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ADVANCING SIMULATION IN HEALTHCARE AND LIFE SCIENCES: A PANEL DISCUSSION OF FUTURE RESEARCH DIRECTIONS

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ABSTRACT

This paper is motivated by a panel organized by the Healthcare and Life Sciences track at the 2025 Winter Simulation Conference (WSC). We summarize the panelists' perspectives and reflect on current trends and future research directions for simulation applications in healthcare and life sciences. We begin with a brief review of key methodologies and application trends from the past decade of WSC proceedings. We then present expert insights from a range of application areas, including (bio)pharmaceutical manufacturing, hospital operations, public health and epidemiology, and modeling human behavior. The panelists provide diverse perspectives from academia and industry, and highlight emerging challenges, opportunities, and future research directions to advance simulation in healthcare and life sciences.

1 INTRODUCTION

Simulation methods are widely used in healthcare and life sciences, with applications ranging from pharmaceutical manufacturing, hospital operations management, infectious disease modeling, behavioral models in health and humanitarian systems, among others. One of the key benefits of using simulation is the ability to design, analyze, and optimize complex systems that are otherwise too costly, risky, or impractical to evaluate through real-world experimentation. Simulation methods provide a variety of tools and techniques for evaluating different scenarios, managing uncertainty, and informing policy makers and practitioners. As the healthcare industry becomes increasingly data rich, simulation will continue to help develop resilient, efficient, and innovative healthcare solutions.

This paper contributes to the ongoing dialogue about the future of simulation in healthcare and life sciences (HLS) and is motivated by a panel organized at the 2025 Winter Simulation Conference (WSC). This initiative also aligns with the broader theme of the 2025 WSC: "Looking to the Future! Simulation 2050 and Beyond". In this paper, we summarize the key perspectives of the panelists. We reflect on the evolution of simulation research and practice in healthcare and life sciences, identify emerging challenges and opportunities, and outline a vision for future research directions. Based on the diverse perspectives of the invited experts, the panel spans a wide range of application domains: (1) (bio)pharmaceutical manufacturing and supply chains (Tugce Martagan), (2) hospital operations (Anup C. Mokashi), (3) the role of human behavior in medicine (Maria Mayorga), (4) disease simulation and epidemic prediction (Chaitra Gopalappa). These experts provide complementary views in academic, industry, and healthcare policy-making settings. Together, they reflect on the role of simulation research in addressing new scientific challenges and stakeholder needs.

While the specific interests of the WSC community continue to evolve in response to emerging scientific and societal needs, healthcare has long been an important part of the WSC. The online archive of WSC proceedings dates back to 1968, and "health services" appeared as a recognized topic/track as early as

1969.[1] At the 2025 WSC proceedings, the HLS track received the fourth highest number of contributed paper submissions out of 28 tracks, underscoring its continued relevance and growth within the simulation community. In this paper, we therefore begin with a brief review of the track's past decade, analyzing key methodologies and application areas based on WSC proceedings from the past 10 years (Section 2). We then present expert perspectives on current trends and future research directions in simulation for healthcare and life sciences (Section 3). Finally, we reflect on the skills and interdisciplinary collaborations needed to realize the full potential of simulation (Section 4).

2 A REFLECTION ON THE HEALTHCARE AND LIFE SCIENCES TRACK

We considered papers published in the last 10 years in our analysis of the evolution of the HLS track at the WSC. As part of this, we first classified every paper published in the track from 2015 onward until (including) 2024 as belonging to the following important subfields of healthcare modeling:

- Healthcare delivery and healthcare facility operations (HDFO): simulation studies that considered operational aspects of healthcare systems and individual facilities.
- Public health and epidemiology (PHE): simulation studies that considered public health and/or epidemiological impacts of healthcare interventions.
- Regulatory aspects and policy: studies that use simulation to model and optimize healthcare policy and inform formulation of healthcare regulation.
- Other areas.

Results from the first-level classification are provided in Table 1 below.

Table 1: The Healthcare and Life Sciences track at the Winter Simulation Conference, 2015 - 2024.

Year	Total number	Public health & epidemi-ology	Healthcare delivery & facility operations	Regulatory aspects & policy	Other areas
2015	25	4	13	3	8
2016	25	2	18	5	2
2017	24	3	16	2	3
2018	21	2	12	3	4
2019	24	6	14	2	7
2020	21	2	16	0	5
2021	19	2	8	1	7
2022	12	2	1	0	6
2023	30	15	12	3	8
2024	25	13	10	2	5

Papers could be classified as belonging to more than one category: for example, a paper that proposed a new method to extract clinical pathways of patients in a hospital department for use in discrete-event simulations of the department in question could be classified as belonging to the HDFO category as well as the "Other areas" category as it contributed more broadly to healthcare simulation methodology. The distribution of papers by subfield across the decade is depicted in Figure 1.

