Evolution of Simulation and Digital Twin in Health Care: From Discovery to Design and Integration

Yue Dong, Amos Lal, Alexander S. Niven, and Xiang Zhong

Abstract Over the past two decades, simulation and Digital Twin (DT) technologies have become increasingly prevalent in health care. These technologies have significant potential to advance modern medicine, enhance clinical decision-making and team performance, improve healthcare delivery, reduce cost, and improve patient outcomes. This chapter provides an overview of these technologies and their emerging applications in the field of health care, including opportunities to accelerate discovery in basic science, delivery of more realistic training opportunities that advance clinician competence and interprofessional teamwork, and an efficient and cost-effective approach to analyze, improve, and monitor clinical workflows, healthcare delivery systems, and their performance. This emerging field fosters multidisciplinary research among healthcare professionals, information technology experts, engineers, and data scientists, all working together to better serve our society. Widespread adoption of these technologies will require solutions to address several technical, ethical, and regulatory challenges. These solutions will require a close collaboration between industry, academic centers, and government to develop a thoughtful approach that aligns implementation and integration of simulation and DT technologies into the healthcare workplace with measurement of meaningful outcomes to ensure broad-based access benefit from these important tools.

Y. Dong (✉) · A. Lal · A. S. Niven
Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
e-mail: dong.yue@mayo.edu

A. Lal
e-mail: lal.amos@mayo.edu

A. S. Niven
e-mail: niven.alexander@mayo.edu

X. Zhong
Univesity of Florida, Gainesville, FL 32603, USA
e-mail: xiang.zhong@ise.ufl.edu

M. Grieves and E. Hua (eds.), *Digital Twins, Simulation, and the Metaverse*, Simulation Foundations, Methods and Applications, https://doi.org/10.1007/978-3-031-69107-2_11

1 Introduction

Modern health care is a complex adaptive system that requires highly skilled interprofessional team members to work together using advanced equipment and standard processes to care for patients with a wide variety of diseases with steadily increasing acuity over time. While the rapid pace of advancement in medical science offers exciting possibilities and new hope to patients and their family within our global community, it also demands constant changes in an already complicated and strained healthcare delivery system. The practice of medicine and current healthcare outcomes fall far below the level of quality and safety achieved by high-reliability industries, such as aerospace and manufacturing. As a result, institutions have become increasingly focused on the "value equation" of the care they deliver, generally defined as the quality of care divided by the total cost of patient care over time [1].

Over the past two decades, simulation and Digital Twin (DT) technology and their applications have become increasingly prevalent in health care. These tools can provide increasingly accurate representations of the pathobiology behind patient conditions, opportunities to monitor patient health and optimize disease diagnosis and management, enhance and evaluate the performance of clinicians and their healthcare teams, and analyze and improve healthcare delivery and systems. Using a systematic implementation strategy that includes key stakeholder collaboration, these technologies offer the opportunity to accelerate medical research discovery and improve healthcare system performance and patient outcomes with greater efficiency and at a reduced cost. This chapter provides an overview of these technologies and their emerging applications in health care.

1.1 Healthcare Evolution from Individual Treatment to Health Delivery Integration: A Systems Perspective

The twentieth century witnessed a wide range of groundbreaking scientific discoveries in medicine, including antibiotics, anesthesia, blood transfusions, vaccines, Computed Tomography (CT) scans, magnetic resonance imaging (MRI), and extracorporeal therapies, including dialysis and extracorporeal Membrane Oxygenation (ECMO), and more [2]. The twenty-first century promises an even faster pace of discovery, with rapid advances in genomics offering a customized approach to common and complex diseases using precision medicine, and the digital revolution challenging our traditional approach to care delivery.

These advancements have had a profound impact on human health and have significantly shaped both the current practice of modern medicine and the benefits it provides to society. Healthcare delivery systems have evolved into complex ecosystems of clinical practice environments that offer a wide variety of services to scale. However, these healthcare improvements come with their own set of challenges. Population aging and growth, the increasing prevalence of chronic conditions, and advanced diagnostic and treatment modalities are both driving cost and reducing access to and equity of care. As the complexity of disease management has increased, there is a growing demand for a collaborative, multidisciplinary, and team-based approach that includes physicians, nurses, pharmacists, and respiratory therapists and technicians. These teams require a clear understanding of each other's roles and responsibilities and a high level of communication and teamwork to ensure timely and coordinated care delivery.

Given its complexity, health care today has evolved into a "system of systems" of healthcare delivery focusing on not only just safe and timely medical care, but also better management of resources to meet demand at scale across geographic locations and time. The Systems Engineering Initiative for Patient Safety (SEIPS) 3.0 framework could serve as a guiding model in this complex landscape [3]. It offers a holistic approach to integrating various components such as people, tasks, tools, and organization, thereby providing a comprehensive view of healthcare delivery systems. These "systems" are also often stratified using different levels, including biology and disease, patients and clinicians, and care delivery processes at the bedside, within the hospital, and throughout healthcare systems as a whole [4]. A System of Systems (SoS) in health care refers to integrating and interacting various independent systems within the healthcare sector to achieve a more comprehensive, efficient, and effective healthcare delivery.

