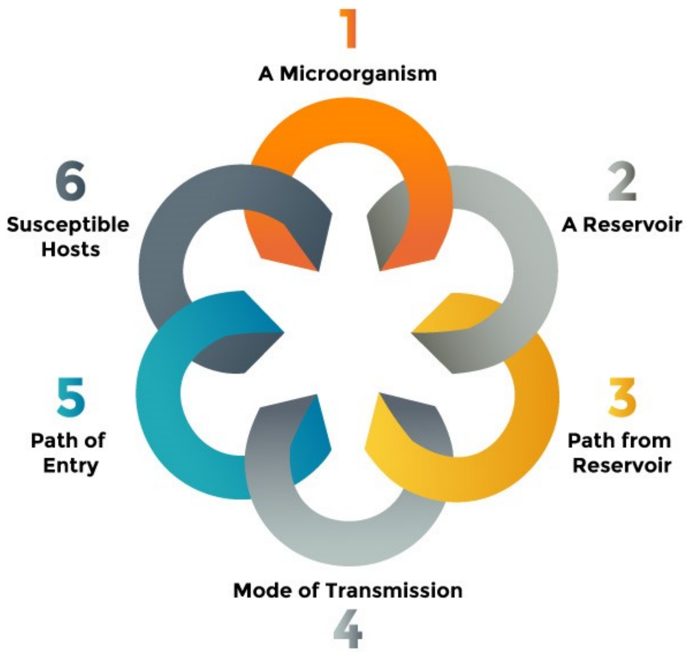


Fig. 7 - The chain of Infection.

The six links include:

1)The infectious agent is the pathogen (germ) that causes the disease.

2)The reservoir is the place where the pathogen lives. This includes people, animals and insects, medical equipment, furniture, environmental surfaces soil and water.

3)The path of exit is the way the infectious agent leaves the reservoir. This could be through open wounds, aerosols, and the splatter of body fluids including bleeding, coughing, sneezing, and saliva, through respiratory tract, mucous membranes, break in host barriers. Hospital acquired pathogens can be recovered not only from infected wounds, but also from frequently colonized areas of intact patient skin. The perineal or inguinal areas tend to be most heavily colonize and hands are also frequently colonized. (World Health Organisation, 2009)

4)The mode of transmission is the way the infectious agent can be passed on. This could be through direct contact like touching, ingestion into the stomach, or inhalation into the nasal cavity or lungs.
To understand the transmission, we should categorize HAIs according to how pathogens that cause them can be acquired. There are two main forms:
HAIs may be caused by a microorganism acquired from another person in the hospital setting (exogenous cross-infection), or may be caused by the patient's own flora (endogenous infection).

Endogenous infection: Bacteria present in the normal flora cause infection because of transmission to sites outside the natural habitat (urinary tract), damage to tissue (wound) or inappropriate antibiotic therapy that allows overgrowth (C. difficile). For example, Gram-negative bacteria in the digestive tract frequently cause surgical site infections after abdominal surgery or urinary tract infection in catheterized patients.

In turn, exogenous cross-infection can be classified according to the transmission route. In fact, microorganisms can be transmitted from their source or carrier to a new host in the air, by vectors, water or through contact (direct or indirect)

exogenous cross-infection are airborne when pathogen is transmitted in the air (droplets nuclei < 5 micron or dust contaminated by a patient's bacteria). Fine dust and droplet nuclei generated by coughing or speaking remain in the air for several hours and can be inhaled in the same way as fine dust. Although, airborne transmission occurs only with microorganisms that are dispersed into the air and that are characterized by a low minimal infective dose. Only a few bacteria and viruses are present in expired air, and these are dispersed in large numbers because of sneezing or coughing.

Vector-borne (exogenous cross-infection) transmission is typical of countries in which insects, arthropods, and other parasites are widespread. These become contaminated by contact with excreta or secretions from an infected patient and transmit the infective organisms mechanically to other patients (Chartier et al., 2014)

Moist environments and aqueous solutions in health-care settings have the potential to serve as reservoirs for waterborne microorganisms. Under favourable environmental circumstances (e.g., warm temperature and the presence of a source of nutrition), many bacterial and some protozoal microorganisms can either proliferate in active growth or remain for long periods in highly stable, environmentally resistant and infectious forms (Sehulster and Chinn, 2003)

In our study, we are interested in modelling and simulating exogenous cross-infection transmitted by contact route.

Exogenous cross-infection by contact are direct if the contamination occurs through direct contact between the human source of infection and the human recipient.

Some examples are:

Pathogen transmitted between patients through direct contact (e.g. hands, saliva droplets > 5 micron or other body fluids).

Pathogen transmitted via contaminated staff members through patient care (e.g. hands, clothes, nose and throat) who become transient or permanent carriers, subsequently transmitting bacteria to other patients by direct contact during care.

Pathogen transmitted via contaminated staff members hands between patient contact or during the sequence of patient care (World Health Organisation, 2009).

Exogenous cross-infection by contact are indirect if the contamination occurs through contaminated objects. This pathogen are transmitted through indirect contact via inanimate objects (including equipment), or environmental furniture recently contaminated from another human source and subsequently transmitting bacteria to other persons (World Health Organization, 2002)

5)The path of entry is the way the infectious agent can enter a new host. In contrast to the means of transmission (which is the movement of the germ from the object another person), the portal of entry is the actual entering in the body. This can be through broken skin, wound, the respiratory tract (nose or lungs), mucous membranes (including the urine), and catheters and tubes. The variety of medical procedures and invasive techniques creates many potential routes of infection.

6)Lastly, the susceptible host can be any person. The most vulnerable are those receiving healthcare, which are immunocompromised, or have medical devices including lines and airways. Infection rates are higher among patients with increased susceptibility because of old age, babies, underlying disease, or chemotherapy (World Health Organization, 2002)

A germ can travel around this circle very quickly. The way to stop germs from spreading is by interrupting this chain at any spot.

2,1,8 TYPES OF PATHOGEN

2,1,8,1 INTRODUCTION

There are multiple types of pathogens that can infect a patient being transmitted by contact route within a healthcare facility.

Some HAIs manifest themselves soon after colonization. This is typical of many viruses, such as norovirus and adenovirus, where susceptibles acquire infection and after an incubation period of a few days suffer symptoms of infection. Such aetiologies are typically associated with outbreaks characterized by 'attack rates' and outbreak durations (Coen, 2012).

In contrast most HAIs are not just about acquiring the organism. Many bacterial infections may be carried for months in the absence of clinical symptoms, such as in the nares (MRSA), the skin (Coagulase-negative Staphylococci), the gastrointestinal tract (Clostridium difficile). This silent infection may last months to years, makes the patient a 'carrier', more or less infectious to others depending on the organism and other circumstances, (see paragraph 4,2,1). Only when natural barriers are breached, often as a result of health-care intervention (e.g. surgery, line and catheter insertion), bacteria will invade hosts, they multiply and cause life-threatening clinical illness (Coen, 2012)

Examples from the Gram-positive bacteria are MRSA (resistant to penicillins and cephalosporins) and C difficile (resistant to fluoroquinolones) and from Gram-negative bacteria is Klebsiellas, for which resistance to carbapenems is emerging (Grundmann et al., 2010).

Apart from the type of pathogen that causes the infection, HAIs can also be classified based on the clinical body sites of the infection. The main body sites that are susceptible to HAIs include blood, urinary tract, respiratory tract, surgical site and gastrointestinal tract. Blood stream infections account only for about 5 percent of HAIs but have a high mortality rate, and are mostly associated with an intravascular device and the admission to intensive care units (ICUs). Urinary tract infections are the most common type of HAIs and are also commonly associated with indwelling catheters. Pneumonia is the second most common HAI and it has a high fatality rate; and patients who are intubated or on ventilators are at a higher risk. Surgical site infections include wound infections or deep cut infections and both patient and surgical factors may affect surgical site infections (Meng et al., 2010).

Even if they share some transmission characteristics and therefore some prevention and control strategies, treatments are different for each of them, however such kind of further considerations are out of the scope of the present work, but it is useful for our purposes introduce some basic notion about distinctive bacteria, so that to become able to recognize differences and similarities.

Currently, the widely known and studied HAIs around the world include Methicillin-resistant Staphylococcus aureus and Clostridium difficile, for its dangerous rising Klebsiella have been also considered in the present work.

2,1,8,2 CLOSTRIDIUM DIFFICILE

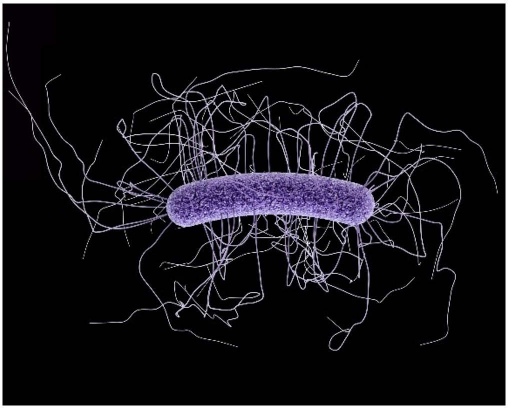


Fig. 8 – Clostridium Difficile Bacterium

Clostridium difficile infection (CDI) is a symptomatic infection due to a gram-positive spore-forming anaerobic bacillus, Clostridium difficile, which is the leading cause of HAI infectious diarrhoea in adults and it is responsible for large outbreaks, Fig. 8 (Butler et al., 2016).

Clostridium difficile is a normal occurring bacterium in the intestinal flora, however certain strains of the bacteria can cause disease, overt infection may be triggered by broad spectrum antibiotic use, hospitalization and the presence of risk factors such as age, anti-diarrhoeal drugs and insertion of tubes into the gastrointestinal tract (Meng et al., 2010).

These infections mostly occur in people who have had both recent medical care and antibiotics.
About half of C. Difficile infections first show symptoms in hospitalized or recently hospitalized patients, and half first shows symptoms in nursing home patients or in people recently cared for in doctors' offices and clinics (Frieden, 2013).

Symptoms include watery diarrhea, fever, nausea, and abdominal pain. Complications may include pseudomembranous colitis, toxic megacolon, perforation of the colon, and sepsis. The severe form of the infection can also lead to death (Frequently Asked Questions about Clostridium difficile for Healthcare Providers | HAI | CDC, no date)

Clostridium difficile infection is spread by spores found within feces. Patients with symptomatic or asymptomatic C. difficile can both contaminate their immediate hospital environment and the spores may persist for several months on surfaces (Meng et al., 2010)
Surfaces may become contaminated with the spores with further transmission occurring via the hands of healthcare workers, other patients, medical equipment and the environmental surfaces.

C. difficile infections occur all over the world. C. difficile diarrhea is estimated to occur in 7,7 out of 100,000 people each year. Among those who are admitted to hospital, the incidence rate is between 3,4 and 8,4 people per 1,000 admissions (Domino, 2014)
Due in part to the emergence of a fluoroquinolone resistant strain, C. difficile-related deaths increased 400% between the years 2000 and 2007 in the United States (Lessa, Gould and McDonald, 2012). In 2011 it resulted in about half a million infections and 29,000 deaths in the United States (Lessa et al., 2015)

C. difficile has become the most common microbial cause of HAI in U.S. hospitals and costs up to $4.8 billion each year in excess health care costs for acute care facilities alone (Hospital Acquired Infections Are a Serious Risk - Consumer Reports, no date)

Prevention to reduces the spread of C. difficile infections is done by limiting antibiotic use, by hand washing, and terminal room cleaning in hospital (Butler et al., 2016)

Infection control measures, are wearing gloves and medical devices used for a single infected person. In addition, washing with soap and water will eliminate the spores from contaminated hands, but alcohol-based hand rubs are ineffective, because chemical action doesn't touch the spores, which in turn should be washed out (Landelle et al., 2014)

2,1,8,2 METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

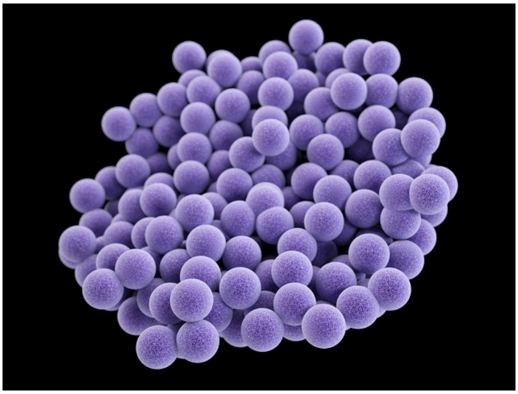


Fig. 9 – Staphylococcus aureus Bacteria

Staphylococcus aureus is normally susceptible to methicillin and several other antibiotics. Methicillin-resistant Staphylococcus aureus (MRSA) is a gram-positive spherical bacterium that is genetically different from other strains of Staphylococcus aureus, Fig. 9.

Methicillin resistant Staphylococcus aureus to often resistant to several antibiotics, methicillin and related antibiotics and to cephalosporins. Strains of S. aureus have emerged that are resistant to oxacillin, clindamycin, teicoplanin, and erythromycin. S. aureus has also developed resistance to vancomycin (VRSA)

(World Health Organization, 2002) In 1997, the first strain of MRSA resistant to vancomycin, the drug usually kept in reserve for treating highly resistant strains, was reported in Japan (Hiramatsu et al., 1997).

Strains unable to resist these antibiotics are classified as methicillin-susceptible Staphylococcus aureus, or MSSA.

MRSA has become endemic in the UK, the USA, some other European countries, and elsewhere. MRSA as a proportion of all Staphylococcus aureus causing blood stream infections has risen from about 2% in 1990 to more than 40% in 2000 (Johnson, Pearson and Duckworth, 2005).

People who are hospitalized, are often immunocompromised and susceptible to infections. Staphylococcus bacteria are one of the most common causes of HAIs and MRSA is responsible for several difficult-to-treat infections. Severe MRSA infections mostly occur during or soon after impatient medical care (Frieden, 2013) The risk of MRSA acquisition is particularly high in elderly patients, in patients with severe underlying disease, patients with open wounds or invasive devices such as catheters (Hryniewicz, 1999)
MRSA infections cause a wide range of illness form skin and wound infections, urinary tract infections, septicaemia, infections of sites for invasive devices, pressure sores, burns to pneumoniae and bloodstream infections that can cause sepsis and death (World Health Organization, 2002)

MRSA cutaneous bacteria colonize the skin and nose of both hospital staff and patients and can live permanently on the skin of some people without showing any symptoms, making them colonized, or temporarily carriers, only people that show symptoms are known as infected. However, all these people could transmit MRSA to another person by physical contact.

The nosocomial spread of MRSA is usually by transiently colonized hands of health care workers, contaminated medical equipment and object (Mulligan et al., 1993)

Severe infections are most common in the intensive care and other high-risk units with highly-susceptible patients (e.g. burn and cardiothoracic units) (World Health Organization, 2002)

CDC estimates 80.461 invasive MRSA infections and 11.285 related deaths occurred in USA in 2011. An unknown but much higher number of less severe infections occurred in the community (Frieden, 2013)
In 2003, the cost for a hospitalization due to a MRSA was $92,363, A hospital stay for MSSA was $52,791 (USD) (Weigelt et al., 2005)
MRSA is important also because staphylococci are virulent and they are associated with high fatality rate. In England and Wales, the number of deaths involving MRSA increased from 51 in 1993 to 800 in 2002; and the mortality data mirrors an increase in laboratory reports of MRSA bacteraemia, increasing from 210 reports in 1993 to 5,309 reports in 2002 (Meng et al., 2010)

To prevent the spread of MRSA the recommendations are to wash hands using soap and water or an alcohol-based formulation; use gloves for handling MRSA-contaminated materials, or infected or colonized patients and consider antiseptic detergent daily wash or bath for carriers or infected patients (Siegel et al., 2006)

2,1,8,3 KLEBSIELLA PNEUMONIAE CARBAPANEMASE

Fig. 10 – Klebsiella pneumoniae Bacteria

In recent years, Klebsiella species have become important pathogens in HAIs, Fig. 10. The most common condition caused by Klebsiella bacteria outside the hospital is pneumonia, a gram-negative bacteria, typically in the form of bronchopneumonia and also bronchitis.

Antibiotic-resistant strains of K. pneumoniae are appearing, which are resistant to the carbapenem class of antibiotics. They are resistant because they produce an enzyme called carbapenemase that disables the drug molecule.
One of many types of carbapenem-resistant Enterobacteriaceae CREs is carbapenem-resistant Klebsiella pneumoniae (CRKP), sometimes known as KPC (Klebsiella pneumoniae carbapenemase). CRKP is resistant to almost all available antimicrobial agents (Frieden, 2013)
Over the past 10 years, a progressive increase in CRKP has been seen worldwide. Infections from carbapenem-resistant Enterobacteriaceae (CRE) are rising as an important challenge in health-care settings (Limbago et al., 2011). This new

emerging pathogen is probably best known for an outbreak in Israel that began around 2006 within the healthcare system there (Schwaber et al., 2011)
Almost all CRE infections occur in people receiving significant medical care in hospitals, long-term acute care facilities, or nursing homes(Centers for Diasease Control and Prevention. CDC, 2015)
In 2012 about 7900 healthcare-associated CKRP infections occur in United States. About 4% of short-stay hospitals had at least one patients with serious CRE infection and about 18% of long-term acute care hospitals had one (Frieden, 2013)
The extent and prevalence of CRKP within the environment is currently unknown. The mortality rate is also unknown, but has been observed to be as high as 44% (Schwaber et al., 2008) The CRKP bacteria can kill up to half of patients who get bloodstream infections (Frieden, 2013)
Carbapenem-resistant Enterobacteriaceae, e.g. CRKP, can also cause infections in the urinary tract, lower biliary tract, and surgical wound sites. Therefore, the range of clinical diseases includes pneumonia, thrombophlebitis, urinary tract infection, cholecystitis, diarrhea, upper respiratory tract infection, wound infection, osteomyelitis, meningitis, and bacteremia and septicemia.

CRE may colonize sites when the host defences are compromised, for patients with an invasive device in their bodies, contamination of the device becomes a risk. Thus, neonatal ward devices, respiratory support equipment, and urinary catheters put patients at increased risk.

As a general rule, CKRP infections are seen mostly in people with a weakened immune system. Most often, illness affects middle-aged and older men with debilitating diseases. For patients with impaired respiratory host defenses, including diabetes, alcoholism, liver disease, pulmonary diseases, renal failure, the mortality rate can be nearly 100%.

Hospitals are primary transmission sites for CRE-based infections. Up to 75% of hospital admissions attributed to CRE were from long-term care facilities or transferred from another hospital (Perez and Van Duin, 2013)

Suboptimal maintenance practices are the largest cause of CRE transmission. This includes the failure to adequately clean and disinfect medication cabinets, other surfaces in patient rooms, and portable medical equipment, such as X-ray and ultrasound machines that are used for both infected and not infected patients (Chitnis et al., 2012)

Researchers found environmental reservoirs of CRE bacteria in ICU sinks and drains. Due to the bacterial resistance to cleaning measures, staff should take extra precaution in maintaining sterile conditions in hospitals not yet infected with the CRE-resistant bacteria.

To reduce transmission from sink to sink is to have sink brushes in each room that would be for cleaning that individual sink alone. Hospital staff should be trained to never dispose of clinical waste down the sinks in patient rooms. (Kotsanas et al., 2013)

One method found effective is to screen and isolate incoming patients from other facilities, and renew focus on hand-washing. Studies have found that CRE incidence and prevalence can be reduced by applying targeted interventions including increased hygiene measures and equipment sterilization, even in populations where the prevalence of infection exceeds 50% of patients (Chitnis et al., 2012)

When a case of hospital-associated CRE is identified, facilities should conduct a round of active surveillance testing of patients with epidemiologic links to the CRE case. Effective sterilization and decontamination procedures are also important to keep the infection rate as low as possible.

One specific example of this containment policy could be seen in Israel in 2007. This policy had an intervention period from April 2007, to May 2008. A nationwide outbreak of CRE necessitated a nationwide treatment plan (Schwaber et al., 2011)
To prevent spreading CKRP infections between patients, healthcare personnel must follow specific infection-control precautions, which may include strict adherence to hand hygiene and wearing gowns and gloves when they enter rooms where patients with Klebsiella illnesses are housed. Healthcare facilities also must follow strict cleaning procedures to prevent the spread of Klebsiella (Centers for Diasease Control and Prevention. CDC, 2015)

To prevent the spread of infections, patients also should clean their hands very often, including:

- Before preparing or eating food;
- Before touching their eyes, nose, or mouth;
- Before and after changing wound dressings or bandages;
- After using the restroom;
- After blowing their nose, coughing, or sneezing;
- After touching hospital surfaces such as bed rails, bedside tables, doorknobs, remote controls, or the phone.

2,1,9 INFECTION OUTBREAK

According to the Hospital Infection Prevention and Control Guidelines the occurrence of two or more similar infection cases relating to place and time is identified as a cluster and it recall further investigations. A possible outbreak is recognized if there is an increase in the number of cases from the same causative agent or a rise in prevalence of a pathogenic organism. Confirmation of the outbreak could come from the comparison between the present rate of occurrence with the endemic rate. If so, specific surveillance and microbiological study must begin to define the outbreak in time, person and place, by developing a case definition, identifying the site, pathogen and affected population. The investigation may include cultures from other body sites of the infected patient, other patients, HCWs and environment. Consequently, should be determinate the magnitude of the problem and if immediate control measures are required. In that case: isolation or cohorting of infected cases; strict hand washing and asepsis; intensification of environmental cleaning and hygiene; strengthening of disinfection and sterilization should be immediately applied. (National Centre for Disease Control, no date)

The investigation should have led to discover the source/s and route/s of transmission to apply all possible measures to prevent further spread. If the cases occur in steadily increasing numbers and are separated by an interval approximating the incubation period, the spread of the disease is probably due to person to person spread. On the other hand, if many cases occur following a shared exposure e.g. an operation, there it is a common source outbreak, implying a common source for the occurrence of the disease.

Following that, specific control measures need to be instituted based on nature of agent and characteristics of the high-risk receivers and the possible sources. These procedures should be devoted to the identification and elimination of the contaminated source or to identification and treatment of carriers. Control measures are clinically effective if cases cease to occur or return to the endemic level. (World Health Organisation, 2004)

2,2 HOSPITAL ACQUIRED INFECTION - POLICIES

2,2,1 INTRODUCION

Effective infection prevention and control is central to providing high quality health care for patients and a safe working environment for those that work in healthcare settings (National Centre for Disease Control, no date). Even if no hospital applies the same infection control strategy as any another. Several interventions are invariably applied simultaneously (Coen, 2012). For instance, in the UK, the Department of Health has outlined in the Health Act not only general measures to prevent and control HAIs, but also specific policies aiming at MRSA and C. difficile (Department of Health, 2008).
Therefore, to realistic depict the phenomenon of infection propagation, it is very important for us to know how the normative approach (by guideline of infection prevention and control programme), outlines main aspects and describe the measures to minimize the risk of infection spread in hospital. In fact, as our model and the simulation will show, the infection spreading is embedded inside the hospital and any change of these processes deeply affects it.

As seen, there are several types of pathogens that can infect a patient, being transmitted within a healthcare facility. Two basic principles govern the main procedures that should be taken to prevent and control the spread of HAI infections in health-care facilities:

- separate the infection source from the rest of the hospital;
- cut off any route of transmission.

The separation of the source should be interpreted in a broad sense. It includes not only the isolation of infected patients but also all aseptic techniques and the measures that are intended to act as a barrier between infected or potentially

contaminated hosts and the environment, including other patients and personnel.
It is impossible to avoid all contact with infected or potentially contaminated people. Even when they are not touched with the bare hands, they may come in contact with instruments, containers, linen, etc. Therefore, all objects that come in contact with patients should be considered as potentially contaminated. If an object is disposable, it should be discarded as waste. If it is reusable, transmission of infective agents must be prevented by cleaning, disinfection, or sterilization (Chartier et al., 2014).

Beside that main principles the first line of defence to prevent and control the transmission of infections in healthcare environment is the application of basic infection control precautions which can be labelled standard precautions, which must be applied to all patients, regardless of diagnosis or infectious status; and additional transmission-based precautions specific to modes of transmission (airborne, droplet and contact) and for selected patients should be applied (World Health Organisation, 2004)
A thorough description of strategies to prevent pathogens transmission through contact route tailored to consider mainly procedures and space related aspects is presented. Such detailed knowledge guarantees for the completeness of the designed model which follow.

2,2,2 STANDARD PRECAUTIONS

In health care facilities, the respect of standard precautions is essential to provide a good level of HAIs protection to patients, HCWs and visitors, these include the following, (World Health Organisation, 2004)(World Health Organization, 2002):

- hand washing and antisepsis (hand hygiene);

- use of personal protective equipment when handling blood, body substances, excretions, secretions and mucous membranes;
- appropriate handling of patient care equipment and soiled linen;
- correct disinfection of medical equipment and invasive medical devices;
- prevention of needlestick and sharp injuries;
- environmental cleaning and decontamination, ensuring that patient-care equipment, supplies and linen is either discarded, or disinfected or sterilized between each patient use;
- appropriate handling of waste.

2,2,3 CONCTACT PRECAUTIONS

Diseases which are transmitted by contact route include colonization or infection with multiple antibiotic resistant organisms, enteric infections and skin infections. Precautions must be taken for patients with enteric infections, diarrhea that cannot be controlled, or skin lesions that cannot be contained. The following precautions need to be taken:

- Implement standard precautions;
- Place patient in a single-patient room when available. if single-patient rooms are unavailable then place him in a room with another patient infected by the same pathogen and provide cohorting of patients if possible. Always consider the epidemiology of the disease and the patient population when determining patient placement. If it becomes necessary to place a patient who requires Contact Precautions in a room with a patient who is not infected or colonized with the same infectious agent. Avoid placing patients on Contact Precautions in the same room with patients who have conditions that may increase the risk of adverse outcome from infection or that may facilitate transmission. Ensure that patients are physically separated (i.e. >4 mt apart) from each other. Draw

the privacy curtain between beds to minimize opportunities for direct contact. Change protective attire and perform hand hygiene between contacts with patients in the same room, regardless of whether one or both patients are on Contact Precautions;

- Wear clean, non-sterile gloves whenever touching the patient's intact skin or surfaces and articles in close proximity to the patient. Don gloves and wear a clean non-sterile gown upon entry into the room or cubicle whenever anticipating that clothing will have direct contact with the patient or potentially contaminated environmental surfaces or items in the patient's room. Remove gown and observe hand hygiene before leaving the patient-care environment;
- Limit transport and movement of patients outside of the room to medically-essential purposes only. When transport or movement in any healthcare setting is required, ensure that infected or colonized areas of the patient's body are contained and covered;
- Ensure that rooms of patients on Contact Precautions are prioritized for frequent cleaning and disinfection with a focus on frequently-touched surfaces and equipment in the immediate vicinity of the patient.

  (World Health Organisation, 2004) (National Centre for Disease Control, no date)

2,2,4 DROPLET PRECAUTIONS

Droplet transmission occurs when there is adequate contact between the mucous membranes of the nose and mouth or conjunctivae of a receiver and large particle droplets (> 5 microns) full of infectious germs. Droplets are usually generated from the infected person during coughing, sneezing, talking or when health care workers undertake procedures such as tracheal suctioning.

Droplet precautions must be taken for patients known or suspected to be infected with pathogens transmitted by respiratory droplets:

- Implement standard precautions. Note that special air handling and ventilation are not required to prevent droplet transmission of infection.
- Place patients in a single-patient room when available; if single-patient rooms are unavailable, then place patients infected with the same pathogen in the same room. If it becomes necessary to place a patient who requires Droplet Precautions in a room with a patient who does not have the same infection: Avoid placing patients on Droplet Precautions in the same room with patients who have conditions that may increase the risk of adverse outcome from infection or that may facilitate transmission. Ensure that patients are physically separated (i.e. >1 mt apart) from each other. Draw the privacy curtain between beds to minimize opportunities for direct contact. Change protective attire and perform hand hygiene between contact with patients in the same room, regardless of whether one or both patients are on Droplet Precautions.
- Don a mask upon entry into the patient room or cubicle. Always wear a surgical mask when working within 1-2 meters of the patient.
- Limit transport and movement of patients outside of the room to medically-necessary purposes. Place a surgical mask on the patient if leaving the room and transport is necessary.
  (World Health Organisation, 2004)(National Centre for Disease Control, no date)

2,2,5 HAND HYGIENE PRACTICE

Hands transmission is one of the most important means of spread of infectious agents in health care facilities. Pathogenic organisms from colonized and infected patients and from the environment transiently contaminate the hands of staff during clinical activities and can then be transferred to other patients (National Centre for Disease Control, no date).

The hands of healthcare staff are the principal cause of contact transmission from patient to patient and most infections are acquired in the hospital through the hands contact, Fig. 11 (Ulrich et al., 2004).

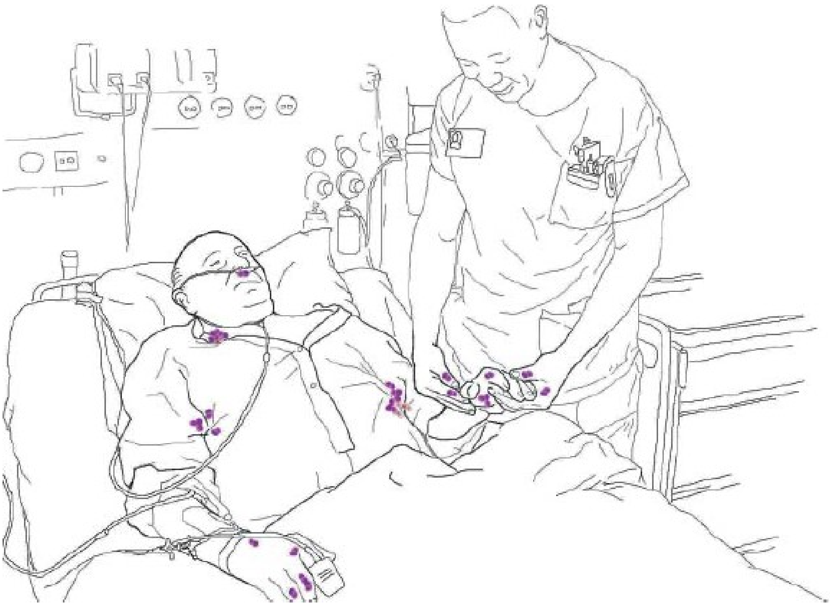


Fig. 11 - Organism transfer from patient to health-care worker's hands: Contact between the health-care worker and the patient results in cross-transmission of microorganisms (Pittet et al., 2006)

While Ulrich seems sure about the importance of assiduous hand washing by HCWs for reducing hospital-acquired infections and Boyce and Pittet agreed that increased handwashing frequency among hospital staff has been associated with decreased transmission of Klebsiella among patients (Ulrich et al., 2004) (Boyce and Pittet, 2002).

According to others only some results have shown that compliance, if raised to high enough levels, could prevent transmission almost entirely where others have shown that hand washing is not a sufficient measure, and that additional policies must be taken to reduce transmission to acceptable levels (Barnes, 2011) (Beggs, Shepherd and Kerr, 2008).

Despite the disagreement about whether hand washing is the ultimate solution to infection control, there is substantial evidence that hand antisepsis reduces the transmission of pathogens and the incidence of HAIs (World Health Organisation, 2009). Evidences suggest that increasing hand-washing compliance by 1.5 – 2 folds would result in a 25-50-% decrease in the incidence of HAI (National Centre for Disease Control, no date).

Then, proper hand hygiene, i.e wash hands in large basins, with ant splash devices, hands-free controls and with a plain soap or antimicrobial soap and running water, or use rub hands with antimicrobial alcohol-based sanitizer, remains the most effective method for preventing the transfer of microbes between people.

Transmission of HAI pathogens from one patient to another via the hands of HCWs requires the following sequence of events:

1. Organisms present on the patient's skin, or that have been shed onto inanimate objects in close proximity to the patient,
2. Organisms must be transferred to the hands of HCWs.
3. These organisms must be capable of surviving for at least several minutes on HCWs hands.
4. Handwashing or hand antisepsis by the worker must be inadequate or entirely omitted, or the agent used for hand hygiene inappropriate.
5. The contaminated hands of the caregiver must come in direct contact with another patient, or with an inanimate object that will come into direct contact with the patient.

(World Health Organisation, 2009)

Thus, almost all the guideline for infection prevention recommend to all the healthcare workers when Hand hygiene must be practiced, known as the “Five Moments in Hand Hygiene”, Fig. 12 (World Health Organisation, 2004):

1. Before touching a patient to prevent cross contamination between different patients.
2. Immediately before performing a clean or aseptic procedure, including handling an invasive device for patient care and between tasks and procedures on the same patient to prevent cross-contamination between different body sites, regardless of whether or not gloves are used.
3. Promptly after contact with body fluids, secretion, excretions, mucous membranes, non-intact skin, or wound dressings regardless of whether or not gloves were used.
4. After touching a patient and his/her immediate surroundings, even when leaving the patient’s side.
5. After contact with known and unknown contaminated objects, equipment or surfaces (including medical equipment and furniture) in the vicinity of the patient.

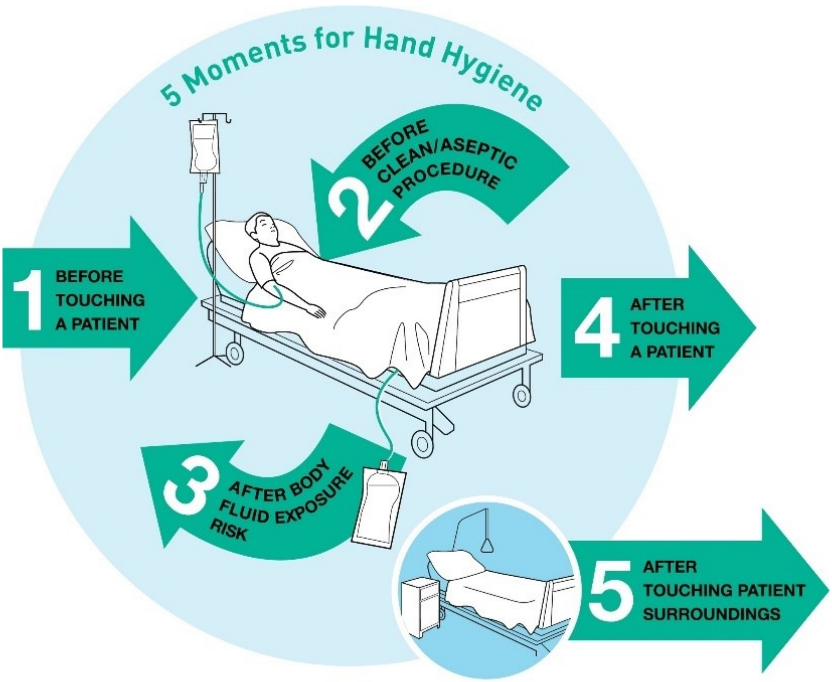


Fig. 12 - Five Moments of Hands Hygiene

Furthermore, they advise to perform always hand wash when hands are visibly dirty and immediately after removing gloves, because hand hygiene is required regardless of whether gloves are used or changed.
And consider the failure to remove gloves after patient contact or between “dirty” and “clean” body-site care on the same patient must be regarded as nonadherence to hand-hygiene recommendations (World Health Organisation, 2004)

In this context, the statistic that rates of hand washing by caregivers are low, represents a serious safety danger. Several studies of hand washing in high-acuity units with vulnerable patients have found that as few as one in seven staff members wash their hands between patients. Compliance rates in the range of 15 percent to 35 percent are typical, rates above 40 percent to 50 percent are the exception.

Education programs to increase hand washing adherence have yielded disappointing or, at best, mixed results. Some investigations have found that education interventions generate no increase at all in hand washing. Even intensive education or training programs (classes, group feedback, for example) produce only temporary increases in hand washing (Ulrich et al., 2004).
There is an urgent need to identify more effective ways to foster sustained increases in hand hygiene. For instance, there is some evidence that providing numerous, easily accessible alcohol-based hand-rub (ABHR) dispensers or hand washing sinks can increase compliance and thereby reduce contact contamination (Ulrich et al., 2004). Evidence suggesting improved hospital design as well as better planned procedural decisions can be effective in elevating hand hygiene, but to prove it is of the utmost importance.

2,2,6 CONTAMINATE SURFCES AND OBJECTS

The hospital environment fosters the dissemination of infectious pathogens.
Hospital surfaces and items frequently come in contact with HCWs, patients and visitors. Spaces occupied by colonized and/or infected people generally become contaminated, Fig. 13. Contaminated surfaces and features act as pathogen reservoirs contributing to the incidence of cross-infection.
Most germs survive for few days on inanimate objects, some longer, therefore their presence on ward surfaces and equipment is common (Kramer, Schwebke and Kampf, 2006). Mostly patient gowns, bed linen, bedside furniture and other objects in the patient's immediate environment can easily become contaminated with patient flora. A study found that in the rooms of patients infected with methicillin-resistant Staphylococcus aureus (MRSA), 27 percent of all environmental surfaces sampled were contaminated with MRSA (Boyce et al., 1997).

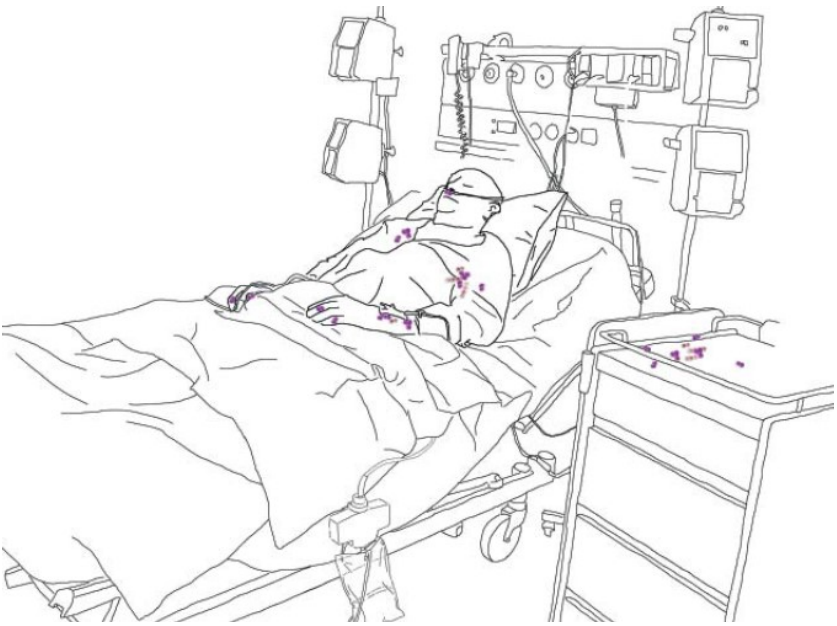


Fig. 13 - Organisms present on patient skin or immediate environment: Bedridden patient colonised with Gram-positive cocci, at nasal, perineal, and inguinal areas (not shown), as well as axillae and upper extremities. Some environment surfaces close to the patient are contaminated with Gram-positive cocci, presumably shed by the patient (Pittet et al., 2006).

Studies have documented that HCWs may contaminate their hands (or gloves) merely by touching inanimate objects in patient rooms. Surface and furniture contamination could be reduced by the correct hands hygiene, but, as already stated, HCWs compliance to this procedure has been reported to be less than 50% (World Health Organisation, 2009).

Harrison showed that contaminated hands could contaminate a clean paper towel dispenser and vice versa. The transfer rates ranged from 0.01% to 0.64% and 12.4% to 13.1%, respectively (Harrison et al., no date)
A study by Barker and colleagues showed that fingers contaminated with norovirus could sequentially transfer virus to up to seven clean surfaces, and from contaminated cleaning cloths to clean hands and surfaces (Barker, Vipond and Bloomfield, 2004).

Microbial transmission between humans and the environment happens both in endemic and outbreak conditions. During outbreaks, environment contamination may be higher, nevertheless, in endemic situations, it was also registered that surfaces were contaminated with patients' microorganisms. In the endemic observation, there was a greater risk for patients of acquiring infections due to bacteria presence. While in outbreaks, there were typically gram-negative bacteria, e.g. carbapenem resistant enterobacteriacae. Environment contamination by C. difficile, which is more resistant to desiccation, was observed either in endemic and outbreak situations (de Oliveira and Damasceno, 2010).

The contamination of apparently clean spots raises the opportunity of pathogens dissemination, surfaces don't have to look soiled or smell bad to be loaded with germs. Places considered clean surfaces, without any visible dirtiness, often make effective cleaning measures to go unattended.
Examples of surfaces found to be contaminated frequently via contact with patients and staff include: overbed tables, bed privacy curtains, computer keyboards, infusion pump buttons, door knobs, bedside rails, blood pressure cuffs, chairs and other furniture, and countertops (Ulrich et al., 2004).

Contamination of surfaces and equipment close to patient, e.g. hand wash surfaces, sinks and taps, monitors and keyboards has been widely detected, corroborating the supposition that surfaces that are frequently touched become more contaminated, Fig. 14.

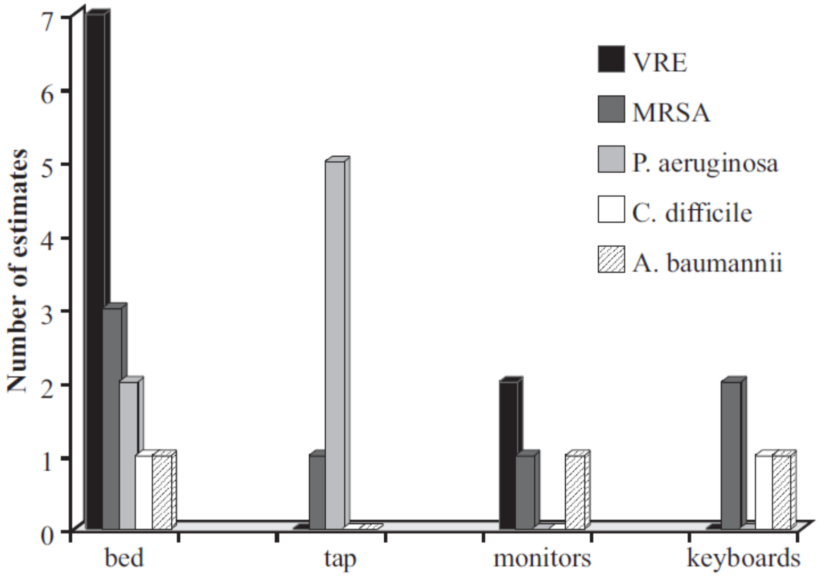


Fig. 14 - Analyzed surfaces and the bacteria recovered from the hospital environment (de Oliveira and Damasceno, 2010)

However, wards are extremely heterogeneous places. Bacterial counts sampled from sites most likely associated with direct patient contact (e.g. hand-rails, soap dispensers, bedding, curtains) are much lower than other sites (e.g. floor) (Coen, 2012).