The HLS track has featured an average of approximately 23 papers each year, with the smallest numbers observed during 2020-22, coinciding with the COVID-19 pandemic. Approximately half were in the HDFO category, followed by the PHE (22%) category. Nearly 20% were classified as belonging to 'other' areas;

[1] https://informs-sim.org/

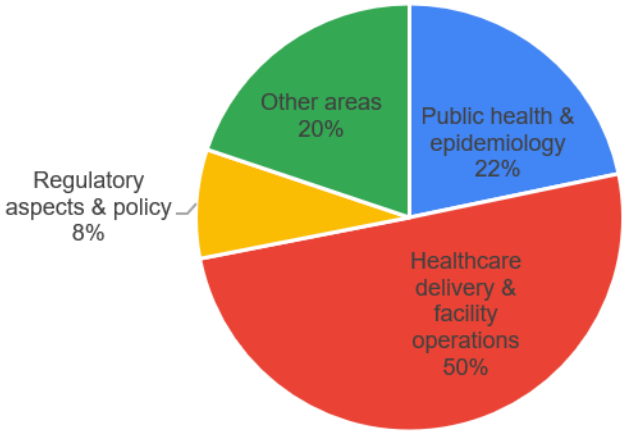

Figure 1: Distribution of healthcare & life sciences track papers across 2015-2024.

however, this included papers classified as belonging to one of the three 'named' categories as well. For example, a paper that proposed a new method for calibrating agent-based simulation models of disease transmission, used to estimate epidemiological and public health impact of interventions designed to combat the disease in question, could be considered as a more general 'healthcare simulation methodology' paper as well as a paper relevant to the public health and epidemiology subfield (Das et al. 2021). There were papers that resisted classification into any of the named categories as well, such as those concerned with modeling the spread of the SARS-CoV2 infection in the human lung (Ayadi et al. 2023).

We begin with the regulatory aspects & policy subfield. While there are a relatively small number of simulation studies over the past decade involving regulatory policy, the diversity of policy applications and methodologies employed is substantial. Policy studies range from cost-effectiveness analyses of screening and treatment strategies for hepatitis C birth-cohorts and of treatment options for type 2 diabetes, to the use of simulation to assess the impact of genetic testing in optimal cholesterol treatment plans and simulation frameworks to model and optimize the clinical trajectories of patients with sepsis in response to therapeutic interventions. Methodologies range from agent-based and discrete-event simulation to individual-level microsimulations and systems dynamics models. The small number of studies combined with their wide variety indicates that this is a growing area of research, and has potential for the development of unified simulation frameworks for specific classes of policy studies. An example is the use of simulation for informing organ transplantation policy, which is a relatively mature area of study, and has seen the development of broadly applicable reusable simulations such as LSAM (Blandon et al. 2024) and LivSim (Kilambi et al. 2018) for liver transplantation.

Between 2015-2019, the HLS track featured an average of approximately four papers each year in the PHE area. Infectious disease transmission dynamics models developed to assess the impact of interventions on population-level outcomes formed the majority of these papers. The diseases studied included tuberculosis, hepatitis C, HIV-AIDS, the human papillomavirus, and the Middle East respiratory syndrome, among others, and the geographies under consideration ranged from the United States, Spain and Colombia to South Korea and India. Agent-based models and differential equation based compartmental and system dynamics models were the key methodologies used in these studies. In a few cases, hybrid models combining one or more methods, such as agent-based and system dynamics models, were also developed. Studies involving noncommunicable conditions were also considered, including the opioid and heroin co-epidemic, urban mental health challenges and, among others, a study assessing the benefits of providing respite care for caregivers of chronically ill patients.

The number of papers in this subfield increased to an average of approximately eight each year between 2020 and 2024, likely due to the increased interest in population-level modeling during and after the COVID-19 pandemic. Interestingly, while the number of papers increased substantially, studies involving COVID-19 did not dominate, and papers considering a wide variety of health conditions in addition to COVID-19 were featured. However, the proportion of studies in this area reporting the use of agent-based and individual-based models has decreased from 66% between 2015 and 2019 to 35% between 2020 and 2024. This is primarily because as the number of PHE studies have increased, the types of problems being considered have also become more diverse, employing more methodologies than just agent-based and individual-based models. Examples of such studies include (a) a queuing-based network model, with individual outcome prediction models, to assess the impact of policies designed to combat recidivism among those released from correctional facilities, and (b) a social simulation developed to identify cooperative strategies to address health-related challenges created due to climate change.

The HDFO area contains nearly half of all papers in the track, and papers in this area can be further divided - in multiple ways - into smaller categories. For example, papers could classified into those dealing with operations within a single facility (such as emergency department [ED] or intensive care unit [ICU] simulations), or into those dealing with a healthcare system as a whole (such as organ transplantation systems or a network of primary and secondary care facilities in a region). In order to provide more insight regarding the types of papers within this field, we further classified papers in the HDFO category into one or more of three subcategories: (a) studies considering operations within a single facility; (b) studies considering emergency medical services (typically involving the ED of a hospital or ambulance services) or the ICU; and (c) those involving a health system as a whole. We performed this next-level classification for papers featured at the WSC between 2020 and 2024, and the results are summarized in Table 2. Note that the proportions in the table are calculated with respect to the total number of papers in the HDFO category, and because each paper could be classified as belonging to more than one subcategory, the sum of proportions in a row may exceed 100%.

Table 2: Types of healthcare delivery and facility operations studies featured at the Winter Simulation Conference between 2020 and 2024.