In complex healthcare systems, the overall system performance is directly linked to the functionality of each subsystem and the interconnections between them. Individual components, such as patient care, administrative processes, and healthcare technology, must not only function effectively in isolation but also integrate seamlessly. The synergy between these subsystems is crucial for the overall system performance. Medical errors and gaps in care quality have been well documented. However, fixing them is not easy due to the complex and unpredictable work environment common in medical practice [5, 6]. The recent global COVID-19 pandemic and its impact further exposed these persistent vulnerabilities in healthcare systems worldwide [7–9]. The pandemic has served as a catalyst for change, underscoring the importance of improving current healthcare delivery mechanisms. It is imperative to enhance the efficiency of healthcare delivery while maintaining the highest standards of quality care and use innovative solutions and technologies to improve healthcare access and distribution on a global scale. This systems view of healthcare delivery also provides a framework that we can use to better understand how simulation and DTs can be used to offer important solutions to these complex problems.

1.2 Technology Advancement in Health Care

Over the past 30 years, we have witnessed a technological revolution that has significantly impacted all aspects of our lives, including health care. Personal computers, mobile devices, the internet, cloud computing, and artificial intelligence/machine learning (AI/ML) have led to an explosion of data related to biology discovery, disease diagnosis, management, and healthcare delivery systems optimization. These data-driven decision support tools can amplify and augment human capacity to improve the efficiency, quality, and safety of health care during the whole journey of patient experience (prevention, management, recovery, and wellness).

Simulation is the imitation or representation of one act or system by another. The Society for Simulation in Healthcare describes four main purposes of simulation—education, assessment, research, and health system integration to facilitate patient safety [10]. Simulation-based training started in the discipline of anesthesiology and has grown rapidly in other areas of medical education, with the development of a growing variety of computer-controlled manikins and task trainers. These simulators can be programmed to recreate a variety of standardized clinical scenarios, allowing students to practice their clinical reasoning, technical (intubation, central line insertion, etc.), and teamwork skills (communication) in a safe and controlled environment. Simulation-based education has been shown to be an effective way to improve student knowledge and skills and translate to better patient outcomes [11].

Computer simulation involves creating a computer-based model or virtual representation of a system or process to study and analyze its behavior.

As an extension to traditional computer simulation, DT is a virtual representation of real-world entities and processes synchronized at a specified frequency and fidelity. DTs' systems transform business by accelerating holistic understanding, optimal decision-making, and effective action. DTs use real-time and historical data to represent the past and present and simulate predicted futures [12]. It is a digital replica of a physical system that can be used to monitor, predict, and optimize the system's behavior. DT is a virtual representation of a physical asset replicated virtually through a data connection, making it possible to link the system with its virtual counterparts in a bi-directional way. The "bi-directional" exchange of information, which synchronizes the virtual system response to match the physical system, distinguishes DT from traditional digital simulation, which is often considered independently operated. Specifically, a digital model has no interaction with the physical system. A digital shadow is updated with data from the physical system but does not inform its control. A DT arises when the physical system data is used to update the digital model, and the resulting simulation is used to control the physical system [13]. Very few works in literature have realized the control loop and are considered as true DTs in use, and thus, our review also includes simulations that are digital models or digital shadows [14].

1.3 Healthcare Applications

DTs have various applications in health care, such as training, diagnosis, management, and care delivery for patients, providers, and healthcare organizations. One way to categorize DTs is based on Siemens' framework, which has three levels of twinning [15].

First, product twining provides a virtual-physical connection to analyze how a product performs under various conditions and adjust in the virtual world to ensure that the physical product will perform exactly as planned in the field. For product twinning, one example is the DTs of medical devices (e.g., digital radiological devices) [16, 17]. These efforts focus on the physical device/product twinning (similar to the concept of DTs for management in manufacturing) and are mostly used to monitor its status, diagnose issues, and test solutions remotely, ultimately optimizing its performance and reducing the risk of malfunctions. From digital devices to digital/virtual patients, precision medicine is one area that exemplifies the application of both product twinning and process twinning. Digitally replicating the human body (from cell to organ biological/physiological systems) allows for in silico clinical trials to examine the prevention, early detection, and targeted treatments of many diseases. These DT human body/organ systems have been used for drug development and treatment recommendations [18]. Another example of virtual patients is optimizing health care at the individual level, i.e., "personalized health monitoring," with the goal of healthcare management and promoting healthy behavior. It can be used to create personalized models of patients that can be used to monitor their health status, predict the course of disease, and optimize treatment plans [19]. This application is still focused on modeling a virtual patient instead of the healthcare system at large and is mainly focused on healthy people's daily life and their living environment instead of a specific healthcare facility. The third level is system twinning, which includes using DTs to improve hospital operation processes and workflows by allowing managers to tweak inputs and see how outputs are affected without the risk of upending existing workflow [20]. The system performance can be captured, analyzed, and acted on operational data, providing insights for informed decisions to maintain effective interactions among the components of the system at the system level.

1.4 Outline of the Chapter

DTs have risen at the intersection of Industry 4.0 and the Internet of Things (IoT), relying on converging technologies in big data analytics, pervasive sensing, and cloud computing infrastructure. In this new era, simulation and DTs promise to enhance healthcare delivery by improving efficiency, flexibility, and patient-centered care, all of which are crucial in a post-pandemic world. This book chapter highlights how technological advancements have enriched health care with valuable data and digital assets, making it imperative to utilize these resources to optimize the entire spectrum of healthcare services. We will delve into the applications, benefits, challenges, and future prospects of DTs and simulation technologies in health care, particularly in the context of a post-COVID-19 world acute care setting. We will explore how these technologies can serve as invaluable tools for healthcare professionals, clinicians, researchers, IT professionals, engineers, and data scientists, all working together to serve society. In Sect. 2, we will explore simulation and DT applications in biology and disease management. In Sect. 3, we will discuss the latest professional training applications using simulation and DTs' technology. In Sect. 4, we will present applications that support decision-making for hospital operations and management. Then, in Sects. 5 and 6, we will provide a vision of simulation and DTs in health care and discuss the challenges and opportunities.