A study conducted in 2010 across 3532 high risk environmental surfaces in 260 intensive care unit rooms in 27 acute-care hospitals (ICUs) assessed the consistency at which these surfaces met base line cleaning standards. Only 49.5% of the high-risk object surfaces were found to meet this baseline criterion. The least-cleaned objects were bathroom light switches, room door knobs, and bed pan cleaners (Carling et al., no date)

According to this general frame, it is imperative to explain the role of the environment (surfaces, equipment and furniture) concerning the contamination and dissemination of pathogens, which to date is still undervalued. It will be valuable to propose strategies to reduce pathogens propagation beyond the indication of the Hands Hygiene increased adherence, toward a more comprehensive understanding of the phenomenon.

One of the most basic measures for the maintenance of hygiene is environmental cleaning whose effectiveness is difficult to measure. Regular cleaning and disinfection of the hospital environment as appropriate is critical to control surface contact transmission of infections.

Routine cleaning is important to ensure a clean and dust-free hospital environment. There are usually many micro-organisms present in “visible dirt” and the purpose of routine cleaning is to eliminate this dirty. Thorough cleaning will remove more than 90% of microorganisms (World Health Organization, 2002).
The microbiological effect of cleaning is mechanical: the dirt is dissolved by water, diluted until it is no longer visible, and rinsed off. Soaps and detergents act as solubility promoting agents. Bacteria and other microorganisms are suspended in the cleaning fluid and removed from the surface. Since neither soap nor detergents possess any antimicrobial activity the efficacy of the cleaning process depends essentially on mechanical action.
Diluting and removing the dirt also removes the breeding-ground or culture medium for bacteria and fungi. Most non-sporulating bacteria and viruses are unlikely to survive on clean surfaces, they survive only when they are protected by dirt or organic matter, otherwise they dry out and die (Chartier et al., 2014). Porous surfaces are more difficult to clean, so that environmental surfaces and materials of architectural elements, must be solid and smooth enough to be able to prevent the suspension of droplets and to facilitate adequate cleaning (Khai, 2016).
There have been reports on the persistence of bacteria in the environment probable due to the incomplete removal of the pathogen in the cleaning procedure. To guarantee respectively the effectiveness of the necessary level of

asepsis, cleanliness, disinfection and sterilization for each hospital area, should be carried out in a standardized manner, e.g. there must be policies specifying the frequency of cleaning and cleaning agents used. To this end classifying areas into hospital zones is needed (World Health Organization, 2002) (World Health Organisation, 2004):

Administrative and office areas with no patient contact require normal domestic cleaning;

- Most patient care areas who are not infected and not highly susceptible, must be cleaned by a procedure that does not raise dust. Dry sweeping or vacuum cleaners are not recommended. The use of a detergent solution improves the quality of cleaning as well as hot water (80°C).
- Disinfection of any areas with visible contamination with blood or body fluids prior to cleaning must be respected.
- Isolation rooms and other areas that have patients with known transmissible infectious diseases should be cleaned with a detergent/disinfectant solution at least daily.
- Highly-susceptible patients or protected areas such as operating suites, delivery rooms, intensive care units, premature baby units, casualty departments and haemodialysis units, must be cleaned using a detergent/disinfectant solution and separate cleaning equipment.
- All horizontal surfaces in the last three cited zones and all toilet areas should be cleaned daily.
- Terminal cleaning method, done when the patient is discharged, should be performed in healthcare environments and isolation rooms to control the spread of infections.

2,2,7 PERSONAL PROTECTIVE EQUIPMENT

Using personal protective equipment (PPE) provides a physical barrier between micro-organisms and the wearer. It offers protection by helping to prevent micro-organisms from:

- contaminating hands, eyes, clothing, hair and shoes;
- being transmitted further to other patients, staff and visitors.

Personal protective equipment includes:

- gloves;
- protective eye wear (goggles);
- mask;
- apron;
- gown;
- boots/shoe covers;
- cap/hair cover.

Personal protective equipment reduces but does not eliminate the risk of acquiring an infection. It is important that it is used effectively, correctly. HCWs must also be aware that use of PPE does not replace the need to follow basic infection control measures such as hand hygiene.

Continuous availability of personal protective equipment and adequate training for its proper use are essential. PPE should be always sited in proximity of isolation rooms, ideally in anterooms or at prompt disposal, since their use is mandatory in case of interaction with infected patients (World Health Organisation, 2004) (World Health Organization, 2002).

Personal protective equipment should be used by:

Healthcare workers who provide direct care to patients and who work in situations where they may have contact with blood, body fluids, excretions or secretions;

Support staff including medical aides, cleaners, and laundry staff in situations where they may have contact with blood, body fluids, secretions and excretions;
Laboratory staff, who handle patient specimens;
Family members who provide care to patients and are in a situation where they may have contact with blood, body fluids, secretions and excretions.

The following principles guide the use of personal protective equipment:

- personal protective equipment should be chosen according to the risk of exposure. The health care workers should assess whether they are at risk of exposure to blood, body fluids, excretions or secretions and choose their items of personal protective equipment according to this risk;
- it must be avoided any contact between contaminated (used) personal protective equipment and surfaces, clothing or people outside the patient care area;
- used personal protective equipment must be discarded in appropriate disposal bags, and dispose of as per the policy of the hospital;
- personal protective equipment mustn't be shared;
- personal protective equipment must be changed completely and thoroughly wash hands must be performed each time an HCW leave a patient to attend to another patient or another duty.

2,2,8 FUNCTIONAL ZONING, TRAFFIC FLOW AND USE OF SPACE

Even if previous aspects are inevitably related with hospital layout, spatial distribution and use of space as well as the following features are somehow more directly connected.
Hospital design is highly involved for what concerns hospital functional zoning, e.g. separation for critical areas like Intensive Care Unit (ICU) from general areas (S K M Rao, 2004).

The architectural segregation should be done stratifying patient care areas by risk of the patient population for acquisition of infection, which in turn partially mirrors the area subdivision previously presented for cleaning practice. For instance, this approach should help to maintain separated infected from immunocompromised patients through the separation of contaminated areas and non-contaminated areas (Rao, 2004).

Four degrees of risk may be considered:

- Low-risk areas: e.g. administrative sections;
- Moderate-risk areas: e.g. regular patient units;
- High-risk-areas: e.g. isolation unit, intensive care units;
- Very-high-risk areas: e.g. operating rooms.

Besides, clear functional zoning and composition of space assure that the traffic flow can be regulated to minimize exposure of high-risk patients, facilitating their transport and eventually easily modifying it in accordance to the emergent needs for infection control and contamination management (Khai, 2016)
From the other hand only limiting the movement and transport of infected patients from the isolation room/area for essential purposes reduces the opportunities for dissemination of micro-organisms in other areas of the hospital (World Health Organisation, 2004).
This twofold facet is significant because the traffic of people, HCWs and visitors, in the ward and their subsequent contact with different patients, objects and surfaces rises the possibilities of pathogen propagation, which fosters the risk of cross infection, especially if the necessary precautions are not observed, sees hands hygiene and ward cleaning. For the same reason of preventing cross-infection separated toilets for staff, patients and visitor must be guarantee and as well overcrowding in nurseries and ward units should be avoided.
Therefore, decision on HAI management requires the consideration of all physical movements and communications and space use interferences. Design or

organize flows to reduce the intensity of travelling and to avoid promiscuous use of space and overlap of all kind of different patients and HCWs minimizes the possibilities of infectious contact transmission, e.g. it answers the need for the easy movement of staff through clean areas without crossing dirty areas.

2,2,9 SINKS AND ALCOHOL BASED HAND RUBS DISPENSERS

An overall low hands hygiene rates by HCWs has been registered. In addition, HCWs education and training and an extensive communication about personal hygiene in the hospital setting, space related aspects as for instance the architectural design of wards, or the spatial organization of patients' rooms could play a major role.

HCWs report several reasons for poor handwashing compliance, inconvenient location and inadequate number wash-hand basins, are two of the main reasons that staff do not comply with hand hygiene protocols. Others reported are lack of time, lack of soap or paper towels and forgetfulness. Generally, they have the perception that unavailability or inadequate hand washing facilities and sinks contribute towards poor compliance (Joseph, 2006). Those results suggest that the position and provision of clinical sinks should ensure that they are all readily available and convenient for use, so their number and disposition should be thoughtfully planned to encourage HCWs and patients to practise hand hygiene.

Having a clinical wash-hand basin easily available at all times is more important than compliance to a precise bed-to-basin ratio. For example, in a multi-bed room, if two clinical wash-hand basins are placed side-by-side, both on the same side of the entrance, only the one closest to the entrance will get significant use, the other will form a dead-leg in the water distribution system. While it may be marginally more complex in terms of plumbing, there should be one clinical

wash-hand basin on each side of the entrance or at opposite sides of the room (Department of Heallth Estates & Facilities, 2013).
Furthermore, healthcare providers should have policies in place ensuring that clinical wash-hand basins are not used for other purposes such as emptying of patient bathing water. Using sinks for both hand-washing and the cleaning of equipment should be discouraged as this will significantly increase the risk of hands and environmental contamination (Department of Heallth Estates & Facilities, 2013).
Ulrich reported numerous studies that examined whether hand hygiene is improved by increasing the ratio of the number of handwashing facilities to beds and/or by placing sinks or Alcohol Based Hand Rubs (ABHR) dispensers in more accessible locations. These studies, on balance, offer support, though limited, for the notion that providing numerous, conveniently located dispensers or sinks can increase compliance (Ulrich et al., 2004).

However, it is not clear how much of the effectiveness in terms of increased hand hygiene or reduced infection rates can be attributed to the installation of more numerous and/or accessible sinks and ABHR dispensers. There is a need for studies that define accessible locations for hand cleaning stations, on the basis of analysis of staff movement paths, visual fields, social interactions and work flows (Ulrich et al., 2004).

2,2,10 SINGLE BED ROOMS, ISOLATION AND COHORTING

Literature suggests significant benefit of single-patient bedrooms in reducing the hospital infection colonization rate (Stiller et al., 2016). Single rooms help prevent the risk of transmission of infection from the source patient to others by reducing direct, indirect contact and droplet transmission (World Health Organisation, 2004).

The key to effective isolation on general wards is the provision of sufficient ensuite single-bed rooms to prevent patients known to be a risk for spreading infections or because susceptible being cared for in open ward areas (Department of Heallth Estates & Facilities, 2013).

While the German Commission for Hospital Hygiene and Infection Control (KRINKO) recommends 10–20% single-patient rooms in a normal care unit, the Facility Guidelines Institute (https://www.fgiguidelines.org/) recommends performing all patient care in single-patient rooms in its Guidelines for Design and Construction of Hospitals and Outpatient Facilities (Stiller et al., 2016).

Ulrich identified many relevant studies answering to the question of whether nosocomial infection rates differ between single-bed and multi-bed rooms. Different mechanisms or factors have been identified as contributing to lower infection incidence in single rooms. One clear set of advantages relates to reducing airborne diseases. In addition to that, several studies show that single-bed rooms also lessen risk of infections acquired by contact, reducing the risk of cross-infection. The findings collectively provide a strong pattern of evidence indicating that infection rates are usually lower in single-bed rooms (Ulrich et al., 2004).

Support for this point is provided by research on contamination of HCWs in units having patients infected by MRSA. Boyce founds that 42 percent of nurses who had no direct contact with an MRSA patient but had touched contaminated surfaces contaminated their gloves with MRSA (Boyce et al., 1997).
In a study of MRSA infections Jernigan reports that risk was lowered by isolation in single-bed rooms, where high risk was associated with spatial proximity to an infected patient and shared exposure to caregivers (Jernigan et al., 1996).
Ben-Abraham asserts that nosocomial infection frequency was much lower in a single-bed paediatric intensive care unit than a unit with multi-bed rooms. The

investigators concluded that single-bed rooms helped to limit person-to-person spread of pathogens between paediatric patients (Ben-Abraham et al., 2002).

As verified many surfaces and furniture close to the patients become contaminated.
Single-bed rooms are far easier to decontaminate carefully after a patient is discharged compared to multioccupancy rooms, such in turn worsen the problem of surfaces acting as pathogen reservoirs. HCWs can touch contaminated spots, the risk of a HCW becoming contaminated is greater in multi-bed rooms, where single rooms with a conveniently located sink or ABHR dispenser may contribute to hand hygiene compliance.

The first essential measure in preventing the spread of nosocomial infections is isolation of infected. Patient isolation confines a detected colonized or infected patient to a single room. An adequate number and type of isolation rooms must be in each unit. Single rooms used for isolation purposes should include an anteroom to encourage the use of personal protective equipment, which should be located in such space (World Health Organization, 2002).

However, the term isolation covers a broad domain of procedures. Isolation of any degree is expensive, labour-intensive, and usually inconvenient or uncomfortable for both patients and health-care personnel, its implementation should therefore be adapted to the severity of the disease and to the causative agent (Chartier et al., 2014).

For infection control purposes, if single rooms are not available, or if there is a shortage of single rooms, patients infected or colonized by the same organism can be cohorted (sharing of room/s).
When cohorting is used during outbreaks these room/s should be in a well-defined area (a designated room or designated ward), which can be clearly

segregated from other patient care areas in the health care facility used for non-infected/colonized patients. Furthermore, cohorting accounts for the solution that each HCW is dedicated to the cure of a fraction, infected/non-infected, of patients. In the case of transmission via HCW hands, the increasing of HCW-to-patient ratios decreases the range of transmission, as infected patients can only transmit the bacteria to others who share their HCW (Barnes, 2011).

2,2,11 BEDS SPACING AND ROOMS SIZE

Along with the number of patients occupying one room, the amount of space assigned for each patient within this room to assure adequate spatial separation of patients, is an important factor to foster or hinder pathogens propagation.
In open plan wards there should be adequate spacing between each bed to reduce the risk of cross contamination occurring from direct and indirect contact or droplet transmission (World Health Organisation, 2004).
The space around beds in a multi bed ward is crucial in controlling infection spread to the environment. Moreover, the fixed space around the single bed is insufficient, the equipment could become contaminated and, could lead to a risk of cross infection.

Theoretically speaking, the less space that is provided for patients and healthcare workers within a room, the higher the risk for the transmission of pathogens and for breaches in infection prevention measures, possibly leading to an increase in infections (Stiller et al., 2016).
Research data correlating the relationship between the patient room size or the patients' proximity in adjacent beds and their colonization or rates of infection is scarce.

Kubbler, J Hosp Inf 1998 investigate the Impact of introducing a fifth bed into a conventional four bed bay, decreasing distance between beds from 2.5 to 1.9m

he found an increased transfer of MRSA 3.15 times (Infection Prevention in Hospitals: Designing Away the Risks - Dr. Brenda Ang Department of Infectious Diseases).
Jones et al. studied the space per cot in a neonatal intensive care unit. They concluded that a significant association exists between a higher square footage per cot and lower late-onset sepsis rates (Resende *et al.*, 2015).
Jou et al. determined an increased risk of nosocomial C. difficile infection in patient rooms with larger square footage Due to the characteristics of the evaluated pathogen C. difficile, it is likely that spores contaminated the surface. This is attributable to the fact that a larger room allows more surface to be contaminated and in the case of larger multi-bed rooms cleaning and terminal decontamination could be performed rather inadequately, which leads to an increased transmission (Jou et al., 2015).

Nowadays, more detailed suggestions could be found, which relate the topic of bed spacing to the sufficient space required around beds for equipment and treatments. Therefore, the volume of care and the degree of intervention, diagnostic equipment and movement of staff around the patient dictates the bed space needed. Similarly, bed spaces for critical care areas need to be greater for reasons of circulation space and the equipment used in these areas.

The UK Department of Health (NHS Estates, 1997) provided guidance on the bed space allowance in multibed bays of between 2.3m and 2.5m to allow sufficient space for nursing and patient activities. Where the latest release (Department of Heallth Estates & Facilities, 2013) suggest to design to provide sufficient space for activities to take place and to avoid cross-contamination between adjacent bed spaces.

Similarly, there is not agreement on the square footage for patient rooms, directives vary in their recommendation.

UK NHS Estates suggests that all beds should have a minimum floor area of 26 m2. 18.58 m2 per bed on critical care units (ICU) in the United States, 25 m2 for single-patient rooms or 40 m2 for multiple-patient rooms on German ICU's where indicated. The FGI recommends 13.94 m2 per patient bed in single patient rooms and 11.15 m2 per patient bed in multiple patient rooms on critical care units. Germany has not established guidelines for medical/surgical units, whereas the FGI proposes 11.15 m2 per patient bed in single patient rooms and 9.29 m2 in multiple-patient rooms (Stiller et al., 2016).

Lawson and Phiri recommend that single patient rooms should be a minimum of 20m2 in area with recommended dimensions of 5m by 4m excluding ensuite facilities (Lawson, B., Phiri, M. and Wells-Thorpe, 2003).

3 MODELLING APPROACHES

3,1 STATE OF THE ART

3,1,1 INTRODUCTION

There is a wide literature concerning epidemiology modelling. Community acquired diseases have been the main areas of early studies with static and dynamic models. Nevertheless, established theories, modelling methods, findings and prevention and control policies may not be tout court translated to HAIs.

Compartmental models arise, to account for fluctuations and stochastic variations in smaller population.

Such kind of models aggregate patient and health-care worker populations into compartments, as for instance colonized or uncolonized patients and contaminated or uncontaminated HCWs.

Usually such models examine the effect of control interventions, such timing of antibiotic prescribing policies, rapid detection and isolation strategies, patient isolation, and patient-to-HCW ratios, various hygiene measures, as well as the importance of patient re-admission.

Nevertheless, compartmental suffer some limitations as for instance behaviour homogeneity inside compartments and homogeneous mixing between individuals. Therefore, Individual Based model and later ABM where applied in this domain.

The interest on simulating healthcare environment is not new, early models were designed to improve hospital performance, workload scheduling, economic indicators, patients flow and so on.

Agent-based applications have seen an incredible growth in many research fields over the past 15 years, with more recent inclusion of HAI topic. This method is

applied to examine more in a fine-grained level the transmission of HAIs within a hospital.
Recently a new modelling approach has emerged based on event, which add to the bottom up structure of ABM a system architecture to manage the coordinated behaviour of many agents in a top down manner. Its capacity to simulate complex and realistic scenarios with a powerful software tool, namely unity 3D engine, drive us to apply it in the context of HAI.

3,1,2 COMMUNITY-BASED INFECTIOUS DESEASE

The application of mathematical models to the study community-acquired infectious disease with large size population was initiated in 1760 when Daniel Bernoulli used a technique to evaluate effectiveness of the practices of variolation (process of inoculation) against smallpox (Anderson and May, 1991)

From such static model, i.e. where the transmission risk is treated as a parameter exogenous to the model, not changing with the number of infectious individuals in the population; in the nineteenth century, dynamic transmission models were applied to epidemiology. These models track the number of individuals (or proportion of a population) carrying or infected with a pathogen over time, where the risk of transmission to susceptible at a given time point is dependent on the number of infected (or colonized) individuals in the community (Jit and Brisson, 2011)

In 1840 William Farr fitted a normal curve to smoothed quarterly data on deaths from smallpox in England and Wales over the period 1837-1839 (Wilson and Wilson, 2003)

in 1855 John Snow published the classical study of cholera On the Mode of Communication of Cholera and a detailed treatise incorporating the results of his investigation of the role of the water supply in the Soho epidemic of 1854. He identified the source of the outbreak as the public water pump on Broad Street (now Broadwick Street) He used a dot map to illustrate the cluster of cholera cases around the pump. He also used statistics to illustrate the connection between the quality of the water source and cholera case.

In the early twentieth century, the application of mathematical models has witnessed noteworthy theoretical and practical advances since several quantitative, but mainly statistical, studies in epidemiology followed Snow. Brownlee in 1906 published a paper entitled "statistical studies in immunity: the theory of an epidemic, in which he fitted Pearsonian frequency distribution curves to a large series of epidemics (Anderson and May, 1991).

In the same year Hammer hypothesized that the course of an epidemic depends on the rate of contact between susceptible and infectious individuals.
This notion has later been slightly modified to become one of the most important notions in epidemiology; it is called the mass-action principle in which the net rate of spread of infection is assumed to be proportional to the product of the number of susceptible and infectious populations divided by the number of individuals in the total population (Wilson and Wilson, 2003)

Ross in 1911 presented a new set of equations as part of a general framework which model the transmission dynamics applied to understand malaria. Where his quantitative method considers the relationships between numbers of mosquitoes and the incidence of malaria epidemics. In 1915, he solved the general equations, and discussed his work in relation to Brownlee's approach (Smith et al., 2012).
In 1927, Kermack and McKendrick published the first of their seminal papers providing a firm theoretical framework for the investigation of observed patterns of the course of epidemic diseases, establishing the threshold theory in which the

introduction of a few infectious people into a community of susceptible will not incur an epidemic outbreak unless the density or the number of the latter is above a critical limit. Kermack and McKendrick's framework has evolved to become the classic SIR (susceptible-infected-removed) model for studying of population biology (Kermack and McKendrick, 1991)

3,1,3 COMPARTMENTAL MODELS

Compartmental models are more suitable to represent HAIs compared to community-based infections.

In a discrete-time compartmental model, the population is divided into groups (compartments), and the number of persons of each compartment are tracked in the model. Each compartment represents a stage of the infection history. The most common compartments are Susceptible (S), Exposed (E), Infectious (I) and Recovered or removed (R). Different combinations of these compartments lead to different model structures, depending on the aims and the level of details. Elaboration of the classic S-I-R model are: S-I, S-I-S, S-I-R, S-I-R-S, S-E-I-S, S-E-I-R and so on. Inside a compartment it is supposed homogeneous mixing of the agents. After the compartments are decided, one can define the governing equations of the model therefore the compartment models are given by closed mathematical equations (Pethes, Ferenci and Kovács, 2017) .

Mathematical compartmental modelling of HAI has been widely used to examine the transmission dynamics of infection spreading and for estimating the impact of multiple factors that may influence pathogen dissemination in hospital facilities, such as various infection control measures. These factors include hand hygiene compliance, nurse staffing levels, frequency of introduction of colonized or infected patients onto a ward, whether cohorting is implemented and so on (World Health Organisation, 2009). Among mathematical models, stochastic compartmental model, in which random variation influences the chance of events, e.g. colonization and infection rates, seemed to be the more appropriate choice for estimating the impact of various infection control measures (Otto and Day, 2011)

It is believed that the first compartmental modelling study on HAIs was carried out by Massad et al. (1993) (Meng *et al.*, 2010). The model investigated the evolution of antibiotic resistance in the hospital setting based on the classical SIR method. The model only considered the patient population which was divided into three compartments: susceptible, infected by antibiotic sensitive strain and infected by antibiotic resistant strain. A system of three ordinary differential equations describe the dynamics of the number of patients in each compartment. Equilibrium analysis was performed to study which strain of the pathogen would dominate, and observed data from other studies were used to configure the model (van Kleef et al., 2013).

In a mathematical compartmental model of MRSA infection in an ICU, Sebille and colleagues (1997) state that the number of patients who became colonized by strains transmitted from HCWs was the most important determinants of transmission rates. Patients and HCWs were explicitly represented in the model and were divided into three compartments: uncolonised, colonised with sensitive strain and colonised with resistant strain. Two transmission routes were modelled: patient-to-patient direct transmission and cross transmission between patients through HCWs. Of interest, they found that increasing hand hygiene compliance among HCWs rates had only a modest effect on the prevalence of MRSA colonization. Their model estimated that it takes >60% hand hygiene compliance to reduce prevalence of MRSA colonization from 30% to below 20% (Sébille, Chevret and Valleron, 1997).

Austin et al. (1999) proposed a mathematical compartmental model to study the transmission dynamics of vancomycin resistant enterococci (VRE) in an ICU setting. The hospital-level model consisted of both patients and HCWs who were classified as either colonised or uncolonised. Transmission dynamics were also described by a system of four ordinary differential equations, each representing the change in the number of paitents/HCWs in one compartment. The model was configured mainly with observed data daily surveillance cultures of patients, molecular typing of isolates, and monitoring of compliance with infection control practices. The Monte Carlo technique was applied to simulate the stochastic process and multiple replications were performed to estimate the mean and confidence interval of model results. The study found that hand hygiene and staff cohorting were predicted to be the most effective control procedures. The model estimated that the basic reproduction number (i.e., the number of secondary transmissions cause by a typical primary case in a large population of susceptible patients) for VRE in the hospital was approximately 3-4 without intervention and 0.7 when infection control measures were implemented (Austin et al., 1999)

Cooper et al. (1999) proposed used a stochastic model of transmission dynamics to study hand-borne HAIs.
The model explicitly considered patients and HCWs and classified them as either colonised or uncolonised.
Stochastic simulation with multiple replications was carried out to measure the effectiveness of various intervention policies under different scenarios. The intervention policies and influencing factors considered in the model include the transmissibility of the pathogen, the probability of colonisation on admission, patients' lengths of stay, hand-washing frequency and infection detection rate.
Direct observed data were not applied to configure or validate the model. The study predicted that improving hand hygiene compliance from very low levels to 20% or 40% significantly reduced transmission, but that improving compliance to levels above 40% would have relatively little impact on the prevalence ('Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects', 1999)

Bonten et al. (2001) review several of the models that have been published and speculate on the usefulness of mathematical modelling for improving the prevention of HAI. The review concluded several potential benefits of the modelling study: (1) models can provide a theoretical basic for evaluating interventions to control the infection transmission and the development of antibiotic resistance, (2) models can suggest explanations of observations that have not been explained yet, (3) models can help illustrate the range of stochastic variation and chance effects, and (4) models can suggest standards for the evaluation of alternative intervention policies (Bonten et al., 2001)

After early studies, the attention of the HAI modelling was focused to the calibration of the model parameters by choosing their values to approximate a set of observed data as well as possible. Examples of model fitting methods are least squares approximation, maximum likehood estimation and Markov Chain Monte Carlo Methods (Meng et al., 2010)

Grundmann et al. (2002) fitted a stochastic mathematical compartmental model to the MRSA observed data in a hospital ICU. The model was then applied to evaluate the effectiveness of control policies of hand-washing, HCW-patient ratio and staff cohorting. He predicted that a 12% increase in adherence to hand hygiene policies or in cohorting levels might compensate for the ill effects of staff shortage and prevented transmission during periods of overcrowding and high workloads (Grundmann et al., 2002)

Pelupessy et al. (2002) also fitted a stochastic Markov model, which was based on previous mathematical compartmental models, to the observed data of two hospital pathogens, VRE and Pseudomonas aeruginosa, in a hospital ICU. The purpose of the model fitting was to evaluate the relative importance of two possible colonisation routes: exogenous cross-transmission by HCWs and endogenous acquisition due to the use of antibiotics. Only patients, who were classified as either colonised or uncolonized, were explicitly represented in the model (Meng et al., 2010)

A mathematical compartmental model was proposed by Cooper et al. (2004) which not only considered the hospital, but also the corresponding community. Only patients were explicitly represented in the model. Apart from colonised, uncolonized and isolated patients in the hospital, people in the community were also grouped into four compartments depending on their colonisation status and re-admission rate to the hospital. The model was evaluated mainly through stochastic Monte Carlo simulation technique. MRSA was the hospital pathogen under study and, for the first time, the effectiveness of isolation as an intervention policy was investigated. Due to the inclusion of the hospital community, the study revealed that although local interventions may control the spread of the pathogens successfully within the hospital in the short-term, the fact that potentially colonised patients can accumulate in the community reservoir and re-admit to the hospital multiple times may lead to long-term control failure (Cooper et al., 2004)

Raboud et al. (2005) applied the model proposed by Austin (1999) to study the transmission of MRSA on a general medical ward using very detailed observed data. The model was evaluated using the Monte Carlo method, and the effectiveness of various intervention policies was evaluated. Most noticeably, improving hand hygiene compliance was likely to be the most effective measure for reducing transmission (Raboud et al., 2005)

Bootsma et al. (2006) proposed what seems to be the most complicated mathematical compartmental model so far. The model comprised three hospitals and each hospital had 36 general wards and 5 ICUs. Both patients and HCWs were represented. Patients were classified as colonised, uncolonised or isolated, and a small proportion of colonised patients were further classified as “super-spreaders”. There were two types of HCWs: one type only interacts with patients in the same hospital unit, while another type interacts with patients in the whole hospital. Regardless of the type, HCWs were classified as colonised or uncolonised. The community of each hospital was also represented in the model. The three-hospital model was evaluated by the Monte Carlo simulation while a single hospital model was evaluated deterministically by analytical methods. The model was applied to quantify the effectiveness of MRSA intervention policies, in particular a rapid screening test. Other interventions evaluated by the model include isolation upon detection, pre-emptive isolation, screening for suspected HCWs, ward closure and decolonisation treatment. Many of these intervention policies such as pre-emptive isolation, screening for HCWs and ward closure were considered for the first time. Noticeably, patient movements within the hospital were captured in the model. Observed data were applied to configure the model when possible (Bootsma, Diekmann and Bonten, 2006).

To estimate the transmission rate of MRSA (2007) in an intensive care unit (ICU) in an 800 bed Australian hospital and evaluate the impact the impact of infection control interventions McBryde et al. (2007) a mathematical model. It consisted of four compartments: colonised and uncolonised patients and contaminated and uncontaminated health-care workers (HCWs).

The model assumes that there is no environmental transmission and that all patients who were colonized were detected on admission. Patient movements, MRSA acquisition and daily prevalence data were collected from an ICU over 939 days. Increasing levels of hand hygiene compliance above 40% to 60% was predicted to be the most effective intervention on reducing MRSA transmission. Where decolonisation was predicted to be relatively ineffective. Increasing. HCW numbers was increase MRSA transmission, in the absence of patient cohorting. The predictions of the stochastic model differed from those of the deterministic model, with lower levels of colonisation predicted by the stochastic model (McBryde, Pettitt and McElwain, 2007)

3,1,4 INDIVIDUAL-BASED MODELS

Computational models which group individuals in classes, i.e. have a compartmental structure (track groups in the population) have predominated the field of HAI modelling until the emergence of individual-based models. Among the early studies to model HAIs, there is only few study that adopted individual-based modelling technique rather than the prevailing mathematical compartmental models.

Before 2013, most (73%) HAI models have taken an aggregate approach, although the proportion of individual-based models has increased over time (van Kleef et al., 2013).

Further use of mathematical models of transmission of HAI is warranted. Potential benefits of such kind of studies include evaluating the benefits of various infection control interventions and understanding the impact of random variations in the incidence and prevalence of various pathogens (World Health Organisation, 2009).

Nevertheless, compartmental models have strong limitations.
One primary drawback of compartmental models is the frequent assumption that each compartment consists of a set of homogeneous individuals with the same condition, e.g. susceptibility for infections, and with the same contact assumption (mass action principle) (Caudill, 2013).

Because they are driven by the macroscopic behavior of the system and even when properly calibrated, mathematical models lack realism because they fail to depict the low-level interactions that drive the system (Barnes et al., 2010).
Moreover, most mathematical models assumed that when HCWs did clean hands, 100% of the pathogen of interest was eliminated from the hands, which is unlikely to be true in many instances. Importantly, all the mathematical models described above predicted that improvements in hand hygiene compliance could reduce pathogen transmission. However, the models did not agree on the level of hand hygiene compliance that is necessary to stop transmission of health care-associated pathogens. In reality, the level may not be the same for all pathogens and in all clinical situations (World Health Organisation, 2009).

In contrast, HAI modelled with individual-based method view Ward population as identifiable and self-contained discrete agents who have some states and which are tracked individually rather than subgroups. Individual based models incorporate heterogeneity, e.g. of patients' populations and HCW behaviors. Hence, each individual can be assigned different characteristics, such as patient demographics and disease history, or the probability of acquiring infection or causing transmission (Jit and Brisson, 2011).

The level of definition which can be reached is the same that is it possible to represent with a computer program. It is possible to define interactions allowing for more realistic modelling of healthcare worker-patient contact patterns (e.g. super spreading events) or incorporate heterogeneity in risk profiles of patients. Therefore, Individual based models assure a greater flexibility in the modelling compared to the compartment-based models.

However, these approaches are computationally far more intensive, are difficult to fit to data and the inclusion of additional factors makes more demand on the data available (van Kleef et al., 2013).

A representative study was conduct by Sebille and Valleron (1997). It applies individual-based model to study the transmission of nosocomial pathogens in a hospital.

Most notably, compared to mathematical compartmental models, the model allowed for the representation of every individual patient and HCW. The authors argued that the model offered a new approach to model the spread of nosocomial pathogens in a hospital unit. The Monte Carlo technique was used to evaluate the model stochastically and the model, which consists of seven modules, was written in the C language. The patients' locations and movements were not represented in the model. Both patients and HCWs had limited behaviour rules and only a few attributes which were considered by previous mathematical models. Furthermore, no direct observed data were applied to configure or validate the model. Nevertheless, this study is valuable in the sense that it is the first attempt to apply individual-based models to study HAIs (Sébille and Valleron, 1997) (Meng et al., 2010)

3,1,5 AGENT-BASED MODELS

In Individual-based models, agents are limited to persons, assuming that transmission of pathogens occurred only via direct contact of HCWs and that contaminated environmental surfaces played no role in transmission. The latter circumstances may not be true for some pathogens that can remain viable in the inanimate environment for prolonged periods (World Health Organisation, 2009). Moreover, individual-based models do not have the ability to represent the explicit location and movements of different type of agents. Each patient and HCW had very limited attributes and no behaviour rules were defined for patients.

The notion of an agent in agent-based model expands the classification of agent beyond an individual person, to include inanimate objects. Non-person agents play a significant role as infection transmission vectors of contaminant microorganisms, as seen the germ can spread when a person touches a surface or object contaminated with infectious droplets and then touches his or her mouth, nose, or eye(s) (Meng et al., 2010)

Moreover, individual based models do not incorporate agent-based approach potentiality, e.g. explicitly model the complexity arising from agents' interactions by means of complex behaviours. In Individual-based models, patients and HCWs are passive and only able to change their states according to pre-defined rules. In contrast to previous techniques, ABMs allow researcher to construct a comprehensive representation of the real world, with a certain level of detail of agents (people and objects) and their individual characteristics, behaviours and interactions.

Several application of ABMs to hospital environments addresses system performances examining: patient flows and admission waiting time, staff workload, economic indicator, patients flow and other hospital functioning matters/ operational issues (Kanagarajah et al., 2008), (Spry and Lawley, 2005), (Cabrera et al., 2011) (Hutzschenreuter et al., 2008) (Jones and Evans, 2008) (Mielczarek and Uziałko-Mydlikowska, 2012)

The modelling of HAI is perhaps the best suited area for ABMs within healthcare environment. This is largely a consequence of being able to address all the model components relative to spatial description and agents' ability of social and physical interaction (Laskowski et al., 2011):

- Patient
- HCW

- Other staff
- Equipment
- Facilities
- Layout
- Other agents

While there is a rich history of mathematical modeling of HAI and despite HAIs features which fit with the ABM approach, relatively little work exists, which applies agent-based models to this domain (Friesen and McLeod, 2014).

Regrettably, the development of verification and validation techniques of the agent based models is much more difficult than traditional approach. Such difficulty is known in research community as literature confirms (Laskowski et al., 2011) (Pethes, Ferenci and Kovács, 2017).

According to Demianyk the role of ABMs as useful simulation technique within healthcare facilities is still in its infancy, but offers tremendous potential for the better understanding and optimization of these complex systems. The emergence of ABMs will likely evolve towards a more integrated simulation and analysis suite, combining with other established techniques (Demianyk, 2015).

In an ABM Bagni et al. (2002) investigates the diffusion of Bovine Leukemia, a pathogen which infects cattle in dairy farms. The case study was used to illustrate the differences between the System Dynamics" and "Agent Based" approaches. The model was built in both the Swarm environment and Java. Interestingly the model was event-driven and has the capability of event-scheduling. In the simulation, it is possible to record the change of each animal states, i.e. healthy or infected and spatial displacements of the animals may also be represented (Bagni, 2002)

In 2006 an agent-based epidemiological simulation system was proposed by Dunham.
The system was built in the MASON toolkit, a set of noncommercially available Java-based agent-simulation libraries. The framework is suitable for community-acquired epidemics with large numbers of agents. Standard epidemic models, SIS (susceptible-infected-susceptible) and SIR (susceptible-infected-removed), were implemented and demonstrated on three diverse examples. However, such tool lack of a proper parameterization to be used for realistic simulations (Dunham, 2006)

A large-scale distributed agent based epidemic model was developed by Parker (2007), a model capable of simulating hundreds of millions of agents and which can be distributed to several compute nodes. Parker's study is addressed at enabling the distributed simulation: allocation of agents to available compute nodes, periodic synchronization of compute nodes, and efficient communication between compute nodes (Parker, 2007)

In two consecutive studies Hotchkiss use ABM to assess the dynamics of nosocomial infectious pathogens spread. The former within an intensive care unit (ICU), advocating for a conceptually simple discrete agent-based model can explicitly address 'geographic' considerations and probabilistic transmission dynamics germane to the spatially intricate environments and small population sizes characteristic of ICUs.
The latter in a dialysis unit using a Monte Carlo model. The dialysis unit is a very good example of where ABMs may be particularly useful as, the frequency of patient visits and intimate, prolonged physical contact with the inanimate environment during dialysis treatments make these facilities potentially efficient venues for nosocomial pathogen transmission. He tries also to evaluate the effectiveness of different infection control protocols or policies, intervention

costs, as well as shedding light on potential confinement failures which would accompany widespread infection dynamics (Hotchkiss et al., 2005) (Hotchkiss, Holley and Crooke, 2007)

Meng in 2010 designed an agent-based simulation to assess and manage the transmission risk of MRSA in a hospital ward and to test the effect of admission and repeat screening tests, shorter test turnaround time, isolation rooms, and decolonisation treatment.
Each patient is identified on admission as being colonised or not, MRSA transmission takes place by interaction between pairs of individuals: colonized and non-colonized patients, patient and healthcare staff (nurse and doctor) transiently or permanently colonized, patient-to-patient contacts and transmission from a contaminated environment is also considered. However, the model assumes that a receiver may acquire MRSA due to the presence of carriers in the proximity, regardless of the mode of transmission or the type of activity (Meng et al., 2010)

In Barnes 2010 the authors presented an agent-based simulation model developed to investigate the dynamics of MRSA transmission within a hospital. It is used to examine the effectiveness of various infection control procedures experiments are performed to examine the effects of hand-hygiene compliance and efficacy, patient screening, decolonization, patient isolation, and health-care worker-to-patient ratios on the incidence of MRSA transmission. The transmission of MRSA between agents is determined stochastically, based on the risk level of the patient and the behavior of the HCWs who visit the patient. The Model shows the interaction between patients-healthcare staff, and patients-visitors, but not consider HCWs – visitors contacts.
Outside of extremely high hand hygiene compliance and single HCW-to-patient ratios, patient isolation appears to be the most effective single measure, reducing transmission.(Barnes et al., 2010)

Temime et al. (2010) present an agent-based model of pathogen transmission in a hospital ward, made with “NosoSim tool”. They illustrate its potential applications through an example to assess the factors which promote so-called “super-spreading events” in hospital setting and to assess the effectiveness of a control systematic hand hygiene. They claim that it could be also used simulating the outcome of various interventions for the benefit of decision makers. Their system lack interactions (and possible pathogen transmission) between HCWs; interactions of patients and HCWs with the outside world, pathogen transmission through the environment (Temime et al., 2010)

Milazzo et al. (2011) use an individual-based and stochastic approach to investigate MRSA outbreaks in a hospital ward. A computer simulation tested the effect of spatial and personnel cohorting with the aim of minimizing the possible interactions between individuals within a ward. This study suggests that a strict spatial cohorting might be ineffective, if it is not combined with HCWs cohorting (Milazzo et al., 2011)

In a 2011 study by Laskowski the spread of influenza like illness in emergency ward, was simulated using ABM. The model examines the dynamics of infection spread within a hospital, contains the immunity of the patients and the spatiality of the ward and tested the effect of infection control policies (Laskowski et al., 2011)

Hornbeck et al. 2012 used a remote-based sensor network to record interactions among healthcare workers and patients in intensive care unit. Then they built an agent-based simulation on the resulting data collection from this network to model the spread of nosocomial pathogens to identify the most- and least-connected healthcare workers. They point out the impact of hand hygiene noncompliance among peripatetic healthcare workers, i.e. individual with measurably high connectivity responsible for infecting many people. They prove that heterogeneity in healthcare worker contact patterns dramatically affects disease diffusion (Hornbeck et al., 2012)

In 2013 Rubin designed an agent-based computer simulation of nosocomial C. difficile transmission and infection, which included components such as: patients and health care workers, and their interactions; room contamination via C. difficile shedding; C. difficile hand carriage and removal via hand hygiene; patient acquisition of C. difficile via contact with contaminated rooms or health care workers; and patient antimicrobial use. It was also possible to test six interventions, alone and mixed together: aggressive C. difficile testing; empiric isolation and treatment of symptomatic patients; improved adherence to hand hygiene and contact precautions; improved use of soap and water for hand hygiene; and improved environmental cleaning. All interventions were tested using values representing base-case, typical intervention, and optimal intervention scenarios. Findings suggest that most of the impact came from improved hand hygiene, empiric isolation and treatment of suspected C. difficile cases (Rubin et al., 2013)

Ferrer in 2013 presented Nosolink, an ABM of an intensive care unit that combines the operational and the epidemiological perspectives used to evaluate the relation between staff organization and nosocomial contagion. Such model they have taken into account the work schedule, sick leaves, workload, fatigue and occupation state of HCWs (Ferrer, Salmon and Temime, 2013)

In the same year Jiménez an initial stage of the study with the aim to develop a highly-detailed, agent-based simulation to compare medical treatments against Clostridium difficile infection. The model was built using patient information and healthcare worker data from electronic medical records, and implemented in EpiSimdemics simulation software that looks at simulation in large social networks. Interactions between people and probability to get the infection are calculated using a stochastic model, such model do not consider the impact of the environment as vector for infections, and simplifies the contact between agents considering them in contact if in the same location at the same time. (Jiménez, Lewis and Eubank, 2013)

In 2015 Codella develops an agent-based simulation model (ABM) to study C. difficile transmission and control in a midsized hospital. He derives input parameters from aggregate patient data from the 2007–2010 Wisconsin Hospital Association. Agents are patients, healthcare workers, and visitors. Natural progression of C. Difficile infection in a patient was also modelled using a Markov chain. The model was used to test the effects of different control measures (Codella et al., 2015)

Recently Pethes presents the preliminary conception of a simulation framework designed in Object-Oriented fashion and using the system in R, which describes the spread of Hospital-Associated Infections (HAIs). The elements of the simulation include among others: admission and discharge patients, pathogen transmission via healthcare workers, colonization and infection, modelling hospital events, scheduling treatments, the interventions against HAI spreading. The development of the model is tracked in discrete time, and the simulation is driven by stochastic events sampled from predefined distributions. The pathogen transmission probability does not depend on the contact length, but it uses fixed transmission probability (Pethes, Ferenci and Kovács, 2017)

3,1,6 CONCLUSIONS

While the reviewed studies have provided new insights into the relative contribution of various infection control measures they investigated only one or few aspects at the time, losing the organised complexity of the phenomenon and all have been based on assumptions that may not be valid in all situations (Weaver, 1948).