Year	Single facility studies	System-wide studies	EMS / ICU studies
2020	78%	39%	22%
2021	33%	44%	44%
2022	33%	25%	50%
2023	42%	42%	42%
2024	60%	30%	30%
Overall	52%	36%	36%

First, discrete-event simulation was the methodology that, as expected, was used the most in this area. Single facility studies, for the most part, appear to form the majority of HDFO papers in the past five years. A wide variety of facilities and units within hospitals are studied, ranging from primary care clinics to the operating theater and the ICU and ED. System-wide studies include those that consider networks of facilities (such as primary care clinics) in smaller regions such as a county or a district as well as deceased donor organ allocation and transplantation systems that may span an entire nation. Unsurprisingly, there is a preponderance of studies concerned with ED and ICU operations. These include studies that examine common queuing-theoretic assumptions made as part of ED operations modeling studies as well as studies that design ED operational policies that are resilient to surges in demand during natural disasters. Studies that have a methodological bent - for example, studies that consider data synchronization approaches for hybrid simulation models that use both historical as well as real-time data to predict wait times in networks of EDs in a region - also have been featured in this space.

Some key avenues of future research in this space include the development of approaches for the faster generation of simulation models of healthcare facility networks in a region to support operational planning during health crises, and improving the computational efficiency of hybrid simulation models developed to model operations in large healthcare systems to facilitate the use of optimization methods and arrive at optimal operational policy.

A wide variety of studies were grouped into the 'Other areas' category. These included, as mentioned earlier, a few studies from each of the three named categories that had contributions beyond only the named caetgory in question. From the HDFO category, the majority of such papers also contributed to healthcare simulation methodology: an example is a study that utilized a combined simulation plus machine approach for predicting whether patients on the waitlist for undergoing surgery at a large Indian hospital would be admitted before a clinically meaningful time duration. This study presented a general methodology - going beyond neurosurgery operations - involving the use of DESs of complex healthcare queuing systems to generate training data for ML models that can then generate real-time delay predictions for queued patients. Other types of studies in this area involved screening and/or treatment planning for infectious as well as noncommunicable diseases, simulations in the biological and life sciences area, and studies using simulation to support clinical trial design for new pharmaceutical drugs.

3 THE PANEL'S VISION FOR FUTURE RESEARCH

This section provides a brief overview of the panel's vision for current and future research directions at the intersection of simulation, healthcare, and the life sciences. This section focuses on a few selected application areas based on the expertise of the panelists, including (bio)pharmaceutical manufacturing and supply chains (Section 3.1), hospital operations (Section 3.2), the role of human behavior in disease models (Section 3.3), disease simulation (Section 3.4) and outbreak prediction (Section 3.5).

3.1 (Bio)pharmaceutical Manufacturing and Supply Chains

Simulation is widely used to design, analyze, and improve (bio)pharmaceutical manufacturing and supply chains. With increasing demand and competition, the competitive advantage of the (bio)pharmaceutical industry is currently shifting towards more sustainable, robust, rapid and cost-effective production and delivery of medicines (Martagan et al. 2024). Therefore, the simulation community will continue to play a key role in helping the industry manage the increasing complexity of (bio)pharmaceutical manufacturing, supply chains, and related regulatory issues.

Current industry challenges. The manufacturing of (bio)pharmaceutical products is inherently complex and poses several challenges to the industry. For example, production processes involve a series of multiple interdependent steps, and each production step is often subject to stringent regulatory requirements (Martagan et al. 2023). The waiting times between production steps can be tightly constrained, as the work in progress can degrade (sometimes within only a few hours or days) while waiting in the production system. Furthermore, (bio)pharmaceutical manufacturing operations face various process uncertainties, such as contamination, batch failure, and yield uncertainty. Stringent regulatory requirements on quality, safety, data collection and process control can further complicate operational decisions. With increasing demand and competition, end-to-end (bio)pharmaceutical supply chains are also under increasing pressure to reduce delivery lead times and increase robustness. The COVID-19 pandemic has underscored the critical role of resilient and reliable supply chains to ensure timely access to medicines. To address these industry needs and challenges, simulation methodologies provide powerful and flexible tools for decision-making, as demonstrated by several successful implementations and industry case studies, e.g., Martagan et al. (2019), Xie et al. (2019), Martagan et al. (2023).

Future research directions. For ease of exposition and brevity, we categorize future research directions into three main areas: process analytics, factory dynamics, and end-to-end supply chains.

To support the industry's initiatives on process analytics, new simulation models and methods can help improve our fundamental understanding of the underlying chemical and biological processes, allowing for better prediction and control of these complex production processes. For example, simulation models of fermentation or purification processes can help identify the critical process parameters and their complex interactions with critical quality attributes. Hybrid models that combine kinetic models from life sciences with process data and machine learning techniques can help streamline real-time process monitoring and control algorithms. In general, the systematic application of simulation models and methods can help improve the transparency and explainability of the models for these complex production processes.