2 Simulation and Digital Twin Applications at the Biology and Disease Management

Modeling and simulation have emerged as a powerful tool for understanding complex biological systems and processes in addition to the traditional theory and experiment [21]. Utilizing mathematical models, simulation allows researchers and clinicians to predict disease outcomes, test treatment interventions, and optimize healthcare delivery. There are two common approaches for physiology and disease modeling: rule-based and data-driven modeling. Each of these approaches offers distinct advantages and challenges [22]. The rule-based approach relies on predefined rules and knowledge about biological systems to model disease processes. These rules are typically derived from clinical guidelines, expert opinions, or well-established physiological pathways and experienced-based learning in clinical settings. It has the benefits of transparency (by incorporation of directed acyclic graphs in the creation and execution of rules), easy control of model behavior, and stability for output, which make it easy to accept for clinicians [23, 24]. At the same time, it also has stability and flexibility limitations because it requires expert knowledge and comes with a possibility of bias. The mechanistic model is designed to represent the underlying mechanisms of a system—the processes and interactions that lead to observed phenomena. They are often contrasted with empirical models, which are purely based on observed data without assumptions about the underlying physiology processes. The data-driven model uses large datasets to investigate inter-relationships using different statistical and data mining methods. It is based on systems' biology and systems' immunology and has expanded rapidly in the last decade because of more accessible data from EMR and more computer power [25, 26].

2.1 Understanding Physiology and Treatment

The simulation technologies have revolutionized medical science by understanding physiology. Various virtual training platforms now offer immersive experiences that closely mimic real-world clinical scenarios based on physiology [11]. These platforms are designed to be interactive, allowing medical students and healthcare professionals to engage in problem-solving, diagnosis, and treatment planning in a risk-free environment. The virtual training modules often include a wide range of case studies covering various diseases, conditions, and patient demographics, providing a comprehensive learning experience. The lab and vital signs will change based on the intervention by user input. The virtual patient offers a practical understanding of disease mechanisms and treatment protocols, thereby bridging the gap between academic learning and clinical practice. This hands-on approach enhances the learner's ability to make informed clinical decisions in a safe environment that will not harm patients, ultimately leading to better patient outcomes.

Archimedes Diabetes Model was designed to simulate individual patients and how they would respond to various treatments for diabetes. It incorporated a wide range of variables, from glucose metabolism to treatment protocols, to generate realistic patient outcomes [27, 28]. This model serves as one of the early successes in utilizing computer-based physiology to understand and manage diabetes. This was also an early implementation of using directed acyclic graphs to explain the complex pathophysiology and rules based on the clinical environment. The model underwent rigorous validation, and its predictions were found to be highly consistent with the results of randomized controlled trials. This level of accuracy made the Archimedes Diabetes Model a valuable tool for clinicians, researchers, and policymakers alike. It not only helped in understanding the complex physiology of diabetes but also played a crucial role in optimizing treatment plans and healthcare policies related to diabetes management.

Agent-based models can simulate the interactions between various biological agents, such as cells and molecules, in each biological system [29, 30]. These agent-based models are particularly useful for understanding complex, multiscale biological systems where traditional modeling approaches may fall short. By providing a more nuanced understanding of biological systems, agent-based models have paved the way for more targeted and effective treatments, bridging the gap between basic biological research and clinical applications. This approach is offering insights that are directly applicable to patient care and treatment optimization. The research group led by Vodovotz explores the use of omics data and mathematical modeling to understand and explore various critical illness management strategies by integrating data-driven and knowledge-based modeling approaches [22]. This approach aims to integrate large-scale data with computational modeling to improve research and clinical applications in diseases involving severe inflammation and immune responses.

BioGears is an open-source, comprehensive human physiology engine that has been instrumental in driving medical education, research, and training technologies [31]. BioGears aims to provide accurate and consistent physiology simulation across the medical community. It can be used as a standalone application or integrated with other simulators and sensor interfaces making it a valuable asset in the healthcare simulation community. Similar to BioGears, the Pulse Physiology Engine offers robust physics-based circuit and transport solvers [32]. It includes a common data model for standard models and data definitions, a software interface for engine control, and a verification and validation suite. Pulse's architecture is designed to reduce model development time and increase usability, making it a go-to solution for many in the healthcare simulation community.

Emerging roles of virtual patients in the age of AI have been explored, and rule-based systems have shown promise in healthcare modeling. These systems can simulate patient responses based on a set of predefined expert rules, making them useful for training and diagnostic purposes. Dr. Lal and team have developed and verified a DTs model of critically ill patients using the causal AI approach to predict the response to specific treatment during the first 24 h of sepsis [23]. This expert rule-based DTs focus on creating individualized patient models for better medical education and clinical decision support [33]. This work was previously developed specifically for sepsis in critically ill patients but has now evolved into multiple commonly seen clinical scenarios in the intensive care setting. The primary goal is to provide a safe testing bed for the learners and the clinicians to evaluate a proposed intervention (useful or otherwise) in an in silico environment, before actually performing those interventions on the patient at the bedside. The envisioned result is to avoid any preventable harm to the patient by pre-testing the interventions that carry any uncertain risks. The utility of such DTs in health care can serve multiple purposes, including advances in medical education delivery, in silico research, and adjunct clinical decision support at the bedside.

