Title page

Title: HYBRID SIMULATION FOR MODELLING HEALTHCARE-ASSOCIATED INFECTIONS: PROMISING BUT CHALLENGING

Running Title: Hybrid simulations for infection control

Authors and Email Addresses

Ms. Le Khanh Ngan Nguyen (MPH): nguyen-le-khanh-ngan@strath.ac.uk

Prof. Susan Howick (Ph.D.): susan.howick@strath.ac.uk

Dr. Itamar Megiddo (Ph.D.): itamar.megiddo@strath.ac.uk

Affiliations

Department of Management Science, Strathclyde Business School, University of Strathclyde, 199 Cathedral Street, Glasgow, G4 0QU, United Kingdom.

Corresponding author

Ms. Le Khanh Ngan Nguyen

Keywords

Healthcare-associated infections, hybrid simulations, simulation modelling

Summary of Main Point

Hybrid simulation for modelling infections is promising as it can help gain deeper insights, assist decision-making at different management levels, and provide a balance between simulation performance and result accuracy, yet challenging to adopt without comprehensive theoretical and technical guidance.

Abstract

Healthcare-Associated Infections (HAIs) are a major public health problem as they pose a serious risk for patients and providers, increasing morbidity, mortality, and length of stay as well as costs to patients and the health system. Prevention and control of HAIs has, therefore, become a priority for most healthcare systems. Systems simulation models have provided insights into the dynamics of HAIs and help to evaluate the effect of infection control interventions. However, as each systems simulation modeling method has strengths and limitations, combining these methods in hybrid models can offer a better tool to gain complementary views on, and deeper insights into, HAIs. Hybrid models can, therefore, assist decision-making at different levels of management, and provide a balance between simulation performance and result accuracy. This paper discusses these benefits in more depth but also highlights some challenges associated with the use of hybrid simulation models for modeling HAIs.

Abbreviations

HAIs	Healthcare-associated infections
DES	Discrete event simulation
SD	System dynamics
ABM	Agent-based modelling
IPC	Infection prevention and control
HCWs	Healthcare workers

Manuscript Body

Introduction

Approaches that attempt to find solutions for preventing and controlling healthcare-associated infections (HAIs), thereby improving quality and cost of care and reducing morbidity and mortality within a healthcare system, need to consider the numerous links to and from different parts of the system (1). Empirical methods associated with linear and reductionist dynamics can mislead how complex adaptive systems such as healthcare systems work (2). The terms linear and reductionist dynamics refer to linear causal thinking and reductionist thinking to explain the dynamic behaviour of a system. Linear causal thinking interprets the behaviour of the system in terms of a unidirectional unfolding of cause and effect; the same cause will always lead to the same effect with a constant relationship of proportionality (3). Reductionist thinking views a system as a machine that could be disassembled into component parts and the behaviour of the system could be explained through the observation and analyses of the behaviour of the individual parts (4, 5). Complex systems are characterized by the interconnectedness and feedback loops between components leading to emergent behaviours which are absent in the individual parts. So, their behaviours cannot be completely explained and anticipated simply by thinking of separate causes and effects, and studying their components individually (4). Simulation modelling could help overcome these limitations.

Systems simulation has made proven impact in the healthcare environment (6, 7). Three key systems simulation modeling methods, each with its own strengths, have been used in healthcare: system dynamics (SD), agent-based modeling (ABM), and discrete-event simulation (DES). These methods can capture the dynamics between patients, pathogens, and the environment. Therefore, they are useful for studying complex systems such as healthcare systems and improving understanding of epidemiological patterns of HAIs. Systems simulation methods can be utilized to evaluate the effectiveness and cost-effectiveness of different infection prevention and control (IPC) interventions that are unsafe, unethical, and/or cost- and time-consuming to test in the real world. The generated prediction can inform decisions on IPC policy and funding, guide IPC practice, and maximize the use of scarce resources.