Future simulation research can support a variety of operational and strategic decisions at the factory level, including the adoption of new technologies, process optimization, and production planning to reduce costs and lead times. For example, digital twins can support new technology adoption decisions for emerging technologies such as continuous pharmaceutical manufacturing and real-time release testing (Martagan et al. 2024). When integrated with cost-benefit analyses and what-if scenario evaluations, digital twins offer powerful tools to help the industry assess risks and strategically navigate the implementation of new technologies. Future simulation research can also guide data collection efforts by identifying critical data gaps, prioritizing data collection efforts (e.g., where to place sensors and what data to collect), and developing adaptive control strategies based on real-time data. In the context of production planning and control, future research can help integrate real-time process data from advanced sensors (e.g., Raman probes) into predictive models, optimal control algorithms, and digital twins. In particular, digital twins can help synthesize historical and real-time data to support optimal design and control, as detailed in Shen et al. (2021). Simulation methodologies can also facilitate the integration of diverse models operating at different levels of the production system. For example, chemical and biological process models, which are used to estimate batch quality and yield, can be combined with factory-level planning and scheduling decisions to reduce costs and lead times.

In the context of end-to-end (bio)pharmaceutical supply chains, digital twins will continue to play a critical role in enhancing the robustness and resilience of patient access to medicines. This is particularly relevant for the growing field of personalized medicine, which presents new opportunities and challenges for simulation-based modeling and analysis. Supply chains for personalized therapies (such as gene and cell therapies) are often highly specialized, time sensitive, and patient-specific. Unlike traditional pharmaceutical supply chains, which typically follow a linear flow of standardized products from manufacturer to patient, personalized medicine supply chains involve complex, bidirectional flows of information and materials: tissue samples (such as blood, cells, or bone) are first collected from the patient, then used to develop individualized treatments, and finally returned to the same patient. These complex and patient-specific supply chains require dynamic coordination between multiple stakeholders. Adjusting to the fast pace of personalized medicine supply chains will require a fundamental re-thinking of current industry practices. Digital twins and other simulation-based tools will be essential to enable the industry to design, monitor, and optimize these unique supply chains.

In the future, simulation models can play a more proactive role in facilitating communication and collaboration between regulators and industry stakeholders. For example, simulation can support model validation and maintenance by aligning data standards, control strategies, and decision support tools. Simulation models can help increase transparency and accelerate regulatory alignment. Simulation models can also inform what data should be collected at what frequency to maintain stringent safety and quality standards. New simulation research can support optimal timing and frequency of interactions between regulators and manufacturers at different stages of the drug lifecycle. In addition, regulators themselves can use advanced simulation methods to streamline compliance, monitoring, and standardization globally. New research can also help harmonize international guidelines for the use of artificial intelligence in drug manufacturing and delivery.

3.2 Hospital Operations

Simulation models have been widely used as operational decision-support tools in healthcare systems for several decades. With advancements in simulation software, development of dedicated operations research/ data science teams in healthcare institutions, and improved access, standardization, and quality of healthcare data, simulation will continue to be leveraged (either on a standalone basis, or in combination with other operations research/machine learning techniques) to deliver meaningful, actionable insights pertaining to increasingly complex hospital systems.

Current challenges faced by healthcare organizations: Some of the key financial challenges faced by hospital systems in the United States are outlined in American Hospital Association (2025). Increasing labor costs to avoid high turnover, and high year-over-year expense growth rates are limiting the ability for hospitals to reinvest in infrastructure upgrades and expand their outreach to under-served populations within their catchment areas. Changes in demographics over the past two decades have resulted in a greater proportion of Medicare patients, and an increase in the volume of patients being treated for chronic conditions. These have contributed to longer lengths of stay and reduced reimbursement as compared to the cost of care per patient.

Operationally, a hospital system is comprised of several distinct components, each with unique characteristics in terms of patient flow patterns, critical resources, staffing needs, data repositories, etc. such as emergency departments, peri-operative spaces, pharmacy, inpatient and critical care units, infusion centers, and outpatient facilities. Additionally, hospital resources are also divided based on clinical specialties such as pediatrics, surgery, pathology, radiology, etc. A patient's treatment journey often requires them to interface with multiple components of this system. However, in many cases, these distinct subsystems operate independently resulting in disruptions to patient flow due to less-than-ideal communication, and lack of an integrated approach to resource allocation/capacity planning. Additionally, in recent years, healthcare systems worldwide have experienced the impact of sudden unexpected changes to their operations resulting from natural disasters such as pandemics, hurricanes, earthquakes, etc.

Thus, hospital systems are required to provide the best-in-class care and adhere to the healthcare quality and patient safety standards set by institutions such as The Joint Commission, while balancing financial constraints and limited resources. As a result, healthcare organizations have sought to adopt the practices of High Reliability Organizations (HROs) in order to build resilience and increased sensitivity into their operations (Carroll and Rudolph 2006; Phillips et al. 2021). Increasingly, hospital systems are also taking a proactive approach to resource and capacity planning through design and implementation of clinical growth strategies (i.e., taking a structured, proactive, and analytical approach to growing certain clinical specialties, expanding into new geographical areas to increase outreach to new patient populations, etc.).

Improving the adoption of simulation-based solutions in healthcare: In a review of Operations Research and Management Science literature focused on integrated planning of different resources in hospitals, Rachuba et al. (2024) note that "successful implementations of integrated planning approaches in practice are still rare." They observe that simulation methods dominate the approaches that showcase practical implementations due to their ability to incorporate considerations around the complexities of the underlying systems.