2.2 *In Silico Clinical Trials*

In silico clinical trials have emerged as a groundbreaking approach in medical research, offering many opportunities and advantages over traditional clinical trials. Utilizing computational models and simulations, in silico trials allow for the testing of medical interventions or devices in a virtual environment, thereby revolutionizing the way clinical research is conducted [34, 35].

One of the most compelling advantages of in silico trials is the significant reduction in costs. Traditional clinical trials often require extensive resources, including patient recruitment, site management, and long-term follow-ups, all of which contribute to high operational costs. In contrast, in silico trials can be conducted with minimal overhead, as they rely on computational power rather than physical infrastructure and human resources. This cost-effectiveness makes it feasible to explore a broader range of research questions and to conduct multiple trials simultaneously, thereby accelerating the pace of medical innovation. Time is another critical factor that holds a distinct advantage for in silico trials. Traditional trials can take several years to complete, from initial planning to final data analysis. In silico trials, however, can be executed in a fraction of the time. The ability to quickly simulate different scenarios and interventions enables researchers to arrive at conclusions more rapidly, thereby speeding up the "time to market" for new treatments and medical devices. Perhaps, the most significant benefit of in silico trials is the elimination of risks to human subjects. Despite rigorous ethical standards, traditional clinical trials always carry some risk to the participants. In silico trials remove this concern entirely, as they are conducted in a virtual environment. This not only ensures the safety of potential patients but also allows for the testing of treatments that might be considered too risky for traditional trials. By offering a safer, faster, and more cost-effective alternative to traditional methods, in silico clinical trials are poised to become a cornerstone in the future of medical research. They offer a promising pathway for the development of new treatments and medical technologies, with the potential to significantly improve patient outcomes and healthcare systems globally. Important components of biomedical ethics, such as informed consent, algorithm fairness and biases, intellectual property law, data privacy, safety, and transparency, should be considered alongside the regulatory issues of DTs [36]. Computer modeling and simulation can be adopted from other industries to aid in various stages of medical device development, testing, clinical evaluations, and failure analysis, leading to cost reduction [37].

Recently, the FDA has published reports to showcase how modeling and simulation can be used for scientific research and regulatory decision-making [38]. FDA also published guidance providing recommendations to assess the Credibility of Computational Modeling and Simulation in Medical Device Submissions [39]. Virtual clinical trials represent a significant shift in how clinical research is conducted. By leveraging DT platforms, researchers can gather large data more quickly and from a broader population base. Simulations and virtual environments offer a unique opportunity for policymakers to test the implications of healthcare policies in a controlled, risk-free setting [40]. By modeling the outcomes of proposed policies, stakeholders can anticipate their effects and refine them before implementation, ensuring that new regulations are both effective and efficient.

3 Health Professional Training Through Simulation and Digital Twin Technology

Over the past two decades, there has been a significant expansion in clinical training for healthcare professionals through various simulation technologies. These technologies range from task trainers, mannequins to more advanced Virtual Reality (VR) and Augmented Reality (AR) systems. The learners include the multidisciplinary clinical team (physicians, nurses, pharmacists, and respiratory therapists). While traditional task trainers have been around for many years, modern technology has allowed for the expansion and sophistication of simulation training programs. These programs now cover a wide array of skills, from procedural skills to non-technical skills like communication, compassion, and empathy. Numerous studies have shown that simulation-based training is associated with improved care processes and better patient outcomes [41].

3.1 Computer-Driven Mannequins and Task Trainers in Medical Training and Assessment

Modern mannequins used in medical training have evolved to become highly sophisticated, computer-driven devices. These mannequins can be controlled remotely or in-room, offering a range of clinical scenarios for trainees to practice clinical skills and teamwork [42, 43]. Those mannequins provide invaluable hands-on experience for clinicians in a controlled, risk-free environment for various specialties and disciplines [41, 44, 45]. The COVID-19 pandemic has forced the healthcare industry to adopt distance simulation using various technologies to find alternative approaches for traditional onsite clinical training [46, 47]. Simulation has been used for skill assessment and evaluation in many disciplines [48–50]. The use of VR and AR in healthcare training is growing rapidly to offer immersive learning experiences for learners that traditional methods cannot match [51–53]. Game-based training modules have also gained popularity, providing an engaging way for healthcare providers to hone their skills [54]. Although the cost of hardware can be a limiting factor, the benefits, such as improved skill retention and real-world applicability, often outweigh the initial investment.

3.2 Research Potential: Investigating System Vulnerabilities

Simulation technologies not only provide clinical skill training but also serve as research tools for human factor analysis. They offer a reproducible clinical environment where the interaction of system factors (clinician, technology, and workflow) can be investigated independently of patient factors [55, 56]. Researchers can use these technologies to investigate system vulnerabilities, test new workflows, new technology innovations, and even simulate the impact of potential policy changes before clinical implementation [57–60]. This simulation-based research extends the utility of simulation technologies as integral tools for overall healthcare system improvement [61].

4 Hospital Operations and Management

4.1 Leverage Data Insights from EMR, IoT, AI

The past 15 years have seen a data revolution in health care fueled by electronic medical records' (EMRs) implementation and adoption. This shift from paper to digital documentation has unlocked a wealth of patient data, improving team communication and clinical decision support, informing disease treatment plans, and tracking outcomes. Further, the integration of EMRs with the IoT and Radio

Frequency Identification (RFID) technologies creates a connected ecosystem for real-time patient flow monitoring and streamlined inventory management benefits from this data influx [62–64].