SD is a top-down continuous simulation modeling method that is ordinarily deterministic and characterizes the structure of dynamic and complex systems, using stocks, flows, feedback and delays within such systems to explore how the system structure determines the system behavior (Table 1) (8). This method is useful for macro-level modeling to investigate the long-term behavior of a system containing large and relatively homogenous patient populations that can be aggregated into compartments. By contrast, ABM is a bottom-up, ordinarily stochastic, simulation method for modeling dynamic and adaptive systems with autonomous entities called agents and their environment (9). This method is well-suited for capturing the spatial detail and microstructure of an intricate healthcare facility, the complexity and heterogeneity of contact networks within a healthcare setting and the stochasticity of interactions within such networks; all are elements which SD ignores. DES is a process-based stochastic simulation method used for modeling the operation of a system as a discrete sequence of activities and events in time (10). Similar to ABM, DES enables incorporation of detailed patient attributes and is suitable for modeling the procedure of activities that patients need to progress through. However, DES models cannot simulate transmission of infections via social interactions among individuals as in ABMs. In DES, transmissions are modelled as events where individuals’ infection status attribute is changed. How frequent transmission events occur could be defined by an overall rate/probability or individually specified based on other attributes such as age and health status. Many studies have compared different aspects of these simulation methods such as assumptions, inputs, outputs, data dependency, advantages and disadvantages (11-16).

The systems research community has found that combining systems simulation methods in hybrid simulation models (i.e., combining the methodological strengths of at least two among SD, DES, and ABM) can provide richer insights, answer questions that are difficult to answer otherwise, and improve the balance between simulation efficiency and accuracy, and these benefits will be useful for modelling HAIs (17-19). For example, the combination of different methods of systems simulation will be particularly useful for understanding the impact of IPC interventions in one part of the system on other components of that system or on the system as a whole because each method considers problems from a different perspective. Additionally, hybrid simulation modeling can help improve the decision-makers model acceptance by enabling modelers to incorporate greater details of particular model components. For example, modelers can integrate an ABM component into an SD model that represents the transmission of HAIs in a hospital to provide greater details on the transmission occurring in a ward of the hospital to address credibility concerns. Increasing the model's credibility leads to the increasing acceptance and adoption of the model by decision-makers in HAIs.

Despite hybrid system modeling's significant potential, it is limited in research developing and applying HAI models. A recent systematic review indicates that healthcare is the largest area of application for hybrid simulation, though only 31 papers representing 22% of total publications in hybrid simulation were found (7). Furthermore, another review merely identified that only nine out of 68 publications modelling HAIs use hybrid simulation; the others use single simulation methods (20). The scant application of this method implies that the systems simulation community and researchers in infection control should work together to increase awareness of hybrid simulations' potential benefits. Although a few recent papers have been published about the need to consider health systems using systems modelling (21, 22) none describe the advantages of combining methods and none consider HAIs. This paper provided discussions to address this gap.

A Method to Promote Richer Insights beyond Single Simulation Approach

Combining the strengths of different simulation modeling methods has the capability for delivering richer insights for specific questions than those based on one simulation method only. As the three types of systems simulation modelling methods, namely SD, DES, and ABM, have different benefits, limitations, strengths, and weaknesses, combining or mixing them potentially overcomes the drawbacks faced by using a single approach and/or provides more plausible explanations, and therefore richer insights, of a problem compared to those offered by a single approach.