They foremost focus on community-acquired epidemics with large numbers, even hundreds of millions, of agents and large-scale distributed. If regarding a single hospital ward, mostly ICU, many of them, if not all suffer the following limitations:

1. include only two members of healthcare staff: doctors and nurses, where other HCWs and visitors are ignored;
2. account only for contact transmission through interaction between the patients – physician or patient - nurse, when contact between patients, HCWs and visitors cannot be included;
3. the contact transmission dynamic does not consider the specific features of the (type) activity in progress or the effective contact between agents, at best considering the agents proximity regardless of the modality of transmission;
4. not consider pathogens removal via a proper hand hygiene or ward cleaning through decontamination procedures, neither the level of accuracy of such procedures;
5. focus on transmission between individuals neglecting the role of the environment and inanimate objects as potential transmission vectors;
6. divide patients into colonized or infected and the healthcare staff into colonized and non-colonized or transiently colonized, therefore representing them with distinct alternative states rather than continuous;
7. do not consider the severity level as well as different levels of susceptibility of patients and ignore patients’ and HCWs heterogeneity, behaviours and personal traits.

Finally, none of them investigate the impact of different architectural design and spatial distribution on the propagation of infections and only a few consider the effective spatial displacements of agents.
Our work applies the Event-Based approach and tries to address many of these under investigated aspects with the aim of building a comprehensive system to handle different pathogens type, spreading conditions and spatial organization.

3,2 EVENT-BASED MODELLING AND SIMULATION

3,2,1 INTRODUCTION

The present work has been developed having the Event Based Modelling and Simulation (EBMS) method as reference framework, which have been developed by Professor Kalay's research group at Architecture Faculty, Technion (IL).
This model combines aspects of Agent-based and Process-based models in a coherent simulation.
Simulation model appears to be the better choice for investigating Human Behaviour Representation (HBR), also known as refers to computer-based models which imitate either the behaviour of a single person or the collective actions of a team of people (MAJID, 2011) (Richard W. Pew, 1998).

Event-Based method considers the users and the processes of use of the space in a hospital environment by modelling events, which take place when different user behaviours occur in that space. Schaumann and Kalay (Schaumann et al., 2015) elaborates the notion of Event, as computational entity that combines information concerning people (who?), the activity they perform (what?) and the spaces they inhabit (where?). Such approach represents users–space interaction, i.e. activities as specific modelling entities on their own, clearly distinct from spaces, but connected with them. The method comprises several modules which are described in the following paragraphs.

3,2,2 SPACE

Event based approach requires us to interpret and formalize the space to provide the conceptual connection between the building use process based on the organization's operational dynamics, and the building design solution provided by the architect. Because to build a space use simulation, two kinds of data must be clearly distinguished: the required data for rendering 3D scene, coming from the design provided by the architect, and data for supporting the human simulation and enabling complex autonomous behaviours, which are drawn starting from the semantic assigned by architects and also from the semantic subsequent to the observation of the current use of the space.

Therefore, in our simulation-driven understanding space represents the spatial place of activities and interactions. It physically corresponds to the structural decomposition of the environment layout. It is hierarchically subdivided into a set of zones and sub-zones, which define the function and afforded activities of the space (Gibson, 1983). For instance, a nurse-station zone affords patient-record keeping activities, administration, consultation, and communication activities. A section of a corridor affords multiple different activities, such as passage and social encounters, as well as medical activities such as patient treatment, if needed (Hadas Sopher, Davide Schaumann, 2016)

Space entity answer "where?" question and assemble static geometry + real time semantic info + real time environmental info in single model integrating all information required to manage realistic behaviours of actors, Table 4.

Static Attributes				**Dynamic Attributes** *(updated during the simulation)*							
Name	**Type**	**Assigned Semantics**	**Affordances**	**Current Use**	**People**	**Equipment**	**Density**	**Temperature**	**Light**	**Noise**	**Smell**
DPR_7 *(example)*	Clinic	Double Patient Room	Rest, Eat, Talk, Medical Check	*Semantics*	*People list*	*Equipment list*	*# of People*	*Value*	*Value*	*Value*	*Value*

Table 4 - Space attributes (Schaumann, Morad, et al., 2016)

Static geometry:

Space is a semi-closed area bounded by static objects (usually walls). Each place may have connections called portals, with its neighbour places, used to ease the interaction between two adjacent spaces.

It comprises static semantic, defined a priori by the designer of the simulation and mirroring the semantic assigned by the architect which remains fixed during the simulation, e.g. permeability of doors and solidity of walls.

Space in such extent provides structural information about the environment to actors. Allowing actors to accomplish simple behaviours consist in avoiding static and dynamic obstacles, which requires only geometrical information on the various objects in the virtual world.
Space in such interpretation provides also topological information about the environment to actors. Required to exhibit complex behaviour in a virtual world, which depend on the nature and position of the objects, associated to each zone, and the global distribution of spaces, for instance to compute and perform the displacement between two spaces, carrying a chart.

Real time semantic information:
Space is defined by its meaning depending on the possible use patterns. There is a list of plausible semantic for each space zone, which correspond to space affordances, e.g. the usability of furniture, the state of occupancy of the space and so on. The space detects autonomously the people present and the activity carried on and change in real time its current semantic accordingly. Competing space affordances determine how a space is currently used, and what are other possible uses.
Space in such interpretation provides dynamic semantics allowing actors for more complex behaviours, which depend on the understanding of the objects affordances.

Real time environmental information:
In addition to determining affordable activities, Space can communicate certain parameters ensuing from the performance of an activity within its place, such as presence of actors and the noise it produces. By doing so, the space construct can be used to replace actor based perceptual capacities (as done by ABM), and save computational resources.
Artificial Intelligence resources distributed in the space components have the task of controlling the simulation of local interaction with the actors by taking

momentary control of their behaviour, as will be explained in the next sections. For instance, a door can include knowledge about the users already inside the room and decide if the approaching user is allowed to enter or not. In this way, the AI resources are balanced among a large amount of entities rather than just concentrated in the 'brains' of the actors, and this makes the simulation process computationally manageable and its outputs more reliable and realistic (Yehuda, 2013)

Environment is a shared structure for agents, where each of them somehow perceive and acts.

3,2,3 ACTORS

Actors are computational entities with physical description that can move and perform activities used to formally represent building users.

Beyond the computational representation, actors have profile and status, which include psychological, social, cultural, and other traits and abilities.

Actors which are anthropomorphic agents answer "who?" question and assemble imported geometry + fixed semantic role + physiological and psychological attributes (fixed and variables), Table 5.

Static Attributes										Dynamic Attributes			
Name	Type	Role	Age	Gender	Experience	Threshold for:			Politeness	Stress	Tiredness	Knowledge	Social Relations
						Density	Noise	Smell					
Nurse_1 *(example)*	Medical Staff	Head Nurse	*Value*	*Type*	*Value*	*Value*	*Value*	*Value*	*Value*	*Value*	*Value*	*Database*	*Database*

Table 5 - Actors attributes (Schaumann, Morad, et al., 2016).

The event based approach comprises actors' abilities as rules that describe the response of actors to their physical and social surroundings, based on the actors' individual features.

Actors do not incorporate autonomous high level decision-making ability, because these are provided by the Event, a process model, which controls them at in real time, as will be described in the next section.
The Actor is the recipient of an Activity that needs to be performed, communicated to it by the Event. The event query for specific physiological and psychological states.
The performance of the activity is modulated by the Actors current surrounding (physical and social), which is communicated by the Space semantic, and affected by the Actors' internal state (e.g., tiredness). For instance, if an actor is an old lady, she might walk slowly, i.e. the activity move can use the actor default speed, causing her to walk slowly.
Together, they produce an individual reaction to the Event's directive, which is communicated back to the Event. (Shaumann)
Therefore, actors are provided with the abilities to autonomously adapt their behaviour within a predefined range, depending on the status of the environment and on the reference process model. In turn, the simulated actors' serendipitous actions outputs are feedback into the process model, and can influence it, providing information to support the event high level decision-making.
However, actors are integrated with some typical agent-based components, intended to control some autonomous low-level aspects of actors' behaviour. For instance, the abilities of a user to compute a path and perform the movement actions is and controlled directly in the actor entity as well as path decision, walking actions, obstacles avoidance, local interactions with other entities, such as doors or other actors.
Finally, the computation of the agent perceptions is not the subject of a specific process in the event based approach. Actors' perception of a certain environmental condition is in fact a process of comparison information stored in the "space entity", under the form of parametrized value, with a certain threshold for that parameter embed in the actor. The system engine coordinates

coherently the response of the actors to the environment. The result is that the actors seems react to the environment like if he perceives and understand the environment condition (for each parameter) acting in accordance to his embed threshold of tolerance. Thanks to that it is possible avoid the overall complex computation of all actors' perceptions.

3,2,4 ACTIVITIES

The event based approach required the simulation environment to provide data about the system of activities and their specific performing.

This is needed because the objective of the model is to simulate not only some specific aspects of users' behaviour (e.g. the displacement), but the main tasks that actors may perform in an hospital ward, leading to visualize the simulation animations.

Every elemental activity, i.e. social activities, movement and physical activities, which can be performed by a single or a group of actors are modelled in the system.

Activity which is a use process related semantic assembling a set of actions and answering "what?" question. It takes arguments the actors involved, the semantics of the space and the duration.

A series of activities form a task, which is a function, called by the event unit, as described in the next section, which the actor needs to complete to resolve the task.

A Patient-check event, for example, comprises of activities such arrival of the relevant actors to a specified destination, carrying out the medical procedure (which involves communication) and recording the results in some form.

Therefore, these lists of activities, which can be sequential or parallel, are communicated by the Event construct to the Actors in a form of a task.

3,2,5 EVENT

An event unit is a process model that that meaningfully combine actors, space and activities Fig 15. Events construct combines three different information (Where, who and what). These types of information representing heterogeneous and independent domains of data must therefore be interpreted (Simeone *et al.*, 2012).

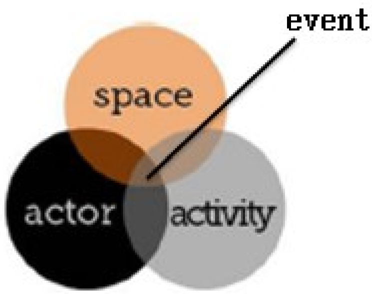


Fig. 15 - Event representation (Simeone et al., 2012).

Events are computational entities that manage the performance of a specific behavior pattern querying the involved actors, spaces, and activities.
An example is the "Patient-check" event, where a doctor and a nurse perform an activity common in hospitals of checking patients: all three actors (doctor, nurse, and patient) must be present at the same place, at the same time, for the purpose of performing a medical activity.
Events are not a direct prediction of how the people will behave in a future building, but rather a knowledge-base necessary for such prediction, to be modified and adapted by local, specific circumstances.
In the simulation the event entity behaves like a sort of movie director, managing and coordinating single actor behaviour during a scene, but leaving to them a low level of adaptation to such direction.

Novelty of this approach lies in making the actions process execution more flexible and partially adaptable to serendipitous "emergent" circumstances in real time during the simulation.

Events embed the knowledge to perform a task in virtual settings. They meaningful interpret information applying space and activity semantics to actors, envisioning the specific use process of that space for a certain time span. When triggered the event reduce the autonomy of the agents and tactically coordinates them through a series of actions, related to the contextual building function. The Event unit for a certain space check the list of possible space semantics and the actual one, to see if can instruct an activity to be performed or not.

The Event works through preconditions, performance procedures and postconditions. The triggering happens if the preconditions are satisfied. According to Weiss's definition of agent goal oriented behaviour: "goal oriented behaviour is in a simplest way is definable like a procedure that run if are recognized certain pre-condition ad such procedure will produce some effects, the post-condition, that have to be the agent goals" (Weiss, 2000).

Preconditions as have been explained fit the definition the multi agent system paradigm "Actions have preconditions associated with them, which define the possible situations in which they can be applied" (Weiss, 2000).

Preconditions ("if something") relate to a state of the world, i.e. they are a set of facts about the virtual world which can be true or false. They account for the decision-making ability of the system, which express the required actors and space for an event to be triggered.

Performance procedures guide the event execution. Procedures are provided by the activity component and it comprehend the duration of the activity itself, unless it concerns a displacement activity, which depends on the space conformation. Activities are operations on the state of the world.

Post conditions ("then something") the simulation engine at the end of each activity collects information and coherently updates the state and statistics of

space and actor entity. Activities being functions cannot be affected or modified, for that reason in Event-Based method actors do not have learning abilities.
Events scripting can be derived from data gathered during contextual survey activities in different ways, such as direct observation of similar, already built cases, previous knowledge formalization, hypotheses reviewed by experts usually involved in such circumstances.

3,2,6 SYSTEM ARCHITECTURE

The previous elements are needed to assemble a building use scenario.
It is an example which describes a real-world process of how an organization (in terms of the people involved) interacts within itself, with the built environment, and with the context in which it operates (Simeone *et al.*, 2013)
The simulated representation of a building use scenario is represented as a game narrative, a story path where events can be considered as milestones: entities that are linearly connected to each other to represent, step by step, what happens in the building, Fig. 16 (Simeone *et al.*, 2012).

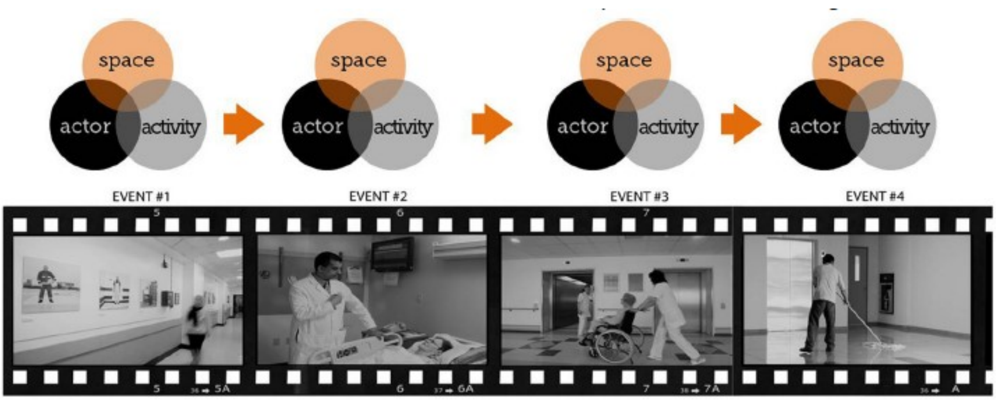


Fig. 16 - The example of a building use scenario (Simeone et al., 2012)

To represent different building in use scenarios events are combined into time-based structured sequences called human behaviour narrative. Which comprises discrete activities, involving a number of users, and performed in specific spaces and time.

Human Behaviour Narrative is made by coexisting building use scenarios, where several activities can be performed simultaneously and affect each other. It is generally intricated as it is reflected by the complexity of its representation, Fig. 17, showing multiple paths of activities to be performed in a temporal sequence, generate an articulated graph, which connects and combines them in an oriented network where the orientation of each branch shows the logical sequence of their performing. In such configuration events can be shared by different use building paths and are connected through connectors to define an operational sequence flow.

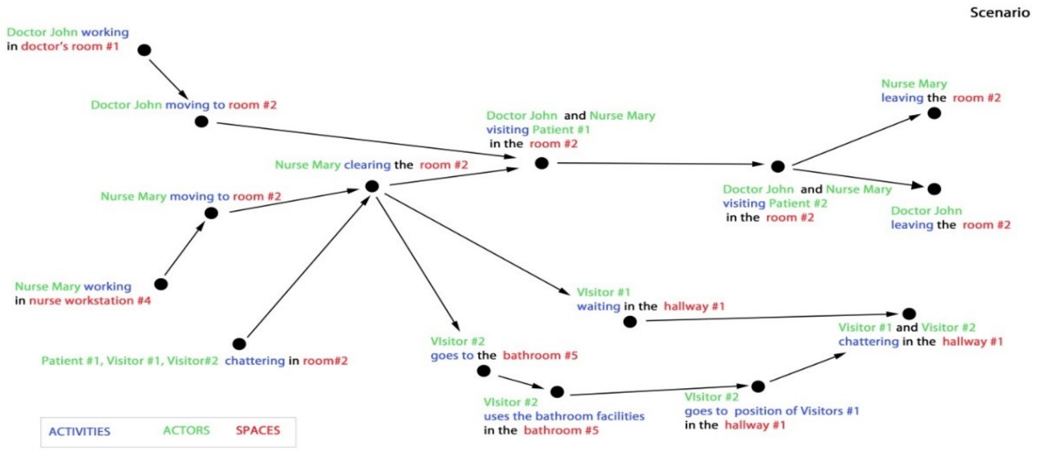


Fig. 17 - Human Behavior Narrative (Yehuda, 2013)

Human Behaviour Narrative before the simulation starts is built thanks to real-life observations, interviews and discussion with experts and it is made up hierarchically aggregating events, nesting events in sub-events and assembly events in: sequence, parallel or selection connections. Which can be exploit using

the rules of structural programming, following the Bohm-Jacopini theorem (Böhm and Jacopini, 1966).
Nevertheless, to provide a reliable prediction of the users’ behaviour a good narrative of humans’ situations should approach the complexities and contradictions of real life. In fact, such daily life narratives are difficult or impossible to summarize into neat scientific formulae, general propositions, and theories (Flyvbjerg)
Therefore, the scenario has to be able to adapt to the different conditions emerging from the performing of determined activities in a specific building layout.
To do so the simulation script is integrated with some typical agent-based components, intended to control some autonomous low-level aspects of actors’ behaviour. In that way, it is possible to simulate serendipitous events generated by the interactions of the actors with the contextual built environment that are not predictable in the Human Behaviour Narrative development. If for instance the paths taken by two agents brings them close, they may choose to stop and talk, or ignore each other and continue their pre-scheduled task.
Moreover, the choice to provide actors with some degrees of autonomy allows to represent some aspects of users’ behaviour that would be difficult and time-consuming to represent and compute at the Human Behaviour Narrative process level, mostly if iterated for each agent.
The system allows the emergence of events because preconditions triggering at the same time situations scheduled in some branches of the Human Behaviour Narrative, as well as unscheduled situation.
Therefore, at the end of the simulation the Human Behaviour Narrative may be composed by a different sequence of events form which it was pre-designed, due to the arising of un-planned events, which take place inside the pre-planned sequence, emerging from the contextual conditions, Fig. 18.

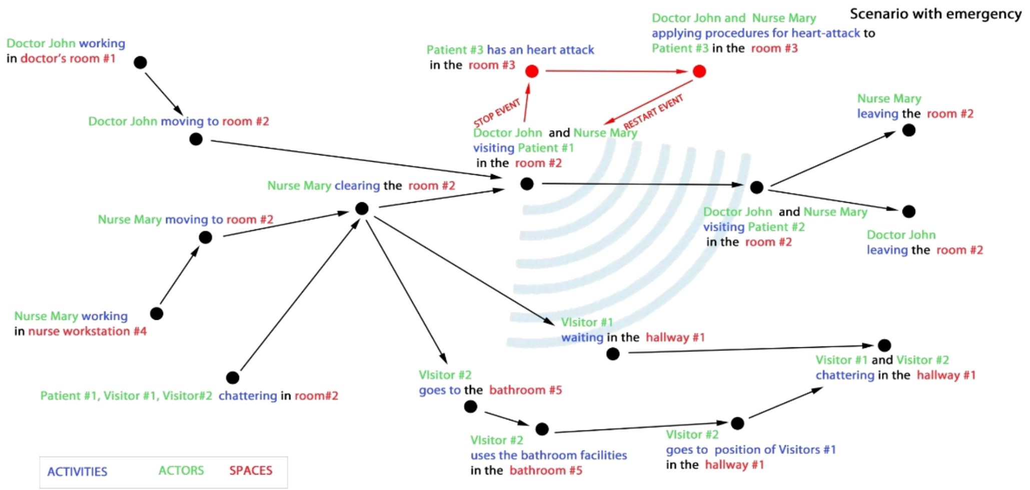


Fig. 18 - Human Behavior Narrative in the case of unplanned event. Image courtesy of Prof. Y. E. Kalay (Yehuda, 2013)

Where planned events are top-down and time based scheduled events inside the Human Behaviour Narrative. Un planned events are never scheduled in a time-based fashion, they emerge unexpected during the simulation run, e.g. code-blue event and random meetings and originate from agents situated interactions with their physical and social environment. However, their configuration in terms of event basic components: actors, space, which can be whatever, but activity function as a clear set of actions, is scripted in advance.

Un planned events depend upon agent individual traits, group serendipitous situations, social and environmental stimuli and so on. They consist in a list of possible events that may occur if some specific preconditions arise.

The existence of planned and unplanned events can produce conflicts, which can lead to the system failure or stuck. To manage this prospect, the upper level narrative management system has been conceived. The main function of the narrative management system in the simulation is to resolve conflicts about resources and priorities between Events.

Narrative Management System manage, coordinating the performing of the different activities, solving interferences and conflicts among them and, most generally, guiding the flow of activities

It practically enables control and simulation of serendipitous events, e.g. the ones triggered by the physical (actually, geometrical) proximity and location of the actors within the simulated built environment. It also supervises the re-arrangement of events as in the case of the need of rescheduling due to a delay.

Narrative Management System consists in a rule data-based system, which is rebuilt for each case study, but it can be generalized. To resolve conflicts, it relies on all the available system information e.g. priorities, actors' traits, urgency, and so on. His selection of event abilities into the real-time development of human behaviour narrative implies the elicitation of a priority function, accounting for a system level decision-making.

Narrative Management System literally develops as a structured Event Based narrative tree composition which operates at strategic level, directing the development of the Human Behaviour Narrative by combining top down planned events with bottom up un planned events into a sequence that develops in real time through the simulation, Fig 19.

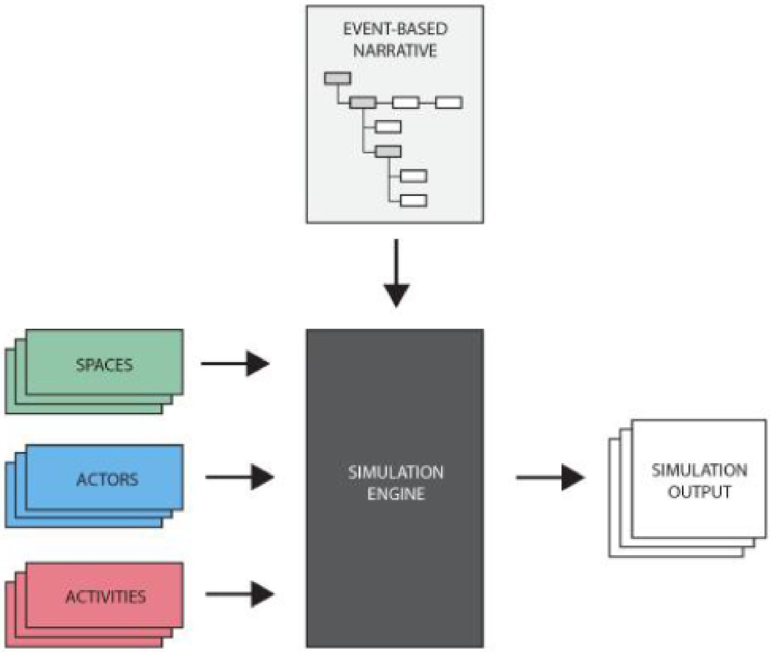


Fig. 19 - Event-Based system architecture. Image courtesy of Prof. Y. E. Kalay (Schaumann, Morad, et al., 2016)

Even though in the following case study we consider only one type of unscheduled event, i.e. the interruptions by visitors on the HCWs work schedule, it is possible to model multiple unscheduled events thanks to the Narrative Management System.

Differently from previous activity-based models where the use process is entirely computed before and then merely visualized, in the proposed model the use scenario is computed in real time during the simulation, providing a better adaptation of the sequence of activities to the built environment and its occupants and, consequently, a more coherent and reliable simulation output

The subsequent step is to animate activating the model within the simulation, running different scenarios with different layouts (space-actors-activities).

3,3 EVENT BASED SIMULATION COMPARISON WITH DES AND ABS

Several methods are used to model and simulate human behaviour. The most well-known are Discrete Event Simulation (DES) and Agent Based Simulation (ABS).

The main differences between them are well documented; see, for instance (Borshchev and Filippov, 2004) (Nehme and Crandall, 2008) (Korhonen et al., 2010) (Mustafee, Katsaliaki and Taylor, 2010)

While DES has been used widely in the field of operational research, ABS is relatively new and applied as part of artificial intelligence and complex adaptive systems.

The use of a bottom-up rather than top-down approach is a key feature of ABS when compared to DES in which the system is centralised and the entity is only one of the many essential elements of the model, Fig. 20.

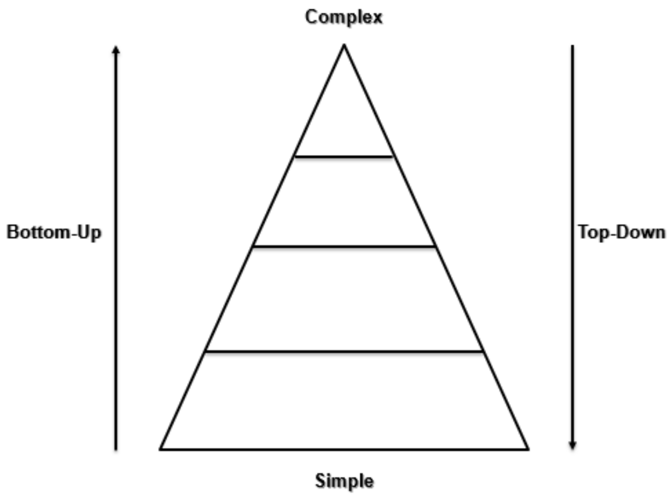


Fig. 20 - Bottom-Up vs Top-Down Outline

Discrete-event simulation models are named after their discrete, dynamic, and stochastic characteristics.

DES involves the modelling of a dynamic evolving system which is stochastic, as it consists of random input components, and discrete because a series of chronological sequences of events change the system's state instantaneously at separate points of time. (Carson, 2004)
DES maintains a future event list and is capable of event scheduling. It is normally applied to describe a system through activity sequences where waiting in a queue between each activity is necessary since the required resources (e.g. people, equipment and spaces) are scarce.
Conventionally, these models are used in engineering to optimize the resource flow. Typical queuing systems include production lines, airports, banks, restaurants, call centres, accident and emergency departments of hospitals. DES has been also applied to study community-based infections, see for instance (Allore et al., 1998) (Cohen, Artois and Pontier, 2000) (McKenzie, Wong and Bossert, 1998) (Rauner, Brailsford and Flessa, 2005).

Despite its wide use and applications, DES cannot account for the human factor of physiological and psychological traits as set out in this study (e.g., HCW's individual knowledge and personality, patients' health condition and more). Nor can it do so for agents' perceptual and cognitive abilities in relation to their dynamic surrounding environment.
To this end, ABS is more suitable as it can represent an agent's health condition and hygiene level along with the interaction between them. One core advantages of ABS compared to DES is its capacity to represent agents' spatial locations and movements, which is critical to the actual contamination transmission in the hospital ward. Indeed, in DES agents are not situated in a spatial context, since spatial features are abstracted in terms of the time required to move within a space (Schaumann, Pilosof, et al., 2016).

As demonstrated previously, spatial features have a significant effect on pathogen dissemination, both directly as well as through agent activities and interaction. Moreover, human spatial behaviour and decision-making are strongly affected by contextual environment. Several studies have attempted to understand such a close relationship. Major concerns include wayfinding, queuing and crowding, spatial compatibility and conflict among activities, the psychological consequences of spatial experience, territoriality, spacescape visualization and more. See for instance (Ostermann, 2009) (Oldenburg, 1999) (Stokols, 1972) (Gehl, 2011) (Hall, 1966) (Linder, 1990) (Whyte, 1982) (Gibson, 1986) (Lynch, 1960) (Marcouiller, 2008) (Weiss, 2000) (Wei and Yehuda, 2007) (Esposito, Mastrodonato and Camarda, 2017)

These aspects of human (spatial) behaviour in simulation can be managed by an Agent Based paradigm.
ABS models a system as a collection of entities called agents.

Several definitions of the term “agent” exist, ranging from the earlier “something that perceives and acts” (Norvig and Russel, 2010) to Maes’ more complete description; “autonomous agents are computational systems that inhabit some complex, dynamic environment, sense and act autonomously in this environment and by doing so realize a set of goals or tasks for which they are designed.” (Maes, 1995).
Wooldridge and Jennings provided a definition of what an agent is and does by through the following properties (Wooldridge and Jennings, 1995):

- autonomy;
- social ability;
- reactiveness;
- pro-activeness.

Autonomy: an agent must be able to operate, follow instructions and take decisions without the direct intervention of humans or others and to have some kind of control over his actions and internal state.
Social Ability: an agent is part of a system of agents. Therefore, he must be able to interact with others in order to complete his tasks and support others in their activities.
Reactiveness (reactivity and situatedness): an agent must be able to perceive his environment and react to it. Generally, if the environment changes, so must the agent in some way.
Pro-activeness: agents do not simply act in response to their environment, they are able to exhibit goal-directed behaviour by taking the initiative when appropriate. They fulfil a series of objectives in a complex, dynamic environment, learning from their experience, their environment and their interaction with others.

In their subsequent study, Wooldridge and Jennings clearly formalised the definition of agent, a key aspect in modelling decision-making support, by stating that: “an agent is a computer system, set in a particular environment, who is capable of autonomous and flexible action to reach his planning objectives.” (Wooldridge, Sycara and Jennings, 1998). For further reading, see (Reynolds, 1987) (Ferber, 1998) (R. M. Axelrod, 1997) (Gilbert, 2008) (Kennedy, 2011) (Macal and North, 2010) (Batty, 2009) (Helbing and Balietti, 2011)

Bonabeau presents a list of decisive factors in the choice of modelling approach from architecture to agents; among these elements, it is interesting to highlight the following as they are appropriate to our situation (Bonabeau, 2002) :

- when individual behaviour is complex. In principle, everything can be done with equations but the complexity of differential equations increases exponentially as the complexity of behaviour increases.

Describing complex individual behaviour with equations becomes intractable;

- when space is crucial and the agents' positions are not fixed, as in our case;
- when the population is heterogeneous, when each individual is (potentially) different. Our agents have multiple concurrent state and feature changes which at the same time regard infection development, hygiene status, location and more;
- when validation and calibration of the model through expert judgment is crucial. ABM is often the most appropriate way of describing what is actually happening in the real world and the experts can easily "connect" to the model and have a feeling of "ownership".

Given these preconditions, it is not difficult to outline what an Agent-Based model is and what it does; it is a system based on autonomous decision-making agents (in social systems, most often people) which are able to perceive, plan and act. In the most general contexts, agents are both adaptive and autonomous. Multiple goal-oriented agents operate and interact simultaneously in a shared environment and each one does so under different initial conditions and constraints. Therefore, the dynamic evolution of the system emerges from local interaction among agents, leading to an unpredictable development of the system which is thus referred to as complex.

The case of a set of agents who interacts in a common environment and can modify themselves and the environment, which in turns impacts and transforms agents' activities and behaviours, typically pertain a Multi-Agent System (MAS). MAS agents show the ability to solve problems at individual level and can interact in order to reach global objectives. This interaction may come about both between agents as well as between agents and their environment.

In ABS and MAS, the modeller defines the behaviour of the single agent at individual level and the system behaviour emerges from multiple interactions between individual entities. Therefore, such approaches are well-suited to simulate human behaviour and interactions. It has been extensively applied to represent particular kinds of human behaviour in space, mainly reactive to social and physical environments. This includes, for instance, fire-exit, pedestrian flows, traffic, evacuation and crowding, all situations in which large number of agents express a clear and standard behaviour pattern without the need for complex reasoning or cognitive abilities, so allowing for an easier and more likely approximation to real life. However, in such cases compound behaviour results are not intuitive, since a small number of rules applied to many agents are capable of generating complex macro-phenomena and emerging circumstances may appear (a factor the modeller investigates). Therefore, simulation outputs may help to predict surprising developments as well as risky situations. See for instance (Pan, Han and Law, 2005) (Camillen et al., 2009) (Hajibabai et al., 2007) (Ronald, Sterling and Kirley, 2007) (Batty, Desyllas and Duxbury, 2003) (Galland et al., 2014) (Chen, 2012) (Ronald, Arentze and Timmermans, 2009)

Nevertheless, the current approaches of ABS and MAS are still limited to representing more complex activity patterns of interaction (e.g. agents-agents-space) because of the high processing requirement of a real-time emulation of the process of human cognition and decision-making, which is still under study (Crooks, Patel and Wise, 2014).

Another limiting factor is that an ABS is still incapable of representing dynamic collaborative behaviour in a reliable way, i.e. multiple autonomous, responsive and interactive agents who co-operate, co-ordinate and negotiate among one another to achieve their objectives. (Schaumann et al., 2015)

Thus, regardless of the apparent advantages of using ABS rather than DES, to be able to describe an agent’s state and location and the impact of the social and

physical environment on individual agents, the use of ABS alone would not be appropriate in our case.
To address this issue, Simeone et al. and Kalay, Schaumann et al. have proposed the Event-Based Modelling approach, which is a feasible trade-off between top-down and bottom-up methods.
EBM bypasses ABS limitations by using the Human Behaviour Narrative, whereby high level decision-making is set to co-ordinate the actors' sequences of activities and cooperation. Conversely, agents retain the low-level decision-making which expresses bounded rationality. This allows them an autonomous response to local conditions, such as path-finding, avoiding obstacles and triggering events, which ultimately is what a current ABS can manage.
Such a choice is reasonable for our purposes, because it avoids situations in which the simulation is blocked due to insufficient agent reasoning capabilities when performing complex sequences of behavioural patterns. These are displayed by the EBM, effectively mirroring the structured organisation of hospital ward workflow.

3,4 CONCLUSIONS

The more we study human behaviour from a cognitive point of view (i.e. the mechanisms that control behaviour), by selecting a specific form of behaviour (e.g. studying the cognitive process which attains an understanding of dimensions in space) the more we can advance its description while attempting to discover how it develops and why it leads to situations occurring. This fact implies that we can then generalize about a specific case study for all types of different settings. This is true, as here we are not referring to the chosen case study, namely spatial events, but rather focusing on the underlying cognitive mechanisms behind human understanding of the world, which naturally contributes to the effect on human spatial behaviour by influencing him to perform (or not perform) a certain activity in a certain manner. Broadly speaking we can, using a certain degree of approximation, fit our findings to different contexts if these rely on the investigated human cognitive process.

On the other hand, since it is insufficient on its own, a thorough depiction of a specific cognitive process underlying specific behaviour prevents us from describing the environment complexity composed of interrelated behaviour, situations and spaces. It means that if we want to represent the dynamic evolution of a case study in terms of space and time, we must reach a trade-off. We must find a level of description which is capable of representing how something happens both coherently and realistically. Moreover, it should allow us to tackle a high degree of real-life situations evolving over time in a complicated setting, such as hospital departments.

RESEARCH ENQUIRY LEVELS	**LEVELS OF REPRESENTATION OF THE SUBJECT**	**RESEARCH APPROACHES TO STUDY THE SUBJECT**
UNDERSTANDING AND DESCRIPTION OF WHY IT HAPPENS	HUMAN SPATIAL COGNITION AND PERCEPTION FUNCTIONS	COGNITIVE SYSTEM ARCHITECTURES
UNDERSTANDING AND DESCRIPTION OF HOW IT HAPPENS	PROCESSES OF HUMAN SPATIAL MOTIVATION AND BEHAVIOUR	HUMAN SPATIAL BAHAVIOUR AND DECISION-MAKING SYSTEMS
UNDERSTANDING AND DESCRIPTION OF WHAT HAPPENS	INTERACTION MECHANISMS ARISING AGENTS AND SPACE	EVENT-BASED MODEL AND SIMULATION OF THE PHENOMENA

Table 6 – Levels of understanding and representation of human behaviour.

We should consider that the levels of understanding and representation for the human behaviour systems, definite in the Table 6, are not directly scalable, even if they are strictly related until those cases when it is not easy to define a border between them. It means that good cognitive architecture (intelligence structure and functions) cannot represent the development of human behaviour (which occurs in space) and a good simulation of a human behaviour has nothing to do with the underlying human cognitive architecture. It is up to the modeller to define to what degree particular aspects of the different description levels should be taken into consideration in order to shape the best model for the specific case study and its purposes.

To facilitate this process, Benenson reports a detailed description of agent properties mirroring the level of detail which may be needed to effectively represent the phenomenon under study, Table 7.

Property	Other names	Meaning
Reactive	Sensing and acting	Responds in a timely fashion to changes in the environment
Autonomous		Exercises control over its own actions
Goal-oriented	Proactive, purposeful	Does not simply act in response to the environment
Temporally continuous		Agent behavior is a continuously running process
Communicative	Socially able	Communicates with other agents, perhaps including people
Mobile		Able to transport itself from one location to another
Flexible		Agent actions are not scripted
Learning	Adaptive	Changes its behavior based on its previous experience
Character		Believable "personality" and emotional state

Table 7 - Properties of agents in Multi-Agents Systems (Benenson and Torrens, 2004)

Nevertheless, as the table hypothetically shows, broadening the description of the agent cognitive abilities means decreasing the possibility of simulating a complex scenario, namely multiple and heterogeneous agents and activities dynamically evolving over time, Fig. 21.

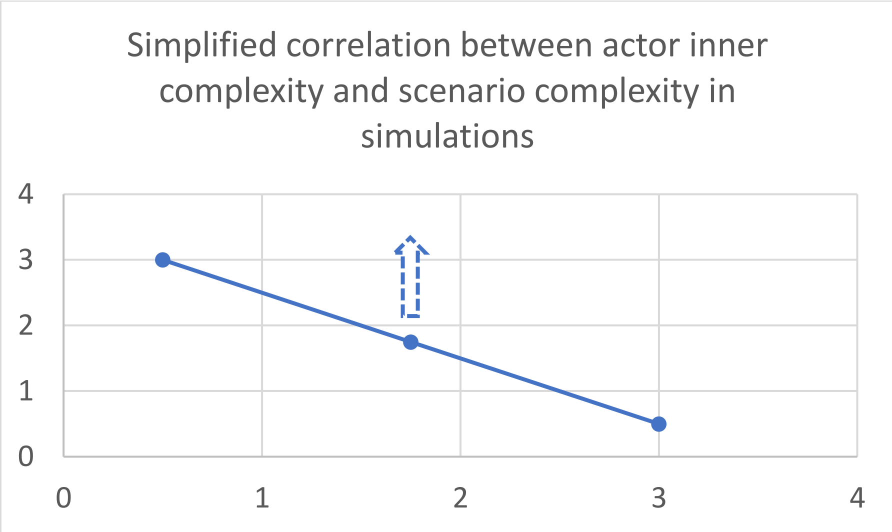


Fig. 21 - Supposed basic relationship between agent complexity and narrative complexity in simulations.

Conversely, the aim of simulating complex scenarios implies the consideration of only certain agent properties (capabilities) and not the handling of complex cognitive abilities, which in real life drive processes up to some extent or are at the very least fundamental.

We find ourselves at the middle point, in which the system simulates complicated series of events while taking into consideration agent simplified decision-making processes by means of the Human Behaviour Narrative and the Narrative Management System.

The EBMS framework that we use shows a narrative made up of a sequence of events (e.g. patient check, medicine distribution, visits) which are pre-ordered in a logical fashion. The simulation platform then visually represents this narrative, allowing the agents some degree of freedom.

Agents within the simulation can only do certain things which have been previously explained to them through a sequence of rules of conduct; therefore, they act accordingly.

It may be the case that the narrative changes unpredictably because unplanned events arise from the contextual situation, modifying the sequence of events. Therefore, the actors must act in response to the new script, meaning that the order of the list of actions has changed, even if the rules of conduct have not. It implies that how the actors could behave is pre-coded and that it is the Narrative Management System which manages the top-down decision-making process of actors. This is not encoded in the actor himself, but is merely a property of the system.

The actor is ordered by the system to perform his next scheduled activity if a pre-condition arises, displaying a certain degree of freedom in decision-making depending on the coded rules of conduct. How he must accomplish the action is out of his decision capability and possibility, since there is no AI engine in the system.

In an agent-based system, with learning agents, if the agent decides to perform the "drink water behaviour", he takes a glass and a bottle of water, fills the former and drinks. To be believable, the agent must show a good trade-off between the task which he must achieve and the autonomy to adapt himself to the environment and modify his planned behaviour if needed. If the glass is not there, he must find different solutions, such as drinking from the bottle, so that he is capable of autonomously finding a solution to overcome an unpredictable problem. If he is an agent without cognitive abilities forced into a rule-based routine system, he is stuck because he will continuously repeat the same pre-planned sequence of actions without reaching the goal.

Weiss and Woolridge explain intelligence in agent-based systems (Weiss, 2000) (Wooldridge and Jennings, 2009) :

"Agents must operate robustly in rapidly changing, unpredictable, or open environments where there is a significant possibility that actions can fail. An agent will not have complete control over its environment, it will have at best partial control, in that it can influence it. This means that the same action

preformed twice in apparently identical circumstances might appear to have entirely different effects and it may fail to have the desired effect.
In certain conditions this explanation is simplified to run well; in particular, it will crash in an environment that changes faster than the procedure velocity, in the case when the reason for executing that procedure, the goal, does not remain valid until the procedure terminates.
Hence in domains that are too complex for an agent to observe completely, or where there is uncertainty in the environment, blindly executing a procedure is a poor strategy.
In such a dynamic environment, an agent must be reactive, it must be responsive to events that occur in its environment, where these events affect the agent's goals or the assumptions which underpin the procedures that the agent is executing.
So, the key problem of comprehending what could be defined as intelligence for an agent becomes the objective to achieve an effective balance and integration between goal-oriented and reactive behaviour".

"We want agents that will attempt to achieve their goals systematically, perhaps by making use of complex procedure-like patterns of action. But we don't want our agents to continue blindly executing these procedures in an attempt to achieve a goal either when it is clear that the procedure will not work or when the goal is for some reason no longer valid. In such circumstances, we want our agent to be able to react to the new situation, in time for the reaction to be of some use. However, we don't want our agent to be continually reacting and hence never focusing on a goal long enough to actually achieve it."