By collecting and analyzing this data, healthcare professionals can leverage predictive modeling to anticipate patient needs and prescriptive analytics to design personalize treatment plans, ultimately resulting in more informed decisions, improved patient care, and efficient healthcare operations [65]. Recent advancements in AI, computer vision, and Large Language Model (LLM) are opening up a new era in the healthcare innovation using simulation and DT [66, 67]. These technologies extend the capabilities of traditional data collection and analysis, offering a more holistic view of healthcare delivery from outpatient settings to inpatient care, and even post-discharge home care.

4.2 Operation Management and Resource Allocation

Healthcare operations' management aims to improve the efficiency of business processes within healthcare facilities to reduce overcrowding, waiting times, and delays. One of the main challenges in healthcare operations is managing the unpredictability caused by variations in patient demand, staffing capacity, and resource availability. For instance, changes in the number of patients or types of cases can affect staff schedules, patient flow, and patient room utilization. According to a rapid literature review of papers published in 2002–2022, the use of DTs for healthcare systems management is an emerging topic [68]. With availability of real-time patient and hospital operation data, healthcare managers can make informed decisions about staff deployment based on patient needs and workflow efficiencies. Similarly, data analytics can be used to optimize inventory levels, ensuring that medical supplies are ordered and utilized most effectively, thereby reducing waste and costs. The key advantage of DTs in health care is the ability to leverage real-time data to model complex systems and processes that involve many interdependent variables [69]. This allows for dynamic, evidence-based decision-making by integrating a large amount of heterogeneous data and real-time data queries to achieve better resource allocation at the hospital level [70].

Trauma centers, emergency departments, and ICUs are systems whose processes are subject to large variability and are very time-sensitive, and thus, have attracted substantial attention for process improvement and patient safety assurance using DTs. For instance, a trauma DT is used to digitize and support the process of severe trauma management, considering it as a physical asset that is mirrored by two DTs [71]. In Augusto et al. 2018, a DT of an emergency unit was developed to optimize the pathway of patient care in the unit. The system accounts for various arrival processes to account for massive arrivals in case of a crisis and determine the best available leverages to optimize the operations of the system [72]. DTs of ICU processes are used to identify inefficiencies in patient flows, optimize patient care by clinical staff at the enterprise level, and use remote monitoring to detect process faults and anomalies [68, 73]. Healthcare leaders can shift from reactive decisions to proactive optimization based on data-driven insights from DTs. Hospital-level model by using predictive decision support model that employs real-time service data is drawn from the systems and devices [74]. Their model enables assessing the efficiency of existing healthcare delivery systems and evaluating the impact of changes in services without disrupting the daily activities of the hospital. Along the same line, Karakra et al. 2020 developed discrete event simulation and DTs through a system called HospiT'Win that allows for tracking the pathways of patients inside the healthcare organization to manage growing demand and decrease waiting times [69]. Rodriguez-Aguilar et al. 2020 proposed a digital healthcare system initiative through multi-paradigm simulation [75]. Computer modeling has also been used to simulate infectious disease transmission dynamics, optimize the vaccination strategy, and test public policies before clinical implementation [76–78].

5 Challenges and Opportunities: Ushering a New Era in Healthcare Simulation and Digital Twins

The adoption of simulation and DT technologies in health care is not without its challenges [79, 80]. One of the most pressing issues is the need for accurate and complete data. Incomplete or erroneous data can significantly impact the effectiveness of these technologies in both training and real-world applications. Also, modeling complex biological systems involves numerous variables and nonlinear interactions, making it challenging. Regulatory hurdles, such as compliance with healthcare standards and data protection laws, further complicate the adoption process. Ethical considerations are paramount when using patient data in the DTs, especially when it comes to patient and clinician data privacy and confidentiality. The collection and use of patient data must adhere to strict ethical guidelines to ensure that individual privacy is respected. Moreover, there is a risk of bias in data collection and analysis, which could inadvertently lead to unequal healthcare delivery. Addressing these ethical and bias concerns is crucial for the responsible deployment of these technologies. Data sharing and interoperability present another set of challenges. Different healthcare systems often use different data formats and standards, making integration a complex task. The lack of interoperability can hinder the seamless exchange of information, thereby limiting the effectiveness of simulation and DTs technologies in a multi-system environment [81].

For simulation and DT tools to be effectively integrated into health care, there needs to be a set of clearly defined performance metrics for systems evaluation. These metrics should measure impacts of simulation and DTs across various domains, including disease outcomes, patient outcomes, system outcomes, and return on investment. The development of such comprehensive evaluation metrics will enable stakeholders to assess the effectiveness of DT technologies objectively.

Despite these challenges, there are numerous opportunities for innovation. For instance, multiscale simulation is a powerful tool for understanding complex biological systems and healthcare processes. By simulating the behavior of individual molecules, cells, and tissues, multiscale simulations can provide insights into how diseases develop and how drugs work. Multiscale simulations are being used to understand the molecular basis of diseases, such as Alzheimer's disease and drug development [82, 83]. Meanwhile, DTs can be used to track the progress of patients, monitor their vital signs, and predict when they may need medical attention. DTs have been used to monitor cardiac and cancer patients for personalized treatment planning [84, 85]. Additionally, AI algorithms can be used to analyze the data generated by simulations and DTs. This data can be used to train AI models to make predictions and identify patterns. AI models can be used to improve the accuracy of diagnoses, recommend treatments, and develop new drugs. The synergistic relationship between multiscale simulation, DTs, and AI offers unprecedented capabilities in health care, from real-time analytics to predictive and prescriptive modeling for disease prevention, diagnosis, and management. The integration of multiscale simulation, DTs, and AI is creating a new era of precision medicine and personalized health care. Data-driven decision-making is revolutionizing disease management and patient care. By leveraging predictive analytics, healthcare providers can anticipate disease progression and intervene earlier. This proactive approach improves patient outcomes and reduces the burden on healthcare systems. Simulation and DTs will empower clinicians and operational managers to use real-time data to streamline workflows and enhance the quality of care. By analyzing patterns in healthcare delivery, they can identify bottlenecks and inefficiencies, leading to policies that align with the goals of all stakeholders and provide safe, effective, efficient, and equitable patient care.