Decision makers in a healthcare operations setting comprise of a group of representatives from the clinical domain such as physicians, nurses, as well as non-clinical areas such as supply chain, facilities management, hospital administration etc. In recent years, there has been a significant increase in the availability of commercial as well as Free and Open-Source Software (FOSS) packages that have enabled analysts to develop and deploy user-facing, web-based/desktop applications that are based on a combination of machine-learning, forecasting, and optimization models, which can be used by these operational leaders with minimal analytical support. While there have been similar advancements in commercial and open-source simulation software, they do not always integrate seamlessly with the ecosystem that is currently in use by data scientists at healthcare institutions. Additionally, development of complex simulation models in healthcare, especially using FOSS packages requires a greater level of programming effort as compared

with other analytical methods, which introduces challenges to knowledge transfer and wider adoption of simulation-based solutions. Thus, development of FOSS simulation software requiring a reduced level of programming effort and offering seamless integration with other analytical techniques would greatly help increase the utilization of simulation-based solutions. Developing frameworks such as those proposed in Monks et al. (2024) could help with sharing and reuse of simulation models among different healthcare organizations and guide the development of standardized approaches for simulation-based solutions.

Future research directions: In light of emerging challenges and trends in healthcare operations management, it is worthwhile to highlight the research opportunities for integrated systems modeling, and integration of artificial intelligence/machine learning (AI/ML) models with simulation to improve the accuracy of recommendations.

Large-scale integrated-system simulation models that can capture the impact of dependencies between various components of a hospital system can be extremely valuable for strategic capacity planning decisions. For example, using an integrated systems modeling approach, the impact of patient growth forecasts over time can be translated into the projected increase in outpatient-and urgent-care visits in a hospital system, and can also be used to plan for the need for additional inpatient beds, operating rooms, clinic space, and staffing needs. Integrated systems modeling could also assist with the development of best practices and guidelines for clinical growth strategies that could be shared among distinct healthcare systems.

Ferdousi et al. (2023) showcase several AI/ML models in use in healthcare. Some examples include models that can provide real-time predictions of estimated wait times in emergency departments, projections for hospital census based on current/future inpatient admissions, prediction models for mortality of admitted patients with chronic conditions, etc. Incorporation of AI/ML model outputs into the simulation modeling framework as inputs can help improve the accuracy and utility of simulation-based tools for short-term/ real-time decision support, due to the inclusion of considerations around several sensitive variables that have a diminished effect when it comes to strategic planning. Digital twin solutions based on simulation and AI/ML methods can help hospital systems build resilience to short-term disruptions, deliver consistent quality of care to patients, and work toward achieving the goals of HROs.

3.3 Modeling Human Behavior

Personalized, or precision medicine, is the idea that instead of a “one-size-fits" all approach to medicine, we should provide each patient with the right treatment at the right time. That is, healthcare interventions should be tailored to an individual’s characteristics. Often, emphasis is placed on an individual’s genetic profile (Institute 2025), although some definitions recognize that phenotype and lifestyle play a key role when considering targeted prevention, diagnoses, or treatment (Council 2003). Simulation modeling has been used extensively in personalized medicine, to optimize treatment for individuals (Jacquemyn et al. 2024; Marrero and Yi 2024), for example.

Fewer studies, however, acknowledge the key role that human behavior plays in medicine. Individuals have preferences which may lead them to choose one treatment over another, or they may face barriers which hinder their ability to adhere to or comply with recommended actions or treatments. Without explicitly considering individual patient preferences or choices, it may not be possible to obtain accurate estimates of the effectiveness of interventions. For example, for colorectal cancer (CRC) the US Preventive Services Task Force recommends that average-risk individuals ages 45-75 be screened for CRC using one of several modalities including colonoscopy or a fecal immunochemical test (FIT) test (U.S. Preventive Services Task Force 2021), yet as of 2021 less than 73% of individuals were up-to-date with CRC screening guidelines, despite substantial efforts over the last decade to reach 80% up-to-date. Previous studies have included choice of modality and compliance with CRC screening to simulate the impact of interventions on long term health outcomes, such as cancer cases averted (Lich et al. 2017; Lich et al. 2019; Powell et al. 2020). In these cases, patient choice of modality and adherence were modeled based on statistical models which consider patient demographics (Wheeler et al. 2016). Other work provides guidance on how to estimate future CRC screening behavior based on past patient behavior (Townsley et al. 2022). Human behavior

is complex, and in some cases, such as with the spread of an infectious disease, it is crucial to capture individual behavior as well as the interaction between individuals to accurately estimate health outcomes.

Grounding in health behavior theories: Behavior theories represent theoretical frameworks that propose factors that predict behavior. These frameworks delineate how these factors interact and mechanisms through which their interactions culminate into specific individual actions. These factors are defined as psychological constructs, which are abstract concepts that encompass a set of human cognitions or behaviors. There are many classical theories commonly used in the literature to explain health behaviors. Some of the more well-known theories include the Health Belief Model (HBM), the Protection Motivation Theory (PMT), the Theory of Planned Behavior (TPB), and the Social-Cognitive Theory (SCT). These theories have been used to explain protective health behaviors for respiratory diseases such as acute respiratory syndrome (SARS), H1N1 and H5N1 flu, COVID-19, and sexually transmitted diseases (STDs) such as the human immunodeficiency virus (HIV). Target behaviors studied include non-pharmaceutical interventions (such as wearing a face mask, social distancing, and self-isolation) for respiratory diseases, engaging in protective behaviors to prevent STDs, and pharmaceutical interventions such as drug treatments and vaccines.