The hybrid model in Barnes et al. (2011) provides an example that demonstrates how a hybrid method can generate richer insights compared to using a single simulation method. This study adopted a hybrid SD-ABM model to investigate the impacts of transferring patients between different healthcare facilities upon the prevalence of HAIs at each facility (23). Each healthcare facility was modeled as an agent in a network of various facilities with a predefined configuration of directed links representing patient movement from one facility to another at a specific rate. An SD model embedded within each healthcare facility agent represents the transmission dynamics within the facility. Like traditional epidemiological compartment models (e.g. Susceptible-Infected-Recovered models) (24, 25), stocks of the SD model represent corresponding susceptible patients, persistently and transiently asymptomatic carriers. Proportions of patients in different infection states constitute a unique state that characterizes each facility agent. The hybrid model helps understand the impact of the heterogeneity and stochasticity of different configurations of patient transfer on the transmission of HAIs within each facility. Reshaping this model to use ABM alone requires the researchers to remove the SD component within each agent health facility or replace this component with an ABM which models each facility in the network at an individual entity level. The former approach does not capture the dynamics of HAI transmission within each facility and thus the impact of inter-facility connections upon this intra-facility transmission dynamics. The latter approach will obfuscate this impact since both the interconnectivity between facilities and the heterogeneity among individuals in each facility would concurrently influence the transmission of HAIs in this approach. It is important to separate these effects to identify whether heterogeneity/interactions within facilities or heterogeneity/interactions across facilities primarily cause the spread of HAIs. This can help inform whether interventions such as active screening and decolonization of all transferred patients are required. Another way to reshape this model is to use SD alone. However, this would provide poorer insights on the heterogeneity and stochasticity in the interconnections between facilities and, thus, their impact on the transmission of HAIs within each facility. There are other examples of hybrid models taking similar approaches in literature (26-28).

A Method to Support Decision-Makers at Different Levels of Management

Another benefit of hybrid simulation modelling is that it permits healthcare decision-makers and policy-makers to study a problem at different levels of abstraction. SD often deals with high abstraction levels, whereas DES is used for low to middle abstraction levels and ABM can be applied across all levels but is preferably used for low levels (29). The modeler will find SD useful to quickly evaluate an IPC program implemented in a large population and provide an integrated and holistic view of feedback systems that can affect outcomes of the program years or decades later without knowing how processes take place at the micro-level within each healthcare facility. Health policymakers at a high level would find this type of simulation modeling helpful to inform their decisions at a strategic-level decision that influence a large-sized population in the long run. By contrast, ABM is well-suited for evaluating the operational level of the program. It can be used when agents, their characteristics, behavioral rules, and interactions are well understood but the emergent and stochastic behaviors of the system are unknown. ABM can also be used to explore and understand unknown characteristics, behaviors, and interactions of individuals at the operational level when the system outcomes for particular scenarios are known.

A hybrid simulation model that combines an SD and ABM approach can be used to evaluate an IPC intervention such as hand hygiene in hospitals at both strategic and operational levels.

Modelers can develop SD and ABM models parallelly which provide two representations of the same system, offering complementary insights into the system. The SD model can generate a general view of the long-term impact of hand hygiene upon the dissemination of HAIs. This would be of interest of decision makers at a high level who are responsible for developing general guidelines or standards for infection control in hospitals. However, ABM is the most appropriate method to capture the spatial intricacies of a hospital ward. It accounts for the stochasticity of transmission events due to individual variations in characteristics (e.g. profile of healthcare workers, daily schedule and patient allocation) and the time and space heterogeneity of their behaviours (e.g. hand hygiene compliance and efficacy) and interactions. Additionally, ABM allows adaptive behaviours of individual healthcare workers to be incorporated such as increasing hand hygiene compliance when performing high-risk medical procedures and providing care for infected patients. The flexibility to explicitly model all of these factors simultaneously also makes ABM more appropriate to address questions for which they are all important. Individual heterogeneity and the interactions of these factors affects the transmission dynamics (14); for example, it can cause super-spreading events in which cross-transmission to a large number of patients is mediated via a single HCW (30). Identifying super-spreaders can help inform the target group for interventions that aim to improve hand hygiene compliance at the operational level.