The multidisciplinary nature of this field allows for the convergence of healthcare professionals, engineers, data scientists, IT experts, AI specialists, etc. Such collaboration can lead to innovative solutions that address the existing challenges. Moreover, as these technologies become more integrated into health care, there will be a growing need for workforce training and upskilling to ensure that healthcare professionals can effectively leverage these advanced tools.

While technological advances in health care are promising, their successful adoption hinges on robust change management, implementation science strategies, and workforce upskilling. Crucially, comprehensive training is needed to equip healthcare professionals with the skills to leverage new digital capabilities effectively. This includes technical competencies, data literacy, human–AI collaboration, cybersecurity, and ethics. Investing in change management, implementation science, and strategic workforce development will be critical for healthcare organizations to capitalize on transformative technological advances. Several major societies and groups are active in related fields. The Society for Simulation in Healthcare (SSH) is a global community of medical educators who use various technologies, such as manikins and task trainers, to deliver educational interventions for skills and teamwork training [86]. The Winter Simulation Conference includes many engineers working on modeling and simulation in various industries [87]. The Interagency

Modeling and Analysis Group (IMAG) is a government group of program officials from multiple federal government agencies supporting research funding for modeling and analysis of biomedical, biological, and behavioral systems. IMAG is focused on research across the biological continuum across different scales or levels of resolution with modelers from multidisciplinary research communities [88]. The Medical Device Innovation Consortium (MDIC) primarily focuses on device innovation, using Computational Modeling and Simulation (CM&S) to reduce product development costs, speed up time to market, and better serve patients with safe and effective medical devices [37]. The Virtual Physiological Human Institute for Integrative Biomedical Research, commonly known as the VPH Institute, is another significant player in this field. Its mission is to ensure that the Virtual Physiological Human is fully realized, universally adopted, and effectively used in research and clinical settings [89]. The Europe Digital Twin in Healthcare (EDITH) project aims to capitalize on the growing trend of interest in Digital Twins [90]. EDITH creates a roadmap for future development, allowing stakeholders to exchange best practices, analyze ecosystems and data flows, and identify vulnerabilities. In addition, groups are working to prepare data for modeling. Mobilizing Computable Biomedical Knowledge is an international community focused on ensuring that biomedical knowledge in computable form is findable, accessible, interoperable, and reusable. A recent report from the National Academies of Sciences, Engineering, and Medicine presented an intergraded research agenda to advance the field. DTs can be a critical tool for decision-making base on the synergistic combination of models and data [91].

6 Conclusion

The emergence of simulation and DT technologies marks the beginning of a new era in health care. These technologies are practical tools that can improve disease management, care planning, and resource allocation. While there are undoubtedly challenges, such as technical complexities, ethical and regulatory hurdles, overcoming these obstacles will enable us to fully integrate simulation and DT technologies to support healthcare system digital transformation that serves all patients with safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity.

References

1. Yong PL., Olsen L, Jm M (2010) Value in health care: accounting for cost, quality, safety, outcomes, and innovation: workshop summary
2. Brandt AM (2012) A reader's guide to 200 years of the New England journal of medicine. N Engl J Med 366(1):1–7
3. Carayon P et al (2020) SEIPS 3.0: human-centered design of the patient journey for patient safety. Appl Ergon 84:103033