From a simulation observer's point of view, if the actor uses some reasoning ability and updated experience (through memory) to overcome the problem or if the system architecture has embedded the solution to the specific problem (no glass left), there is no difference in letting the actor's behaviour follow a different track to the script. Neither does this change from a decision-maker's point of view, whose foremost concern is the use of this framework to exploit the main environmental variables which could affect human behaviour in realistic scenarios. However, this is as long as the narrative is sufficiently detailed to depict all the most important situations which may occur in such a type of layout. This latter condition, the case for this study, involves extensive work in building a narrative with as many branches of evolution as possible; the better the narrative, the more convincing the simulation. Writing the narrative relies on a researcher's in-depth knowledge of the context and of the numerous potential situations which may arise when changing the script.

This knowledge is tested when the system architecture, which manages the script, can rearrange the script in a number of different ways (mirroring the wide range of possibilities that can arise from unplanned situations using system control parameters) without an expert recognising its difference from real life conditions.

If, for example, the problem is a lack of water in the fridge, the agent must display good decision-making to choose among the many different possibilities (such as give up the action, drink directly from the sink, go to the beverage machine to buy a new bottle, or other). This is correlated to the actor's psychological and physiological status, motivations and desires which drive certain choices, including his capacity to detect and adapt autonomously to the possibilities offered by the contextual environment.

More than that, the major property of a liveable actor is his capacity of projecting himself into the future, planning in advance situations which may come about (such as that described previously) thanks to his cognitive ability (Vernon, 2014). This ability acts as a constant function which relates variables exploiting the relational quality of life development (Bateson, 1977).

The Event-Based method tries to capture and effectively characterize the relational structure between the three circles, comprising the essence of real-life, focusing on the overlap between different aspects of reality, mimicking human

cognitive ability and simplifying them by the use of space-semantic, pre- and post-conditions to instruct activities to occur.
It assumes that the agent's decisions are based on what people think is true about the contextual situation and on what they want to achieve. Therefore, the knowledge of the situation could be translated into a tree-shaped if-then rules system up to the desired level of accuracy inside the Narrative Management System.
Using these parameters does not mean knowing the end of the story before fully simulating it in a virtual environment. They merely provide certain conditions for its development if certain conditions arise, enlarging the spectrum of options available for an agent's behaviour accomplishment and making the simulation more realistic. This trade-off brings the simulation to a level of depth which ensures plausible agent behaviour, since the performance of such an agent varies automatically. Moreover, such an approach does not avoid considering how the human cognitive system works in relation to the extent to which it is needed to simulate realistic behaviour, without conflicting or violating real-life physical laws.
Nevertheless, detailed studies should support this type of system architecture by providing data to exploit the correlations between environmental parameters and agent choices and learning (which represent the ways in which agents develop behaviour over time and receive feedback from the experience). These concerns do not compromise the structure of the system.
In this respect, our hidden agenda is to move straight on from the central point of the table shown above, maintaining the narrative level of complexity and forcing the system architecture to represent more likely human perception processes (dashed arrow in Fig. 21). This has been achieved by detailing agents' features and through an expert system architecture which works as a medium to relate an agent to his surroundings in a more realistic way.

4 DEVELOPED MODEL

4,1 MODELLING HAI PROPAGATION THROUGH THE CONTACT ROUTE TRANSMISSION

4,1,1 INTRODUCTION

The role of the model can be seen as a crucial step along a path that moves from the analysis of human traits and cognitive functions through the observation of human spatial behaviour and capabilities towards the realization of plausible computer simulations of them.
As noted above, decision makers relying solely on the analysis phase are unable to ensure acceptable outcomes. On the other hand, the computer simulation of phenomena pathogens contamination cannot ignore the modelling phase, which, located upstream in the work flow, sets the ground and the boundaries in which the simulation can operate, allowing for an understanding of alternative developments of system patterns and for the elaboration of what-if scenarios.

Coen concurs: "When designing the structure of a model it is necessary to strike a balance between realism and generality. A model needs to be complex enough to capture all those essential features of the process under study, ensuring realism and providing sufficient information so that all questions can be addressed using the model framework" (Coen, 2012).

The quality of a model is largely a function of its fitness for the purpose, rather than of its capacity to describe the real system (Box and Draper, 1987). Therefore, the model must reach a manageable trade-off between realism and usefulness. Key factors must be carefully chosen to guarantee completeness. Situations where factors provide only a negligible contribution to the model should be avoided. However, such a passage is not straightforward.

During the model building process, the abstraction phase is critical. When creating a new and above all living model (as opposed to a mechanical project which adheres to rational laws of the physical world), it is not possible to know beforehand what the essential variables will be.

It is often the case that if the completed model is incapable of reproducing the total behaviour under examination, it is because the scale of detail chosen is insufficient for the inclusion of determining variables.

Coen continues, arguing: “Yet models must not be too complex lest conclusions are only generalizable to a small number of situations of little interest for much of the health care public. As complexity increases, providing information for a model may become prohibitive, less tools for analysis may be available for checking errors in formulation, and exact solutions may not exist so that approximations are needed (Coen, 2012).

Indeed, the more variables are used as input and allowed to vary, the greater the variance in the model prediction can be expected. This could lead to a situation in which having incorporated all uncertainties, the model prediction varies so wildly as to be of no practical use (Saltelli, Ratto and Andres, 2009).

A last consideration is that all complex realistic models have a philosophical problem. They may never mirror the precise circumstances of reality and estimated parameters may not be truly representative of the target situation; even when abundant and accurate data is available for a specific setting, it is by no means certain that it is representative of a common, “true” underlying model. A more pragmatic approach, such as that presented here, is to illustrate a point by using a set of parameter values vaguely consistent with the observed fact (Coen, 2012).

The present study proposes a model which is designed to be as flexible and open as possible to adapt to various situations, such as different hospital units, pathogens, agents involved and activities. It also needs to be easily modifiable to take into account new areas of interest, with the aim of setting out wider and more effective boundaries to understand the circumstances of HAIs from exogenous cross-infection by a contact transmission route.

To date there are no general rules to define HAI spreading in a hospital ward setting and it is not possible to propose universal responses. Therefore, the model developed in our work is based on international scientific literature on HAIs.

A number of well-known scientific factors have been considered, accounting for a full current understanding of the phenomenon, while others whose role is still uncertain or unknown have not. This means that the model is based on assumptions deriving from the problem domain and thus tries to achieve the same level of accuracy and coherent vision with the references from which it is drawn.

When designing a model based on agents, e.g., the model arises from the consideration and definition of the agent's environment, the agent's characteristics and the agent's interaction (physical and social). The worth of the model depends on how local conditions have been interpreted (e.g., patients' activities, aetiological agent, prevention and intervention strategies, and so on). These choices become design decisions unique to the context and objectives of the model (Friesen and McLeod, 2014). Such considerations must fit with the expression of the technique chosen to model the agents, which in turn represents the scale of the phenomenon representation that is able to deal with the simulation.

Our work develops using Event Based Modelling and Simulation (EBMS) techniques to investigate HAI transmission by contact and its propagation dynamics within a hospital ward. Indeed, the topic of HAI serves as a foundation for the conceptual modelling, in fact we investigate the contamination risk through the behaviours of agents. To such extent HAI is a lens to interpret agents' spatial behaviour. HAI is also worthy to expand on the potentialities which the EBMS technique offers us.

The purpose of building a simulation in a Unity 3D environment with different virtual scenarios was to visualise contamination transmission and be able to assess the potential outcome on the infection spread caused by the implementation of control strategies. Of further interest was to understand the effects of different architectural design and space distribution on the propagation of the pathogen. These were the key factors which dictated the development of the model.

Considering the agent (either actor or space), pathogens and activities, the following Fig. 22 represents the elements involved in the model of transmission dynamics. The features of each element will be described below.

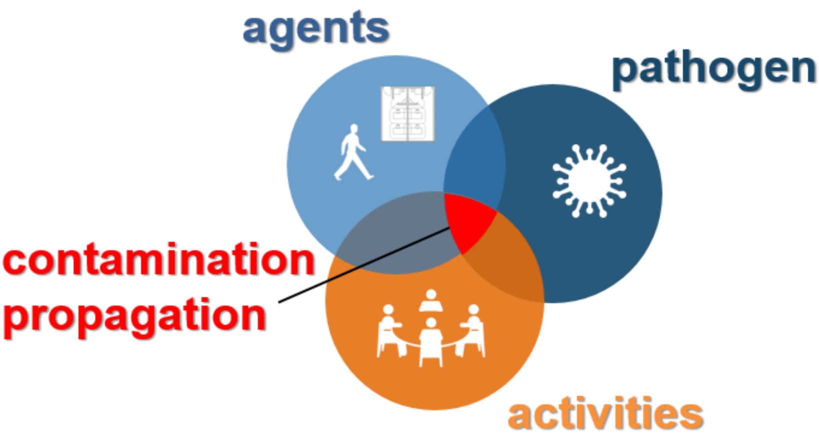


Fig. 22 - Components framework for the contamination propagation.

In order to help understand the framework, key factors concerning the elements of our model are put forward in the following Table 8:

	C	Ct	It	Cl	Du	Ty	Tr	Dt
Actor	✓	✓	✓	✓				
Space	✓			✓				
Activity					✓	✓		
Pathogen							✓	✓

- C = Contamination level;
- Ct = Carrier threshold;
- It = Infection threshold;
- Cl = Cleanness factor;
- Du = Duration feature;
- Ty = Type factor;
- Tr = Transmissibility factor;
- Dt = Decaying timer.

Finally, it must be stated that the system model was built in a modular way, allowing it to develop by elaborating descriptions of the phenomenon and plugging and unplugging components as and when required by the case study application.

4,1,2 ACTORS

The model developer's initial task is the selection of actors. In our EBMS we model four types of actors:

- Patients;
- Nurses;
- Physicians;
- Visitors.

In most hospital ABMs, the logical selection of agents includes patients and hospital staff members. Basic ABMs for hospitals may only include patients, nurses, and physicians, while more detailed ABMs include allied healthcare providers who also operate within a hospital, potentially reaching as far as including visitors and facility personnel not directly involved in healthcare delivery (e.g. maintenance staff) (Friesen and McLeod, 2014) Fig. 23.

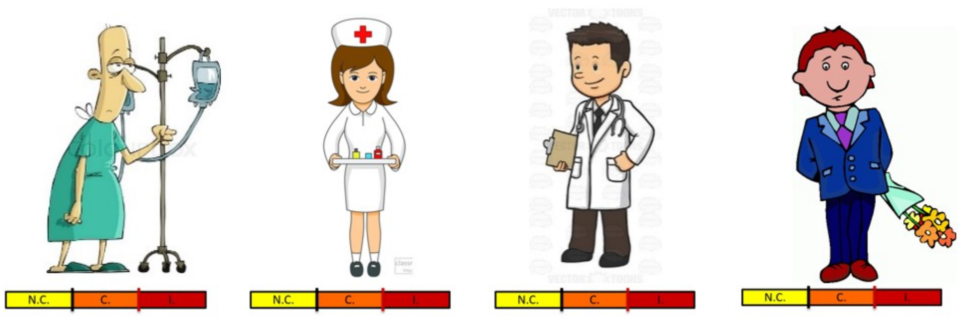


Fig. 23 - Hospital actors with their Contamination Status Bar

In health-care facilities, actors can be the sources of infection and of preceding contamination. Infected actors, e.g. patients, or simple carriers of pathogenic microorganisms admitted to hospital are potential sources of infection for other patients, staff and visitors.
For instance, if a person tests positive but has no symptoms, this is known as C. difficile colonization rather than an infection (Frequently Asked Questions about Clostridium difficile for Healthcare Providers | HAI | CDC, no date). Patients who later become infected (sick) become a further source of infection in the hospital (World Health Organization, 2002).
To visualise this condition each actor is equipped with a Contamination Status Bar, which discretely changes colour depending on the amount of bacteria present on the actor, i.e. his level of contamination, to ease status display Fig. 24. This modelling choice, which differs from the common dual-purpose representation of condition, allows us to simulate the changes in each actor's internal pathogen population over time. This can lead, among other things, to the possibility of bacterial exchange during actor-interaction events.

Fig.24 – Contamination status bar.

Inside the bar, two thresholds are present and modifiable to represent each actor as non-colonized, colonized or infected Fig. 25.

Fig. 25 - Contamination status bar with thresholds.

How do these two thresholds work and how can they be set?

The Black Threshold “Ct” accounts for the presence of a minimum level of pathogen, indicating the limit when an actor is labelled non-carrier or carrier. However, our formalization is capable of accounting for a minimum, yet present, contamination exchange even for the lowest level of contamination.
Therefore, only formally it can be seen that:

- Non-colonized = non-carrier
- Colonized or infected = carrier

The Red Threshold “It” accounts for the infection limit.
Health care settings are an environment where both infected people and people at increased risk of infection congregate. Patients are constantly exposed to a variety of microorganisms during hospitalization. Contact between the patient and a microorganism does not by itself necessarily result in the development of clinical disease for two main reasons:

1) Minimal Infective Dose:
   The most important determinants of infection are the nature and number of the contaminating organisms. Microorganisms range from the completely innocuous to the extremely pathogenic: the former will never cause an infection, even in immunocompromised individuals, while the latter will cause an infection in any case of contamination. When only a few organisms are present on or in a tissue, an infection will not necessarily develop. However, when a critical number is exceeded, it is very likely that the host will become infected. For every type of microorganism, the minimal infective dose can be determined; this is the lowest number of bacteria, viruses, or fungi that cause the first clinical signs of infection in a healthy individual. For most causative agents of nosocomial infections, the minimal infective dose is relatively high. For Klebsiella and Serratia spp. and other Enterobacteriaceae, for example, it

is more than 100 000, but for the hepatitis B virus it is less than 10 (Chartier et al., 2014).

2) Susceptibility:

Whether or not a tissue will develop an infection after contamination depends upon the interaction between the contaminating organisms and the host. Healthy individuals have a normal general resistance to infection. Health-care workers are thus less likely to become infected than patients.

Patients with underlying disease, newborn babies, and the elderly have a decreased resistance and will probably develop an infection after contamination.

Important patient factors promoting acquisition of infection include decreased immunity status, underlying disease and diagnostic and therapeutic interventions; malnutrition is also a risk.

Many inpatients have co-morbidities that put them at special risk of infection such as patients with chronic diseases such as malignant tumours, leukaemia, diabetes mellitus, renal failure or HIV cases, diabetics, bone-marrow transplant patients, those on chemotherapy and those undergoing surgery. In fact, they have an increased susceptibility to infections with opportunistic pathogens. The latter are infections with organisms that are normally innocuous, e.g. part of the normal bacterial flora in the human, but may become pathogenic when the body's immunological defences are compromised.

Immunosuppressive drugs or irradiation may lower resistance to infection. Injuries to skin or mucous membranes bypass natural defence mechanisms. In effect, local resistance of the tissue to infection also plays an important role: the skin and the mucous membranes act as barriers in contact with the environment. Infection may follow when these barriers are breached. Local resistance may also be overcome by the long-term presence of an irritant, such as a cannula or catheter; the likelihood of infection increases daily in a patient with an indwelling catheter.

Many modern diagnostic and therapeutic procedures, such as biopsies, endoscopic examinations, catheterization, intubation/ventilation and suction and surgical procedures increase the risk of infection. Contaminated objects or substances may be introduced directly into tissues or normally sterile sites such as the urinary tract and the lower respiratory tract (World Health Organization, 2002)

In order to describe a condition arising from the combination of the Minimal Infective Dose for that kind of pathogen and of the Susceptibility Factor of each actor, the infection threshold limit can be set differently and can be modified for each actor, marking the passage between not infected and infected status Fig.26.

Fig. 26 – Infection Limit.

As a result, we can also show the lower or higher risk of HAIs for certain actors, e.g. accounting for the presence of susceptible patients. It is possible to run a scenario in which a percentage of total patients have a predisposition to the acquisition and development of infection caused by a specific pathogen, as in the case of the presence of immunocompromised individuals or virulent pathogens, Fig. 26.

Minimum risk:

Medium risk:

High risk:

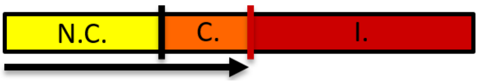


Fig. 26 – Infection threshold sets for different risk conditions.

This reflects the Table 9 on the differential HAI risk by patient and interventions:

Risk of infection	Type of patients	Type of procedures
1 Minimal	Not immunocompromised; no significant underlying disease	Non-invasive No exposure to biological fluids *
2 Medium	Infected patients, or patients with some risk factors (age, neoplasm)	Exposure to biological fluids or Invasive non-surgical procedure (e.g. peripheral venous catheter, introduction of urinary catheter)
3 High	Severely immunocompromised patients, (<500 WBC per ml); multiple trauma, severe burns, organ transplant	Surgery or High-risk invasive procedures (e.g. central venous catheter, endotracheal intubation)

* Biological fluids include blood, urine, faeces, CSF, fluid from body cavities.

Table 9 - Differential HAI risk by patient and interventions (World Health Organization, 2002)

It is important to note that in our model we suppose that patients are permanent carriers after colonization and do not yet consider the process of patient decolonization. In the case of MRSA, this process involves a regimen aimed at reducing or eradicating the presence of bacteria on the skin of a patient, which can be done effectively through the use of antibiotics and chlorhexidine (Pethes, Ferenci and Kovács, 2017).

Therefore, in our model patients carrying germs on their skin, nose or injured skin act as a constant source and this assumption affects the pathogen transmission dynamic, which seems reasonable comparing to the short length of the simulation. Neither do we consider antibiotic usage protocols, which obviously have a key impact on blocking the emergence and spread of HAIs.

Nevertheless, the model is open and it is worth noting that in future it will be extended to encompass these further features.

Asymptomatic carrier:

The source of an outbreak of HAI may be any colonized actor (carrier) who at the same time is an asymptomatic carrier (not-infected). Indeed, asymptomatic carrier actors are contaminated or colonized by potentially pathogenic organisms, e.g. pathogen strains are in different parts of the host's body, but do not develop any infection.

Many HAIs, such as MRSA and C. difficile, may stay in a healthy people for a long time without causing any clinically recognisable symptoms, but still have the ability to transmit to others, such as susceptible patients (Meng et al., 2010). Later on, if symptoms of clear infection are revealed, it will make the potential of transmission apparent to that person and/or to managerial staff and the recognized infected host will be dismissed from patient care duties.

How does this happen? One possibility is that the infection threshold may change for the same actor under different conditions. Healthy people are naturally contaminated. Faeces contain about 1013 bacteria per gram, and the number of microorganisms on skin varies between 100 and 10000 per cm2. Many species of microorganisms live on mucous membranes where they form a normal flora. None of these tissues, however, is infected. Microorganisms that penetrate the skin or the mucous membrane barrier reach subcutaneous tissue, muscles, bones, and body cavities (e.g. peritoneal cavity, pleural cavity, bladder), which are normally sterile (i.e. contain no detectable organisms). If a general or local reaction to this contamination develops with clinical symptoms, there is an infection (Hygiene and infection control). In epidemiology, asymptomatic carriers are normally known as colonised persons while clinical symptomatic carriers are known as infected persons.

Our model visualizes these states, as the system engine can update the value of contamination of an actor in real-time in line with his interaction with others and with the environment and compare it with his infection threshold limit, exploiting the actor's contamination condition. As an example, let us consider the case in which two actors with the exact same amount of pathogens expresses a different condition according to the relative level of their infection threshold Fig. 27.

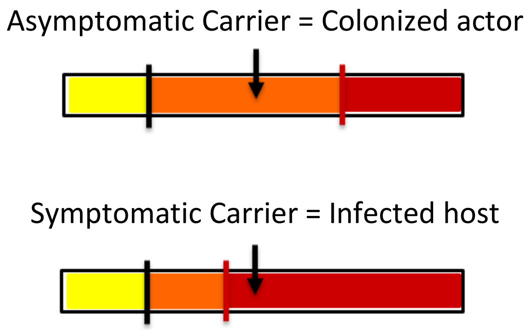


Fig. 27 Infection threshold and contamination level for asymptomatic and symptomatic carrier.

Asymptomatic carriers are very difficult to identify and consequently prevent these actors from transmitting the pathogen to other susceptible actors (mainly patients). The existence of asymptomatic carriers and the lack of a pre-emptive screening strategy in most hospitals implies that detailed transmission dynamics of HAIs are normally a hidden process and are difficult to observe (Meng et al., 2010).

For this reason, active surveillance policy is carried out in some cases, i.e. patient screening in the hospital, at admission and with some frequency during their stay. This strategy allows for the detection of asymptomatic carriers so that procedures can be taken to prevent further transmission.

Our model uses colours to visualise the changes to the contamination status of each actor, thus allowing us to understand this phenomenon. Colonised actors are essential for infection propagation since they can transmit pathogens to other actors (e.g. susceptible patients) leading to the development of infections. Therefore, our model fully takes into account the range of the contamination status of an actor as the transmission mechanism works independently of the semantic classification of the actor's condition.

4,1,3 OBJECTS AND SPACES

As a source of infection, the hospital environment is an extremely complex, heterogeneous entity and difficult to model explicitly. Hospital surfaces can harbour live HAI agents (e.g. Staphylococci, Enterobacteriaceae, C. difficile spores and so on). The problem is that even where it is possible to establish associations between bacterial flora on patients and their immediate environment, the direction of the causal arrow is not known (Coen, 2012).

Generally, ABMs developed to model infection spread include the role of equipment and hospital textures as agent-vectors for infection, e.g. medical instruments, room furniture and so on (Friesen and McLeod, 2014).

Actors behave in space according to the accomplishment of various activities specific to their own function, such as medicine distribution, visiting relatives and patient check and environment furniture and medical equipment are used during the activities. Even if objects such as medical equipment do not have their own initiative, they can be contaminated with pathogens and became vectors. Thus, we model a status bar for them which accounts for their contamination level Fig 28. Obviously, being inanimate objects, they cannot develop any infection.

Fig. 28 - Common hospital objects, equipment and medical equipment and their Contamination Status Bar

The same consideration is valid for space as the environment and its related furniture can be a carrier of pathogens Fig. 29. It is important to note that different levels of asepsis are needed for each space. Therefore, each one could have its own limit as to what could be considered «dirty» or «clean», but from the point of view of pathogen transmission, this label is irrelevant.

Fig. 29 - Common hospital spaces and furniture and their Contamination Status Bar.

Because it is not possible to consider all the objects and equipment present in a hospital ward, we consider that objects belong to the space or to the actor depending on whether they are explicitly utilized by actors in an activity which has been already modelled and simulated by the system or not. Some examples could be door knob, tap and more. A contaminated object as part of the room, its contamination level is considered as part of the space.

A contaminated object such as a cart, is part of the simulated activity (medicine distribution) which implies that its contamination level is considered as part of the actor. In fact, patients could be colonized even if pathogen strains are on different parts of the host's equipment or carried objects. Thanks to this assumption, we can deal with the hypothetical representation of bacteria transported by common objects like smartphones.
During the development of the simulation, actors interact with each other and with the environment. This interaction is the mechanism by which HAIs transmission occurs in the virtual hospital ward Fig. 30.

Fig. 30 - Example of patient-check activity performed with medical instruments and without gloves.

4,1,4 PATHOGEN DECAYING FEATURE

The lifetime of a specific pathogen affects how contamination propagates. In our model, actors, objects and spaces may be equipped (if needed) with a decaying timer "Dt", which counts the decreasing level of contamination from the moment

of their contamination and whose pace is set depending on the type of pathogen. Moreover, the presence of the decaying timer changes the vector label from “permanent” to “transient” and the actor from “reservoir” to “carrier”.
In the specific case of infected actors, the pathogen may reproduce and therefore the level of contamination, without external intervention, will grow accordingly (this occurrence is not yet considered or simulated).
In our case study in colonized actors, the level of contamination is steady unless specific procedures are followed, i.e. hand hygiene and decolonization. In addition, under certain conditions an inanimate environment could be a reservoir of pathogens (e.g. Clostridium Difficile).
As verified HCWs, hands could become colonized during patient care.
Moreover, Pittet demonstrates that in optimal conditions (temperature, humidity, absence of hand cleansing, or friction), microorganisms not only survive on hands, but continue to multiply. In the absence of hand hygiene action bacterial contamination increases linearly over time (Pittet et al., 1999), Fig. 31.

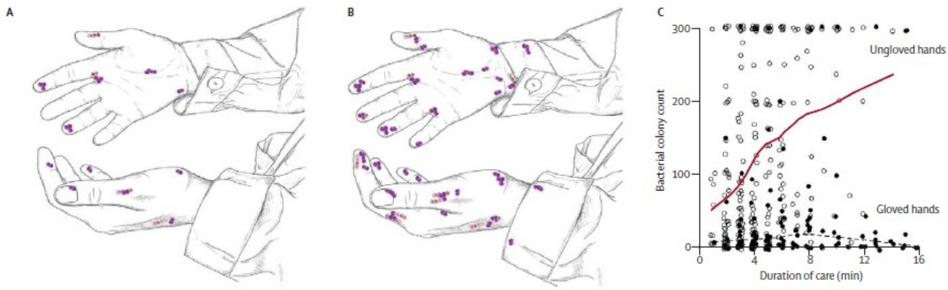


Fig. 31 - Organisms survival on HCW hand: (A) Microorganisms, in this case Gram-positive cocci, survive on hands. (B) When growing conditions are optimal (temperature, humidity, absence of hand cleansing, or friction), microorganisms can continue to grow. (C) Bacterial contamination increases linearly over time during patient contact (Pittet et al., 2006).

Due to the apparent disagreement between different research studies, we chose to model this aspect of the phenomenon according to the scope of our model.

On the one hand, where its purpose is only to represent a few hours of daily work flow, we have inserted the decaying counter only for spaces. In addition, it will only run for those empty spaces such as corridors where no actors stay permanently, and no specific treatment is carried out.
On the other hand, to permit the results of the simulation to account for "security conditions", we should consider the worst-case scenario. For instance, let us consider the fact that virulent pathogens such as MRSA bacteria can live more than 90 days on different surfaces and that this period is much longer compared with the average patient stay in a hospital setting (Kramer, Schwebke and Kampf, 2006). Using a simulated time span in our model, we can assume that the lifetime of the pathogen is endless on inanimate surfaces (objects, furniture and medical equipment) until microorganisms are eliminated through cleaning or disinfection procedures. However, in future case studies our model is open to applying the decaying timer to certain types of actors, e.g. HCWs and spaces full of actors.

4,1,5 TRANSMISSION FRAMEWORK

To simulate the infection propagation, we identify the sufficient and necessary conditions for transmission to occur. Bacteria, viruses and fungi could be introduced to a hospital ward through colonized or infected people or objects.
Patients and health-care workers (HCWs) frequently interact, creating the opportunity for the transmission
of infectious diseases. If someone becomes colonized with a pathogen, germs could spread by way of HCWs to many others within the hospital population (Barnes et al., 2010). It is also important to consider patient-to-patient routes when there is a non-negligible or high probability that two patients come into direct contact such as in a paediatric ward or in the case of room sharing.
The primary source of most hospital epidemics is infected patients, i.e. patients contaminated with pathogenic microorganisms. These germs are often released into the environment in very high numbers, exceeding the minimal infective

dose, and contaminate other patients who subsequently develop (hospital-acquired) infections (Chartier et al., 2014).
For instance, strains of MRSA can survive and remain viable on dust particles or skin scales for many weeks and months. It has also been verified that low densities of MRSA can initiate infections (Pethes, Ferenci and Kovács, 2017).
Pathogen transmission or colonization does not mean infection in itself, but rather that the pathogen moves from one agent to another. However, as pointed out in the section above (Actors), a likely result is that many patients fall victim to hospital-acquired infections.

As noted in paragraph 2,1,7, there are two ways to acquire HAI:
-Endogenous infection (self-infection or auto-infection): the causative agent of the infection is present in the patient at the time of admission to hospital but there are no signs of infection. The infection develops during the stay in hospital because of the patient's altered resistance.
-Exogenous cross-contamination followed by cross-infection: during the stay in hospital the patient comes into contact with new infective agents, becomes contaminated, and subsequently develops an infection.

While there is no clinically significant difference between endogenous self-infection and exogenous cross-infection, the distinction is important from the viewpoint of our modelling and simulation purposes. In our study, we are interested in exogenous cross-infection.

As regards the routes of transmission, our area if focus is the contact route (direct and indirect).

Direct contact :
Direct contact between patients does not usually occur in health-care facilities, with the exception of particularly crowded locations such as waiting rooms. It is

more probable that an infected health-care worker can touch a patient and directly transmit numerous microorganisms to the new host.

During general care and/or medical treatment, the hands of health-care workers often come into close contact with patients. Thus, the hands of the clinical personnel are the most frequent vehicles for HAIs.

Transmission by this kind of direct route is much more common than vector-borne or airborne transmission or other forms of direct or indirect contact (Chartier et al., 2014). However, many other common social interactions such as shaking hands, touching for empathy and so on, which do not trigger an intrinsic need to wash hands although if performed in a health-care environment, they may lead to hand contamination with the risk of cross-transmission (World Health Organisation, 2009).

Indirect contact  :

Indirect contact occurs when infected actors touch and contaminate an object, an instrument, or a surface. Subsequent contact between that item and another actor is likely to contaminate the second individual who may then develop an infection.

Droplet transmission  :

Droplet transmission refers to droplets > 5 micron in diameter that fall rapidly under gravity to the ground or onto objects and are transmitted only over a limited distance, i.e. < 1 m, which may transmit germs directly or indirectly (Atkinson et al., 2009)

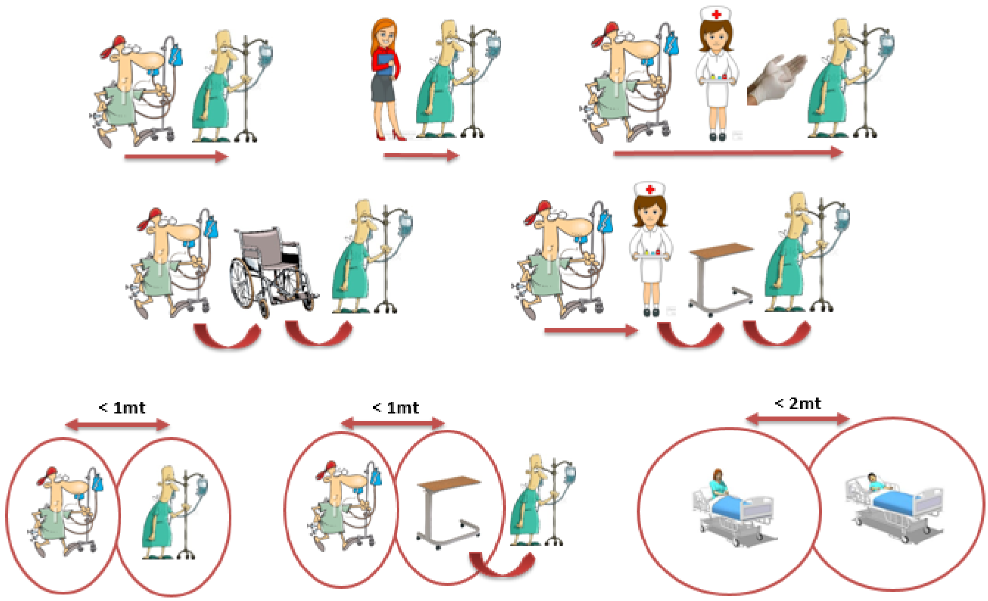


Fig. 32 - Routes of contact transmission, direct, indirect and droplet and their possible combination.

From a modelling point of view, it is useful for us to classify the contact-mediated pathogen transmission mechanism into the parameters of:

Touch-based (actors and objects). When someone touches a person carrying the bacteria or when someone touches an object that a contaminated person has touched, transmission occurs, Fig. 33.

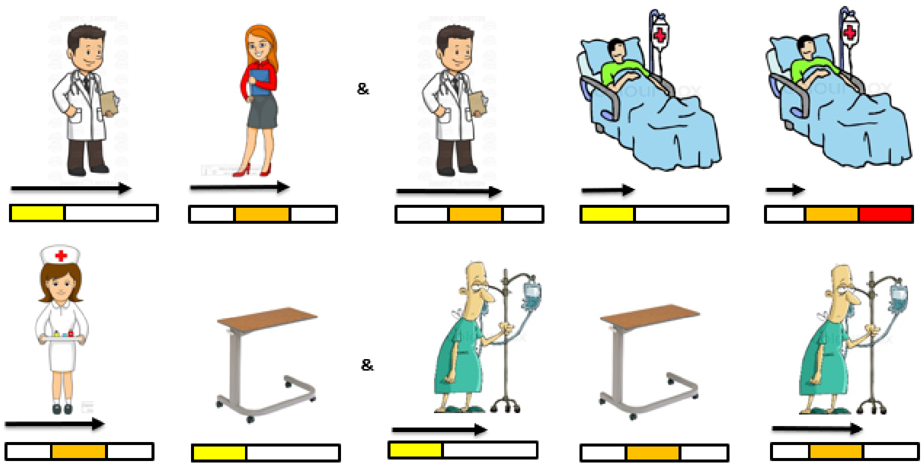


Fig. 33 - Sequence of events with touch-based transmission, with susceptible and without susceptible patients.

Environment-based (space and furniture). Transmission occurs through the environment when a contaminated person interacts with a space (e.g. enters or passes through) and later, or at the same time, someone else interacts with the same space, Fig. 34.

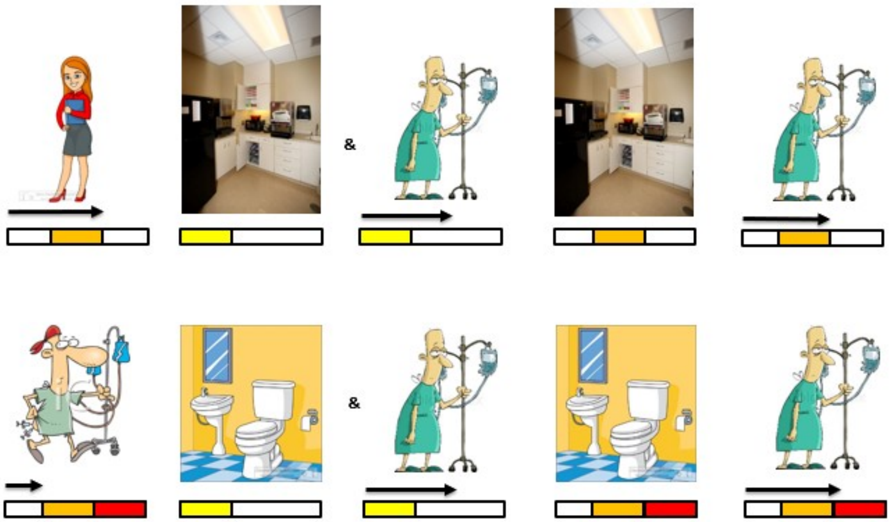


Fig. 34 - Sequence of events with environment-based transmission, without susceptible patients.

Therefore, we can state that touch-based transmission is represented by direct transmission (person-to-person) among patients, healthcare workers and visitors, and through indirect transmission (person-to-object-to-person) by the means of objects or medical equipment which belong to one of the involved actors.

Environment-based transmission is represented by indirect transmission (person-to-surface-to-person) between actors through the means of objects and furniture belonging to the environment. Environment-based transmission usually happens for promiscuous use of space. When an actor interacts with certain furniture in the hospital room and the bacteria is transmitted to that surface and if another actor has later contact with the same surface, he/she acquires the bacteria.

4,2 TRANSMISSION FLOW FORMALIZATION

4,2,1 INTRODUCTION

Whenever an interaction happens by touch or by environment (between actors or actors and spaces), a pathogen transmission occurs. There is a wide range of factors which affect the strength of the transmission flow influencing the contamination status of the receiving actor, changing him from non-colonized to colonized and infected and thus from non-carrier to carrier. Alternatively, if the bacteria are removed by cleaning procedures, the contamination status of the actor consequently decreases at the same time as the amount of pathogens transmitted by contact.

The section on the transmission framework explains how pathogens are transmitted by contact routes, but to assess the strength of transmission we still need to determine the quantity of the contamination flow, translating the following question into a formula.

How much contamination is transferred by contact (interaction) with contaminated actors (or actor-space and vice versa) during the development of an activity or during permanence in a given space?

So that the following reasoning is valid for actor-actor transmission and for actor-space (and space-actor) transmission, the form of the flow equation is practically the same. In the system, there are two different functions which calculate the equation in the two cases. Therefore, different values of the variable factors can be set for each case.

Firstly, we made some reasonable assumptions:

- If actors, objects and spaces involved in an event have the same level of contamination, there is no gradient between them and therefore no flow of contamination, thus they will maintain their initial level of contamination.

- If the actors with different levels of contamination enter into contact each other (or with a space or object) there will be a flow of contamination from that with the major level to those with the minor level, increasing the contamination level of the less contaminated (agent, object or space).

How does this flow work?
We should consider the main aspects which clarify the major effects of the phenomenon. Therefore, we can focus on the following aspects of HAI transmission; the characteristics of an activity, the type of pathogen and the compliance and effectiveness of prevention policies (hand washing or ward cleaning).

The first aspect depends on the activity. We introduce “Ty” Type of activity coefficient.
Thanks to this variable we can represent each risk level of acquiring infections which varies with the type of activity (see table on the differential HAI risk by patient and interventions) and depending on the need and the type of physical contact between agents.
Therefore, we could assume that there is no contact and therefore no opportunity to transmit the pathogen during zero-risk activities. In contrast, examples of high risk activities could be wound care, changing nappies, taking a pulse, taking blood pressure, performing physical examinations, lifting the patient in bed, oral temperature or cleaning blood spills.
It has been proved that HCWs can contaminate their Klebsiella strains during “clean” activities e.g., lifting a patient, taking a patient’s pulse, blood pressure, or oral temperature or touching a patient’s hand. Similarly, in another study, hands of HWs who touched the groins of patients heavily colonized with P. mirabilis were cultured and 10–600 CFUs/mL of this organism were recovered from glove

juice samples from the nurses' hands. Data are limited regarding the types of patient-care activities that result in the transmission of patient flora to the hands of staff and equipment. In the past, efforts have been made to stratify activities into those most likely to cause contamination, but such stratification schemes were never validated by quantifying the level of bacterial contamination that occurred (Ehrenkranz and Alfonso, 1991) (Pittet et al., 1999) (Casewell and Phillips, 1977)

The second aspect depends on the characteristics of the pathogen.
We introduce "Tr" Transmissibility coefficient.
The nature and frequency of nosocomial infections depend partly on the characteristics of the microorganisms, including their resistance to antimicrobial agents, intrinsic virulence, and amount (inoculum) of infective material (World Health Organization, 2002).
The transmissibility coefficient stands for the propagation capacity by contact of a particular type of pathogen, i.e. its strength in moving from to surfaces and from one host to another. It is worthy to note that "Tr" does not consider microorganism time of persistence outside organic hosts as this has already been accounted by the Dt factor. Neither does it represent the virulence of a specific pathogen, which has already been accounted for by the red infection threshold.
In our system, two different values of "Tr" can be set, depending on whether the transmission is directly between actors or is to (or from) space. This accounts for different transmission capabilities in the two conditions of certain pathogens.

The final feature depends on a compliance with prevention policies, i.e. hand hygiene procedures or ward cleaning. We introduce "Cl" Cleanness coefficient.
Cl is a variable indicating the level of cleanliness of the involved actor (objects and spaces) with the higher level of contamination (i.e. the spreader). It is a proxy to signify the occurrence or frequency of hand hygiene and ward cleaning as well as the level of accuracy in performing such procedures. Washing hands

improperly may not be effective in removing a sufficient amount of bacteria and the same is true for environmental cleaning.

We can now write an equation to represent the flow of contamination during contact (between two actors or actor and space) which will then be calculated by the system with a certain time rate explained in the next section.
From a modelling point of view such equation represents the behaviour of each agent in his contamination activity. Agents' contamination characteristic if two agents interact varies as the equation shown:

Set C = Contamination level from 0 to 100.
-Actor 1 (or Object or Space) = C1 old;
-Actor 2 (or Object or Space) = C2 old;

If C1 old is > than C2 old:

$$\Delta C = C1old - C2old$$

The new level of contamination of the Actor2 is:

$$C2new = C2old + \Delta C\ (\mathrm{Ty\ Tr\ Cl}) \quad (1)$$

Which could be written as:

$$(\mathrm{Ty\ Tr\ Cl}) = K$$

and

$$C2new = C2old + K\Delta C \quad (2)$$

with K parameter accounting for the power of the flow.

It is interesting to note that a parallel representation could be applied to represent the flow of pathogens from an actor while he his performing a hands hygiene procedure, subtracting ΔC and associating a different meaning to K. For instance, this could establish the sink (e.g. a certain dedicated location in the simulated layout) as an absorbing spot for the contamination flow. Then Ty varies from the use of a traditional sink or ABHR, with Tr as a factor evaluating pathogen endurance on hands and the Cl will not be present. The flow equation will also show right or wrong practices, depending on the duration of the activity (namely a hand washing action) if the length required to perform properly the procedure would have been set in advance. Such early reasoning is to be developed in the near future when a proper hand hygiene event will be added to the simulation.

4,2,2 DURATION, INTERRUPTION, PERMANENT STAY AND MULTIPLE PRESENCE EFFECT

The duration of actor-actor and actor-space contact is a central factor in the transmission process, as the probability of transmission rises with contact duration. We know that the duration of patient-care activity is strongly associated with the intensity of bacterial contamination of HCW hands (Boyce and Pittet, 2002), i.e. the longer the duration of care, the higher the degree of HCW contamination (World Health Organisation, 2009). However, apart from this initial consideration, there is a lack of statistical data about the correlation between treatment duration and HAIs (Pethes, Ferenci and Kovács, 2017).

In the next future an aid to parameterising such a detailed feature could be provided by an observation of the proximity patterns of agents in the hospital and the frequency of social interactions through an electronic medical record system and spatial tracking systems collecting detailed level data. This kind of information is priceless if we want to fully understand the spreading phenomenon. For example, the SocioPatterns project (www.sociopatterns.org) has developed a platform that allows for physical proximity measurements using wearable sensors (RFID) (A. Barrat, C. Cattuto, A.E. Tozzi, P. Vanhems, no date).

If we obtain statistics concerning contact duration correlated with pathogen transmission, we will be able to build and apply a more accurate time-dependent transmission rule. However, until then our model focuses on expressing how contamination varies depending on contact length, mirroring the increasing risk of being colonized and becoming infected with the duration of contact (or duration of the stay inside a contaminated space). This feature in our model signifies that the overall quantity of contamination transmitted by the flow increases over time and is expressed by the integer of the transmission flow equation.
The duration "Du" of contact is not necessarily the same as the duration of the activity itself (as they are two different entities) but it must be less or equal to the latter.
The total length of one contact (between two actors or actor and space) can be measured in seconds, thus Du = a certain number of seconds.

$$\frac{dCfinal}{dt} = \int_0^{Du} C2new\, dt$$

In the simulation, Du consists of numerous subsequent touch steps (ts). In our case, this is set as equal to 1 sec, we chose such a small time-step to approximate real time dynamics:

Du = N * ts + fraction of the last ts.