Brailsford et al. (2010) argued that although using one simulation method is possible to represent problems at a macro- and micro-level at the same time, they described this approach as “a case of hammering in a screw” because it forces modelers to use a simulation method that may not be suitable for all components of the problem (31). Morgan et al. (2011) also agreed that it may not possible to develop a model using one method to obtain all of the intended objectives without the need for additional assumptions which risks making the model less representative of reality (32).

A Method to Balance Simulation Performance and Result Accuracy

Hybrid simulation modelling is helpful for handling trade-offs between simulation performance and the accuracy of results, which is the degree to which the model results/predictions conform to the actual outcomes (macro-level predictions), and avoids the need for an excessive amount of input data (33). The accuracy of results in this case could be measured using methods such as hypothesis statistical testing, mean absolute scaled errors, root mean square error, and mean absolute error (34). As deterministic models yield a single outcome for each parameter set while stochastic models produce a distribution of possible outcomes, literature recommends to average a sufficient number of simulations to assess the accuracy of stochastic models' results (35). In addition to the single-valued forecast, probabilistic forecasting which aims to quantify the inherent uncertainty in predicting the future in stochastic models can be assessed by methods such as marginal calibration plots, probability integral transform histograms, sharpness diagrams and proper scoring rules (36, 37).

Running SD models is extremely quick because they are deterministic and do not need several replications to gain insights into a system's behavior. Also, the data requirements of SD models are generally less than those of DES models or ABMs as they are typically used at a higher and more aggregated level. However, Forrester (1960), who first introduced SD, contended that SD models are "learning laboratories" (38), and later research even argued that outcomes produced by SD models are seldom greater than 40% accurate (39). DES and ABM are capable of modeling a problem in much more detail than SD, providing the flexibility for a closer representation of reality. However, they require a vast amount of data and several simulations to generate reliable results, which is time-consuming to collect and to run. Hybrid simulation modelling offers a top-down approach where researchers can model a problem at a macro-level using SD and then zoom in on certain aspects of the problem that require microscopic understanding, using DES or ABM. Modelers often try to keep their models as simple as possible whilst seeking to still produce reasonably accurate results. An abstract SD model that represents a system at a macro-level, where causal relationships and feedback effects are revealed, is often faster to run and requires fewer data inputs compared with a micro-level DES or ABM model that represents the spatial details and microstructure of the same system. Hybrid simulation modelling can be used to solve the issue of balancing the simulation performance and the accuracy of results.

Mustafee et al. (2017) used the study of Djanatliev (2015) as an example to demonstrate this benefit of hybrid simulation modelling methods (33). In this study, three models that represent the same problem in healthcare were developed using a single method of SD and ABM and a hybrid simulation modelling method where SD and ABM were combined. The first model had been developed using only SD, and it took a few seconds for this model to finish running, even for nationwide population size. By contrast simulations of the second model, using ABM, took 1.5 hours to run and the model comprising more than 20,000 agents was not able to complete. However, the author stated that the ABM produced much more accurate results because of a more detailed presentation of the problem. They then developed a hybrid simulation model by using ABM to model and represent specific parts of the SD model whose greater details were of interest to the problem being considered. Agents with similar properties that had been created in the ABM were also aggregated into one "super-agent". This hybrid simulation model generated results comparable to those of the ABM in an acceptable runtime. When weighing result accuracy and model simplicity, it is important to emphasize that the level of accuracy is dependent upon the research problems and objectives. For example, estimating costs of an IPC intervention for resource planning and allocation would require a higher level of result accuracy than evaluating the clinical effectiveness of the intervention for directing further research.

The ecology dynamic hybrid SD-AB model in Wallentin and Neuwirth (40) is another example of the use of hybrid simulation that optimizes the trade-off between the predictive and computational modeling performance. The model dynamically alters among different SD-ABM configurations where, for instance, one entity may be represented by stocks and another entity is represented by agents. The switching point is informed by a threshold determined by the size of the population of interest. This results in heterogeneity and spatial networks among individuals of each entity type having more or less impact on the model's outcomes. A similar approach is adopted in Bobashev and his colleagues' epidemiological modelling study in which the model begins as an ABM when the number of infected people is small and individual variation is critical, and switches to a SD model after the infected population becomes large enough to apply the population-averaged approach (19).