4. Wickramasinghe N et al (2007) Healthcare system of systems. IEEE Int Conf Syst Syst Eng 2007:1–6
5. Institute of Medicine Committee on Quality of Health Care (2000) In A., To Err is human: building a safer health system, In: Kohn LT, Corrigan JM, Donaldson MS (eds) To Err is Human: building a safer health system. National Academies Press, National Academy of Sciences, Washington (DC)
6. Makary MA, Daniel M (2016) Medical error—the third leading cause of death in the US. Br Med J 353
7. Blumenthal D et al (2020) Covid-19—Implications for the health care system. N Engl J Med 383(15):1483–1488
8. Kaye AD et al (2020) Economic impact of COVID-19 pandemic on healthcare facilities and systems: international perspectives. Best Pract Res Clin Anaesthesiol 35:293–306
9. Domecq JP et al (2021) Outcomes of patients with coronavirus disease 2019 receiving organ support therapies: the international viral infection and respiratory illness universal study registry. Crit Care Med 49(3)
10. Society for simuation in healthacre: what is simulation? (2024) 22 Apirl 2013. Available from: http://ssih.org/about-simulation
11. Cook DA, Erwin PJ, Triola MM (2010) Computerized virtual patients in health professions education: a systematic review and meta-analysis. Acad Med 85(10):1589–1602
12. Digital Twin Consortium (2024) Available from: https://www.digitaltwinconsortium.org/faq/
13. Kritzinger W et al (2018) Digital Twin in manufacturing: a categorical literature review and classification. IFAC-PapersOnLine 51(11):1016–1022
14. Cockrell C et al (2022) Generating synthetic data with a mechanism-based critical illness digital twin: demonstration for post traumatic acute respiratory distress syndrome. bioRxiv, p 517524, 22 Nov 2022
15. SIEMENS (2024) What is a digital twin? 2024; Available from: https://www.sw.siemens.com/en-US/technology/digital-twin/
16. Pesapane F et al (2022) Digital twins in radiology. J Clin Med 11(21)
17. Bjelland Ø et al (2022) Toward a digital twin for arthroscopic knee surgery: a systematic review. IEEE Access 10:45029–45052
18. Hernandez-Boussard T et al (2021) Digital twins for predictive oncology will be a paradigm shift for precision cancer care. Nat Med 27(12):2065–2066
19. Rivera LF et al (2019) Towards continuous monitoring in personalized healthcare through digital twins. In: Conference of the centre for advanced studies on collaborative research
20. Vallée A (2023) Digital twin for healthcare systems. Frontiers Digital Health 5
21. Pool R (1992) The third branch of science debuts. Science 256:44–47
22. Vodovotz Y (2023) Towards systems immunology of critical illness at scale: from single cell 'omics to digital twins. Trends Immunol 44(5):345–355
23. Lal A et al (2020) Development and verification of a digital twin patient model to predict specific treatment response during the first 24 hours of sepsis. Crit Care Explor 2(11):e0249
24. Lal A et al (2020) Artificial intelligence and computer simulation models in critical illness. World J Crit Care Med 9(2):13–19
25. Alquraishi M, Sorger PK (2021) Differentiable biology: using deep learning for biophysics-based and data-driven modeling of molecular mechanisms. Nat Methods 18:1169–1180
26. Yue R, Dutta A (2022) Computational systems biology in disease modeling and control, review and perspectives. NPJ Syst Biol Appl 8
27. Eddy DM, Schlessinger L (2003) Validation of the archimedes diabetes model. Diabetes Care 26(11):3102–3110
28. Schlessinger L, Eddy DM (2002) Archimedes: a new model for simulating health care systems–the mathematical formulation. J Biomed Inform 35(1):37–50
29. An G (2022) Specialty grand challenge: what it will take to cross the valley of death: translational systems biology, "True" precision medicine, medical digital twins, artificial intelligence and in silico clinical trials. Frontiers Syst Biol 2

30. An G et al (2009) Agent-based models in translational systems biology. Wiley Interdiscip Rev Syst Biol Med 1(2):159–171
31. McDaniel M et al (2019) A whole-body mathematical model of sepsis progression and treatment designed in the BioGears physiology engine. Front Physiol 10
32. Bray A et al (2019) Pulse physiology engine: an open-source software platform for computational modeling of human medical simulation. SN Compr Clin Med 1:362–377
33. Rovati L et al (2024) Development and usability testing of a patient digital twin for critical care education: a mixed methods study. Front Med 10
34. Pappalardo F et al (2019) In silico clinical trials: concepts and early adoptions. Briefings Bioinf
35. Viceconti M et al (2021) In silico trials: verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. Methods 185:120–127
36. Lal A et al (2022) Regulatory oversight and ethical concerns surrounding software as medical device (SaMD) and digital twin technology in healthcare. Ann Transl Med 10(18):950
37. Landscape report and industry survey on the use of computational modeling and simulation in medical device development (2023). Available from: https://mdic.org/resource/cmslandscapereport/#download_form
38. Successes and opportunities in modeling and simulation for FDA (2022)
39. Guidance document (2023) Assessing the credibility of computational modeling and simulation in medical device submissions, U.S.F.D. Administration, Editor
40. Romero-Brufau S et al (2021) Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study. BMJ 373:n1087
41. Cook DA et al (2011) Technology-enhanced simulation for health professions education: a systematic review and meta-analysis. JAMA 306(9):978–988
42. Cooper JB, Taqueti VR (2004) A brief history of the development of mannequin simulators for clinical education and training. Qual Saf Health Care 13:i11–i18
43. Gaba DM (2004) The future vision of simulation in health care. Qual Saf Health Care 13:i10–i12
44. Schmidt E et al (2013) Simulation exercises as a patient safety strategy a systematic review. Ann Intern Med 158(5_Part_2):426–432
45. McGaghie WC et al (2014) A critical review of simulation-based mastery learning with translational outcomes. Med Educ 48:375–385
46. Buléon C et al (2022) The state of distance healthcare simulation during the COVID-19 pandemic: results of an international survey. Adv Simul 7(1):10
47. Flurin L et al (2022) International virtual simulation education in critical care during COVID-19 pandemic: preliminary description of the virtual checklist for early recognition and treatment of acute illness and iNjury program. Simul Healthc 17(3):205–207
48. Ryall T, Judd BK, Gordon CJ (2016) Simulation-based assessments in health professional education: a systematic review. J Mult Healthc 9:69–82
49. Boulet JR, Murray DJ (2010) Simulation-based assessment in anesthesiology: requirements for practical implementation. Anesthesiology 112(4):1041–1052
50. Hayden JK et al (2014) The NCSBN national simulation study: a longitudinal, randomized, controlled study replacing clinical hours with simulation in Prelicensure nursing education. J Nurs Regul 5(2, Supplement):S3–S40
51. Kononowicz AA et al (2019) Virtual patient simulations in health professions education: systematic review and meta-analysis by the digital health education collaboration. J Med Int Res 21
52. Foronda CL et al (2024) A comparison of virtual reality to traditional simulation in health professions education: a systematic review. Simul Healthc 19(1s):S90-s97
53. Woodall WJ et al (2024) Does extended reality simulation improve surgical/procedural learning and patient outcomes when compared with standard training methods?: A systematic review. Simul Healthc J Soc Simul Healthc 19(1S):S98–S111
54. Gentry SV et al (2019) Serious gaming and gamification education in health professions: systematic review. J Med Internet Res 21(3):e12994