Sheeran et al. (2017) provide a summary of the main factors used in health behavior theories and synthesize descriptions into a unified conceptual definition. They group constructs into four categories: perception about the health threat, perception about the target behavior, volitional factors (related to the will to perform an action) and implicit perceptions. Perceptions about the health threat and the target behavior are commonly found in classical behavioral theories; whereas, volitional factors and implicit perceptions are proposed in more novel theories. Because of their flexibility in representing individual agents and accounting for agent-to-agent interactions, Agent-Based Models (ABMs) have been a natural choice for incorporating human behaviors grounded in behavioral theories into simulation models. For example, Grefenstette et al. (Grefenstette et al. 2013) developed FRED, an agent-based simulation framework that incorporates the application of the HBM proposed by Durham and Casman (Durham and Casman 2012). de Mooij et al. (De Mooij et al. 2023) developed a large-scale agent-based simulation framework that incorporates the attitudes of the agents as input for their decision-making process. In a recent study which models COVID-19, Rodriguez-Cartes et al. (Rodriguez-Cartes et al. 2024) demonstrate how to incorporate human behavior accounting for personal beliefs and perceptions by using the HBM within an ABM to drive an agent's decision to wear a face mask.

Challenges in modeling human behavior: There are several challenges to incorporating human behavior in an ABM, or any simulation framework. Badham et al. (2018) name model specification as one of these challenges; that is, the modeler must decide which psychological constructs to consider, how these determine the behavior of the agent, and how these can be represented in the simulation environment. The most appropriate behavior theory will depend on the problem context, the purpose of the study and the research question of interest. Authors should conduct a literature search to identify which theories have been employed to model the target behavior. For example, the HBM and PMT frameworks are often used when considering risk perception and perceived severity. Then, there are many ways to incorporate these constructs into a simulation model. A recent review by Hamilton et al. (2024) cataloged studies that had endogenously incorporated behaviors into models of COVID-19 transmission. They found that most studies used feedback loops while a substantial number used game or utility theory and a few studies used a model of information or opinion spread.

The next challenge is finding data associated with the behavior. The most common way to measure psychological constructs is through survey instruments. The usual approach is to employ Likert scale questions, where participants respond to statements that relate to specific constructs. For example, the Preventive Health Survey: COVID-19 Beliefs, Behaviors & Norms Survey conducted by MIT and Facebook asked questions that measured beliefs and perceptions in relation to COVID-19 and protective behaviors (Collis et al. 2022). Rodriguez-Cartes et al. (2024) used responses from from this survey to map to specific constructs in the HBM framework to model an agent's decision to wear a mask. While survey design is usually guided by the chosen behavioral theory and the behavior studied, these surveys are not usually

designed with simulation modeling in mind. Longitudinal studies allow researchers to assess changes in perception over time, which helps to examine the effects of variations on behavior. However, longitudinal studies are more challenging to execute due to the need for continued engagement from respondents. In contrast, cross-sectional studies provide a simpler approach to collecting data but lack information on how behaviors may change over time. The information collected from survey instruments or other empirical studies helps to inform the effect of each construct in predicting behavior. Statistical models (i.e., linear and logistic regressions, structured equation modeling) are useful for quantifying these relationships and assessing the importance of each psychological construct.

Other challenges in modeling behaviors in simulation models include operationalizing behaviors using data or information endogenous to the simulation study and calibrating simulation parameters. For example, if social norms are important in determining vaccination decisions, one may model perceptions about the vaccination behaviors of connected agents, and parametrize how much influence agents have on each other depending on their closeness (e.g. agents within a household may influence an individual more than agents within a community). ABMs require extensive parameter calibration, especially when incorporating multiple psychological constructs, leading to increased computation complexity.

Future research directions: Despite the rich literature that exists in behavioral theories that propose the main factors driving behavior from the psychology and social science fields, there is a lack of clear guidelines for incorporating health behaviors into simulation models. It would be useful to have a unified framework to aid in the operationalization of agent actions grounded in behavioral theories. Furthermore, while it may be important to incorporate human behavior into some health models, due to computational complexity, this must be done only when it necessary to answer the research question of interest. There is a trade-off between simple representations of behaviors that may adequately capture population level estimates and models with high granularity and heterogeneous behavior that can accurately represent what is happening at the individual level. Meta-modeling, or equation learning may offer a happy medium, where realistic ABMs are used to capture complex individual behaviors and are then are abstracted to be represented as simpler models. For example, equation learning can be used to derive ordinary differential equations, like the classic SEIR model which can provide easily interpretable results for decision-makers (Nardini et al. 2020). Machine learning and other techniques such as artificial neural networks can be used either to directly create meta-models, or for equation learning itself. There are many challenges associated with meta-modeling techniques, such as how to capture the stochasticity within simulation models, how to choose the right level of granularity and how to adapt to changes in the underlying disease dynamics. While incorporating human behaviors in simulation modeling is challenging, accurately capturing these in models of disease spread will allow decision-makers to test and tailor interventions to better alter individual behaviors, ultimately making interventions more efficient and effective.