However, if necessary the length of the time-step could be modified inside the function coded in the system.

Hence, the flow equation is calculated for every ts of contact and correspondingly the ΔC in the formula is updated following this rate.

The total amount of the transmitted flow during a single contact whose length is equal to Du could be calculated as the sum of the flow for each touch step:

$$Cfinal = \sum_{i=1}^{n} C2newi$$

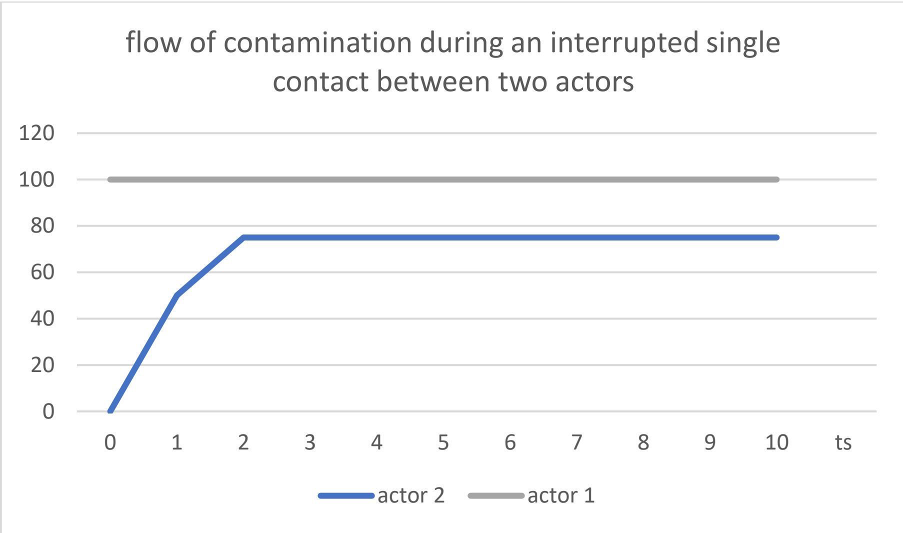
Where:

$$C2newi = C2oldi + \Delta Ci\ (\mathrm{Ty\ Tr\ Cl})$$

Interruption:

The previous assumption is useful as we want to account for cases of interruption, i.e. if an unplanned event interrupts an activity and therefore the contact in progress.

In the following examples, two actors are supposed to interact for a length Du = 10 ts. The first actor is infected = 100 (level of contamination) and the second is not colonized = 0 (level of contamination). All the other variables are pre-set accounting for an assumed K = 0,5. The contact and therefore the total flow is interrupted after two ts from the start. As shown in the plot, only the quantity flowing in the first 2/10 of the total duration has been transmitted and consequently the second actor's new level (Cnew) of contamination reached a value of 75.



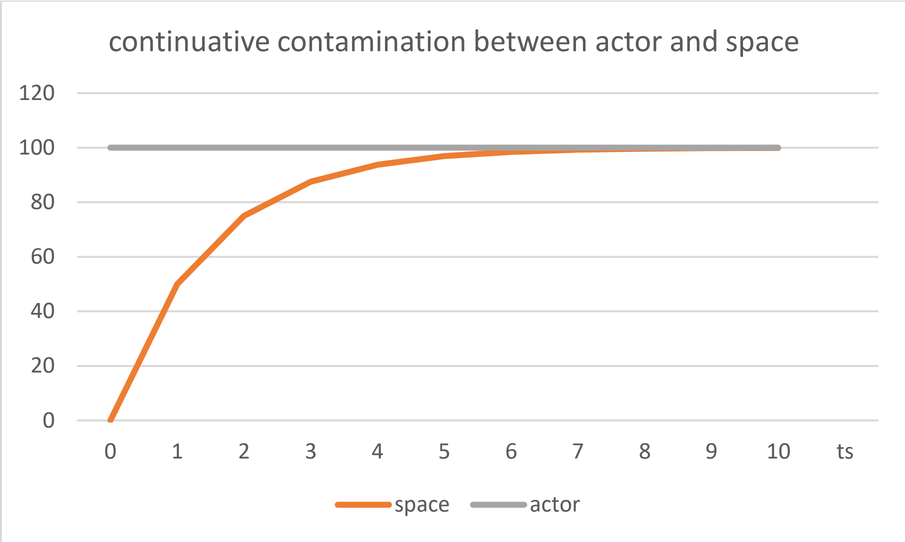
Permanent stay:

How does the contamination transfer by contact (interaction) from actor to space or vice versa (depending on the gradient direction ΔC) if the actor stays in that space permanently?

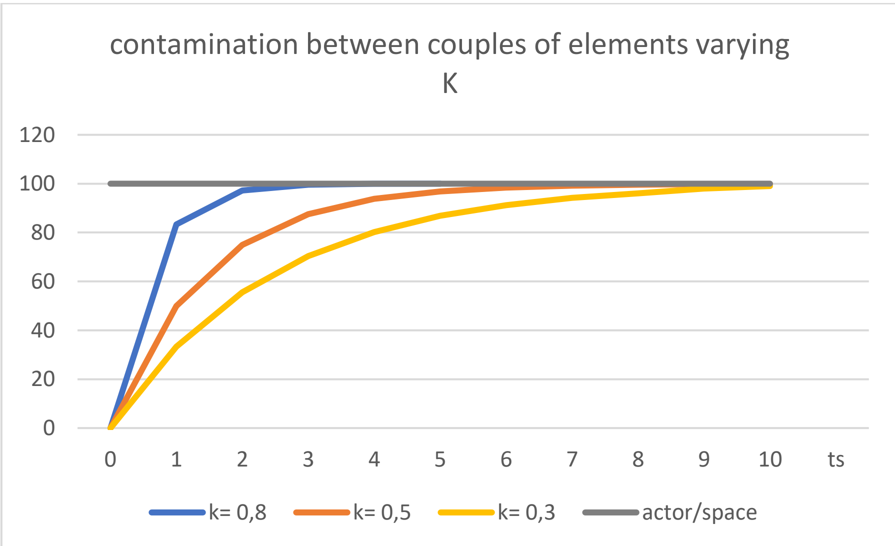
In the case of a patient remaining permanently in his room, we will not simulate every single activity (contact) he performs inside that space. The total amount of the transmitted flow during the total permanence is the sum of the flow calculated for each ts of his permanence. Therefore, the previous equation works also in this case.

The results show that the level of contamination of the patient and that of the space will asymptotically reach the greater of the two.

The following plot shows the pace of the contamination flow between two elements, with one of the two contaminated at the maximum level 100 (e.g. infected if actor) and the second not colonized (e.g. decontaminated space), with K assumed as equal to 0.5.



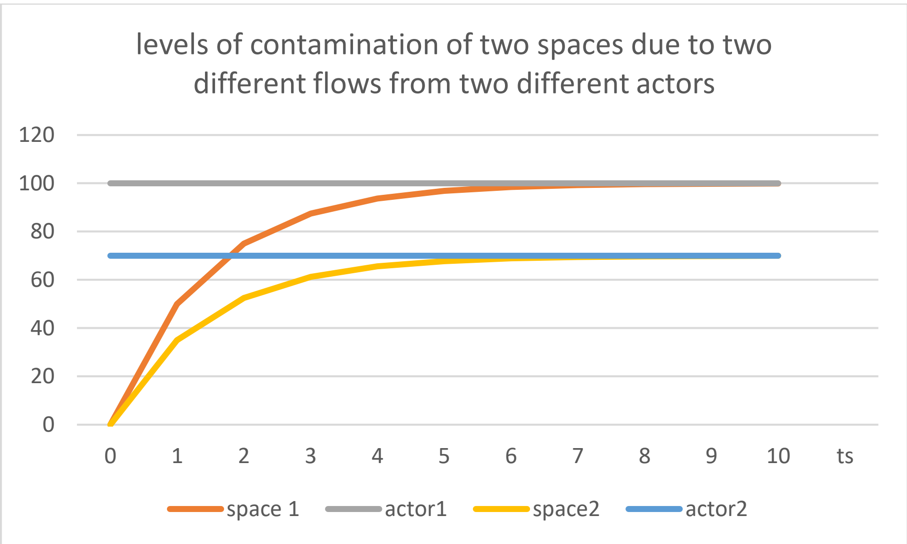
It can be interesting to compare the trends for different values of K parameter. The following plot visualizes how fast the contamination flows depending on K while assuming two elements (actor-actor or space-actor), the first one with a 100 level of contamination and the second with 0 level of contamination, interacting for a Du = 10 ts.



Multiple presence effect:

We must also deal with the crowding aspect, which here is intended as the case of multiple actors staying in the same room without interacting among themselves but with the space. This occurrence affects the way the space is contaminated and the how contamination spreads among occupants.

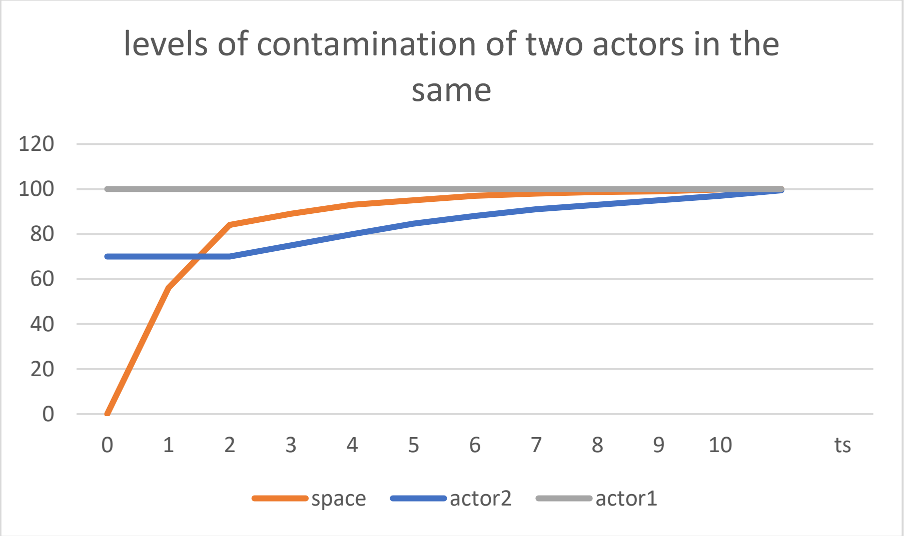
Firstly, the next plot compares two different flows of contamination. The first takes place between an Actor1 100 (level of contamination) with a space 0 (level of contamination) and the second between an Actor2 70 (level of contamination) with a different (separated) space 0 (level of contamination).



What if there is more than one actor in the same space, i.e. room?

The Cnew of the space is calculated for each actor present in the space at each ts, therefore the space will receive the sum of the two contributions. The following plot shows the trend of each element, considering actor-actor contact and actor-space contact, assuming each touch steps (ts) equal to 1 sec and K equal to 0,3.

The orange curve represents the value of contamination acquired by the space due to the presence of actor 1 and actor 2 in each ts. At the same time, each actor can be affected by the flow from the space, according to the direction of the gradient ΔC. Therefore, in our example from the ts in which the C value of the space becomes higher than the C of one of actors. This is what happens between the space and Actor2 from the second ts onwards, where the level of contamination starts to rise after the level of contamination of the space exceeds its level, as shown by the blue curve.



The trends show both the space contamination level and the actors' contamination level reaching the level of the greater among them asymptotically over time.

The system will calculate the flow since the C levels become equal and if one actor leaves the space, it will continue for the remaining one.

4,2,3 AGENTS' RELATION LAW

The last case in the previous paragraph forces us to generalize the transmission flow expression in cases of multiple agents, as well as extend it from a discrete to a continuous equation as set out below.
We suppose n agents (actors, spaces and objects) in our hypothetical ward.
Each has its own level of contamination C^i , whose value may change depending on the occurrence of contact among them:

$$C \in R^n$$

$$C = \begin{bmatrix} C^1 \\ \vdots \\ C^n \end{bmatrix}$$

The value of contamination of the nth agent will be identical to its previous value plus the difference between its previous value and that of the agent with which it came into contact, multiplied by parameter K. This is independent of time and the ΔC between the two agents, but dependent on three other factors, namely; type of activity Ty, type of pathogen Tr and level of cleanliness of the more contaminated agent of the two Cl. Considering the discrete process for each case of contact, we have a temporal unit, between $n-1$ and n:

$$C_n^i = C_{n-1}^i + \sum_{\substack{j=1 \\ j \neq i}}^{m} \left(C_{n-1}^i - C_{n-1}^j\right) K_{ij}\, \beta_{ij} \qquad (3)$$

with $1 \leq i \ \in N$

$$\left(C_{n-1}^i - C_{n-1}^j\right) > 0$$

The contact indicator β_{ij} assumes a value of 0 in the case of no contact and a value of 1 where contact occurs; the matrix NxN shows which contacts occur over temporal unit $n-1$ and n.

The parameter K_{ij}, describes the strength of contagion in j over i and the zero diagonal matrix NxN, since the agent cannot interact with himself.

Considering the entire duration of contact Δt :

$$C_n^i = C_{n-1}^i + \sum_{\substack{j=1 \\ j\neq i}}^{m} \left(C_{n-1}^i - C_{n-1}^j\right)_+ \Delta t\, K_{ij}\, \beta_{ij}$$

$$C_n^i - C_{n-1}^i = \sum_{\substack{j=1 \\ j\neq i}}^{m} \left(C_{n-1}^i - C_{n-1}^j\right)_+ \Delta t\, K_{ij}\, \beta_{ij}$$

$$\frac{C_n^i - C_{n-1}^i}{\Delta t} = \sum_{\substack{j=1 \\ j\neq i}}^{m} \left(C_{n-1}^i - C_{n-1}^j\right)_+ K_{ij}\, \beta_{ij}$$

$$\frac{d}{dt} C(t) = \sum_{\substack{j=1 \\ j\neq i}}^{m} \left(C_{n-1}^i - C_{n-1}^j\right)_+ K_{ij}\, \beta_{ij}$$

A differential formula was obtained for (1), which is the extended formulation over continuous time, in which the increase is a derivative.

In each contact case, this expression gives the C^i of element i. Thus, at the time t of contact there will be a certain $C^i(t)$. As this is a linear function of C^i, the solution (derived over time) is an exponential function.

In cases of a new interaction with contact, the process must be repeated. Thus, the new C^i at the starting time of t will be precisely the value of C^i obtained at the end of the previous interaction.

Extended over the total time of the simulation, we have $\frac{d}{dt}C(t)$ which depends on the history S, the specific sequence of contact events between agents; due to interaction, the contamination of each agent depends on the contamination of the others. Therefore, we obtain a differential integral function, with the following general expression:

$$t \in [0, T]$$

$$\begin{cases} \frac{d}{dt}C(t) = \dot{C}(t) = \int_0^t f\big(S, C(S)\big)\, dS \\ C(0) = C_0 \end{cases} \tag{4}$$

with S = system history (of the simulation).
This assumes the form of a Volterra integral equation.

The choice, as always when modelling real-life phenomena, is in that of assigning a form to the function f which at moment S of system history will show how the C^i have interacted until that time. Function f is not constant and in its most simple form is linear with a quadratic integral.

For complex systems, only the history of the system itself allows us to understand what will happen at a certain time t from now; there are no solutions within closed systems (e.g. linear equations) which are able to predict evolution accurately. Thus, the general behaviour of a complex system is unpredictable.
The system analysed in the study also evolved in this way, which indicates that any state of a complex system depends on the specific history which that system has covered. If it were possible to delete the history of a system and restart it (as occurs in simulations), the results of a determined time t could be different for each repetition. This concept expresses "path dependency", an irreversibility typical in complex systems (Bar-Yam, 1997).

This was previously written as the f linear function, whereby at the i-th agent, a linear sum of contamination contribution is revealed, the sum of ΔC between single agents multiplied by K.

If $K = K_{n\times n} = for\ example\ K_{2\times 2}$

Since the contamination is that of n agents, the new variable is no longer the C of a single agent but a vector, an nth number of all the agents together.

If $C = C_{n\times 1} = for\ example\ C_{2\times 1}$

Thus, at time t of the simulation, the entire system is contaminated based on the history S of events occurring up to that moment.
At the time of S, f shows that the level of contamination is given by a matrix for C(S)

$$f\big(S, C(S)\big) = K(S)\ C(S)$$

$$K\ C = \begin{bmatrix} K_{11} & K_{12} \\ K_{21} & K_{22} \end{bmatrix} \begin{bmatrix} C^1 \\ C^2 \end{bmatrix} = \begin{bmatrix} K_{11}C^1 + K_{12}C^2 \\ K_{21}C^1 + K_{22}C^2 \end{bmatrix} \quad (5)$$

where $K_{i,j}$ gives the weight of interaction for C^i with agent C^j.
The interaction is always between two different agents.

$$K_{i,j} = \begin{bmatrix} 0 & K_{12} \\ K_{21} & 0 \end{bmatrix} = \begin{bmatrix} K_{11} & K_{12} \\ K_{21} & K_{22} \end{bmatrix} - diag\ (K_{11}, K_{22})$$

For the nth agent, expression (3) gives the history of the various different contributions.
Thus, to study the contamination variation over the whole simulation, history S is integrated.
The linearity of f shows that the variation of the nth agent depends on the contamination level of all the other agents with whom he has interacted.

$$\dot{C}^1(t) = \int_0^t (K_{11}C^1(S) + K_{12}C^2(S))\ dS \quad (6)$$

From here, the explicit solution can be written.

If $C(t)$ is the solution of (2), then $C(t)$ can be calculated for the entire duration of the simulation T.

$$\int_0^T C^i(t)dt$$

Where events of decontamination are inserted, for example hand washing, K provides negative values and so:

$$\int_0^T \left|C^i(t)\right|\ dt$$

Our area of interest is to identify the inferior threshold values (e.g. the minimum time of environmental saturation) or the maximum time after which intervention is required through decontamination protection.

In this contamination expression, we have not considered the agent's spatial "X" position variable since the simulation provides us with this information in its clear visualisation of an agent's position in space.

It is to be hoped that these mathematical expressions will be developed further to the point where they consider all the factors contributing to the phenomenon in a detailed way, thus allowing for the use of a purely mathematical approach to describe and understand the phenomenon.
Instead, the approach presented in this study is of a hybrid type. The mathematical equations support the modelling process since within the simulation, factors are considered (e.g. agent position in space) that do not form part of the mathematical expression. Besides this, in order to formalise the phenomenon in more detail, a collection of data is required which focuses on the construction of a refined mathematical model. For the purposes of this study, further complication of this expression would be unreasonable, even if it should not be excluded as an interesting future development of the research topic.

4,2,4 PRELIMINARY CONSIDERATIONS ON THE VARIABLES

Moving back to the discrete formulation (2) we can make some considerations, based on our starting assumptions. To happen a contamination variation in the actor2, (i.e. for the flow to occur) it must be:
C2old < C1old.
Hence it must be:

$$0 \leq K \leq 1$$

which means that:

$$0 \leq (\mathrm{Ty\ Tr\ Cl}) \leq 1$$

In this formulation, the K parameter could be seen from another perspective a way to interpret the probability of the contamination occurrence. Whereas in previously reviewed models the probability assumes a pure stochastic value and is calibrated with data coming from observation to fit the model results to the real trends. In the present study we attempt to exploit its composition and determine a ratio for its variation. Therefore, we must understand if K varies depending on the weight of each coefficient and select a plausible criterion to express their variation.

- Tr: Transmissibility coefficient.

The transmission of infections from one individual to another cannot be accurately represented without considering the characteristics of the causative organism. Therefore, in our formulation the transmission rate per second of contact depends on the characteristics of the pathogen involved.
We know that there are multiple pathogen types at the same time in a hospital, and that a single actor can be a carrier for each of the pathogen types. However, at the time of writing such an aspect has not yet been included in our simulation since only one type of pathogen at a time will be considered in each simulation run.
Because transmission models concerning HAIs have strongly focused on Meticillin-resistant Staphylococcus aureus MRSA (van Kleef et al., 2013), Clostridium difficile enhances a strong propensity toward environment surface contamination (Jou et al., 2015) and the emergence of Carbapenem Resistant Enterobacteriaceae, like Klebsiella, pose a major threat regarding antibiotic-resistant bacteria (Frieden, 2013). We theoretically take in considerations such three strains.

We also suppose that there can be two different values for each pathogen taken into consideration, depending on whether transmission occurs between actors or to and from space, thus accounting for the different transmission strengths of certain pathogens in the two cases. Nevertheless, because there is no official scale to weight this factor or compare among different pathogens, our main interest is to compare three different simulation scenarios changing the value of this variable in accordance with hypotheses albeit far from reality about transmissibility capacities of the chosen pathogen types. (Kramer, Schwebke and Kampf, 2006)

	Clostridium D.	MRSA	Klebsiella
Tr -> actor			
Tr -> space			

- Ty: Type of activity coefficient.

This variable is set to vary in a discrete way, mirroring the diverse activity and treatments which can be practised in a hospital ward.

	Meet Visitors	Medicine Distribution	Patient Check
Ty			

It is important to note that at the time of writing, explicit activities involving explicit interaction between space and actor and vice versa have not yet been coded in the simulation. Therefore, the relative impact value in the function changes in consideration of a patient staying permanently in his room and performing more or less contact with his surroundings.

- Cl: Level of cleanness of each actor or space coefficient.

Hand hygiene, the cleaning of actors' hands, has two dimensions (Beggs, Shepherd and Kerr, 2008): compliance (the proportion of staff that actually clean their hands) and effectiveness (the probability of effective removal of contaminants during hand-cleaning). The problem with traditional hand hygiene models is their assumption of a linear relationship between hand-washing compliance and the reduction of the transmission coefficient, for which there is no evidence. According to Coen, if effectiveness is inversely proportional to compliance then non-linear effects are expected (Coen, 2012). The same reasoning could be applied to ward cleaning, whose effectiveness, as already stated, is difficult to measure.

For these reasons, we do not know how Cl may vary. Perhaps there could be a function describing the variation in time, which for instance could be asymptotic or exponential or have no relationship; this will be identified over time.

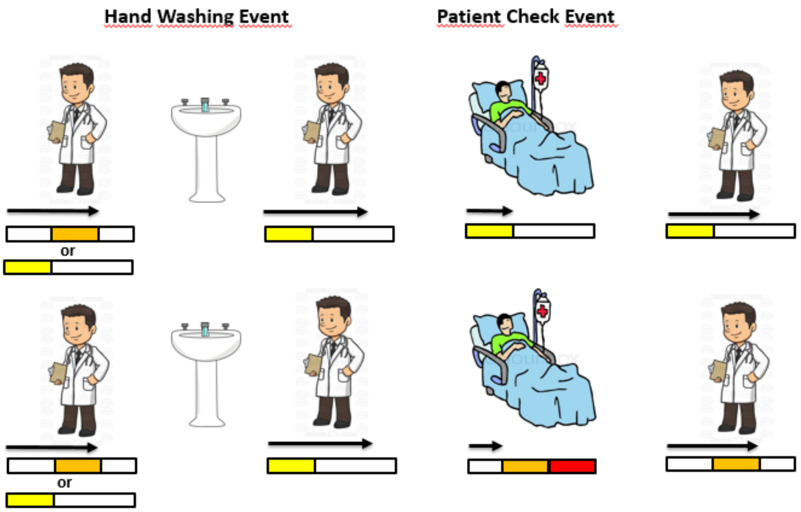
It is not our aim to demonstrate how a possible correlation develops, as this will doubtless form the basis for other future experimental research, which will allow us to gather the data needed to feed the equation. Until then, we can approximate by equal tracts and discretizing the values we need, taking their average value.

For instance, hospital managers subdivide the dirtiness of a space according to the dust shade they remove from it into three rising classes: white, grey and black. Thus, it seems reasonable for our purposes also to use the same triadic scheme for actors.

	Clean / White	Normal / Grey	Dirty / Black
Cl			

In our system, the value of the Cl variable changes for each actor and space. Since the flow equation describes a transmission from the more to the less contaminated, inside that equation the value of the more contaminated actor (or space) between the interacting two elements must be considered.

Nevertheless, because in the near future we need to code a Hand Washing Event, a thorough description of a plausible approach to assign the right value to the Cl factor for each actor and space is explained in the next section through the building of an expert system which will eliminate the need for artificial discretization. Finally, we can suppose what the outcome of different simulations should be due to the changes of the value of these variables and maintaining the same layout Fig. 35.



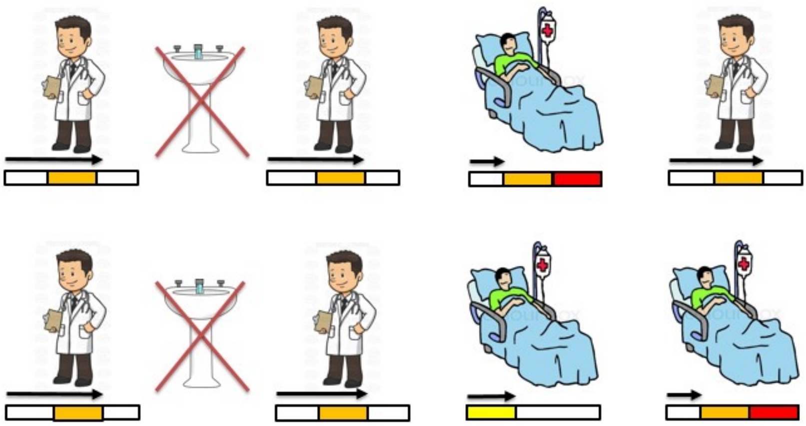


Fig. 35 - Actors (doctor and susceptible patient) contamination outcome from a sequence of events.

These variables affect the intensity of the contamination flow, so they directly influence the velocity of pathogen propagation (i.e. the dynamics), which can also be accounted for through the simulation duration.
Moreover, varying the intensity of the contamination flow, the spatial diffusion of the pathogens changes. Because it impacts on the level of contamination of each actor, the actor contamination level consequently changes (e.g. lowering it from infected to colonized, or not colonized), varying how much pathogen could be transmitted and because it triggers with the number and the location of interactions, how many colonized, not colonized, or infected actors and spaces there will be totally changes.

4,2,5 EXPERT INTERVIEWS AND QUESTIONAIRES

To verify that the selected variables are the optimal representation of the phenomenon and understand if there could be others to consider and correlate inside the equation as well to weight them according to expert knowhow, we interviewed experts in the field through the use of questionnaires.

The first was created to rank, by importance, the behaviour and situations (from literature and synthesized through equation variables) which determine or influence the phenomenon of contamination diffusion in hospital wards. We asked experts to assign weight to each of them and if needed to add other aspects to the list which, based on experience, they considered critical.
Subsequently, to rank factors affecting behaviour and situations by importance (e.g. the conditions identified in the first answer), we asked experts to assign weight to each of them, Fig. 36.

	A	S	O
Non adeguata pulizia / disinfezione delle mani	10		
Non adeguata pulizia / disinfezione degli oggetti di uso comune			
Non adeguata pulizia / disinfezione degli equipaggiamenti			
Non adeguata pulizia / disinfezione degli strumenti			
Non adeguata pulizia / disinfezione degli spazi			
Mancato uso dei dispositivi di protezione individuali	8		
Sovrapposizione di flussi di persone (persone diverse contemporaneamente nello stesso luogo)	8		
Interferenze di percorso (persone diverse attraversano lo stesso spazio in momenti differenti)	6		
Uso promiscuo degli spazi (persone diverse usano lo stesso luogo e arredi in momenti differenti)	5		
Spazi insufficientemente ampi (affollamento)			
Uso inappropriato degli spazi (persone che accedono e usano spazi non consoni alla loro presenza o ruolo)	2		
Indisponibilità di stanze di isolamento	5		
Non presenza di zone filtro per il passaggio fra zone contaminate e zone non contaminate	4		
Non disponibilità di anticamere filtro nelle stanze di degenza			
Non presenza di un bagno per ogni stanza di degenza	10		
Non presenza di un bagno dedicato ai visitatori	5		
Non presenza di un bagno dedicato allo staff medico	7		
Disponibilità solo di stanze quadruple	8		
Disponibilità solo di stanze triple	6		
Disponibilità solo di stanze doppie	2		
Non presenza di stanza destinata allo stoccaggio del pulito	10		
Non presenza di stanza destinata allo stoccaggio dello sporco	10		

	A	S	O
Il livello di contaminazione delle persone coinvolte	10		
La durata dell'attività	2		
Il tipo di attività	8		
La percezione o consapevolezza del livello di rischio per quella attività	10		
Il tipo di patogeno	10		
La conoscenza dello stato di contaminazione della persona con cui si entra in contatto			
La conoscenza dello stato di contaminazione dell'oggetto con cui si entra in contatto			
La conoscenza dello stato di contaminazione dello spazio con cui si entra in contatto			
La disponibilità di tempo sufficiente per compiere l'attività			
La accessibilità dei lavandini	7		
La accessibilità dei dispenser di disinfettante alcolico	7		
La visibilità dei lavandini o dei dispenser di disinfettante			
La disposizione dei lavandini o dei dispenser di disinfettante			
Il numero dei lavandini o dei dispenser di disinfettante			
La disponibilità di dispenser di disinfettante al posto dei lavandini			
L'affollamento temporaneo del padiglione	7		
La superamento della capacità del reparto (numero di pazienti)	9		
La sotto-disponibilità di personale rispetto al necessario	10		
Il ruolo o categoria professionale	1		
Medico	1		
Infermiere	5		
Visitatore	1		
Paziente	1		
Paziente immunodepresso	5		
Il sesso	0		
Uomo	0		
Donna	0		

Fig. 36 - Questionnaires to rank by importance and weight coefficients.

The results of the survey confirmed our choices of the parameters affecting transmission flow. The weight assigned to each of the considered coefficients, i.e. Ty, Tr, Cl, was practically the same, meaning that each of them impact in the same way on the contamination flow. In the near future, a wider survey will be carried out, until then we can consider each factor composing K, ranging from 0 to 1. In the simulation the assignment of attempted values verifies the coherency of the simulation output. For instance, Cl varies from 1 to 0. If it reaches the maximum value (= 0), the contamination flow (pathogen transmission) is prevented, as the equation (1) shows. It is important to note that this Cl factor does not affect the actor’s personal level of contamination, but his capacity of transmit the contamination, being a variable in the flow equation.

Besides, a lack of perception associated with the diffusion of contamination through objects and space was verified. This was mostly because the risk of contagion was understood to be only a consequence of a direct possibility of infection development through humans, ignoring the possibility of indirect paths through objects or space; this aspect must be investigated further.

4,3 CONCEPTION OF AN EXPERT SYSTEM APPROACH

4,3,1 INTRODUCTION

As stated previously, a detailed description of the method proposed to evaluate the Cl factor is introduced in this section.
It is important to note that this further step of the model formalization widens the breadth of the research towards a second range human-related element affecting the main one, i.e. Cl factor, and attempts to further enhance the causative aspects (often hidden) of HAI diffusion. In fact, one great weakness of the infection control research domain is the neglect of knowledge of human factors (Ulrich et al., 2004).

The Cl variable inside the equation represents the compliance (occurrence) of hand hygiene or ward cleaning and the efficiency of this activity.

The quality of hand cleansing should be taken into consideration in accordance with observations and experimental studies on the correct practice of hand washing (Lankford et al., 2003).
For instance, in one study, nurses were asked to touch the groins of patients heavily colonized with gram-negative bacilli for 15 seconds — as though they were taking a femoral pulse. Nurses then cleaned their hands by washing with plain soap and water or by using an alcohol hand rinse. After cleaning their hands, they touched a piece of urinary catheter material with their fingers, and the catheter segment was cultured. The study revealed that touching intact areas of moist skin of the patient transferred enough organisms to the nurses' hands to result in subsequent transmission to catheter material, despite handwashing with plain soap and water (Ehrenkranz and Alfonso, 1991).

It is worth noting that the Cl factor considered here does not affect the actor's (or space's) own level of contamination, but rather modifies the pace of the flow equation. In effect, it accounts for the circumstances whereby an actor, even an infected one, has just performed the correct hand washing procedure and during the next contact is less likely to transmit pathogenic microorganisms. Therefore, unless the actor (or space) is decontaminated by a specific and simulated activity, e.g. hand washing (or ward cleaning), which are not yet coded, his level of contamination cannot decrease autonomously.

In truth, neither can his level of contamination grow if interactions with actors or space do not occur, or an infection develops. The former option is not realistic and not admitted to our model, because each actor is always situated in space and cannot avoid this condition, the latter neither for our aims as previously explained.

At this point, a threat arises which it seems convenient to reflect on now, before the upcoming development of the Hand Hygiene Event; actors moving in space to reach the spot where they perform hand hygiene with a consequent reduction of their own level of contamination. Is it correct to reduce the level of contamination of an actor who performs a hand hygiene procedure even if his level of contamination exceeds the infection threshold? Or does this occurrence imply pathogenic flora growing autonomously on the actor's skin, therefore requiring a growing timer which is independent from the contamination reduction effect of the hand washing occurrence?

To solve this issue, it is useful to remember that the aim of the present work is to visualize the propagation of pathogens on surface and skin, not to consider their effect on the health of actors, e.g. actor's death, clinical treatments or decolonization procedures to eradicate the infection, which moreover have a longer average duration than the timespan simulated in our scenarios.

From this perspective, it seems reasonable to consider hand hygiene activity (and the cleaning of spaces) an adequate procedure to reduce the level of contamination in all cases, i.e. even if the pathogen is growing on an infected actor’s skin because of infection (or on surfaces due to favourable environmental conditions).

The following reasoning is developed for the Cl variable representing hand hygiene procedures. A parallel argument could be proposed for the Cl variable for space, i.e. ward cleaning procedures.
There are two main factors when dealing with hand hygiene:

1. the actor’s awareness and perception of the risk of being contaminated;
2. the availability of time to perform the hand-hygiene action.

The former (1) depends on two conditions:

1.A) Complete knowledge of the level of contamination of other actors (objects or spaces), or at least if the approaching actor is infected or not.
However, self-protection is not always a response purely to a microbiological basis but also to emotive sensations including feelings of unpleasantness, discomfort, and disgust. These sensations are not normally associated with the majority of patient contacts within a health-care setting. It may frequently occur when a nurse touches a patient who is regarded as “unhygienic” either through appearance, age or demeanour, or after touching an “emotionally dirty” area such as the axillae, groin or genitals (Whitby, McLaws and Ross, 2006).
Consequently, if a patient is touched who is regarded as unhygienic or infected, HCWs are more likely to wash their hands because they perceive the risk of infection (Boyce and Pittet, 2002). From this point of view Hand Hygiene plays the role of ritualized behaviour carried out to ensure, on the whole, self-protection from infection.
Therefore, the previously defined Cl factor is a reasonable proxy to define whether the actor approaching (or leaving) the interaction will perceive the risk of contamination or not.

1.B) Type of activity combined with the duration of the activity (i.e. in our case of the contact) stands for the perception of high or low risk. Factors that may influence (fostering or lowering) hand hygiene include those reported by HCWs as reasons for lack of adherence to hand-hygiene recommendations such as the type and intensity of patient care.

In Dedrick (Dedrick et al., 2007) adherence to hand hygiene practices was correlated with the duration of the encounter, with overall adherences of 30.0% after encounters of ⩽1 minute, 43.4% after encounters of >1 to ⩽2 minutes, 51.1% after encounters of >3 to ⩽5 minutes, and 64.9% after encounters of >5 minutes

In this study, adherence to hand hygiene practices was lowest after brief patient encounters (i.e, <2 minutes). Brief encounters accounted for a substantial proportion of all observed encounters and opportunities for hand contamination occurred during all brief encounters.

Therefore, the previously defined Ty factor is a reasonable proxy to define whether the actor approaching (or leaving) will perceive the risk of contamination or not.

The latter (2) depends on three conditions, which relate to perceived barriers to compliance with hand hygiene practices, depending on the environmental context:

2.A) One of the barriers impeding Hand Hygiene is a lack of sufficient number and accurate arrangement of facilities i.e. sinks or gel dispensers.

If hand washing facilities are inadequate, i.e. wash-hand basins and supplies (soap, medicated detergent, alcohol-based hand-rub solution or disposable towels) are inaccessible, inconveniently located or in scarce supply, the adherence to hand hygiene prescription drops. Increasing the availability of hand hygiene facilities at convenient locations, e.g. providing antimicrobial hand-rub dispensers in patient rooms at the point of care, can be a contributing factor to hand hygiene compliance (Stiller et al., 2016).

Furthermore, this occurrence significantly increases the length of time for HCWs to perform care tasks (Taylor, 2015)

The fact that a long time is required for nurses to leave a patient's bedside, go to a basin and wash and dry their hands before attending to the next patient is a deterrent to regular handwashing. Instead, visible and easily accessible sink and gel dispenser locations could permit the total time spent in performing the action to be no more than 60 sec (Voss and Widmer, 1997)

Architectural design choices are not always fully compatible with care tasks (e.g. hand hygiene facilities located at the back of the room or far from where hand hygiene is needed), preventing correct hand hygiene procedures from being incorporated within the workflow and maximizing HCWs time in direct patient care. Consequently, environmental design influencing behaviour patterns may lead to compensating for some of the other deficiencies which cause HAI propagation.

2.B) High workloads and the multi-tasking demands of overcrowding and understaffing lead to low hand hygiene compliance (Taylor, 2015).

Outbreak investigations have shown an association between infections and understaffing and overcrowding and this association was consistently linked with poor adherence to hand hygiene. Numerous cases have been reported in literature (Borg, 2003)

During an outbreak investigation of risk factors for central venous catheter-associated bloodstream infections, the patient-to-nurse ratio remained an independent risk factor for bloodstream infection, indicating that nursing staff reduction below a critical threshold may have contributed to this outbreak by endangering adequate catheter care. The understaffing of nurses can facilitate the spread of pathogens in through relaxed attention to basic control procedures (e.g. hands hygiene) (Fridkin et al., 1996).

In an outbreak of Enterobacter cloacae in a neonatal intensive-care unit, the daily number of hospitalized children was above the maximum capacity of the unit, resulting in an available space per child below current recommendations. At the same time, the number of staff members on duty was substantially less than the number required for the workload, which also resulted in relaxed attention to basic infection-control measures. Adherence to hand-hygiene practices before device contact was only 25% during the workload peak, but increased to 70% after the end of the understaffing and overcrowding period (Harbarth et al., 1999).
High patient bed occupancy rates and understaffing were documented in the largest nosocomial outbreak attributable to Salmonella spp. ever reported; in this outbreak in Brazil, there was a clear relationship between understaffing and the quality of health care, including hand hygiene (Pessoa-Silva et al., 2002).
Observations have documented that being hospitalized during this period was associated with an increased risk of acquiring HAI. This studies not only demonstrates the association between workload and infections, but it also recognises the intermediate cause of contamination spreading: poor adherence to hand-hygiene practice.

2.C) Alcohol-based hand-rubs (ABHR) are a time-saver. Therefore, by introducing ABHRs experts expect to reduce the infection spread by 50%.
ABHRs have been welcomed by HCWs as they are more likely to use an alcohol-based hand rub than to wash their hands. Because the time required for traditional hand washing may render full adherence to previous guidelines unrealistic, more rapid access to hand hygiene facilities and less time required to use them helps improve compliance (Taylor, 2015).
One study conducted in an intensive-care unit demonstrated that it took nurses an average of 60 seconds to leave a patient's bedside, walk to a sink, wash their hands and return to patient care. In contrast, an estimated one quarter as much time is required when using an alcohol-based hand rub placed in a more

convenient location thanks to its small size, for example at patient's bedside (Basurrah and Madani, 2006)

Providing easy access to hand-hygiene materials is mandatory for appropriate hand-hygiene behaviour and is achievable in the majority of health-care facilities due to the use of ABHRs.

Furthermore, using alcohol-based hand rubs may also be a better option than traditional hand washing because they act faster, even if not valid for all the pathogens (Landelle et al., 2014).

Several studies have shown a significant increase in hand hygiene compliance after the introduction of alcohol-based hand-rub solutions. In most of these studies, baseline hand hygiene compliance was below 50%, and the introduction of hand-rubs was associated with a significant improvement in hand hygiene compliance. In contrast, in the two studies with baseline compliance equal to or higher than 60%, no significant increase was observed. These findings may suggest that high profile settings may require more comprehensive strategies to achieve further improvement.

However, hand hygiene behaviour will continue to require handwashing with water and soap, especially when there is visible soiling on hands especially if ABHR solution is ineffective. Hence, the accessibility of sinks (2.A) must be carefully considered.

To help with the understanding of the updated framework, in the following Table 10 new key factors concerning the elements of our model have been added to the list and marked in red cross:

	C	Ct	It	Cl	Du	Ty	Tr	Dt	ABHR	Oc	Us	Sd	Ro
Actor	✓	✓	✓	✓✗									✗
Space	✓			✓✗									
Activity					✓	✓✗							
Pathogen							✓	✓					
Hospital									✗	✗	✗	✗	

- C = Contamination level
- Ct = Carrier threshold
- It = Infection threshold
- Cl = Cleanness factor
- Du = Duration feature
- Ty = Type factor
- Tr = Transmissibility factor
- Dt = Decaying timer
- ABHR = Presence of ABHR in the setting
- Oc = Overcrowding condition of the context
- Us = Understaffing condition of the context
- Sd = Sink Disposition estimation
- Ro = Role of the actor, e.g. doctor, nurse, patient

4,3,2 EXPERT SYSTEM

Knowledge at the level of beginner consists specifically of the reduced formulas which characterize theories, while true expertise is based on intimate experience with thousands of individual cases and on the ability to discriminate between situations, with all their nuances of difference, without distilling them into formulas or standard cases (Flyvbjerg, 2006). In our case study, we discovered this insight in specific situations and therefore crafted an in-silico system to approach the level of brilliant human expert.

The Cl variable shows how the contamination flow can strengthen depending on the cleanliness of the actor and space involved. The actor's (and space's) cleanliness in turn depends on the occurrence and the effectiveness of prevention policies, i.e. hand hygiene procedures or ward cleaning.
In the following formalization, the Cl is evaluated through certainty factor (CF) as described in detail below.

Certainty factors are combined to be built into Knowledge-Based Systems (rule-based systems, or expert systems) which are able to solve problems in a limited domain, structuring a solution incrementally with a performance similar to that of a human expert of the domain.

The inference engine of the rule-based system does not create new solutions, but responds with a degree of plausibility for each pre-built competing hypothesis by combining all available evidence. Each CF, defined through a value of confidence, represents a contribution of the rule, which is the sum of all considerations of the situation in order to validate the hypothesis.