55. Small SD (2007) Simulation applications for human factors and systems evaluation. Anesthesiol Clin 25(2):237–259
56. Deutsch ES et al (2016) Leveraging health care simulation technology for human factors research: closing the gap between lab and bedside. Hum Factors 58(7):1082–1095
57. Ahmed A et al (2011) The effect of two different electronic health record user interfaces on intensive care provider task load, errors of cognition, and performance. Crit Care Med 39(7):1626–1634
58. Arriaga AF et al (2013) Simulation-based trial of surgical-crisis checklists. N Engl J Med 368(3):246–253
59. Patterson MD et al (2013) In situ simulation: detection of safety threats and teamwork training in a high risk emergency department. BMJ Qual Saf 22(6):468–477
60. Yeh VJ et al (2024) Using mobile and remote simulation as a research methodology for health care delivery research. Simul Healthc
61. Goldshtein D et al (2020) In situ simulation and its effects on patient outcomes: a systematic review. BMJ Simul Technol Enhanc Learn 6(1):3–9
62. Asamoah DA et al (2016) RFID-based information visibility for hospital operations: exploring its positive effects using discrete event simulation. Health Care Manag Sci 21:305–316
63. Haddara M, Staaby A (2018) RFID applications and adoptions in healthcare: a review on patient safety. Procedia Comput Sci 138:80–88
64. Abkari SE, Jilbab A, Mhamdi JE (2020) RFID medication management system in hospitals. Int J Online Biomed Eng 16:155–168
65. Sutton RT et al (2020) An overview of clinical decision support systems: benefits, risks, and strategies for success. NPJ Digital Med 3
66. Cristofoletti M et al (2023) Towards a computer vision-based approach for digital twin implementation. Int Conf Intell Metaverse Technol Appl (iMETA) 2023:1–6
67. Wang Y et al (2024) TWIN-GPT: digital twins for clinical trials via large language model
68. Elkefi S, Asan O (2022) Digital twins for managing health care systems: rapid literature review. J Med Internet Res 24(8):e37641
69. Karakra A et al (2019) HospiT'Win: a predictive simulation-based digital twin for patients pathways in hospital. IEEE EMBS Int Conf Biomed Health Informatics (BHI) 2019:1–4
70. Peng Y et al (2020) Digital twin hospital buildings: an exemplary case study through continuous lifecycle integration. Adv Civil Eng 2020:1–13
71. Croatti A et al (2020) On the integration of agents and digital twins in healthcare. J Med Syst 44(9):161
72. Augusto V, Murgier M, Viallon A (2018) A modelling and simulation framework for intelligent control of emergency units in the case of major crisis. Winter Simul Conf (WSC) 2018:2495–2506
73. Zhong X et al (2022) A multidisciplinary approach to the development of digital twin models of critical care delivery in intensive care units. Int J Prod Res 60(13):4197–4213
74. Karakra A et al (2018) Pervasive computing integrated discrete event simulation for a hospital digital twin. In: 2018 IEEE/ACS 15th international conference on computer systems and applications (AICCSA), p 1–6
75. Rodríguez-Aguilar R, Marmolejo-Saucedo JA (2020) Conceptual framework of digital health public emergency system: digital twins and multiparadigm simulation. EAI Endorsed Trans Pervasive Health Technol 6:e3
76. Currie CSM et al (2020) How simulation modelling can help reduce the impact of COVID-19. J Simul 14:83–97
77. Romero-Brufau S et al (2021) Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study. The BMJ 373
78. Zhang T et al (2023) Data-driven modeling and analysis for COVID-19 pandemic hospital beds planning. IEEE Trans Autom Sci Eng 20:1551–1564
79. Fackler J, Hankin J, Young T (2012) Why healthcare professionals are slow to adopt modeling and simulation. In: Proceedings of the 2012 winter simulation conference (WSC)

80. Combs CD, Combs PF (2019) Emerging roles of virtual patients in the age of AI. AMA J Ethics 21(2):E153-159
81. Jacoby M, Usländer T (2020) Digital twin and internet of things—Current standards landscape. Appl Sci
82. Stefanovski L et al (2021) Scales in Alzheimer's disease: biological framework for brain simulation with the virtual brain. Frontiers Neuroinformatics 15
83. Joshi A et al (2020) Opportunities for multiscale computational modelling of serotonergic drug effects in Alzheimer's disease. Neuropharmacology 174:108118
84. Coorey G et al (2022) The health digital twin to tackle cardiovascular disease-a review of an emerging interdisciplinary field. NPJ Digit Med 5(1):126
85. Stahlberg EA et al (2022) Exploring approaches for predictive cancer patient digital twins: Opportunities for collaboration and innovation. Front Digit Health 4:1007784
86. Society for Simulation in Healthcare (SSH) Council for accreditation of healthcare simulation programs accreditation standards
87. 2024 Winter Simulation Conference (2024). Available from: https://meetings.informs.org/wordpress/wsc2024/
88. IMAG: Interagency Modeling and Analysis Group (2024)
89. Virtual Physiological Human Institute (2024). Available from: https://www.vph-institute.org/
90. Europe Digital Twin in Healthcare (2024). Available from: https://www.digitaleurope.org/projects/ecosystem-digital-twins-in-healthcare-edith/
91. National Academies of Sciences, Engineering, and Medicine. Foundational Research Gaps and Future Directions for Digital Twins (2024). Available from: https://www.nationalacademies.org/our-work/foundational-research-gaps-and-future-directions-for-digital-twins