Challenges in Developing and Applying a Hybrid Simulation Model

Developing and applying a hybrid simulation model is a challenging task. First, although there have been some conceptual publications and guidelines on the development of frameworks for combining different simulation methods (33, 41-43), these works studied hybrid simulation modeling only at a high level and did not provide overarching methodological frameworks that explicitly guide and specify how modelers can apply them to develop their model. Indeed, there is not yet any evidence that these frameworks are comprehensive, useful and practical enough to apply when building a hybrid simulation model. Zulkepli and Eldabi (2016) also asserted that most attempts to hybridize different simulation modeling methods have been "ad hoc and pragmatic with no clear methodology" (44). Additionally, although a few studies (i.e., none of these is about modeling in HAIs or healthcare) reported the validation and verification for single-method sub-models in a hybrid simulation model using existing standard approaches for single-method models (7), more comprehensive propositions to validate and verify the overarching hybrid models are needed. These barriers make it difficult and time-consuming to develop, verify and validate a hybrid simulation model which in turn prevents this approach's wider adoption.

Second, although the selection of a simulation modelling method should be objective-driven, the best modelling approach is often ambiguous and modeler expertise, experience, and preference may bias the decision on when the use of a hybrid simulation model is needed and beneficial.

Thirdly, the reasons for choosing a specific simulation modeling approach are inseparable from the intention of solving a problem more efficiently requiring less time, effort and cost inputs. The research community has yet to conclusively determine when using a hybrid simulation model offers a quicker, easier and cheaper approach to solve a complex problem than using a single simulation modeling method (33). The development of multi-method simulation modeling tools, which is more user-friendly to modellers and offers a free version for personal learning, can counteract the resistance to use hybrid modeling and help reduce time and effort inputs. Further studies which explore when to use which simulation modeling method (i.e., single or hybrid simulation) in modeling HAIs can guide modelers to choose appropriate methods. Encouraging and/or requiring modelers to rationalize the simulation method used in published works can help prevent them from selecting a particular method just because they feel comfortable with it. This approach also leads to the availability of case studies of hybrid models in HAIs which offer an explicit clarification to justify the use of hybrid simulation.

Finally, it can be argued that the need for hybrid simulation models potentially initiates from attempts to model a problem as close to reality as possible to improve the prediction capability of the models. However, this purpose may be achieved at the tradeoff of their generalizability, the degree that they can be validated and verified, and without the guarantee they will capture more detail that results in more insights (18). The development of more comprehensive validation and verification approaches, along with promoting the collection of relevant clinical data in HAIs for model inputs and validation, can help address this challenge. Addressing these challenges will facilitate the process of developing valid and credible hybrid models, and therefore, improve the acceptance and adoption of the models among healthcare professionals and policymakers whose decisions will drive impacts on health outcomes such as improvements in HAIs.

Conclusions

Like any other research method, hybrid simulation modelling has both benefits and drawbacks. It can generate richer insights compared with a standalone simulation method for specific questions, allow for modeling a system at different abstraction levels which supports decision-making at different levels of management, and balance simulation performance and result accuracy. Thus, its application in modeling HAIs can improve the understanding of HAIs as well as aid strategy and planning for infection prevention and control. Additionally, it is increasingly recognized that when finding solutions to healthcare problems it is important to consider the system as a whole, rather than focus on individual parts. Therefore, hybrid simulation is promising and potentially beneficial for capturing the links and interdependencies between different parts within the system. However, applying hybrid simulation in HAIs and other healthcare problems is complex and challenging due to the unavailability of comprehensive guidance and technical obstacles. Deciding when and why this method should be chosen for a particular question and judging whether it is worth the challenges it creates will be a subjective decision, depending on the researcher's objective and expectation. Future research developing a comprehensive guideline for building hybrid simulation models, further collaborations between modelers with expertise in different simulation methods, and innovation in software packages can help overcome its drawbacks and facilitate its application.