In our case study, we wanted to know if the hand-washing procedure would be performed or not. Thus, CFs provided a measurable strength of confidence (plausibility, more or less possibility) that hand hygiene or a generic cleaning procedure would be performed when certain conditions are verified.

In our case, we do not use multiple hypotheses but only one and its negation:

- h_1: the actor does not perform a hand hygiene procedure;
- $\neg h_1$: the actor performs a hand hygiene procedure.

CFs are a way to approximate the Bayesian conditional probability in case of uncertainty or unreliable data. Up to a certain extent (clarified below), each CF could be seen as the evidence of conditional probability of a pure Bayesian System, which assumes the probability that H verifies if E occurs:

$$Pr\,(\mathrm{H}\,|\,E)$$

Therefore, we must assume that the only relevant evidence for H is E. Alternatively, if there is more than one example, we must ensure that all evidence is statistically independent, otherwise we must consider the joint probabilities (Adams, 1984).

This case represents a conditional probability deriving from an alignment of evidence. Given n different hypotheses to take into consideration, the number of combined probability sets needed to calculate the Bayesian function rises to 2 to the nth power. Thus, the Bayes theory becomes unmanageable, while systems experts use compromise mechanisms to avoid this limit (Rich and Knight, 1991).

Certainty factors are used to prove and compare hypotheses, which are traditionally exploited thanks to the judgments provided by experts or textbooks. In our case, these were references agreed on through expert knowledge (healthcare managers and practitioners), partly based on experience and partly on regulatory principles and which were acquired through questionnaires.

However, in the case of knowledge acquired from experts, conditional probabilities and their complex inter-relationships can not be acquired in an exhaustive manner. Indeed, it is termed uncertain and the extent to which it can be quantified and manipulated as probabilities is not clear (Shortliffe and Buchanan, 1975). To overcome this problem, CFs were developed to describe possibilities suggested by evidence and were applied for the first time in the MYCIN expert system by Shortliffe and Buchanan.

4,3,3 BAYESIAN PROBABILITY

In line with procedures carried out in the development of MYCIN, we can start by considering our problem using Bayesian theory;

Data:
Cl is the variable which varies from 0 to 1

- With Cl = 1 in the case of certainty of do not perform hand hygiene procedure: h_1 is thus our hypothesis 1
- With Cl = 0 in the case of certainty of do perform hand hygiene procedure: $\neg h_1$ is thus our hypothesis 2

We must assign the probability of hypothesis 1 occurrence only after considering the evidence e.

Thus, the conditional probability that the actor will not perform a hand hygiene procedure in the light of evidence e =

$$P\ (h_1 \mid e)$$

The Bayesian theory allows us to calculate the conditional probability of the component ('Sheldon M Ross - Probability and Statistics For Engineering and Science.pdf', no date).
Therefore, we can apply the Bayesian theory, whereby:

$$P\ (h_i \mid e) = \frac{P(h_i)\, P(e \mid h_i)}{\sum P(h_i)\ P(e \mid h_i)}$$

we find:

$$P\ (h_1 \,\big|\, e) = \frac{P(h_1)\ P\ (e \,\big|\, h_1)}{P\ (e)}$$

$$P\ (\neg h_1|e) = 1 - \ P\ (h_1 \,\big|\, e) = \frac{(1 - P(h_1))\ P\ (e \,\big|\, \neg h_1)}{P\ (e)}$$

where:
h_1 is our hypothesis and e the evidence;
$P(h_1)$ is the a priori probability that h_1 is true (i.e. the actor does not perform a hand hygiene procedure) in the absence of evidence;
$P\ (e \,\big|\, h_1)$ is the probability that since h_1 is true (i.e. that the actor does not perform a hand hygiene procedure) evidence e is referred to (i.e. it was not carried out due to evidence e).

Evidence is acquired incrementally piece by piece; e is a set of observations or data; it is also composite of all our conditions c_k.
A conditional probability statement is, in effect, a statement of a decision criterion or rule. For example, the expression

$$P\ (h_1|c_k) = \mathrm{x}$$

can be read as a statement that there is a 100% chance that an actor under certain observed conditions c_k will not perform a hand hygiene procedure. Stated in rule form, it would be:

IF: the c_k condition occurs

THEN: the actor will not perform a hand hygiene procedure with probability x
The value of x for such rules may not be obvious ("y strongly suggests that z is true" is difficult to quantify), but an expert may be able to offer an estimate of this number based on experience and domain knowledge.
A large set of such rules, with a single one for each condition (as in our case) or one for a certain composition of different conditions obtained from references and experts, would clearly contain a vast amount of knowledge. It is conceivable that a computer program could be designed to consider all such general rules and to generate a final probability of each hypothesis based on data regarding a specific case.

Unfortunately, Bayes' Theorem would not be appropriate for such a program if values for $P\ (c_1 \,|\, h_1)$ and $P\ (c_1 \,|\, h_1\ \&\ c_2\ \&\ \dots)$ can not be obtained.

As has been noted, these requirements become unworkable when the subjective probabilities of experts are used together with uncertain data or in cases where a large number of hypotheses must be considered. The first requires acquiring the inverse of every rule (our case) and the second requires obtaining explicit statements regarding the interrelationships of all rules in the system. Conditional probability provides useful results if sufficient data are available to permit its appropriate use, for instance huge amounts of observations and questionnaires to exploit the exact values of inverse probabilities $P\ (c_1 \,|\, h_1)$ and $P\ (c_1 \,|\, h_1\ \&\ c_2\ \&\ \dots)$ and so on for all conditions c_k.

Hence, the usefulness of Bayes' Theorem is limited by practical difficulties, principally the lack of data with resulting imperfect knowledge; consequently, a rigorous probabilistic analysis is not possible.

Therefore, we chose the Shortliffe and Buchanan approach to devise an approximate method that will allow us to compute a value for $P\ (h_1 \,|\, e)$ solely in terms of $P\ (h_1 \,|\, c_k)$ where e is the composite of all the verified c_k.

It is true that this technique will not be exact, but since the conditional probabilities reflect judgmental knowledge, a rigorous application of Bayes' Theorem would not necessarily produce accurate cumulative probabilities either. Instead, we look for ways to handle decision rules as discrete packets of knowledge and for a quantification scheme that permits accumulation of evidence in a manner that adequately reflects the reasoning process of an expert using the same or similar rules (Shortliffe and Buchanan, 1975).

4,3,4 MYCIN: A MODEL OF INEXACT REASONING APPLIED TO A SUBDOMAIN OF MEDICINE

While researchers have sought to develop techniques for modelling clinical decision-making, the design of such programs has required an analytical approach for medical purposes and several programs have successfully modelled the diagnostic process.

Introduced for the first time in the MYCIN Expert System (Shortliffe and Buchanan, 1975), MYCIN was developed at Stanford University and was designed to aid physicians in the diagnosis and treatment of meningitis and bacteraemia infections.
Its scope was to:

1. decide whether the patient has an infection that needs to be cured;
2. if so, determine what the infectious organism most probably is;
3. choose the most appropriate therapeutic regimen for treating the infection.

MYCIN uses a simple type of classification is to identify certain unknown objects or phenomena as belonging to a known class of objects, events or processes. Typically, these classes are hierarchically organized types and the identification process corresponds to the matching of observations of unknown entities with known class characteristics. MYCIN's backward-chaining methods collect data by regressing from possible conclusions to related previous conditions and from this to their required data, recursively if necessary (Hayes-Roth, Waterman and Lenat, 1983).

Although conceived with medical decision-making in mind, as demonstrated in our case study (Cl), it is potentially applicable to any problem area in which real-world knowledge must be combined with expertise judgments before an informed evaluation can be obtained to explain the consequences of observations (conditions) or to suggest a future course of action.

To illustrate MYCIN purposes, we shall use the following rule-based approach:

IF:
1) The strain of the organism is gram positive and
2) The morphology of the organism is coccus and
3) The growth conformation of the organism is chains
THEN:
There is suggestive evidence 0.7 that the identity of the organism is streptococcus.

This rule reflects an expert's belief that gram-positive cocci growing in chains are apt to be streptococci. When asked to weight his belief in this conclusion he indicated a 70% belief that the conclusion was valid. The prompt used for acquiring the certainty measure from the expert is as follows: "On a scale of 1 to 10, how much certainty do you affix to this conclusion?”

Translated to the notation of conditional probability, this rule appears to say:
$P\ (h_1 \mid c_1\ \&\ c_2\ \&\ c_3)$ = 0.7

Where:
- h_1 is the hypothesis that the organism is a Streptococcus;
- c_1 is the observation that the organism is gram-positive;
- c_2 that it is a coccus;
- and c_3 that it grows in chains.

Questioning of the expert gradually reveals, however, that despite the apparent similarity to a statement regarding a conditional probability, the number 0.7 differs significantly from a probability.

In fact, the expert may well agree that:
$P\ (h_1 \mid c_1\ \&\ c_2\ \&\ c_3)$ = 0,7
but he becomes uneasy when he attempts to follow the logical conclusion that therefore:
$P\ (\neg h_1 \mid c_1\ \&\ c_2\ \&\ c_3)$ = 0,3
He claims that the three observations are evidence (to a degree of 0.7) in favour of the conclusion that the organism is a Streptococcus and should not be construed as evidence (to a degree of 0.3) against Streptococcus.

It is tempting to conclude that the expert is irrational if he is unwilling to follow the implications of his probabilistic statements to their logical conclusions. Another interpretation, however, is that the numbers he has given should not be construed as probabilities at all, but that they are judgmental measures that reflect a level of "belief" and therefore an interpretation of the 0.7 in the rule above should be given (Shortliffe and Buchanan, 1975).

4,3,5 BELIEF MEASUREMENT

We can no longer consider the value of 0.7 as a real conditioned probability but rather as a measure of belief (i.e., how much more the expert believes in the hypothesis is realised by the set of conditions c_k, which form the evidence e).
We have chosen belief and disbelief as our units of measurement. The need for two measures was introduced above in our discussion of a disconfirmation measure as an adjunct to a measure for degree of confirmation.

The notation is as follows:

- MB[h,e] = x, (0<x<1) means "the measure of increased belief in the hypothesis h, based on the evidence e, is x"
- MD[h,e] = y, (0<x<1) means "the measure of increased disbelief in the hypothesis h, based on the evidence e, is y"

Thus, MB and MD measure how much the evidence validates the hypothesis or its negation and are so increments or decrements of the Probability P(h).

The evidence e need not be an observed event, but may be a hypothesis (itself subject to confirmation). Thus, one may write MB[h1,h2] to indicate the measure of increased belief in the hypothesis h1, given that the hypothesis h2 is true. Similarly MD[h1,h2] is the measure of increased disbelief in hypothesis h1 if hypothesis h2 is true.

To illustrate this in the context of the sample rule from MYCIN, consider e = "the organism is a gram-positive coccus growing in chains" and h = "the organism is a

Streptococcus." Then MB[h,e] = 0.7 according to the sample rule given to us by the expert.
The number 0.7 reflects the extent to which the expert's belief that h is true is increased by the knowledge that e is true. On the other hand, MD[h,e] = 0 for this example; i.e., the expert has no reason to increase his or her disbelief in h on the basis of e.

In accordance with subjective probability theory, it may be argued that the expert's personal probability $P\ (h)$ reflects his or her belief in h at any given time. Thus $1 - \ P\ (h)$ can be viewed as an estimate of the expert's "disbelief" regarding the truth of h.

If $P\ (h|e)$ is greater than $P\ (h)$, the observation of e increases the expert's belief in h while decreasing his or her disbelief regarding the truth of h. In fact, the proportionate decrease in disbelief is given by the following ratio:

$$\frac{P\ (h|e) - \ P\ (h)}{1 - \ P\ (h)}$$

This ratio is called the measure of increased belief in h resulting from the observation of e, i.e., MB[h,e]:

$$MB\ (h|e) = \frac{P\ (h|e)\ - \ P\ (h)}{1 - \ P\ (h)}$$

Therefore, we can calculate the conditional probability increased by the belief in the hypothesis:

$$P\ (h|e) = MB\ (h|e) * (1 - \ P\ (h))\ + \ P\ (h)$$

If the starting $P\ (h) = 0$ then:

$$P\ (h|e) = \ MB\ (h|e)$$

Suppose, on the other hand, that $P\ (h|e)$ were less than $P\ (h)$. Thus, the observation of e would decrease the expert's belief in h while increasing his or her disbelief regarding the truth of h. The proportionate decrease in belief in this case is given by the following ratio:

$$\frac{P\ (h) - \ P\ (h|e)}{P\ (h)}$$

We call this ratio the measure of increased disbelief in h resulting from the observation of e, i.e., MD[h,e]:

$$MD\ (h|e) = \frac{P\ (h) - \ P\ (h|e)}{P\ (h)}$$

Therefore, we can calculate the conditional probability decreased by the disbelief in the hypothesis:

$$P\ (h|e) = P\ (h) - \ (MD\ (h|e) * \ P\ (h))$$

If the starting $P\ (h) = 0$ then:

$$P\ (h|e) = 0$$

We consider the measure of increased belief, MB[h,e], to be the proportionate decrease in disbelief regarding the hypothesis h that results from the observation e. Similarly, the measure of increased disbelief, MD[h,e], is the proportionate decrease in belief regarding the hypothesis h that results from the observation e, where belief is estimated by $P\ (h)$ at any given time and disbelief is estimated by $1 - \ P\ (h)$.

Note that since one piece of evidence cannot both favour and disfavour a single hypothesis, when MB[h,e] > 0, MD[h,e] = 0, and when MD[h,e] > 0, MB[h,e] = 0.

Numerical example:

We chose as standard probability P(h) the even chance 0.5, which reflects no effects of any condition on the chance of hand washing.

$P\ (h) = 0{,}5$
$MB\ (h|e) = 0{,}7$
$MD\ (h|e) = 0$

$$P\ (h|e) = MB\ (h|e) * (1 - \ P\ (h))\ + \ \ P\ (h)$$

$$P\ (h|e) = 0{,}7 * (1 - \ 0{,}5) + \ \ 0{,}5 = 0{,}85$$

$P\ (h) = 0{,}5$
$MB\ (h|e_1) = 0$
$MD\ (h|e_1) = 0{,}4$

$$P\ (h|e) = P\ (h) - \ (MD\ (h|e) * \ P\ (h))$$

$$P\ (h|e) = 0{,}5 - \ (0{,}4 * 0{,}5) = 0{,}3$$

Furthermore, when $P\ (h|e) = P\ (h)$ the evidence is independent of the hypothesis (neither confirms nor disconfirms) and MB[h,e] = MD[h,e] = 0.

4,3,6 WEIGHT CONDITIONS ACCORDING TO EXPERTS

We plan to use this approach to evaluate CI use and data derived from literature and estimates provided by expert physicians, which reflect the tendency of a piece of evidence (condition) to prove or disprove the given hypothesis h_1 .
We would like to use experts' knowledge to judge the influence of each condition identified from literature to verify the hypothesis of full compliance with hand hygiene procedures. Thus, thanks to the information from references weighted from experts through questionnaires, the value quantifying the confidence on hand hygiene procedures could increase or decrease.

We asked experts:

On a scale of 0 to 1, given the fact that the condition occurs, how much does your belief in the hypothesis increase?

At the moment of writing, some reasonable supposed values or those from information taken from references have been assigned.
Note that in the following formalization, each condition c_k was chosen from reported observed risk conditions for poor adherence to recommended hand hygiene practices (World Health Organisation, 2009) and from (Dedrick et al., 2007), (Roehr, 2007). They were considered as a single, independent piece of

evidence. Otherwise, as seen, this approach would require dependent pieces of evidence being grouped into single rules, but we do not know how such variables correlate.

Actor types:

- Physician: MD 0.5
- Nurse: MD 0.5
- Nurse assistant: MD 0.3
- Visitor: MB 0.3
- Patient: MB 0

Self-protective requirement = pleasing perception = other actor status of cleaning = other actor Cl value:
If Cl < 0.5 then MD = 0.5
If Cl > 0.5 then MD = 0.5

Activity type and duration = Activity danger, i.e. depends on Ty:
If Ty < 0.2 then MD = 0; e.g. Meet Visitors
if Ty < 0.5 then MD = 0.2; e.g. Medicine Distribution
if Ty > 0.5 then MD = 0.7; e.g. Patient Check

Environmental conditions, i.e. condition related to the ward setting and context:
Device location = time needed to use it:

- If t < 60 sec.: MD 0.7
- If 60 < t < 120 sec.: MD 0.2
- If 120 sec. < t: MB 0.3

Overcrowding:

- Yes: MB 0.5
- No: MD 0.5

Understaffing:

- Yes: MB 0.5
- No: MD 0.5

Presence of ABHR:

- Yes: MD 0.5
- No: MB 0.5

N.B. For the particular case of Clostridium Difficile, the presence of ABHR has different values:

- Yes: MB 0.5
- No: MB 0

4,3,7 CERTAINTY FACTOR

Shortliffe and Buchanan define a third measure, termed a certainty factor (CF), that combines the MB and MD in accordance with the following definition:

CF[h, el ^ ea] = MB[h, el] - MD[h, ea]

The certainty factor is an artefact for combining degrees of belief and disbelief, derived from different pieces of evidence, into a single number.
Such a number is needed in order to facilitate comparisons of the evidential strength of competing hypotheses, which, with just one hypothesis, is not our case.
Furthermore, the certainty factor is used as a weighting factor for the credibility of the hypothesis h_1, which is supported by evidence el into MB and reduced by evidence ea into MD, as in our case.

The following observations help to clarify the characteristics of the three measures that they have defined (MB, MD, CF):

Characteristics of the Belief Measures

1. Range of degrees:
a. 0 ≤ MB[h,e] ≤ 1
b. 0 ≤ MD[h,e] ≤ 1
c. -1 ≤ CF[h,e] ≤ +1

2. Evidential strength and mutually exclusive hypotheses:
If h is shown to be certain $P\ (h|e) = 1$:
a. MB[h,e] = $\frac{1 - P\ (h)}{1 - P\ (h)} = 1$
b. MD[h,e] = 0
c. CF[h,e] = 1

If the negation of h is shown to be certain $\mathrm{P}\ (\neg \mathrm{h}_1|\mathrm{e}) = 1$:
a. MB[h,e] = 0
b. MD[h,e] = $\frac{0 - P\ (h)}{0 - P\ (h)} = 1$
c. CF[h,e] = -1

Note that this gives MB[~h,e] = 1 if and only if MD[h,e] = 1 in accordance with the definitions of MB and MD above. Furthermore, the number 1 represents absolute belief (or disbelief) for MB (or MD).
Thus MB[hl,e] = 1 and hI and h,~ are mutually exclusive, MD[h2,e] 7= 1.

Lack of evidence:
a. MB[h,e] = 0 if h is not confirmed by e (i.e., e and h are independent or e disconfirms h)

b. MD[h,e] = 0 if h is not disconfirmed by e (i.e., e and h are independent or e confirms h)
c. CF[h,e] = 0 if e neither confirms nor disconfirms h (i.e., e and h are independent)

Numerical example:

$$P\ (h) = 0{,}5$$
$$MB\ (h|e) = 0{,}7$$
$$MD\ (h|e) = 0$$

$$P\ (h) = 0{,}5$$
$$MB\ (h|e_1) = 0$$
$$MD\ (h|e_1) = 0{,}4$$

CF (h | e_i) = 0,7 - 0,4 = 0,3

$$CF = \frac{P\ (h|e) - \ P\ (h)}{1 - \ P\ (h)} - \ \frac{P\ (h) - P\ (h|e)}{P\ (h)}$$

$$0{,}3 = \frac{P\ (h|e) - 0{,}5}{1 - \ 0{,}5} - \ \frac{0{,}5 - P\ (h|e)}{0{,}5}$$

$$P\ (h|e) = 0{,}575$$

4,3,8 FORMALIZATION OF "CL" THROUGH CERTAINTY FACTOR

In our scenarios, the final evidence which supports our hypothesis h_1 is composed of two parts of evidence e+ & e-, each of them in turn composed of certain occurring conditions c_k (piece of evidence).

e = e+ & e-

where e+ represents all confirming conditions acquired to date and e- represents all disconfirming conditions acquired to date.
Therefore:

CF[h, e] = CF[h, e+ ^ e-] = MB[h, e+] - MD[h, e-]

Shortliffe and Buchanan present a function to combine different conditions to obtain MB[h, e+] and MD[h, e-] which represent how each item of evidence (e+ and e-) is incrementally acquired.

$$MB\,[h, c_1 \wedge c_2\,] = \begin{cases} 0 & if\ MD\,[h, c_1 \wedge c_2\,] = 1 \\ MB\,[h, c_1\,] + MB\,[h, c_2]\,(1 - MB\,[h, c_1]) & otherwise \end{cases}$$

$$MD\,[h, c_1 \wedge c_2\,] = \begin{cases} 0 & if\ MB\,[h, c_1 \wedge c_2\,] = 1 \\ MD\,[h, c_1\,] + MD\,[h, c_2]\,(1 - MD\,[h, c_1]) & otherwise \end{cases}$$

This function satisfies the commutative property: the order in which pieces of evidence (conditions) are discovered should not affect the level of belief or disbelief in a hypothesis.
Combining function simply states that, since an MB (or MD) represents a proportionate decrease in disbelief (or belief), the MB (or of a newly acquired piece of evidence) should be applied proportionately to the disbelief (or belief) still remaining.
Numerical example for our case:

Yes Overcrowding

$$MB\ (h|c) = 0{,}5$$
$$MD\ (h|c) = 0$$

Doctor

$$MB\ (h|c_1) = 0$$
$$MD\ (h|c_1) = 0{,}5$$

Patient Check

$$MB\ (h|c_2) = 0$$
$$MD\ (h|c_2) = 0{,}7$$

$$MB\ \left(h \,\middle|\, c_1\ \&\ c_2\right) = 0{,}5 + 0{,}7\ (1-0{,}5) = 0{,}85$$
$$CF\ \left(h \,\middle|\, e^{+} \&\ e^{-}\right) = 0{,}85 - 0{,}5 = 0{,}35$$

4,3,9 EXPERT SYSTEM INCREMENTAL GROWTH OF CONFIDENCE

Expert systems are developed and maintained incrementally with the active involvement of one or more experts.

Unlike traditional computer programs which are very difficult to modify, expert systems are easy to change. Each of their rules is a separate module, since the rules are not explicitly related to one another.
Any particular rule can be removed or modified or a new rule can be added and the system will still run. The ability to add rules and modify reasoning is a key characteristic of expert systems.
The only mandatory constraint for the modeller in the use of Expert Systems is that he must assure that the rules are statistically independent.
When a new rule is found to be true, either MD or MD could be updated using the combining function. When all the rules have been executed, the final CF may be re-calculated as equal to MB – MD.
In such a way, the evidence can be built incrementally piece by piece, and such pieces of evidence are combined to obtain the CF of the hypothesis, as the example below explains.

Suppose, for example, that the hypothesis h_1 that the actor will not perform the Hand Washing procedure has been confirmed by a single piece of evidence $c_1$with $MB\ [h_1 \mid c_1] = 0{,}3$, therefore $MD\ [h_1 \mid c_1] = 0$ and $CF\ [h_1 \mid e^{+}] = 0{,}3$

If a new piece of evidence c_1 is now encountered, confirming h_1 with $MB\ [h_1 \mid c_2] = 0{,}2$ that has $CF\ [h_1 \mid e^{+}] = 0{,}2$ in support of h_1, the e should be updated to include the latter piece of evidence, we use the combining function to obtain $MB\ [h_1 \mid c_1 \wedge c_2] = 0{,}3 + 0{,}2 * 0{,}7 = 0{,}44$, $MD\ [h_1 \mid c_1 \wedge c_2] = 0$.

Suppose a final piece of evidence c_3 emerges for which $MD\ [h_1 \mid c_3] = 0{,}1$. Thus, e is once again updated to include all current pieces of evidence and again we use the combining function to obtain $MB\ [h_1 \mid e^{+}] = 0{,}44$ and $MD\ [h_1 \mid e^{-}] = 0{,}1$.

If no further knowledge allows new insights on the possibility that the actor will not perform the Hand Washing procedure, we calculate a final result, $CF\ [h|\ e] = 0.44 - 0.1 = 0.34$.

This number is a confidence value that the hand washing (cleaning procedure) will not be performed when selected scenario conditions c_k occur. It is also a measure of the probability of Hand Hygiene when an explicit Hand Hygiene Event is coded in the future. Until then it will account for the value of Cl in the flow equation, namely the strength of the contamination flow depending on the cleanliness level of the involved actor (and space).

4,3,10 HAND HYGIENE EVENT

In the near future, when a Hand Hygiene Event is coded, the Cl factor should be removed from the flow equation, otherwise the drop of contamination level will be considered twice in the equation (as a variable factor as well as inside the ΔC modified by the specific activity).
However, the approach to formalize the Cl factor explained previously will work in future when an explicit Hand Hygiene Event is fully simulated, accounting for the probability of this event occurring based on identified key conditions. Subsequently, the actor's level of contamination will decrease, thanks to the given efficacy of the procedure. In this case, the Cl will be considered as representing the only hypothesis of compliance of the cleaning procedure without accounting for the effectiveness of it.
From another point of view, since the Cl (as for the other variables, Ty and Tr) is now fixed at the start of the simulation for each actor/space and it cannot dynamically increase or decrease, when a Hand Hygiene Event is coded it will vary during the development of the simulation due to the incidence of the events.

At this point, it seems appropriate to present a straightforward consideration on the Hand Hygiene Event. In line with HAI prevention guidelines Fig. 12, we should implement the following rule for the Hand Hygiene Event:

1. Perform hand-hygiene procedures before any “meet” (during an event) with patients, or any “do” (during an event) with objects surrounding the patient.
2. Perform hand-hygiene procedures after any “meet” (during an event) with patients, or any “do” (during an event) with objects surrounding the patient.
3. Do not perform the hand-hygiene procedure twice in sequence.

5 DEVELOPED SIMULATION

5,1 SIMULATING HAI PROPAGATION THROUGH THE CONTACT ROUTE TRANSMISSION

5,1,1 INTRODUCTION

In a hospital context it is not feasible to manipulate the real world of people due to logistics, expense and the ethical implications of full scale trials. Such strong limitations support our choice to manipulate a simulated version of it in an inexpensive way that does not place patients at risk and, at the same time, allows us to draw a number of conclusions while remaining aware of all the premises and assumptions made in its design.

A simulation is a simplified replica of a real-world system in order to predict the system behaviour by asking “what-if” questions. It offers us the potential to identify improvements and new understanding of how a healthcare environment operates.
Simulation has the potential to model spatial influences and social dynamics in order to observe pathogen dissemination effects and is a way to gain insights into the relative impacts of infection control measures. It may also reduce the costs of planned interventions and the risk of errors in implementing changes (Friesen and McLeod, 2014).

The progression of contamination spread and the effectiveness of infection control procedures are strictly related to other hospital processes. Thus, we need to simulate the hospital events flow at the same level of detail. In reality the HAI phenomenon happens contemporary and within its real-life context, boundaries between phenomenon and context are not evident, therefore we must simulate real-life and take out what is interesting for us.

This means that our case study reveals a narrative nature. Narrative inquiries cannot start from explicit theoretical assumptions or mathematical formulations. Instead, they begin with an interest in a particular phenomenon that is best understood narratively. Our narrative inquiry, which fits well with the EBMS approach, develops descriptions and interpretations of the phenomenon through the built model (Flyvbjerg, 2006).

Our simulation is drawn from the Event Based framework, established by Shaumann et al. for modelling human use of buildings and where spaces, actors and activities are modelled in a computational environment. Such a system provide us a variety of behaviour and interactions during the simulation of hospital workflow and use (Schaumann, Morad, et al., 2016)

Once the model has been established, the next stage is to select the simulation software and program the simulation model. We chose to encrypt the spatially explicit model coded in C# for a simulation built in a Unity3D platform of a hospital ward case study.

For us, the advantage of the simulation environment is that it can 'close in' on real life situations and test views directly in relation to phenomena as they unfold in practice. This differs from numerical simulations which require a very large number of iterations to generate meaningful findings. Simulation environments allow for a real-time dynamic 2D or 3D visualization of the phenomenon and data can be stored while being accumulated.

Simulation scenarios are built once the scope and level of EBMS models have been determined. Up to a certain degree we are applying an established approach to a new case study, but we are also developing the Event Based approach further by means of the HAI problem-domain. We widened the capabilities of the Shaumann et al. approach to fit it within the specific case study of HAI. Basically, the HAI dynamic model has been added to the modified script to integrate the simulation with the effect of the contamination propagation on spaces and actors. This increases the overall expressive nature of the framework as a means to an end, still guarantying enough flexibility to be tuned to high degrees of sensitivity in agent behaviour and interactions.

In the simulation, some hospital procedures and daily activities are translated in terms of work events as system inputs and the infection map, updated every second, as output. In the simulation, the agents' relation law for the contamination developed in the model overlaps with algorithms that guide agents' behaviours and those that coordinate unexpected events.
We develop the simulation to envision correlations between human traits, behaviour, activities and the propagation of pathogens, as well as to give us hints on how the spatial design of buildings affects the risk of HAIs.

First and foremost, the research group at the Technion Architecture faculty is interested in showing how space influences people (and consequently the phenomena), while our goal is to discover this through emergent observable patterns. To date, what people think or what they believe is too abstract to deal with as part of a visual-spatial simulation, even if, as already stated, the way we adapted the Cl factor makes it geared to embrace human factors such as awareness, perceived barriers and highly variable local conditions.

The simulation illustrates the potential applications of the framework through a simple case study. On the other hand, this case study also demonstrates the potential of the simulation approach.
To verify the simulation capability to depict HAI diffusion many different preliminary conditions were generated within different scenarios and their simulation outputs have been analysed.

Each initial condition and parameter can be pre-determined at the beginning of the simulation in the dashboard interface (when they are not generated randomly), making this a model driven by deterministic rules and suitable for visualizing the exact development of the system following certain inputs. However, the role of chance in the system exists, both through the occasional opportunities for interactions among actors and the random entrance of visitors. Therefore, for any run, the way the system elements combine to increase the phenomenon is both apparent and unpredictable before the simulation ends, mirroring how the real system works.

In the remainder in order to make scenarios more accessible, the model is developed in a deterministic way. So that to display propagation patterns consistent with the agents' relation law and with the initial conditions and agents' characteristics that have been set upped.
Nevertheless, to the simulation a random parameter can be added, e.g. through a variable accounting for the chance variations of the pathogen survival, the infection development, exposure and more. So that estimating the probability distributions of potential outcomes by allowing for random variation inputs over time. As has been seen, in literature random parameters are used so that the model can adhere better to the data used for phenomenon estimation.
However, at the moment of writing, this hypothesis is a further configuration of the present study. In fact, to handle stochasticity a large number of multiple simulation replications must be carried out for each scenario, followed by a statistical analysis of the results to extract relevant information. However, such an advantageous upgrade to the system architecture would demand added complexities to the case study with the inclusion of further events, above all Hand Hygiene and Ward Cleaning, as descripted previously.

This future application of the model has not been developed in the current study as our aim is not so much to draw final and detailed conclusions (for example,

procedures or treatment to deal with an epidemic of a given pathogen) as to develop and demonstrate the validity of the simulation and the model itself.
This can be achieved by demonstrating that the proposed approach is able to deal consistently with the mass of different factors which give rise to contamination propagation phenomena and that it is sufficiently robust to adapt to a variety of contingent and physical contexts.

In effect, rather than a prognostic model focused on predicting the future accurately, our approach is diagnostic, i.e. model used to understand and exploring a law which has been exploited to describe the system through what-if scenarios (Saltelli, Ratto and Andres, 2009). To this extent, the simulation model, built as a knowledge support tool, is useful in assisting decision-makers to forecast possible outcomes based on informed speculation and when thoroughly validated and integrated taking real world data, it would most likely be used to make predictions (Crooks, Patel and Wise, 2014).

5,1,2 THE SETTING OF THE CASE STUDY

This research was carried out in association with Professor Yehuda E. Kalay and his research group at the faculty of Architecture and Town Planning, Technion, Haifa (IL). To implement our approach, we chose as the setting the Sammy Ofer Heart Building, Sourasky Tel-Aviv Medical Center, by Sharon Architects & Ranni Ziss Architects 2005-2011, where we received the important collaboration of the internal healthcare staff and management, Fig. 37.

Fig. 37 - Sourasky Medical Center and Sammy Ofer Heart Building

This choice is useful because the Cardiology Unit does not share the extremely regimented situations and procedures of ICU or surgery wards. Moreover, it involves multiple categories of users and shows emergent phenomena and actor behaviour which are influenced by the architecture of space and the presence of other people.

The layout on which agents operate is the initial decision in any simulation development. Environments can be a real-world setting or synthesized from real-world. Real-world environments represent the hospital floor plans as they are, while synthesized environments can be generated by the modeler with simplifications or assumptions compared to real floor plans (Demianyk, 2015).

In our case, the layout reflects a synthesized, slightly modified prototypical Ichilov ward layout.

The clear benefit of this choice is to allow for real-world environments to enhance the validity and credibility of the model, to ease the interpretation of simulation results and to assist in knowledge transfer (Friesen and McLeod, 2014) Fig. 38, 39, 40.

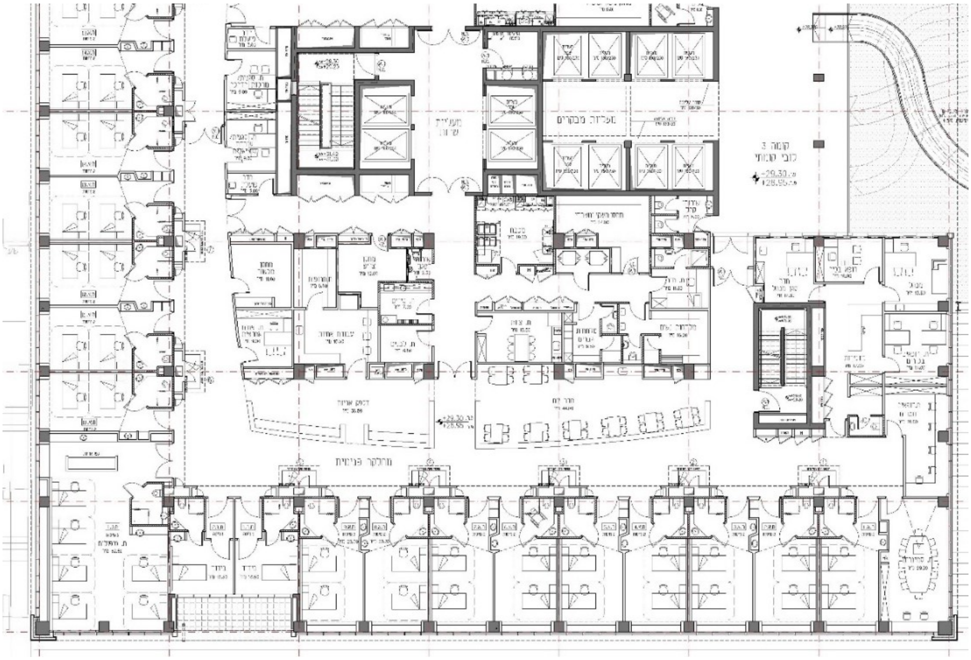


Fig. 38 - The Real-world Ward Plan.

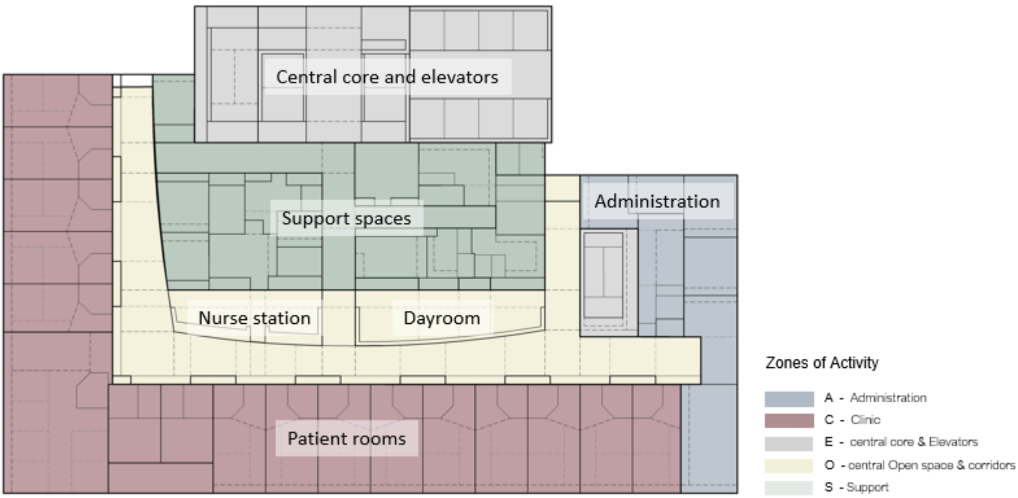


Fig. 39 - The synthesized hospital Ward Layout (Brodeschi, Pilosof and Kalay, 2015)

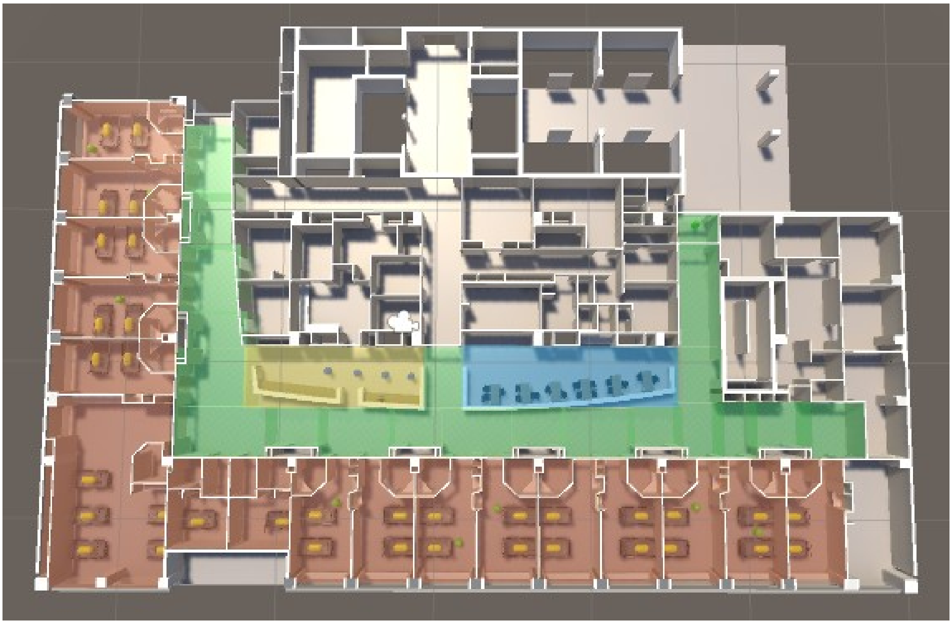


Fig. 40 - The simulated ward plan.

5,1,3 FROM SURVEY DATA TO SYSTEM KNOWLEDGE

A hospital department is a complex system since its environment is heterogeneous and constantly changing as technology improves medical practice changes.

Operations are not linear and depend on several factors such as the acuity level of the patient, the configuration of the healthcare staff and the physical facilities of the unit, among other factors.

Moreover, hospital inpatients are difficult subjects for study. They are only 'available' for a short time window, measured in days. Furthermore, they are too debilitated to all cooperate to the same degree, they are an extremely heterogeneous population and major ethical issues are met when it comes to experimentation. While, data is often technically available, political barriers may exist to access the data, e.g. privacy regulations (Cooper et al., 2003).

Nevertheless, the observation and analysis of human behaviour in built environments is usually considered the best way to understand and evaluate how a building fits the needs and activities of its intended users. On this basis, the Post Occupancy Evaluation (POE) paradigm has proposed several approaches and techniques to assess if the project brief has been met (Zimring, 2002). POE approaches have, of course, one major limitation: they can be applied only after the building has been completed and occupied, and at that point it is usually too late or too costly to intervene in order to solve errors, critical failures, and in-consistencies with the needs of users, e.g. safety requirements (Hadas Sopher, Davide Schaumann, 2016).

Under all these circumstances, HAI simulation models have a distinct advantage over uncontrolled observational studies, and many solutions proposed to address the HAI issue could be tested in the simulation environment.
When applying a tool which simulates human behaviour in space, one needs to make sure that the underlying theory of the process is firmly grounded in people's real-world experience. The role of real data in the assignment of agents' behavioural rules is just as significant as the assignment of agent characteristics or profiles.

To construct the behaviour for each agent and environment so as to model the case study, two descriptions were required; on the one hand, the content of the hospital domain and on the other hand the actor's knowledge of this domain and real-life situations. Simulating the activities performed in the unit required extensive observations and long meetings with medical staff. Despite this, we were still only able to reproduce them computationally within a residual degree of abstraction.

Professor Kalay's research group at Technion used a variety of research techniques to collect data.
The data collection phase involved direct-experience observations, i.e. monitoring what happens, tracking people and interviewing medical and administrative staff, patients and visitors.
The observation lasted 54 hours over 6 days during a period of 3 weeks in which 36 staff were followed by 8 students, Fig, 41, 42. A quantitative method was used to gather data which was then elaborated; for example, the numbers and flow of patients, recording HCWs arrival and exit times, physicians' service activities and so on. Several treatment events were also observed.

Fig. 41 - Shadowing of hospital workers. Image courtesy of Prof. Y. E. Kalay.

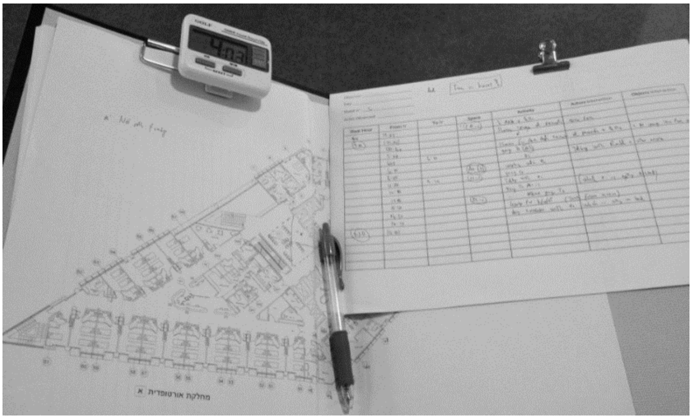


Fig. 42 - Data collection sheets. Image courtesy of Prof. Y. E. Kalay.

While quantitative data are used as input data in our simulation models, qualitative data are used for conceptual EBMS development.

Qualitative methods such as interviewing are involved in the data gathering process. Interviews with hospital architects were conducted and further interviews were carried out with the HCWs (doctors, nurses, medical staff), visitors and hospital directors at the Sammy Ofer Heart Building to gain knowledge about current workflows and daily life in the department.