3.4 Mechanistic modeling social determinants of health (SDH) into disease simulations

Disease simulation models play a critical role as disease prediction and intervention decision-analytic tools to inform national or global public health strategies or clinical guidelines. The general mechanistic approach is to simulate the direct mechanisms or pathways to disease risk, such as health behaviors or other health conditions. For example, infectious disease simulations model transmissions as functions of behaviors that influence contact networks, and infectiousness of infected contacts, and chronic disease simulations model disease risk as a function of healthy lifestyles, pre-existing health conditions, and/or screening behaviors. Accordingly, intervention analyses have focused on pharmaceutical and/or behavioral interventions. However, numerous studies have shown that social-economic-demographic features, such as race, geography, income-level, insurance-status, and housing and food insecurity, etc., are core predictors of disease risk or health outcomes, challenging the approach of focusing on pharmaceutical and/or behavioral interventions alone. These factors, simply referred to as social determinants of health (SDH) given their significant associations with a wide range of diseases and multi-comorbid (i.e., multiple co-occurring) health conditions (Álvarez Gálvez et al. 2023), highlight the need for structural interventions, alongside

pharmaceutical and behavioral interventions, as a critical component of public health response. In addition, there are correlations between diseases due to common behavioral mechanisms or biological interactions. As these associations can influence the cost-effectiveness of interventions, there is increasing interest in integration of the associations between SDH and diseases, and between diseases, into intervention decision analytic models to inform public health resource allocation strategies.

Broadly, there are two types of models used in above analyses, dynamic simulations and statistical methods. While statistical methods help identify associations between SDH, behaviors, and disease risk, or evaluate effectiveness of structural interventions using data from controlled studies, they have two interrelated challenges. First, they do not model the mechanisms between SDH, behaviors, and disease risk, and are thus unsuitable for intervention analyses. Second, measuring joint intervention effects through controlled studies become infeasible as the number of features (e.g., SDH, behavioral, or health conditions) to experimentally control increase. While dynamic simulation methods can address these gaps, challenges had included high computational burden and model parametrization. With the availability of high compute and data, recent literature has seen a growth in simulation studies that jointly model SDH and related diseases. We provide some examples below on methods used for model parameterization.

Estimating mechanisms between SDH, behavior, and disease-risk: Models under the Cancer Intervention and Surveillance Modeling Network (CISNET) traditionally simulated natural disease progression, measuring the impact of screening and treatment combinations on disease progression to inform screening and treatment guidelines. In recent work, motivated by bias in data and barriers to screening access, they additionally incorporated screening and treatment *access* into the modeling framework, to infer through the simulation, the causal factors (biological v. SDH) of disparities in cancer mortality by race (Mandelblatt et al. 2023). Another example are studies by the Progression and Transmission of HIV (PATH 4.0) modeling group. They incorporated copula probability theory with machine learning probabilistic graphical modeling to integrate disparate datasets (from literature studies and large national surveys) to first infer the joint distributions of SDH and sexual behaviors, and subsequently to parameterize a mechanistic simulation of HIV and STIs (Khosheghbal et al. 2024; Zhao and Gopalappa 2023), to enable joint evaluation of pharmaceutical, behavioral, and structural interventions.

Joint modeling related diseases and intervention effectiveness: One study developed a model to collectively evaluate the impact of blood pressure control on stroke, cardiovascular diseases, and dementia (Burke et al. 2024). They parameterized the model using a combination of statistical methods, meta-analyses of randomized control trials, well-characterized prospective cohort studies, and multiple population surveys to generate risk, state transitions, and treatment effects. A second study developed a model to evaluate the impact of combinations of behaviors such as physical activity, healthy diet, smoking, and screening on multiple interacting health outcomes such obesity, CVD, hypertension, cancers, and chronic pulmonary disease (Clennin et al. 2022). They parametrized the casual structure using associations from the literature and subject matter expertise. A third group developed a joint STI model, to quantify the biological v. behavioral mechanisms for high risk of HPV and cervical cancer among women with HIV, and the impact of structural interventions on HIV, HPV, and cervical cancer outcomes (Zhao and Gopalappa) developing a deep-learning assisted hybrid agent-based and compartmental model to overcome the parametrization challenges of modeling diseases of varying epidemiological scales (Eden et al. 2021; Gopalappa et al. 2023).