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Conflict of Interest

All authors declare no potential conflict of interest

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Table 1: Overview of the assumptions, inputs, outputs, and data dependency of system dynamics, agent-based models, and discrete-event simulation (Adapted from Table 1 in Nguyen LKN, Megiddo I, Howick S. Simulation models for transmission of health care-associated infection: A systematic review. American journal of infection control. 2020;48(7):810-21.)

Feature	**System Dynamics**	**Agent-Based Models**	**Discrete Event Simulation**
Similar Models	Compartment model (mathematical epidemiology and ecology), equation-based modelling, macrosimulation	Microsimulation, individual-based model, multi-agent modelling, cellular automata	N/A
Assumptions	Entities within each stock are mixed homogeneously	Entities can be heterogeneous and autonomous decision-makers, who can learn and adapt to their environment; entities can interact with each other	Entities are passive and do not interact with one another or learn from or adapt to the environment, but they can be heterogeneous
Stochasticity	Ordinarily deterministic but stochasticity could be incorporated.	Typically stochastic but could be deterministic	Stochastic
Inputs	Stock and feedback and accumulation structures; initial levels of stock/sub-	Agent types and definitions in terms of their characteristics,	Structure of queuing network; types of entities and resources

	populations aggregated by particular characteristics; rates, which characterize the inflows and outflows of a stock.	possible actions and rules of behavior; initial number of agents; environment characteristics and rules; definition of agent-agent (eg, network), agent-self, and agent-environment interactions.	(eg, healthcare-workers, hospital beds and equipment), and their characteristics; time between entity arrivals, and number of entities per arrival; service time or delays.
Outputs	Deterministic time series of population/stock levels and flows and insight into behavior of the system.	Stochastic (typically) time-series of population and sub-population outputs such as number of entities in a specific state, frequency of actions, and frequency of events as well as state of the environment; insights into the system emergence behavior; tracking individual entities.	Stochastic time series of, and insight into, operational performance outputs such as queue lengths, utilization of resources, and frequency of events; tracking of individual entities.
Data dependency	Objective data at aggregate levels supplemented by judgmental, subjective	Depending on simulation aims, these methods can be highly data-dependent because they model entities at the individual level and try to	

	data, and informational links	describe variations in their characteristics and other inputs.	
Typical use cases	Model transmission dynamics of infections and evaluate impact of strategic interventions at global/national/regional level (e.g. public health policies) Provide a strategic overview of the system, accounting for competing demands and feedback effects (e.g. workforce planning for health and social care sector at a national level to cope with future epidemics)	Model transmission dynamics of infections and evaluate impact of interventions at organizational/ individual level affected by social and spatial networks, demographic and health characteristics (e.g., age and underlying conditions), and behaviours (e.g., compliance to hand washing, self-isolation practice) Determine how interventions (e.g. screening/testing and vaccination) can be tailored/targeted to specific groups of individuals at high-risks due to their characteristics (e.g. elderly, individuals with comorbidity),	Model capacity planning and allocation of resources (e.g. staff, hospital beds, medical equipment) at an operational level under various intervention strategies (e.g. self-isolation/quarantine strategies affect staffing and workflows in a hospital, required staffing level to maintain quality care and services in a care home when social distancing and isolation are implemented) Determine system reconfiguration, and care and treatment pathways that reduce waiting times, disruption of services, impact on other patients, and pressure on the system, and optimize use of available resources (e.g. earlier discharges

	contact patterns (e.g. bank/agency staff working at multiple care homes who can spread the infection) and/or behaviours (e.g. ancillary workers with low compliance to hand hygiene)	of patients, adjourning scheduled operations, changes in hospital flows and transfers under the pandemic conditions)