A series of meetings were held with the inpatients unit director, who explained to the observer the list of procedures performed during treatments (e.g. medicine distribution procedure), and the ways in which interruptions occur because of social interactions among staff members or with visitors (Schaumann, Pilosof, et al., 2016).

Aside from this input, the developer must be aware of limitations and gaps within the data and how those limitations impact on the veracity of the dataset for the simulation objective. Data processing is generally required for a single dataset as well as the consolidation of varied datasets (Friesen and McLeod, 2014).

Our analysis involves the process of extracting useful information from data, i.e. moving from data gathering to a qualitative hypothesis of how the behavioural system works to the formalization of a “computational model”.

A following elaboration encompasses the phase of making data available, i.e. translate the hypothesis in the appropriate language for their implementation in the Unity platform. This phase consists of converting information into knowledge, namely extracting quantitative manageable metrics from qualitative understandings (e.g. rules) to include in the “event” database. These express how actors’ behaviour is affected by relevant environmental parameters.

Discovering behaviour led us to establish schematic occupancy schedules (i.e. highly detailed lists of activities) from which users can count by type and other essential understanding of the actual use of space can be derived. As a consequence, space use patterns for every 30 minutes or less were drawn up, Fig. 43.

Fig. 43 - Examples of schematic space use patterns. Image courtesy of Prof. Y. E. Kalay.

Our model parameters are based on existing studies and taken directly from observation. Our case study was built based on the synthesized ward using data coming from this process of survey, analysis and elaboration, unfortunately no observed data on infections prevalence were available to support the evidence found in the simulation results.

The area of real data is likely to be an area where EBMS within healthcare facilities will more fully evolve as they install in-house systems to capture the data themselves; this, in turn, will support the ability to fine-tune ABMs. Such systems may include electronic records and dashboards as well as technologies such as RFID. In the case of RFID, both inanimate and animate agents can be tracked (Lowery-North et al., 2013)

5,1,4 UNITY 3D SIMULATION ENGINE

To implement our HAI transmission model and develop the simulation in a virtual environment we chose Unity 3D software.

Unity 3D is a cross-platform game engine developed by Unity Technologies, which is primarily used to develop video games or other interactive content such as architectural visualizations, real-time 3D animations and simulations.

Unity 3D is used to develop applications for a number of platforms. It can export to include HTML, PC, Mac OS, Iphone, Droid, Xbox 360, PS3 and Wii. 3D assets can be created within the Editor or imported if they were created with any industry standard 3D modelling program (Maya, Blender, Lightwave, Google Sketchup, 3D Studio Max).

Unity 3D is used by the gaming industry and educational community and it can be used for simulations in a virtual world platform to develop standard applications and to provide interactive 3D visualizations. Architects, industrial designers and anyone involved in product development can use it as a way to visualize creations. Researchers and teachers use simulations and applications to

demonstrate lessons. Computer scientists use Unity3D for its object-oriented programming capabilities using Java, C# or Boo.
Developing the EBMS within an object-oriented framework from the ground up gives the developer an additional degree of understanding of the modelling technique. In contrast to the Unity 3D platform, others such as netlogo SWARM, Repast, and Anylogic are commonly used.

The simulation in a 3D environment is not always required; in most cases, simpler environmental structures may be used. However, many applications require a maximum level of accuracy and the use of a true 3D environment, mainly to enable agent 3D perception. Allowing agents to perceive their world in 3D enables the simulation of complex real situations like smoky environments, testing the visibility of security features like emergency exits or environmental detailed characteristics affecting actors’ behavioural choices.

The Unity 3D game engine consists of two main parts: a 3D graphics simulator, and a manager level for entities and behaviour. The first part defines the place where the entities (people, physical objects, biological agents) are graphically represented in space and where the objects dynamics (people’s behaviour, object use, space transformations, etc.) are visualized while the simulation is running. The second part is where entities and behaviour data and scripts needed to run the simulation are allocated and computed (e.g. the HAI transmission flow script). In this component of the game engine, each entity is associated with a system of property slots and related values that will be changed and updated in real time during the simulation (Schaumann, Morad, et al., 2016).

We selected the Unity 3D simulation environment for its dynamic visualization capabilities, so that the HAI spreading process could be effectively computed, simulated and visualized at the same time.

Spatial semantics, Actors' profiles, Activities and Events were also scripted in Unity by means of C# scripting language. The building use process, previously formalized in an abstract way together with the HAI transmission model, are connected to the virtual model of the built environment where activities are explicitly performed.
The user-friendly graphic interface allows users to define almost all simulation parameters without intervening on the script. This includes ward layout (including - but not limited to - the number of rooms), starting contamination level, contamination and infection threshold for each actor and the characteristics of circulating pathogens.

Visualising specific instances of the process allows us to verify the model setup, simulation in progress, and simulation results. Traditional statistical simulation requires a very large number of iterations to generate meaningful findings whereby the visualization methods are halted while data is accumulated (Friesen and McLeod, 2014).

We implemented the contamination function, coded in c#, in programming simulation framework, which works in object oriented fashion. In the annex is the Pseudocode Description.

5,2 CASE STUDY DESCRIPTION

5,2,1 INTRODUCTION

A case study is defined as “the detailed examination of a single example of a class of phenomena, a case study cannot provide reliable information about the broader class, but it may be useful in the preliminary stages of an investigation since it provides hypotheses, which may be tested systematically with a larger number of cases” (Abercrombie, Hill and Turner, 1984).

Critics of the case study method believe that the study of a small number of cases can offer no grounds for establishing reliability or generality of findings. Others feel that the intense exposure to study of the case renders the findings biased. Some dismiss case study research as useful only as an exploratory tool (Soy, 1997).

Indeed, the view that one cannot generalize based on a single case is usually considered to be devastating in using the case study as a scientific method.

According to Flyvbjerg, it is correct that the case study is a “detailed examination of a single example”, but it is not true that a case study “cannot provide reliable information about the broader class”. Concluding that one cannot generalize from a single case is not true in any case.

The case study may be central to scientific development via generalization as a supplement or alternative to other methods. Moreover, formal generalization is overvalued as a source of scientific development, whereas ‘the force of example’ is underestimated (Flyvbjerg, 2006).

It is true that a case study can be used ‘in the preliminary stages of an investigation’ to generate hypotheses, but it is misleading to see the case study as a pilot method to be used only in preparing the real study’s larger surveys, systematic hypotheses testing and theory building.

Therefore, the case study is useful for both generating and testing hypotheses but is not limited to these research activities alone.

Researchers continue to use the case study research method with success in carefully planned and crafted studies of real-life situations, issues and problems. The testing of their hypotheses relates directly to the question of 'generalizability', and this in turn to the question of case selection. The strategic choice of case in relation to the research objectives may greatly add to the generalizability of a case study.
In this regard, to investigate the capabilities of the proposed approach a case study was built and a scenario analysis was set.

Our proof-of-concept case study primarily serves to present the usage of the framework, i.e. to grasp insights into the simulation system and evidence about the model potential.
To this end, we identified the most significant parameters exploiting correlations that are able to characterise the development of the whole narrative. Therefore, the designed case study interprets the overall course of human spatial behaviour, starting from human states and contextual conditions and ending with activities set in space. The series of events composing the scenario shows the infection spreading by means of the contamination mechanism that we have coded.
The simulation is based on Simeone's previous studies which explicitly represented patients, HCWs and visitors through a simulation engine which activates Actors, Spaces, Activities, and Events to generate a dynamic time-based representation of the building use (Simeone et al., 2013).
The case study contemplates several component Actors, Activities, Pathogens and Spaces whose characteristics are presented below. Their interaction during the simulation drive the contamination transmission and pathogen propagation.

For the current stage of development, this simplified case study displays a building use situation where HCWs start from their staff station before moving to the central medicine room to prepare medicines and medicaments. Afterwards, they move through the patients' rooms to look after them one by

one, e.g. distributing medicines. In this case study, patients do not leave their rooms. In agreement with the cohorting principle, each HCW is assigned a cohort of patients and operates in a different zone, which only comprises some patients' rooms in the ward. After visiting some patients in certain randomly initialized cases, the HCWs return to the medicine room to prepare additional medication or to take new equipment before returning to their workflow.
During the simulation, a random number of visitors enter the hospital to meet their relatives under treatment, each one visiting a single patient in the ward. They walk through the hallway to reach the patient's room, where a social interaction takes place (e.g. talk) for a certain amount of time. Afterwards, visitors leave the ward from the same entrance.
Besides those two types of events, termed "scheduled" because of the sequence of activities, the involvement of actors and the location of the actions are known in advance; emergent events could be activated/triggered when specific spatial and social conditions arise.
There is also the occurrence of a HCW coming to check the patients in a room, forcing the visitor to leave and wait in the corridor until the nurse has finished and so moves to the next patient's room. Occasionally it may also occur that when a visitor encounters an HCW, the close proximity between the two drives the visitor to interrupt the HCW scheduled duties to start a social interaction in that very place (e.g. visitor asking information about his family member condition), before the HCW returns to his planned events, as does the visitor.

Case study reference parameters:

- 2 single rooms
- 14 double rooms
- 1 five-patient room
- 4 HCWS (single HCW type)
- 35 patients
- 9 visitors

Each HCW is assigned a cohort of patients and operates only in some patients' rooms of the ward, as specified below:

- HCW1: 5 rooms 10 patients
- HCW2: 1 room 5 patients
- HCW3: 6 rooms 10 patients
- HCW4: 5 rooms 10 patients

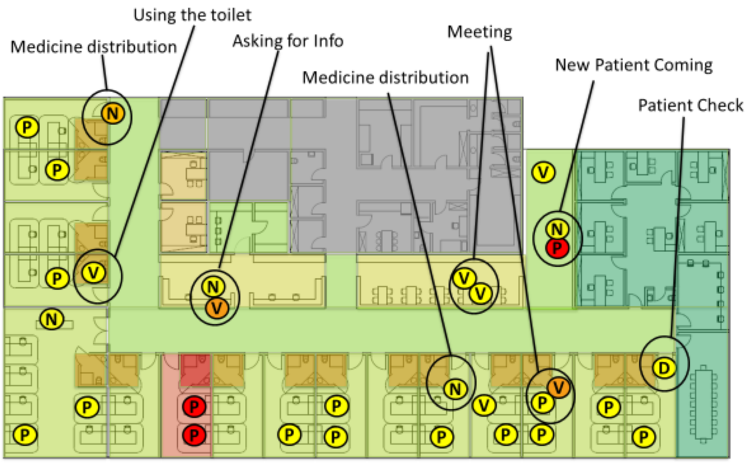
Transmission options:
In our case study, pathogen transmission occurs in four ways, temporally combined through the dynamic development of the simulation:

1. from a colonized (or infected) patient to a HCW and vice versa;
2. from a colonized (or infected) patient to a visitor and vice versa;
3. from a colonized (or infected) HCW to a visitor and vice versa;
4. from a colonized (or infected) actor to a space and vice versa.

In the present case study, touch-based interactions between same-type actors do not occur, because at the moment of writing activities involving two or more same-type actors have not been coded.

To exemplify the simulation-flow, a wider and illustrative discrete time-step scenario is set in the real-world floor plan involving two different types of HCWs (i.e. nurses and doctors), and four types of activities (i.e. meeting, patient check, medicine distribution, using the toilet), as follows, Fig. 44:

Time-step scenario set up

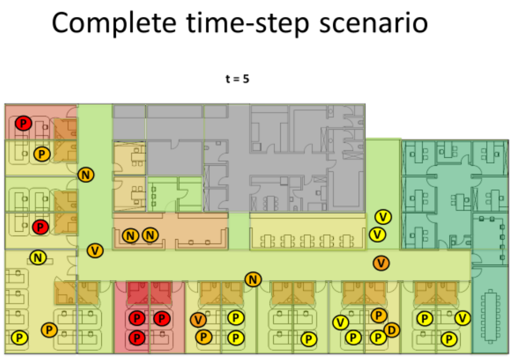


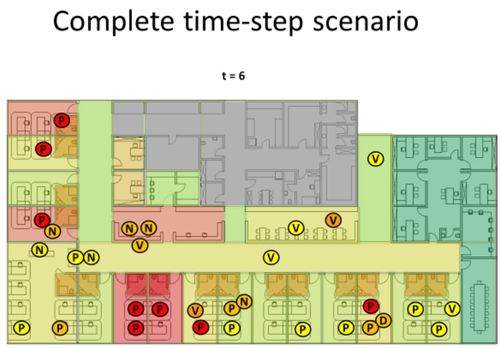
Complete time-step scenario

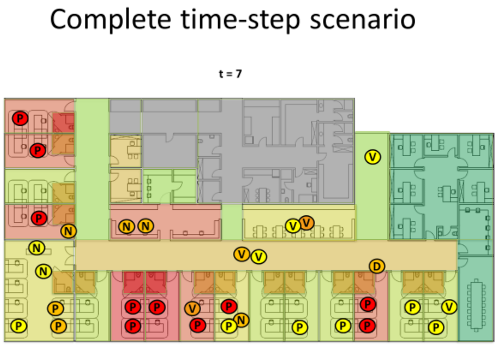
Complete time-step scenario

Complete time-step scenario

Complete time-step scenario







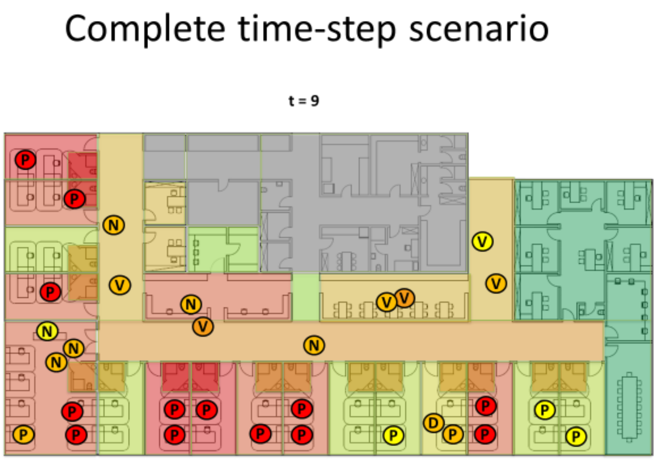


Fig. 44 – Illustrative complete time-step scenario

5,2,2 ACTORS

In our case study, three types of actor generated at the beginning of the simulation populate the virtual setting: HCWs, patients and visitors.

The preliminary step is the assignment of individual characteristics to each actor. Within this virtual representation, each actor is defined by his traits and behaviour. Relevant factors for users' profiles are determined by the objective of the model. For actor profiling we drew from previous works by the Kalay research group, which includes sex, age, and other demographics such as abilities, preferences, knowledge and both fixed and variable states (Hadas Sopher, Davide Schaumann, 2016). As shown, the attributes are user accessible, Fig. 45.

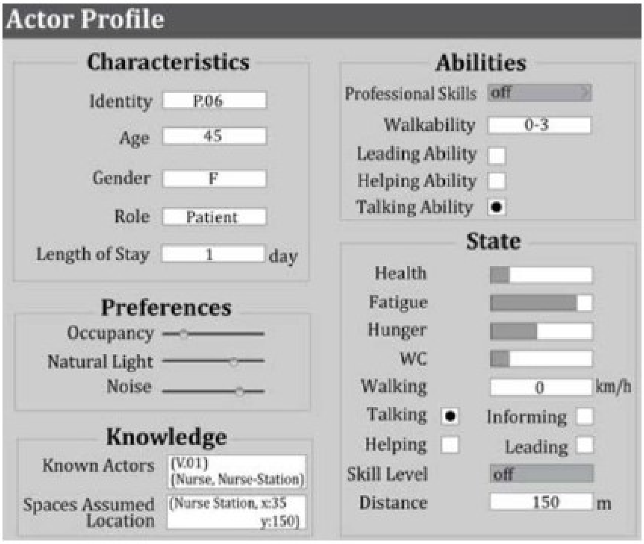


Fig. 45 - Actor profiling dashboard (Hadas Sopher, Davide Schaumann, 2016)

Actors display properties that define their role in the hospital organization (e.g. whether they are nurses, patients or visitors), their current status (e.g. the activity they are currently engaged in) and their relation with other actors (e.g.

nurses are associated with patients to medicate and visitors are associated with a patient to visit) (Schaumann et al., 2015). Every Actor has some basic capabilities of navigation through the space and a dynamic physical location (e.g. an origin and destination within the layout) and perception abilities that allow them to detect the presence of other actors if they are in the same zone and within a certain distance.

The starting level of the contamination status can be adapted at the start of the simulation for each actor or it can be randomly generated with the *setrand* button. As shown in literature, any person arriving in a hospital ward has a probability of being colonized by pathogenic microorganisms. Therefore, the number of non-colonized, colonized and infected actors can be adjusted to reflect the proportion of colonized patients that may be admitted to the hospital or transferred from other hospitals. Both colonized and infected actors can contaminate other actors (or spaces) with a lower level of contamination, so augmenting their contamination level according to the flow transmission equation rate. Each actor is unaware of the actual contamination level of others (or of spaces). The level of contamination of each actor (or space) cannot fall until the end of simulation. It is likely that in the near future, a hand hygiene event (and ward cleaning event) will be coded, overcoming this limitation, Fig. 46.

Fig. 46 - Actor contamination console.

As presented, our model associates risk factors to each actor for the infection spread. Indeed, actors may carry pathogens on their skin, dress and equipment. Their status of contamination, from 0 to 100, is visualized by a range of colours (slightly different from that presented in the model description) which changes when the level of contamination exceeds pre-settable thresholds, Fig. 47.

- White = un-colonized status;
- Green and yellow (two sequential levels) = colonized status;
- Red = infected.

Fig. 47 – Actors range of colours

The threshold values (Ct and It) can be adjusted at the beginning of the simulation for each actor, accounting for the possibility that some of the patients could be more susceptible than others, such as patients with open wounds or catheters, among other reasons. Another important risk factor could be the age of the patient (e.g. people over 65 years old), who are more likely to be infected with HAIs than younger people, Fig. 46.
The red threshold represents the infection threshold of contamination for a particular type of pathogen and is needed to set the limit between colonized or infected actor. In this case study, the risk of becoming infected is the same for all the patients involved and it is pre-set at “minimum risk”, but as stated previously, it is easy to account for particularly susceptible patients, or to simulate the presence of asymptomatic carriers, like HCWs or incoming visitors. The red threshold is set at a lower risk for all HCWs and visitors involved, reflecting their healthier status compared to patients.

However, as this is a simulation which condenses hours of activity into a few minutes, the contamination map develops at the same rate. Because of this, when an actor reaches the infection level it does not imply that he will suddenly manifest sickness but rather that he is sufficient contaminated to likely develop the disease in the following days. For instance, approximately one-third of the patients who acquire C. difficile colonization develop infection, whereas the remaining two-thirds become asymptomatic carriers (Donskey, 2010).

A Cl value can be set in the profile of each actor and for our case study this was done according to a particular ratio which is explained in the scenario building section, Fig. 46.

Unfortunately, as this was a representative case study, each scenario considered a fixed value of the Cl variable and as such the Cl for each actor was fixed during the whole simulation. However, in the near future when a hand hygiene event is coded and simulated, the Cl factor will be removed from the transmission flow equation, as has already been explained.

Finally, because interaction does not always imply contact, at the start of the simulation it is possible to select which actors do not touch others while performing activities, Fig. 46. This option aims to represent the case of actors devoted to tasks where physical contact is negligible, e.g. admission workers. Nonetheless, in our case study, every simulated activity involves contact.

5,2,3 SPACE

A geometrical layout in which actors can move and perform a set of activities was developed. Inanimate agents are modelled without explicit agency or decision-making capability, apart from their role as vectors for infection.

Space consists of a synthesized version of a hospital ward including patients' rooms, a medicine room and a HCW station. The different rooms are connected by a corridor in which the HCW station is located. The HCW station is adjacent to a central medicine room where medicines and medicaments can be prepared before their distribution to patients.

Our virtual setting comprises 2 single, 14 doubles and one five-patient room, housing in total 35 patients. Patients are accommodated in patient rooms during diagnosis and treatment procedures. To investigate the impact of shared and single rooms, in a scenario dominated by double rooms, two single rooms and a big multi-bed room are introduced. The first two play the role of potential isolation rooms and the latter are designed as an acute treatment room which can be found in every internal medicine department. In these rooms, 5 patients with artificial respiration can be accommodated.

The Space representation includes furniture and equipment needed for patient care as we consider them an integral part of each space. Even if not shown through defined activities, we assume that actors operate in rooms, e.g. patients living in it or interacting with objects and furniture, so that the contamination level of the room (space and objects) is affected by their presence and vice versa.

Each space has its value accounting for the contamination level. Indeed, spaces may become vectors containing contaminated surfaces, furniture and objects. Their contamination level, from 0 to 100, is visualized through a range of colours (slightly different from that presented in the model description) Fig. 48:

- Transparent;
- Green;
- Blue;
- Yellow;

- Red.

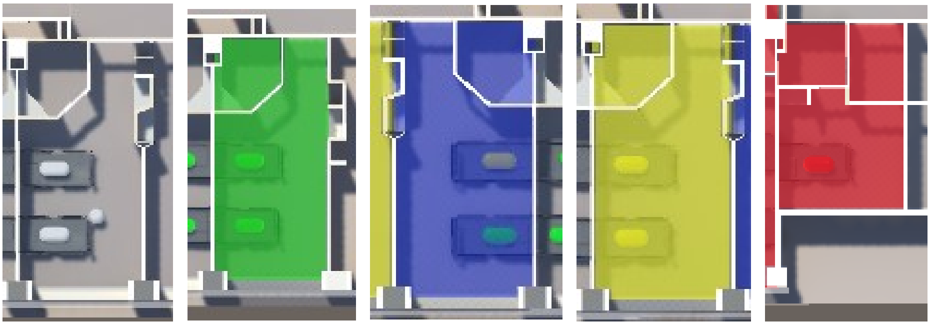


Fig. 48 - The colour changes when the level of contamination exceeds the pre-set thresholds.

In our case study, we assume that neither objects nor spaces are the primary source of contamination but only carriers. Therefore, their initial state is “all clean” and “not-colonized”. Yet, the starting level of the contamination can be randomly generated with the *setrand* button, Fig. 49.
However, if an investigation into how infection propagates from the flora of a health care environment is required (as in the case of epidemic exogenous environmental infections), it is straightforward at the beginning of the simulation to set a scenario whereby the initial cause of infection spread resides in a contaminated space, adjusting the starting contamination level for the selected spaces.

Finally, a CI value can be set in the description of each space. For our case study, this was done according to a ratio which is explained in the scenario building section, Fig. 49.

Setrand	☐
Contamination	0
Lack_of_env_cleaning	0.5
Rate_touch_env	0.5

Fig. 49 - Space contamination console

Unfortunately, as this was a representative case study, each scenario considered a fixed value of the Cl variable and as such the Cl for each type of space was fixed during the whole simulation. However, in the near future when a ward cleaning event is coded and simulated, the Cl factor will be removed from the transmission flow equation, as has already been explained.

5,2,4 ACTIVITIES

A further initial task of the developer is to define the pattern instructions that drive the interaction progression between agents and with space in order to reflect the processes within the hospital.
Here, the inclusion of field expert supervision (e.g. doctors and nurses) is evident. Observable behavioural patterns were established from the lexicon of practitioners and referring to real-world hospital situations (e.g. treatment processing, nurses and physicians' commitments) in order to shape a valid and reliable simulation.
Actors are associated with a set of activities to perform in relation to their role in the setting. In turn, activities provide a set of actions that drive actors toward the accomplishment of their goals and which are the main hospital processes in promoting infection spread towards actors and spaces.

In our case study, three different activity types were simulated:

- Invasive Treatment = Patient Check
- Medicine Distribution = Non-Invasive Treatment
- Meeting visitors

Each type of activity is associated with a certain risk factor Ty. The value of Ty for each activity type was supposed and set at the beginning of each simulated scenario according to a ratio which is explained in the scenario building section Fig, 50.

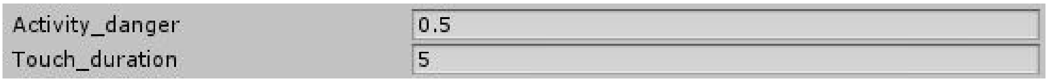


Fig. 50 - Activity contamination console

For each type of activity, a plausible length and contact duration were considered Fig. 50. As this was a simulation, the duration of the activities was proportionally reduced to condense several hours of activity into a few minutes Table 11.

Patient check contact Du approximately 200 sec.	Patient check contact simulated Du 10 sec.
Medicine distribution contact Du approximately 100 sec.	Medicine distribution contact simulated Du 5 sec.
Meet visitors contact Du approximately 500 sec.	Meet visitors contact simulated Du 25 sec.

Table 11 – Activities duration conversion.

Thanks to the openness of the system, the type of each activity and the duration of each contact can be easily modified in the user interface at the beginning of the simulation. Unfortunately, as this was a representative case study, each type of actor performs a single type of activity and therefore for each actor the value of Ty and Du are fixed during the whole simulation. However, it is likely that in the near future a more elaborate pattern of activities for each actor will be coded, leading to a dynamic variation of Ty and Du values.

5,2,5 PATHOGENS

The simulation scenario reveals the propagation dynamic for the chosen type of pathogens, i.e. those we chose for the case study.
For each simulation run, users may define new features for the pathogens which are essential for the investigation. Therefore, at the beginning of the simulation the value of the transmissibility coefficient is set according to the chose type of pathogen. Since the simulation is intended to be representative of the framework potential, the coefficient values were arbitrarily supposed mainly to enhance the difference between the types of microorganisms through the comparison of different pathogen aptitudes which drive scenarios, rather than exhaustively fit the characteristic of each specific kind of pathogen Table 12.
However, in future additional accuracy can easily be implemented thanks to the openness of the system to fine-tuning parameters for specific diseases.

Moreover, in our case study two different values of “Tr” were set, depending on whether transmission occurs between actors or to and from space. Therefore, the rate of contamination can be different if directed to or from surfaces and furniture rather than actors, mirroring the pathogen’s aptitude in spreading. For example, Clostridium difficile was chosen for this study due to its pervasiveness in the hospital environment under certain circumstances.

	Clostridium D.	MRSA	Klebsiella
Tr - actor	0,2	0,5	0,8
Tr - space	0,8	0,5	0,2

Table 12 – Hyothtical value of transmissibility for each pathogen.

The contamination propagation changes depending on the lifetime of the specific pathogen. In our simulation, the level of contamination starts to decrease with a particular speed only when a space (e.g. the corridor) is empty, according to the decaying timer “Dt” whose pace is set in advance. As this was a simplified case study with a very short duration, no decaying timer for pathogens was set to account for the survival duration on actors. As already explained, our simulation does not account for the option of a reproducing pathogen and therefore no contamination growing timer was set for space or actors. Consequently, the level of contamination increases depending only on the transmission mechanism.

Unfortunately, as this is a representative case study each scenario considers only a single type of pathogen. In the real world a composite of several microbial flora, viruses and fungi coexist in the hospital environment and competitive dynamics arise to populate surfaces and hosts. Furthermore, they may interact with each other e.g., the presence of MRSA may increase the risk of acquiring C. difficile and Klebsiella and vice versa. However, is likely that in the near future, a suitably detailed level of description to address this will be included in the simulation.

5,3 SCENARIO ANALYSIS

5,3,1 INTRODUCTION

Scenario analysis is a process of analysing the future events of a system while considering its alternative possible outcomes. It helps planners to conceptualize what type of situations they will need to manage in the future and then plan accordingly.
The scenario analysis is not based on deductions from the past or the extension of past trends. It does not rely on historical data and does not expect past observations to remain valid in the future.
Scenario analysis does not examine one exact picture representing the future. Instead, several alternative scenario developments are shaped and possible future outcomes and the paths leading to those outcomes are revealed.
Indeed, a scenario analysis is based on hypothesized "what-if" scenarios, each one made up of different combinations of system factors.
In our case research, the scenario analysis method implied making assumptions about a number of independent (or inter-related, in the case of expert systems) variables of the system (e.g. environmental features) and to consider their combined impact on the outcomes of the simulation.
We pre-determine certain scenarios (e.g. system critical cases) adjusting the full set of variables within the model to align it with the set-up of interest. A credible picture of the phenomenon is necessary in advance because all aspects of scenarios must be plausible and it is the underlying model structure that plays this role. The starting conditions of scenarios were determined in collaboration with the experience and intuition of a domain specialist.
In the scenario analysis, the developer, knowing the potential of his method, attempts to suppose the range of outcomes and pre-figure an initial understanding of what the outcomes would signify. However, more interesting still are those outputs which are counterintuitive and emergent. Therefore, the

main purpose of the scenario analysis is to validate the user starting points and support (or reject) his previous ideas and subsequent decisions; from his standpoint, the created model is a system to support decisions (DSS) (Jit and Brisson, 2011).

It is important to note that in the real world, precise predictions are impossible due to the complex state of things. Therefore, a scenario analysis must deal with a number of uncertainties and with the possible ways in which they could play out. In this respect, to minimize errors the developer could, for instance, take a decision based on which of the outcomes he has identified as most likely to happen.

The developer usually selects three different but consistent combinations of variables. One set gives rise to the optimistic/best outcome, one to the most likely outcome and the third to the pessimistic/worst outcome. This is commonly called the three-point estimate and mirrors the three states of nature; prosperity, steady and decline.

Even if nobody knows exactly what the future holds, planners are able to formulate effectively for different future possibilities by using such a "what-if" analysis approach.

5,3,2 APPLICATIONS

In our work, the case study is projected in three different prototype scenarios starting with calibrated set-ups.

Two critical types of situation were simulated: in the first scenario, some patients are colonized or infected, whereas in the second scenario, HCWs act as pathogen carriers. Furthermore, for both experiment scenarios, input parameters in the user interface were variated, namely the effect of different kinds of comparable pathogens. The impact of prevention procedures such as hand hygiene compliance and ward cleaning were tested as well as the risks connected with performing different type of activities. A last scenario was then set to assess the impact of the architectural configuration of the hospital setting on the pathogen propagation dynamic. Only the most meaningful cases previously identified were tested within the different spatial layout. An additional purpose of such multiple set-ups is to gain a better understanding on the potential of the simulation system in modelling human behaviour in relation to HAI.

Colonized patients scenario.

As mentioned in the problem domain section, it is possible for some antibiotic-resistant pathogens to emerge caused by the selective pressure of antibiotics. However, it is more common for newly admitted patients to be colonized or infected by one or more pathogens carrying strains into the ward.

Newcomer patients, newly admitted or moved from other units, are usually put in the first available double room, or in a single room only if an infection state has been pre-determined.

However, screening tests to identify MRSA colonised patients take seven days to obtain results. This may have limited value for patients staying in the hospital for less than a week, which may include most of the patients in the hospital itself (Meng et al., 2010).

Therefore, patients may either begin the simulation already colonized or acquire colonization while they are in the ward, whereas HCWs generated at the beginning of the simulation are initialized at a non-colonized state. Moreover, HCWs may become transiently colonized with the pathogen.

HCWs carriers scenario.

Because HCWs work on the ward for much longer than the average patient length of stay, they have a huge potential to spread infection. Hence, they cannot play as large a role in transmission as inpatients lest we expect every inpatient to become infected (Beggs, Shepherd and Kerr, 2008).

However, thanks to the cohorting guidelines, HCWs may transmit the pathogen to the patients assigned to them but are unable to directly transmit pathogens to any other patients in the ward, unless there are interruptions, e.g. visitors asking for information, which change this behaviour pattern.

Architectural design comparison scenario.
Finally, a third scenario is to be developed in the near future which compares two slightly different spatial configurations of the physical environment, while maintaining all the other variables and starting conditions fixed. This further simulated scenario experimentation is designed to exploit analysis into whether the architectural layout alone affects, by fostering or hindering, HAI propagation. The results analysis enables the evaluation of how an intended design meets infection control and prevention requirements. This application aims to support the design team and hospital managers in the evaluation of functional design qualities connected with safety requirements and potential improvements.

5,3,2 SCENARIO-BUILDING

If only best, baseline and worst values for each variable composing K parameters are considered, then in total 729 possible combinations could be variated in the simulation for each case scenario as input parameters in the transmission flow formulation. The following Table 12 summarises the list of variables:

Clostridium D.
MRSA
Klebsiella
HCW High Hands Hygiene
HCW Baseline Hands Hygiene
HCW Low Hands Hygiene

PAT High Hands Hygiene
PAT Baseline Hands Hygiene
PAT Low Hands Hygiene
VIS High Hands Hygiene
VIS Baseline Hands Hygiene
VIS Low Hands Hygiene
High Ward Cleaning
Baseline Ward Cleaning
Low Ward Cleaning
Non-invasive Treatment
Baseline Treatment
Invasive Treatment

Table 12 – List of variables admitted values.

In our study, three different types of condition have been considered for HAI dynamics for each selected scenario:

1. In the first experiment, we study the effect of changing the pathogen type, modifying the transmissibility Tr parameter;
2. In the second experiment, we examined the effects of hand-hygiene compliance and ward cleaning on the propagation of pathogens, varying the Cl variable to test the impact of prevention strategies;
3. In the third experiment, two treatments with different danger levels were compared, e.g. medicine distribution and wound medicament or inserting catheter procedure. Thus, the Ty variable was set accordingly.

When the objective is to obtain the greatest possible amount of information for a given problem or phenomenon, a representative case or a random sample may not be the most appropriate strategy.
Even if random sample selection is useful in avoiding systematic biases and achieving a representative example of the phenomenon which allows for the generalization of average situations, random samples emphasizing representativeness will seldom be able to produce interesting insights. Atypical cases often reveal more information because they activate actors and more mechanisms differently in the situation under study. In addition, from both an understanding-oriented and an action-oriented perspective, it is more important for us to clarify the deeper causes behind a given problem and its consequences than to describe the symptoms of the problem and how frequently they occur (Flyvbjerg, 2006).

A big hospital usually has at most a few thousand inpatients at the same time. For many studies which focus on a single hospital unit, the patient population size ranges from 10 for an ICU to about 40 for a medical ward. Within a small population, it is common to observe large fluctuations in infection prevalence and stochastic chance effects may govern the transmission dynamics (Meng et al., 2010).
Due to the randomness effect, prevalence may be high and outbreak may occur even when effective interventions are implemented. On the other hand, even with ineffective interventions or no interventions at all, there may be a chance that an outbreak does not happen and the prevalence remains low for a certain time span. Therefore, conclusions drawn from a single or few observations within a shorter time span may not represent the reality of the transmission dynamics for the HAI of interest.

Another typical feature of HAI is the rapid turnover of patients' population. Even if the actual length of stay may vary for patients with different diseases and risk factors, patients normally only stay in a hospital for a few days or weeks. According to this facet has many implications for the transmission dynamics. On the one hand, the positive effect is that, even without explicit intervention strategies, contaminated patients who can transmit the pathogen may be discharged in a few days and no longer pose a threat to other people. (Meng et al., 2010). On the other hand, even with every possible intervention strategy, due to the short timespan new cases of infection may still be introduced to the hospital by admitting patients who carry the pathogen. (Cooper et al., 2004).

In light of these considerations, for our aims it is more appropriate to choose a few cases among those simulated for their distinctiveness and validity.
Flyvbjerg identifies four types of cases associated with information-oriented sampling. To maximize the utility of information from small samples and single cases, cases are selected based on expectations about their information content. The Table 13 below summarises various forms of sampling:

Sampling	Purpose
Extreme/deviant cases	To obtain information on unusual cases, which can be especially problematic or especially good in a more closely defined sense
Maximum variation cases	To obtain information about the significance of various circumstances for case process and outcome; e.g., three to four cases which are very different for one dimension: size, form of organisation, location, budget, etc.
Critical cases	To obtain information which permits logical deductions of the type, 'if this is (not) valid for this case, then it applies to all (no) cases.'
Paradigmatic cases	To develop a metaphor or establish a school for the domain which the case concerns

Table 13 - Forms of sampling (Flyvbjerg, 2006).

No universal methodological principles exist by which one can identify a critical case with certainty. However, it can be defined as having strategic importance in relation to the general problem. In breaking down the problem, it also helps to facilitate identification of those elements and aspects of the problem that are likely to foster a risk of the situation. From such understanding, our two case-study scenarios can be classified as critical case studies, and for each of them maximum variation and baseline conditions were investigated and compared.

Such key cases in relation to their impact on pathogen propagation are discussed later. Results are shown for fixed simulation length and fixed number of interactions, while for the remainder these background variables have not been changed.

As stated, the process which leads to case selection firstly involves the investigation of the three-state condition for each scenario and for each kind of pathogen. After this, variable values are combined to shape the intended scenarios.

The simulation of such scenarios proved to be useful in understanding the effectiveness of various infection control procedures (e.g. hand-hygiene compliance and efficacy) and the effect of patient distribution and health-care worker-to-patient ratios on the incidence of pathogen transmission. Moreover, it helped explore more specific questions relevant to hospital managers and policy makers.

5,4 SIMULATION ASSESSMENT

5,4,1 EXPERIMENTAL RESULTS

This section presents a discussion of the significant scenario experiment results. Our contamination model is designed in unity 3D with a hospital unit as virtual environment. It provides both dynamic simulation and visualization of the system performance.

The system allows us to profile individuals and their behaviour, characterise the pathogens and the role of inanimate objects and furniture as agent-vectors and code the development of the interactions occurring among such elements.

This in turn allows the system user to run controlled experiments which reveal the dynamics of pathogen circulation, visualize clusters of infected patients and demonstrate how dynamics may vary depending on initial conditions (e.g. human factor) or because of spatially related features (e.g. space distribution).

The simulation of contact-mediated pathogen transmission permits qualitative estimation of single factor impacts: patient numbers and distribution, staffing conditions, ward spatial organization, pathogen colonization capacity, frequency of interactions and so on, either while the simulation is running (the simulation can be paused to analyse conditions of all the involved agents) or through a set of information extracted after it has ended from the data log. Correlations between factors can also be established. Moreover, the scenario simulation allows us to understand the relative merits of different HAI management strategies and their implementation in contamination propagation control (e.g. prevention measures), although the scope of the present study is more to visualize the propagation of pathogens on surfaces and skin without considering their effect on the health (e.g. development of diseases, death or antibiotics prescribed to cure infections).

Some intuitive and straightforward simulation results, namely those confirming former ABM research, are useful in verifying tool functionality. Some other counter-intuitive results, giving rise to more interesting and unexpected insights, are well suited to the falsification of unprompted assumptions and verifying underestimated correlations, as well the system sensitivity of influencing factors.

Infection policy initiatives, such has Hand Hygiene and Ward Cleaning were simulated to gain qualitative insights into the relative effects of such interventions for the case study.
In the real world, the wide-ranging decisions of intervention policies complicate the management of HAI hazards and the impact of diverse choices may well result in them becoming entangled. Evaluating the weight of every countermeasure as well as its potential interference with others is problematic and impractical in the real world. Our system exploits the effectiveness of each single intervention policy to prevent and control contamination diffusion, as well providing visualization of their co-presence with others at the same time. The scenario experimentation provides results that are consistent with literature by demonstrating varying degrees of improvement within the range of prevention strategies.

As presented above, the outcomes of scenario analysis were analysed for low, moderate, and high hand hygiene compliance and low, moderate, and high ward cleaning compliance. In order to evaluate the effectiveness of each control policy, they were applied separately and in a co-ordinated way. This form of simulation path helped us understand the extent to which a hospital can be subject to outbreaks even if strictly observing prevention regulations.

There is frequently uncertainty concerning the primary source of transmission. In certain circumstances, HCWs are the cause for transferring bacteria to patients, whereas in others, patients or visitors could be the primary source of transmission.

Our system allows for the design of simulation scenarios including asymptomatic carriers, i.e. actors with hidden contamination status. These scenarios challenge the user to detect the initial cause/s of the outbreak. In the same way, environmental epidemics sometimes occur. In this case, the infecting role of space and its evolving consequences can be revealed. Such a scenario takes place in MRSA baseline conditions and is used to understand the effect of a visitor approaching carrying hidden strains of MRSA, Fig. 51.

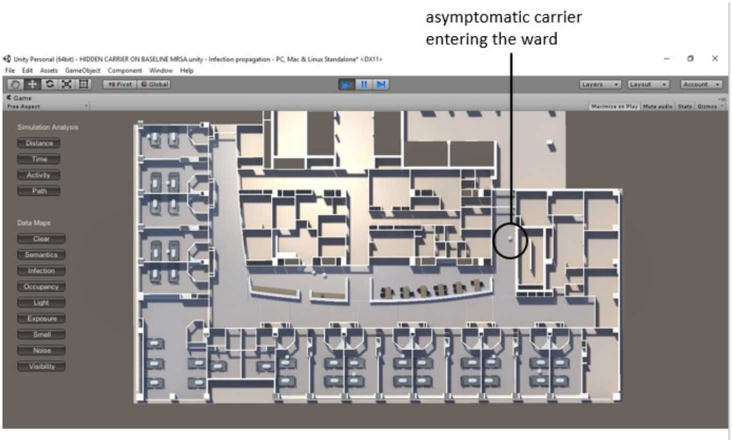
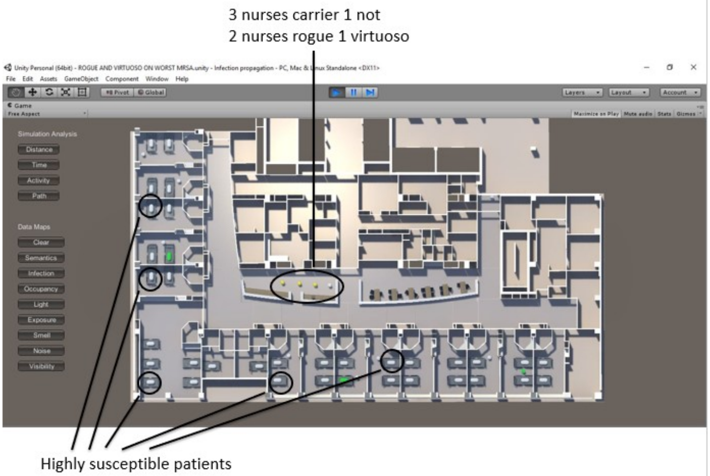
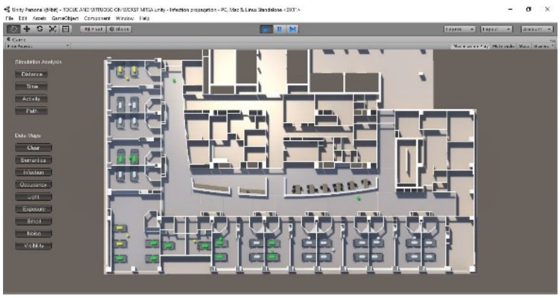


Fig. 51 - Asymptomatic carrier scenario

Thanks to the simulation’s level of detail and real-time visualisation, it is possible to track the colonized actors directly attributable to each HCW. It demonstrates the detrimental effect of a rogue HCW who adheres to Hand Hygiene less than the rest of the medical staff, as well as the remarkable incidence of a virtuoso HCW who is more compliant with prevention protocols. This could be in the case of a worst MRSA scenario condition setting, which means low patient hygiene, invasive treatments and low ward cleaning. Three out of four nurses start as carriers and spread the contamination. Only one of them strictly adheres to hand hygiene protocol. In the scenario, some highly susceptible patients are inserted, Fig. 52.