Gaps and future research directions: Though there are many other significant work in recent years, and we highlight only a few studies above as samples of recent research topics, there are many open challenges and opportunities for research. First, there are significant gaps in methods to identify causal structures. As the casual pathway between behaviors and health risk are biological mechanisms, they can be inferred through controlled studies. However, estimating the casual pathway between SDH and behaviors is a complex area of research, as they are highly heterogeneous, influenced by factors such as socio-economic, social context, systemic racism, and stigma, which are difficult to measure. Thus, most studies typically focus on associations and not on casual structures. A multidisciplinary approach, drawing from concepts

from behavioral psychology, social sciences, community-based health sciences, and data sciences (Bedson et al. 2021), used in conjunction with simulation modeling to incorporate temporal or spatial dynamics, could be one direction of research. The second challenge is with data availability. Individual-level data are most suited for casual inference, and thus, studies that infer casual structures between SDH predominantly use randomized control trials, individual-level longitudinal surveys, or individual-level electronic health records (EHR). Individual-level surveys are only available for a subset of SDH and behaviors, and only for some subgroups. There is no consistency in EHR record keeping for SDH (ICD codes for SDH are only now being considered and not universally adopted), and additionally, can be biased towards populations with higher access to healthcare. One direction of research could be methods to combine evidence and data from disparate datasets (health, behavioral, and SDH), including surveys and surveillance systems that are regularly administered, to add community context. Third, effectiveness of structural interventions from controlled studies typically do not scale in a realistic setting. To address these gaps one direction of research could be methods to estimate intervention effects from ongoing public policies and programs, using longitudinal and spatial program data in conjunction with other population and individual-level data. Along with multidisciplinary research to learn from concepts from behavioral psychology, social sciences, community-based health sciences, and data sciences (Bedson et al. 2021), innovative use of AI and simulation could play a role in addressing the above gaps. Use of artificial intelligence (AI) in public health for disease risk prediction and epidemic forecasting, intervention analyses, identifying associations between SDH and diseases, or extracting knowledge graphs from literature are rapidly evolving. While there is potential for AI to play a critical role in achieving the complex challenges described here, there are multiple issues related to robustness, interpretability, reliability, and ethical and privacy issues that are barriers to be addressed. Suitable directions of research could include innovative use of AI for scalability and methods from mathematical sciences (including causal inference methods, simulation, and reinforcement leaning) for robustness, interpretability, and reliability.

3.5 Contact network generation using multi-modal data for rapid detection of disease outbreaks

Contact network generation in simulation models are a critical component of epidemic prediction. However, they are challenging to generate given the complexity of temporal and spatial dynamics (mobility) and spatial scale (geographical spread), that can make it computationally intractable. Taking advantage of scalability of machine learning methods, there is significant growth in recent work in use of multi-modal data such as from mobility, contact tracing, behavioral surveys, and household co-residence datasets. Among these, a subsection of studies that are gaining high interest, because of their ability for rapid detection of new outbreaks, are those that combine molecular methods of contact generation.

Molecular methods use nucleotide sequences of the virus isolated from persons with infection to identify transmission networks (molecular clusters). As viruses mutate, the difference between two viruses' nucleotide sequences, called genetic distance (GD), indicates how closely they are related in transmissions. Network clusters are detected by applying a threshold on GD; any sequence within a given GD of at least one other sequence is considered part of a cluster. Unlike other surveillance methods, as molecular clusters directly detect networks of rapid transmissions and are not restricted by demographic or geographic boundaries, it helps early, rapid, and targeted intervention response. Recognizing its critical role in outbreak detection and response, public access to data has rapidly increased in recent years through worldwide initiatives, e.g., SARS-Cov-2 (virus that caused COVID-19) saw an unprecedented amount of data made available in a short time. Molecular cluster detection is increasingly used for detection and response to outbreaks of not only newly emerging viruses, but also chronic infectious diseases including sexually transmitted infections (e.g., HIV, Gonorrhea), intravenously transmitted infections (e.g., Hepatitis C (HCV)), and respiratory infections (e.g., tuberculosis(TB), COVID-19).

Gaps and future research directions: As molecular cluster detection can only be applied to diagnosed cases with sequence, they have certain limitations. First, infections with long asymptomatic durations, e.g., HIV, COVID, tuberculosis, hepatitis C, gonorrhea, and human papilloma virus, have delayed diagnoses,

and thus, 'detected' clusters are only the tip of an iceberg, i.e., part of a larger 'full' cluster (iceberg) of unknown composition. Second, barriers to testing, diagnoses, and sequencing can limit sequence availability, and thus, response operations could be biased towards populations with higher access, adding to health disparities. Third, it is retrospective, detects outbreaks in the past but cannot predict networks at-risk of future outbreaks, i.e., may miss opportunities for prevention. Combining molecular methods with simulation modeling to address above gaps is a newly emerging area in the epidemic modeling literature (applied to COVID-19, Hepatitis C, TB, and HIV) (Fujimoto et al. 2023; France et al. 2024), however they are limited in geographical scale. Nationally or globally scalable models are critical for rapid detection and response in the event of new and emerging infectious diseases. Combining model-based methods with data-driven AI could enable development of scalable tools for rapid response.

4 CONCLUSIONS

In this paper, we synthesize domain-specific insights and reflect on the evolving role of simulation in healthcare and life sciences. As challenges grow in scale and complexity, advancing the field will require multidisciplinary approaches that integrate expertise in modeling, machine learning, optimization, and healthcare. Close collaboration with stakeholders in government, industry, academia, and clinical settings will help ensure that simulation models remain timely, relevant, and impactful. Finally, university curricula that emphasize rigorous simulation training will continue to play an important role in preparing a workforce equipped to address future challenges in healthcare care.

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