3 nurses carrier 1 not
2 nurses rogue 1 virtuoso
Highly susceptible patients



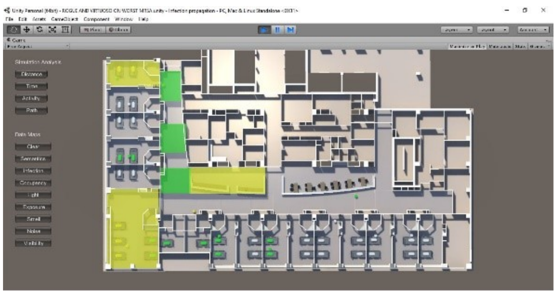
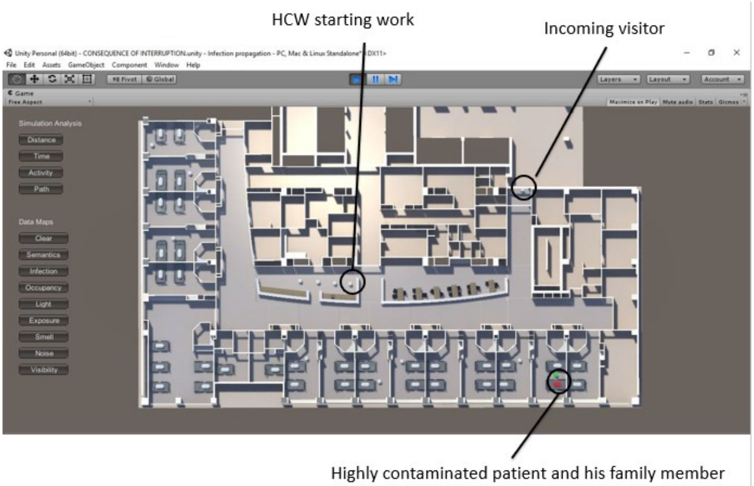


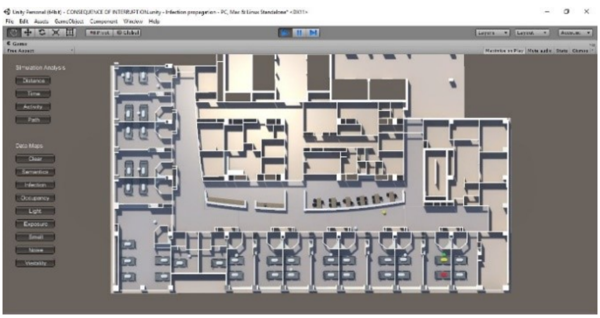
Fig. 52 – Rogue and virtuoso HCWs comparison scenario.

Nurses start their respective treatment rounds in three different cohorts. Nurses 1 and 2 contaminate each patient with whom they interact one by one. Subsequently, the space becomes contaminated due to the presence of contaminated patients. Nurse 3 makes contact with a highly susceptible patient, further raising his contamination level. The presence of numerous actors in the same multiple room increases the contamination level of the space faster compared than that for spaces crossed by Nurse 1. Meanwhile, even if we set the worst-case scenario, Nurse 3 affects patients only marginally and without a considerable effect on susceptible patients. Nor does this affect the space contamination level. If Nurse 2 interacts with a highly susceptible patient, infecting him, the major effect of a contaminated big multiple space impacts on other patients present.

The previous scenario experimentation proves the valuable role played when cohorting is adopted if acceptable HCW-to-patient ratios are maintained and where HCWs respect prevention guidelines. In fact, in such cases, transmission take place across the cohort, especially when the patient population is well mixed, allowing asymptomatic carriers to remain hidden. This condition is more likely to occur if too many patients share the same HCW or if the ward is understaffed. In dangerous situations, minimizing the size of patient cohorts could be suitable.

The following scenario, built on the MRSA baseline, shows a visitor leaving his relative’s room when an actor enters the room to attend to the other patient. This situation forces him to wait in the corridor and then unexpectedly interrupt the HCW workflow while he is performing a round of visits. The visitor who has been in direct contact with his infected relative (who has contaminated him, making him a carrier), in turn contaminates the HCW. In such a situation, if the HCW fails to observe Hand Hygiene, it is likely that he will spread contamination to subsequent patients. In the meanwhile, the space populated by these contaminated actors also becomes contaminated and contributes to the spread, Fig. 53.


HCW starting work
Incoming visitor
Unity Personal (64bit) - CONSEQUENCE OF INTERRUPTION.unity - Infection propagation - PC, Mac & Linux Standalone* <DX11>
File Edit Assets GameObject Component Window Help
Pivot
Global
Layers
Layout
Account
Game
Free Aspect
Maximize on Play
Mute audio
Stats
Gizmos
Simulation Analysis
Distance
Time
Activity
Path
Data Maps
Clear
Semantics
Infection
Occupancy
Light
Exposure
Smell
Noise
Visibility
Highly contaminated patient and his family member



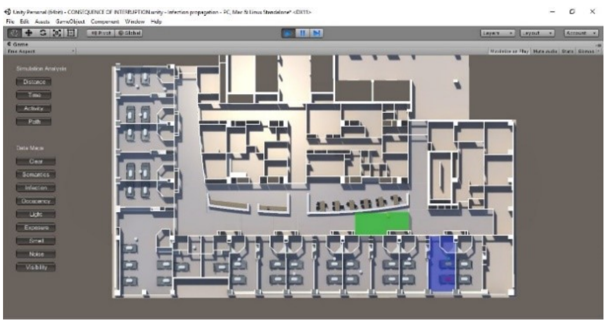


Fig. 53 – HCW workflow interruption scenario.

Simulated scenarios can also be useful in addressing questions relevant to hospital management. Interestingly, the economic return of increasing cohort size compatibly with the workload of HCWs is related to the essential need of reduction in transmission rates, which may likewise be reached thanks to higher Hand Hygiene adherence; this should be assessed.

In this regard, our model could support broader considerations about the correlation between environmental or human factors and contamination prevalence. Awareness of contamination danger and perceived contextual barriers (e.g. local and contextual conditions and the effect of architectural design) are designed to enhance their indirect/high level of influence on Hand Hygiene practice adherence.

As an indirect effect, in our scenarios the following proved to be contributory factors in the spread of germs:

- Crowded conditions within the ward, e.g. many visitors interrupting the HCW's planned work schedule;
- Condition of patient full ward and presence of highly susceptible patients;
- Perception of negligible infection risk due to faster or non-invasive treatments, as well as wellbeing feeling of others;
- Insufficient or unavailable facilities for cleansing.

One further scenario shows the validity of the measure of isolating patients suspected or recognized as infected (if HCW hand hygiene procedures are followed), so that colonized patients are prevented from transferring the bacteria to others through HCWs.

In this case two hidden infected patients occupy two rooms, a double and a single. The nurse caring the first cohort (the double) is compliant to Hand Hygiene measures, where the nurse combined with the second cohort is not. Infected patients start contaminating their surrounding at the same rate and they receive the same treatment. The infected patient sharing the room contaminate his roommate through the environment, in the case of the patient in the single room it doesn't happens. Even if both nurses become equally contaminated after touching the infected patient, the one compliant with hygiene procedures prevents to transmit further, namely in other rooms, the contamination, where in the other case the contamination propagates in subsequent rooms. The spreading proceeds through a single and many double rooms, due to the double presence the latter case obtain a higher contamination than the single, in which the patient has more chances of stay safe, Fig. 54.

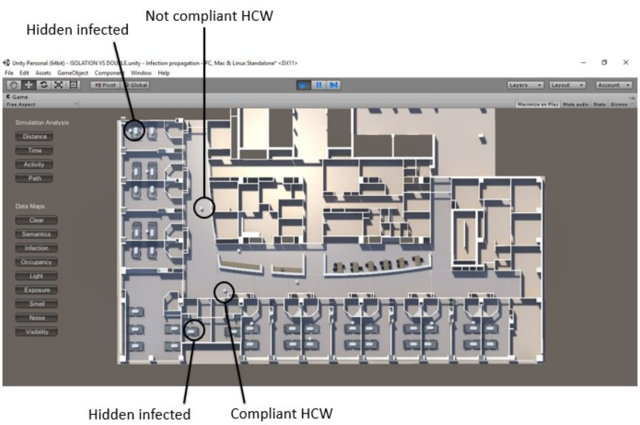


Fig. 54 - infected Patients scenario.

Self-protective perception promotes compliance with hand hygiene procedures and the use of self-protective equipment, e.g. gloves and gowns. Nevertheless, sometimes the latter behavior may lead to an underestimation of its combined need with the former, fostering the spread of pathogens even if the HCW has ensured his own personal safety (Fuller et al., 2011).

As the following scenario demonstrates, the Event Based approach is directly correlated with the pathogen dissemination dynamic. Its development follows the rate of events taking place in the environment, those explicitly coded such as treatment interactions, as well of those implicitly simulated such as patient-surrounding contacts.

Therefore, in each scenario the contamination development visualizes its strong correlation with the number of contact interactions. Such a fundamental parameter is of the utmost importance in the evaluation of the capability of a pathogen to pose a threat for a rapid outbreak or alternatively the chances of contamination control. Certainly, interaction cannot be totally avoided, but minimizing the number of daily contacts could help. At the very least, preventing overcrowding makes it more likely that HCWs will observe Hand Hygiene requirements. For the same reason, a threshold value can be studied which focuses on the risk-shifting from a pathogen displaying a strong aptitude to colonize an environment to one which prefers skin.

Here we compare different scenarios (i.e. best cases and worst cases) for Clostridium and Klebsiella. The results show that while in best cases there is no significant output difference, in worst cases the high rate of interaction taking place in the Klebsiella scenario strongly affects the contamination level of spaces, even if the pathogen’s aptitude to spread through the environment its far less than that of Clostridium, Fig. 55.

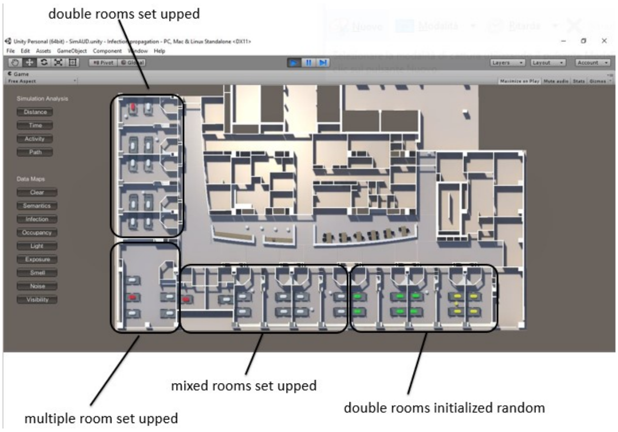

double rooms set upped
mixed rooms set upped
double rooms initialized random
multiple room set upped

Fig. 55 – Pathogens types comparison scenario.

Case study results demonstrate the capacity of the simulation system to detect changes that are not obvious. Our simulation scenarios proved to be highly reliable both in situations when a clear sequence of observable, planned factors can be recognized and when emerging unplanned behaviour complicates situations.
The proposed approach subdividing the complex phenomenon in component pieces help to identify precise spatial and procedural problematic nodes. It is able to deal with the variety of factors that are responsible for contamination propagation in a robust, consistent and flexible way, adapting to the most diverse physical and contingent situations.

Hence, we can assert with confidence that, once calibrated with data from an ad hoc survey, the system output will be coherent and consistent with real world occurrences, making it useful in predicting the development of infections in real world hospital wards.

A visualization illustrating the simulation is included in this thesis as an on-line video.

While the validity of weighting hypotheses, and branching potential outcomes from them has been proved, reliance on scenario analysis without reporting some parameters of measurement accuracy is a poor second to traditional prediction. In a scenario analysis there are no ex ante expected values, only hypotheses, and one is left wondering about the roles of modelling and data decision.
Nevertheless, in a complex real system, factors and assumptions do not correlate in lockstep fashion and therefore causative relations are not always knowable, as they are in other strong science research fields (Anderson, 1972) (Alexander, 1966).
In fact, this bias is the main issue of all the models based on agents, i.e. what is the reliability of the model output for a given what-if scenario which nobody knows for certain or which has never previously occurred and therefore no exact correspondence with real circumstances could be proved?
However, comparisons of "scenarios" with outcomes are prejudiced by not deferring to numbers and once a specific sensitivity is undefined, it may call the entire study into question.
Thus, verification and validation steps were carried out in an attempt to overcome such verification limitation.

5,4,2 VERIFICATION

Case study research studies are often seen as less rigorous than quantitative methods. The supposed deficiency of these approaches relies on the belief that they ostensibly allow more room for the researcher’s subjective judgment and preconceived notions. However, even if a bias toward their verification exists, according to other experts the case study shows a relevant proximity to reality and generates a learning process in which the researcher constitutes a solid prerequisite for advanced understanding (Flyvbjerg, 2006)

In line with this, our simulation system allows for an iterative process of fitting the case study to reality with the aim of perfectly matching virtual environment to reality. Moreover, such a method supports the process of learning through the demolition of old-knowledge categories where truth is proven by scenarios and the building of new ones.

This process is quite a central element in any learning activity, especially in achieving new insights on natural phenomena. More simple forms of understanding must yield to more complex ones as the simulation moves deeper into the case study, leading to new discoveries through the combination of numerous simple understandings.

Through the perspective of the learning process, we can understand why the researcher who conducts a case study often ends up casting off preconceived notions and theories. The case study is well suited for generalisation by using the type of test that Karl Popper called “falsification”, one of the most rigorous tests that a scientific proposition can be subjected to: if just one observation does not fit with the

hypothesis, it is considered generally not valid and must therefore be revised (Flyvbjerg, 2006)

Through this iterative research path, simulated case studies have wide-ranging significance and stimulate further investigations and theory-building.

The strong benefit of our approach is the visualization of virtual environments which can increase the credibility of the model by facilitating the interpretation of simulation results.

The verification phase was undertaken to prove the reliability of simulation progression and results through two iterative processes that were conducted during the model building phase for the case study scenarios. Such a practise was

designed to reduce the gap between model capabilities, simulation expressiveness and real contamination spreading situations.
Two verification procedures were conducted: checking the code with a simulation software expert and visually checking the simulation with HAI experts.

From a software development perspective, a specialist in the Unity3D engine was chosen as an advisor. He inspected the simulation code to verify the validity of the complex decision logic behind the formalized use process. Moreover, he determined whether the simulation computer program performed as intended, i.e. debugging the computer program (Law and Kelton, 1991). Consequently, any simulation errors were noted and adjustments on the code carried out.

The system provides a visual animated description of the model, allowing the user to view the simulation while it is running. System parameters were calibrated and the model informally validated by a medical consultant who assisted the developer. In undertaking this visual verification, scenarios were run separately while the modeller and his consultant monitored agent behaviour.

Both verification by the expert and the modeller's visual checks were conducted iteratively until the correct expected performances of the simulation for the reference case study scenario were carried out.
Even if visual simulation renders potentially complex system dynamics more intelligible to consultants and decision makers, verification remains different from validation.

5,4,3 VALIDATION

Model validation generally shows how well the current model fits the data at hand. Ideally, a model should be validated by means of comparing simulation

outputs/results against external data observations from a dataset different from the one used for model fitting.
Such an arrangement is only possible if data from the real system are available, although this is rare in HAI modelling. Van Kleef reports only four studies with some kind of model validation based on at least two different data sets, where traditional mathematical models sometimes incorporate some form of quantitative methods to model calibration to empirical data (van Kleef et al., 2013)
In the field of HAI modelling, work is ongoing in terms of validation. Recently, to construct biologically plausible transmission risk models that can guide cross-infection control, researchers have developed an RFID tracking system with which to extract agent high-fidelity contact data on the understanding of the critical role that contact patterns play in cross-infection diffusion (Hornbeck et al., 2012).

At the time of writing, we cannot perform this type of validation in the absence of a level of real data comparison and the impossibility of collecting all the dataset needed in a single survey to feed the model at the same time. Moreover, access to sensitive data is highly restricted.
Therefore, a qualitative validation was carried out.
We decided to examine the sensitivity of the simulation results, namely how sensitive the change in outputs is when varying the simulation input by means of sensitivity analysis. The input here is defined as what can vary in order to study its effect on the output. This can also exploit the relative importance of different input factors on the model outputs (LIU, 2011) (Saltelli, Ratto and Andres, 2009).

The European Commission recommends sensitivity analysis in its impact assessment guidelines 2009: “When assumptions underlying the baseline scenario might vary result of external factors, you need to do a sensitivity analysis to assess whether the impacts of the policy options differ significantly for different values of the key variables” (European Commission, 2009).

It could be useful to clarify to what extent a sensitivity analysis validation is different from a scenario analysis. Instead of looking at how all different factors that are adjusted in a scenario could impact on the simulation by giving a certain situation development (as carried out in our scenario analysis), in a sensitivity analysis we examine how every possible value of each variable influences the outcomes. A sensitivity analysis is a logical, methodical process created to understand the impact that a range of variables has on a given outcome, i.e. isolate each variable or group of them and record the range of possible outcomes (Rappaport, 1967).

Hence, the sensitivity analysis validation is based on the variable impact value, which our model can describe using the discussed variables (e.g. transmissibility, type of pathogen, and so on), as well as other simulation parameters such as the number of visitors or the time length of treatment. The latter, even though not a part of the formulation of the contamination transmission, is directly connected with the simulation output through the Event-Based structure of the system and thanks to the Unity interface may be variated in the same way as the other parameters.

Such a method may exploit what the key drivers of the simulation results are, i.e. a sensitivity analysis will instruct the modellers as to the relative importance of the inputs in determining the output (Saltelli, Ratto and Andres, 2009). This subsequently allows him to discover interesting correlation patterns between what the model treats as input and output variables.

Determining the impact of a variable under sensitivity analysis through the process of recalculating simulation outcomes under alternative assumptions can be useful for other purposes, including:

- Searching for errors in the model, e.g. by encountering unexpected relationships between inputs and outputs.
- Testing or increasing the robustness of the results of a model in the presence of uncertainty, namely understanding how the uncertainty in the output of system can be apportioned to different model inputs.
- Model simplification – fixing model inputs that have no effect on the output, or identifying and removing redundant parts of the model structure.

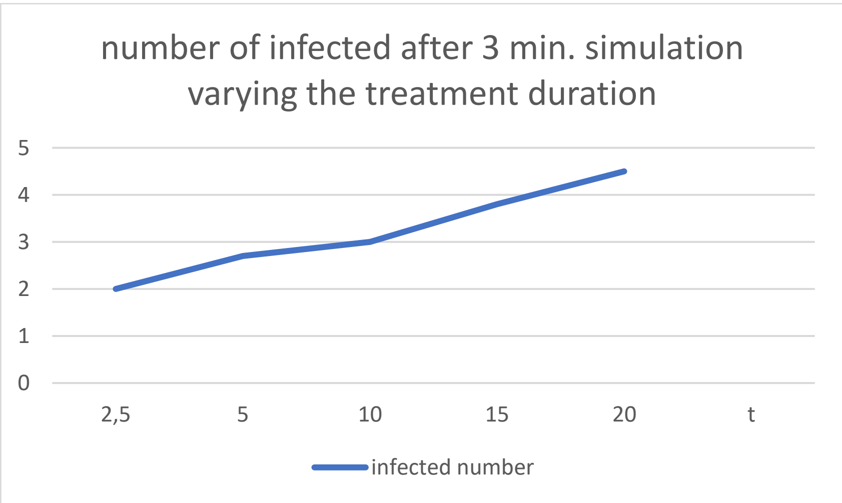
If observation data is available (regrettably not, in our case), a further application of sensitivity analysis is model calibration and improvement. Sensitivity analysis can be used to identify important connections between observations, model inputs and outcomes. Results are likely to help locate errors in the data collection method, in the dataset or in the model development and addressing these issues will lead to a fixed model. (Wikipedia)

Sensitivity Analysis can be univariate or multivariate depending on whether one or more parameters are altered at a time in the same run. If multiple runs of the simulation are performed with a random selection of input parameters, this is known as a probabilistic sensitivity analysis (van Kleef et al., 2013).

To conduct a univariate sensitivity analysis, the value of a certain variable involved in the model is modified to see how that change affects the overall HAI dynamic. The user changes a single variable while keeping the others fixed (e.g. at their base-case value), to investigate what kind of effect this has on the overall output.

By adjusting this variable to either a lower or higher value, the developer can partially determine several eventualities. This helps him to make informed decisions about prevention and control strategies in the light of understanding what could happen to the infection spreading dynamic if variables vary.

To perform our sensitivity analysis validation process, we estimated how sensitive the chosen dependent variable (i.e. number of infected patients) is to a change in an independent variable, i.e. time spent in performing treatment. This investigation was continued for the baseline MRSA case scenario with a random starting contamination level for patients, i.e. a random spatial distribution of colonized and infected patients.
The contact duration was variated linearly and for each case the average number of infections recorded over 100 simulation repetitions at the end of 3 minutes of simulation. The main purpose of the sensitivity analysis validation is to study and compare the sensitivity of the simulation outcome in each run. It is therefore clear that the percentage of increase for treatment length is not crucial.



Following hundreds of repetitions, it is likely that we will be able to estimate that an X% increase in time will result in a Y% increase in infected cases. While this may be an ideal result for a sensitivity analysis, but it does not have to be quantitative. In this sensitivity analysis validation test, we simply wanted to understand how the factor within our control impacts on the outcome. The measurement was expected to increase along with the increase of treatment length and as expected, our hypothesis was verified. However, once the simulation is completed with new events, allowing for more than three minutes of continuous simulation, it is likely to be possible to verify whether the increase in the number of infected cases will rapidly increase at some point and mimic the infection dynamic of outbreaks, so letting us identify a safety threshold. The same method will be used considering the number of interactions as input parameter in the sensitivity analysis.

Interpreting the validation is a process which determines whether the conceptual simulation model is an accurate representation of the system under study (Law and Kelton, 1991). We can assert that the sensitivity analysis validation test provides some level of confidence that the simulation model of this study is already sufficiently valid to represent the performance of the real system.

Our future aim is to carry out a thorough survey which aims to gather the exact type of data required to calibrate the model. This can be achieved through an extensive sensitivity analysis process aimed at searching for errors and so properly validate the model. This may include, verifying the correlation between C and K in the chief equation, and a complete definition of the coefficients composing K, because the quality of this method as a Decision Support System strongly depends on that knowledge. Such a step is needed if we want to understand in detail how the outcomes of the model could help to evaluate how the conditions for the variation in pathogen transmission resulting from management decisions can lead to significant increases or decreases in the incidence of HAIs.

6 CONCLUSIONS

6,1 DISCUSSION

The study presents a model and simulation of HAI transmission by a contact route through exogenous cross-infection and its propagation dynamics in a hospital ward.
We applied the Event-Based method, an extended agent-based approach, to investigate the contamination risk.
The nature of the HAI problem domain requires us to develop the potential of the chosen technique further, as it had never previously been applied to this field.
The model considers the profile and states of agents and pathogen features and includes objects and spaces.
The simulations display agents' displacements and behaviour in a spatially explicit, heterogeneously mixed virtual environment.
The developed framework handles a wide range of pathogen types, allowing us to graphically represent any hospital-unit layout and account for many diffusion scenarios with different agents, activities and spatial distributions.

More specifically, in the simulation, considering "agent" as both space and actors:

- every type of actor, healthcare worker, patient and visitor can be set;
- the heterogeneity of actors is encompassed and their traits, characteristics, abilities and knowledge can vary;
- the contamination status can be set for each actor as well as his susceptible and asymptomatic conditions;
- interactions with or without contact between all the actor types its possible;
- the role of space as an agent source and vector of pathogens with its own level of contamination is included;

- medical instruments, equipment and furniture are included either for actors or in space;
- the transmission law varies depending on the type of activity, the type of pathogen and the cleansing of involved agents, which represents the level of efficacy in hand hygiene or ward cleaning;
- each actor level of cleansing varies depending on the following: the type of planned activity, the level of cleansing of others, the role of the actor in the organization, the contextual situation (i.e. overcrowding or understaffing), the number and location of hygienic facilities and the existence of Alcohol Based Hand Rubs.

The model was built with information gathered from real-life observations and on real work procedures and activities carried out within hospital wards. It was developed taking into consideration scientific literature on HAIs, which reveal established scientific features in understanding HAI propagation.
Prevention and control guidelines and sessions with hospital managers broadened our knowledge on measures and policies to manage HAIs.

The condition of contamination, which is simultaneously the contamination capacity of each agent (actor and space), is the element on which pathogen dissemination depends. The contamination relational law between agents, formalized and presented here, drives the transmission.
The mathematical formalization between agents is complemented by an expert system to include intangible human factors such as the awareness, sensations, perceived barriers and local conditions for each agent which influence his tendency to comply with prevention and control procedures (i.e. hand hygiene).

Our system is founded on the Event-Based approach established by Shaumann et al. which is a modelling and simulation technique of human building use where spaces, actors and activities are modelled in a computational environment.

Events are designed to co-ordinate temporal, goal-oriented routine activities performed by agents. Rather than describing collaborative behaviour from the point of view of each actor, events allow for the description of behaviour from the point of view of the procedures that need to be performed to achieve a task (Schaumann et al., 2017)

It was from this framework that our model derived its event system architecture, the structure of activity simulation and the basic characteristics and behaviour of agents, including those of interaction.

The Event-Based Modelling and Simulation was expanded to consider the HAI phenomenon, i.e. contamination propagation on spaces and actors. Agent attributes were added and scripts modified, while the C# code was integrated with our model of transmission dynamic and the expert system and translated into system functions.

The system was tested in a virtual simulation of the use of space in a building correlated with the contamination propagation through a contact transmission route in a hospital ward. It was built with a tool under development on the Unity3D platform by Professor Yehuda Kalay and his research group at the faculty of Architecture, Technion (Israel).

To illustrate the potential of the developed system, we simulated a trial case study in a Unity 3D environment.

The visual-spatial simulation represents the building and its users in a dynamic situation of HAI risk in a coherent system, where behaviours and outcomes can be measured over space and time.

In the case study, some hospital procedures and daily activities are coded in terms of events such as system inputs while the contamination map is the dynamic output.

The main advantage of the simulation environment is that it allows for a real-time dynamic visualization of the phenomenon and data can be accessed during the simulation run or after being stored in a data log.
To demonstrate potential applications of the simulation, several virtual scenarios are hypothesized. Accordingly, initial conditions and parameters are set up on the dashboard interface or generated randomly, if needed. Simulation outputs are then analysed.
In addition to the capacity of the system to reveal all kinds of situations occurring in space (i.e. agent-agent and agent-environment interaction, as well as interference and unplanned events), the simulation allows for the real-time visualization of contamination transmission. Although tangible in reality, this is a phenomenon that is hidden from cognitive agents within the hospital up until its appearance with symptoms.
The simulation exposes correlations between human states, traits, knowledge, behaviour and activities with the propagation of pathogens.
Moreover, it visualizes the chain of infection which represents the circulation path of an infectious pathogen, while suggesting where it may be more feasible and convenient to operate in order to break the chain.
It reveals clusters of infected patients and patterns of spatial occurrence, demonstrating how transmission dynamics change depending on initial causes and conditions and because of spatially related features.
It gives us hints on how the spatial design of buildings and placement distribution can affect the risk of HAI.
Of further interest is the potential to assess the outcome on the infection spread caused by the implementation of different organizational procedures, e.g. agent hygiene behaviour and contact precautions.
Finally, the simulation shows that the proposed framework is able to consistently consider the wide combination of factors that leads to contamination propagation and that it is sufficiently robust to adapt to numerous environmental and social contexts.

Once the model will be extended with more events, primarily Hand Hygiene and Ward Cleaning, more facets of the contamination phenomenon will be handled by the system and it would be possible:

- to evaluate in detail the role and impact of hand hygiene measure in different risk context as well the improvement correlated with the use of ABHR dispensers;
- to evaluate policies controlling the frequency of ward cleaning in relation with the number of interaction with the environment (rate of space use), to discover more efficient conduct rules and frequency to perform such activity;
- to test specific paths to divide people flows, e.g. HCWs and visitors, in relation to their effectiveness in lowering the pathogens dissemination and the consequent the risk of cross infection;
- a narrow evaluation of the amount of space needed for each patient within his shared room, to assure adequate spatial separation of patients, once integrated in the system;
- to suggest explanations for observations that have not been previously explained;
- to simulate paradoxical situations so that their resolution leads to the progress of knowledge of the problem.

At the end of the process, the re-elaborated knowledge presented through the simulation acts as the basis on which decision makers rely to synthesize their desired solutions, encompassing regulations, guidelines and field expertise.

To decide is to choose in a reasonable way an appropriate alternative in a situation of choice where several solutions are possible (Simon and Alexander, 1977). Our framework functions as a decision support system (DSS), assisting the

decision-making process which is the fundamental meaning of hospital management by imitating real-world phenomena of interest by representing the system's evolution over a set period of time. Where the hospital system is something which evolves under our nose, as a contemporary process rather than an historical.
Our approach fits the established technique for the simulation of future global scenarios since our system is suitable for investigating "what-if?" scenarios, providing evidence in support of underlying decision-making processes. In fact, the scenario-building mechanism is designed to improve decision-making by providing a consideration of scenario outcomes and their implications. In our case-based scenario, analysis was used to illuminate critical cases which, while unlikely, have repercussions which are so dangerous that the event is much more important than its low probability alone would suggest.

It is suggested that this framework allowing the user to understand the phenomena through experimentation, which is a traditional goal of science, can be used as a decision support system (DSS) for practitioners and policymakers alike when employed as a forecasting tool for the evaluation of interventions. In fact, a system user (even the modeler himself) can generate new input conditions and after system parameter tuning (e.g. actor profiles and behaviour and setting re-configuration), by simulating scenarios she/he may figure out possible states in the development of a situation. The subsequent comparison of the experiment's qualitative results is valuable in assessing the effectiveness of the implementation of control strategies, namely measures and procedures, as well as shedding light on potential control protocol breaches in infection outbreak management. In this respect, a key potential advantage is to prove that if the organization does not work, a different design could help and consequently address the design of future hospital environments and the restructuring of existing ones. Finally, the system could be useful in facilitating managers to issue instructions and recommendations to healthcare staff members, as well as using realistic simulation scenarios to act as a knowledge support tool for HCWs training. In this regard it can helps to reduce noncompliance to policies while optimizing hospital resources, where typical control procedures are expensive e.g. materials, additional capacity, dedicated personnel, labour-intensive and generally uncomfortable for both patients and health-care personnel. Finally, and most of all, even if only a small number of infections could be prevented it will repaid our work hundred times.

In conclusion, we explored the potential of using a multi-agent simulation of human behaviour in buildings through modelling to generate several scenarios of system futures. Such approach, applicable in multiple domains, provides measurable insights of different qualitative factors, allowing us to bridge the gap between theoretical knowledge and applied decisions. In this respect, it may support the design of urban infrastructures from the point of view of user behaviour. Through understanding and representing user needs, context constraints and hidden risks, human factor and behaviour could be integrated into the decision-making process and the impact of a built environment and environmental threats on them could be assessed. We recommend that this approach might be considered for future studies on the predictive model construction and risk factor analysis.

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8 ANNEX - PSEUDOCODE DESCRIPTION

```
Object Pathogen added
{
	Attributes:

	Transmission_factor  //variing from 0,0 to 1,0
	Degeneracy //variing from 0,0 to 1,0
}
```

```
Object Hospital added
{
          Attributes:

                    Overcrovding = true;
                    crovding_MB = 0.5f; //if flg true
                    crovding_MD = 0.5f; //if flg false

                    UnderStaffing = false;
                    Staffing_MB = 0.5f; //if flg true
                    Staffing_MD = 0.5f; //if flg false

                    ExistABHR = true;
                    ABHR_MB = 0.5f; //if flg false
                    ABHR_MD = 0.5f; //if flg true

                    DeviceLocationLT100sec = true;
                    Dev_MB = 0.5f; //if flg false
                    Dev_MD = 0.5f; //if flg true


          MB;
          MD;

          Functions added:

  void compute_hospital_MB_MD() //environmental lack_of_cleaning
components
   {
      //return 0.5f;
      //float lack_of_act_cleaning;

      MB = 0f;
      MD = 0f;

      if (Hospital.Overcrovding == true) MB = MB + Hospital.crovding_MB * (1 -
MB);
```

```
        else MD = MD + Hospital.crovding_MD * (1 - MD);

        if (Hospital.UnderStaffing == true) MB = MB + Hospital.Staffing_MB * (1 -
MB);
        else MD = MD + Hospital.Staffing_MD * (1 - MD);

        if (Hospital.ExistABHR == false) MB = MB + Hospital.ABHR_MB * (1 - MB);
        else MD = MD + Hospital.ABHR_MD * (1 - MD);

        if (Hospital.DeviceLocationLT100sec == false) MB = MB + Hospital.Dev_MB
* (1 - MB);
        else MD = MD + Hospital.Dev_MD * (1 - MD);


    }

    // Use this for initialization
    void Start()
    {
        compute_hospital_MB_MD();

    }

}
```

Object Actor modified:

{

Attributes added:

setrand //to abilitate randomic function to initial values
toucher //to abilitate the actor to touch other actors or obiects
contamination // variing from 0.0 and 10.0
lack_of_cleaning //varriing from 0,0 to 1,0 can mute if hygiene procedure is performed
infection_limit //from which depends red colour on the map
colours; limit //to abilitate colours on actor

function modified:

Start{

added:

Start Colour handling to actor;

If set rand flag is enabled:

apply contamination start value to various type of actors in random mode

}

function added:

```
MysetColor(contamination )
{

  if (contamination <= 0F)
  {
    Colour =white;
  }

  if (contamination < 4.0F)
  {
    Color = green;
  }
  else if (contamination < infection limit)
  {
    Colour = yellow;
  }

  else //if (contamination >= infection limit)
  {
    Color = red;
  }
}

}
```

Object space modified :

{

Attributes added:

contamination // starting value variing from 0.0 and 10.0
lack_of_env_cleaning = 0.5f; //variing from 0,0 to 1,0

Function modified : // Every second the UpdateContaminationMap function is performed

Start {

InvokeRepeating modified every sec
}

UpdateMapValues
{

Function UpdateContaminationMap call added
}

Function added :

```
        UpdateContaminationMap
   {

      For each actor in zone {
         if (actor is toucher) {
            if (actor contamination > contamination of env) //from actors to
environment

               contamination = contamination +
                 (actor contamination – env contamination) *
                     Pathogen transmission factor *
                     Actor lack of cleaning *
                    }

            if (env contamination > actorcontamination) // fom environment to
actors
               actorsGODetected contamination = actorsGODetected
contamination  +
                 (env contamination – actor contamination) *
                     Pathogen transmission_factor *
                     Lack of env cleaning *
            actor color = update color (contamination)
         }
      } // end of loop
      if (no actor in zone)
                   env contamination =
           env contamination – Pathogen degeneracy
   }


}
```

Object DrawMaps modified :

{

Infection zones mode visualization added :

Function DrawMap modified addin colour depending on infection values

}

Class Activities modified ;

{

Attributes added:

Activity danger //variing from 0 to 1 depending on type of intervention on patient

Touch duration

Function added: // When an actor performs an activity the Touch function is called

```
Touch (actor, otherActor, duration, lack of cleaning)
   {

          Update lack of cleaning adding to environmental factors
          actors and activities components
      MBact = MBother = MB;
      MDact = MDother = MD;

      //compute actors MB_MD_COMPONENTS

      MBact = MBact + actor.GetComponent<Actor>().MB * (1 - MBact);
      MDact = MDact + actor.GetComponent<Actor>().MD * (1 - MDact);
      MBother = MBother + otherActor.GetComponent<Actor>().MB * (1 -
MBother);
      MDother = MDother + otherActor.GetComponent<Actor>().MD * (1 -
MDother);

      MDact = MDact + ((activity_danger >= 0.5f) ? 0.7f : 0.2f) * (1 - MDact);
      MDother = MDother + ((activity_danger >= 0.5f) ? 0.7f : 0.2f) * (1 -
MDother);

      MDact = MDact +
((otherActor.GetComponent<Actor>().lack_of_act_cleaning >= 0.5f) ? 0.7f : 0.2f)
* (1 - MDact);
      MDother = MDother +
((actor.GetComponent<Actor>().lack_of_act_cleaning >= 0.5f) ? 0.7f : 0.2f) * (1 -
MDother);

      //end of compute actors MB_MD_COMPONENTS

Compute actors lack of cleaning
      new_lack_of_act_cleaning_ACT = MBact - MDact;
      new_lack_of_act_cleaning_OTHER = MBother - MDother;
```

```
//end of compute actors lack of cleaning

SetTime( duration);

 extract fractional part of duration;

for (i=0;i< duration ;i++) { // SUM from 1 to N….
   if (actor is toucher )
      if (otherActor contamination > actor contamination)
      {
         Actor contamination = actor contamination +
            (otherActor contamination – actor contamination) *
              Pathogen transmission  factor *
              This activity danger *
              new_lack_of_act_cleaning_OTHER
         update actor colour
      }
      else //if (actor contamination > otherActor contamination)
      {
         otherActor contamination = otherActor contamination +
          (actor contamination – otherActor contamination) *
            Pathogen transmission factor *
            Activity danger *
           new_lack_of_act_cleaning_ACT;
         update otheActor colour
      }
} //end of multiple of unit tyme elaboration
```

```
      //begin fractional part of time elaboration
    if (actor toucher )
      if (otherActor contamination > actor contamination)
    {
      Actor contamination = actor contamination +
         (otherActor contamination – actor contamination) *
            fracpart *
             activity danger *
             Pathogen transmissionfactor *
             new_lack_of_act_cleaning_OTHER;
            update actor colour
    }
    else //if (actor contamination > otherActor contamination)
    {
      otherActor contamination = otherActor contamination +
       (actor contamination – otherActor contamination) *
                        Pathogen transmission factor *
            fracpart *
             activity danger *
            new_lack_of_act_cleaning_ACT;
            update otheActor colour
    }
}
```

CURRICULUM

Con l'obiettivo di affinare la conoscenza del territorio inteso come organismo complesso e supportare i processi decisionali relativi ad esso, la mia attività di ricerca è rivolta all'indagine delle relazioni spaziali fra agenti cognitivi, ambientali e fisici. A tal fine ho sviluppato e applicato metodi di analisi, modellazione e simulazione mirati allo studio della dinamica evoluzione dei sistemi interconnessi afferenti al territorio.

I principali temi da me approfonditi sono:

Metodi di interpretazione attraverso mappe cognitive di percorsi partecipativi atti alla definizione di condivise visioni di sviluppo delle comunità e territori e studio delle implicazioni in termini decisionali;

Approfondimento su cognizione e comportamento spaziale umano, al fine di modellare lo sviluppo spazio-temporale delle interazioni fra agenti e ambiente (spazio pubblico e infrastrutture), comprenderne le regole di relazione e anticiparne le emergenze;

Simulazione computazionale basata su sistemi ad agenti di situazioni e comportamenti ad alto rischio per la salute umana, per la verifica e miglioramento delle funzionalità e design di infrastrutture e servizi per la cittadinanza.

ACKNOWLEDGEMENTS

I deliziosi ringraziamenti hanno resistito per un po' a svelarsi nero su bianco così da posizionarsi l'un dietro l'altro dove sono ora a comporre con un pizzico di nostalgia le ultime pagine di questo mio lavoro che con essi si chiude.

Questa ricerca è stata per me una storia d'amore iniziata con l'idea che tutto è possibile. È stata capace di sorprendermi e l'ho trattata con rispetto e dedizione. Mi ha regalato molto più di quanto mi sarei immaginato e la ringrazio profondamente. Sebbene sia sempre di più il futuro ad occupare i miei pensieri sarà con me ovunque sarò io.

Alla stessa maniera lo saranno i volti e gli insegnamenti di chi ha costellato questo mio percorso, aiutandomi a tracciare la giusta rotta nel mare di idee che illuminavano ogni sera il cielo della conoscenza, al quale mi affacciavo coraggiosamente rimirando a testa in su, sporto sul soglio dell'ingenuo mio sapere.

Ringrazio il Prof. Dino Borri per la disponibilità dimostratami in questi anni nell'accogliere con benevolenza la mia più vasta e libera curiosità e per avermi incoraggiato a incanalarla per ricercare le giuste domande, piuttosto che accontentarmi di risposte comode o altrui.

Ringrazio di cuore il Prof. Domenico Camarda per la serenità e sicurezza che mi ha trasmesso durante il dottorato, che mi hanno permesso di svolgere con fiducia questo percorso anche nei momenti più complicati o di incertezza.

Ringrazio il Prof. Yehuda E. Kalay, Davide Schaumann e il folto gruppo di ricerca presso il Technion di Haifa che mi ha accolto con sincera amicizia e che con grande professionalità e cordialità mi ha aiutato ad integrarmi a pieno nel loro ambiente di ricerca, stimolante e all'avanguardia.

Ringrazio il Prof. Michele Mossa per la operosa e disponibile persistenza nella conduzione del corso di dottorato, il ché ha agevolato enormemente i compiti e le esigenze di noi dottorandi.

Ringrazio la Dott.ssa Rafaschieri, il Dott. Calabrese e l'amica Ida Milella del Policlinico di Bari per essersi resi disponibili ed avermi aiutato ad approfondire in prima linea le caratteristiche salienti del problema da me analizzato.
Ringrazio sentitamente il Prof. Francesco Maddalena e il Prof. Filippo Notarnicola per il tempo e supporto dedicatomi nella ricerca della formalizzazione matematica del fenomeno studiato.
Ringrazio il Prof. Giovanni Ferraro per le salutari escursioni sulle alte vette della complessità ed il Prof. David Vernon per avermi fornito la lente cognitiva alla ricerca del possibile oltre ogni ovvietà.
Ringrazio i colleghi Rossella, Caterina, Giulia e Mauro per i caffè, le opinioni, i consigli e gli amichevoli suggerimenti. Ringrazio gli amici Irene, Alessandro, Claudio e Alfredo, in tanti casi esempi e maestri.
Grazie infine alla mia famiglia tutta per il supporto costante e l'amore grande dimostratomi. Grazie a mia moglie e ai miei figli per donarmi il senso profondo di ogni mio giorno e nuova vita ad ogni suo inizio.