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ARCHIVES OF
CLINICAL AND
BIOMEDICAL RESEARCH

ISSN: 2572-5017

Research Article

Digital Twins in Healthcare: A Survey of Current Methods

Siddharth Ghatti[1*], Livvy Ann Yurish[1*], Haiying Shen[1#], Karen Rheuban[2], Kyle B. Enfield[2], Nikki Reyer Facteau[3], Gina Engel[2], Kim Dowdell[2]

Abstract

Digital twin technology has been increasingly applied in healthcare and patient well-being in recent years. This paper provides an overview of the current methods and applications of digital twins in the healthcare field. One such application is digital twins in precision healthcare, where digital twins are used to create patient-specific models to assist in diagnosis and treatment planning. Digital twins are also used in hospital/clinic management, where they help to optimize resource allocation and workflow processes. In response to the COVID-19 pandemic, digital twins have been utilized to detect outbreaks and predict disease spread. In addition, digital twins have been applied in bio-manufacturing and pharmaceutical industry to improve manufacturing processes. Another application area is machine learning and modeling, where digital twins are used in machine learning, data generation, and system modeling for applications in healthcare and disease prediction. Security and ethical issues related to digital twins are also discussed in this paper, as privacy concerns and data protection remain important considerations in the application of digital twin technology in healthcare. Finally, the paper concludes by discussing the future challenges and directions of future work in this field. These include the need to develop more accurate and sophisticated digital twin models, addressing interoperability and integration issues, and further exploring the potential of digital twin technology in emerging areas such as telemedicine and personalized medicine.

Keywords: Digital Twins; Health Care

Introduction

The technology of digital twins, which involves creating virtual replicas of physical objects or systems, has been gaining popularity in a range of industries, from manufacturing to transportation. In recent years, digital twins have also been finding applications in the field of healthcare, where they have the potential to revolutionize patient care and improve outcomes. The concept of digital twins was first introduced by Michael Grieves in 2003 and was later put into public use by NASA in 2012 [1]. The technology has continued to evolve and improve since then, making it more useful and accessible for a wider range of applications. Formally, digital twins are defined as digital representations of physical assets, reproducing their data models, behaviors, and communication with other physical assets [2]. Digital twins can be created for living and non-living things, and these computational models are calibrated to individual patients using multiple heterogeneous data streams [2]. This allows for the digital twin to act as a near replica of the physical asset, enabling near realtime monitoring and evaluation of the physical asset

Affiliation:

[1]University of Virginia, Department of Computer Science, Charlottesville, VA, USA

[2]University of Virginia, School of Medicine, Charlottesville, VA, USA

[3]University of Virginia, UVA Health System, Charlottesville, VA, USA

#Corresponding author:
Haiying Shen, University of Virginia, Department of Computer Science, Charlottesville, VA, USA, E-mail: hs6ms@virginia.edu

* - Primary authors with equal contribution.

Citation: Siddharth Ghatti, Livvy Ann Yurish, Haiying Shen, Karen Rheuban, Kyle B. Enfield, Nikki Reyer Facteau, Gina Engel, Kim Dowdell. Digital Twins in Healthcare: A Survey of Current Methods. Archives of Clinical and Biomedical Research. 7 (2023): 365-381.

Received: February 22, 2023
Accepted: March 21, 2023
Published: May 30, 2023

Ghatti S, et al., Arch Clin Biomed Res 2023
DOI:10.26502/acbr.50170352

[3]. Digital twins combine artificial intelligence (AI), big data, and mathematical modeling to make predictions about the future and take advantage of potential opportunities [4]. The field of health information technology is expected to continue to grow, with a projected valuation of $390.7 billion by 2024 [1]. This growth is driven by the increasing demand for innovative solutions that can improve patient outcomes and reduce healthcare costs. Digital twins have the potential to play a significant role in meeting this demand by enabling healthcare professionals to create virtual replicas of individual patients and their unique health needs. Digital twins offer several advantages within healthcare that traditional models cannot provide. By creating a digital replica of a physical asset, such as an individual patient, medical professionals can simulate potential outcomes and develop personalized treatments. In this way, digital twins can improve the efficiency of healthcare delivery and reduce the potential for negative outcomes. For example, digital twins can be used to simulate surgical procedures or test the efficacy of drug treatments before administering them to the patient. Additionally, the ability of digital twins to monitor patients in realtime allows for early detection of potential health issues and enables doctors to take preventative measures, such as altering treatment plans or conducting additional tests. The use of digital twins can also improve patient engagement and increase their understanding of their own health by providing a visual representation of their body and how it is functioning. Overall, digital twins have the potential to revolutionize healthcare by providing individualized care and improving patient outcomes. In recent years, the field of healthcare has seen a significant increase in the use of digital twins as a technology. As a result, it has become essential to discuss the different aspects and areas of application of digital twins in the healthcare field. One of the main advantages of digital twins is the ability to improve precision healthcare by creating personalized models of individual patients. This allows for a more tailored approach to treatment and care, which can ultimately lead to better outcomes. In addition, digital twins have shown promise in hospital/clinic resource management, allowing for the optimization of resources such as beds, staff, and equipment. Moreover, digital twins have been utilized in the detection and response to pandemics, such as the ongoing COVID-19 pandemic, where they have been instrumental in predicting the spread of the disease and informing public health interventions. Furthermore, digital twins have been utilized in the bio-manufacturing and pharmaceutical industry, where they have been used to model and optimize drug development and production processes. Finally, digital twins can also be used in machine learning and modeling applications, enabling the identification of trends and patterns in healthcare data. In this paper, we aim to provide an overview of the current methods and applications of digital twins in the healthcare field. Specifically, we will focus on four key areas: Digital Twins in Precision Healthcare, Digital Twins in Pandemic Response, Digital Twins in Bio-Manufacturing and Pharmaceutical Industry, and Digital Twins in Machine Learning and Modeling. In the section on Digital Twins in Precision Healthcare, we will present how digital twins have been used to create personalized treatment plans for individual patients. By creating a virtual replica of a patient's body and simulating different treatment options, healthcare professionals can identify the best course of action for that patient, reducing the risk of complications and improving outcomes. In the section on Digital Twins in Hospital/Clinic Management, we will discuss how digital twins have been used to optimize resource management in healthcare facilities. By combining data from different sources, digital twins can provide a real-time, comprehensive view of the operations in a hospital or a clinic. This can help healthcare providers to identify bottlenecks in patient flow, predict patient demand and adjust staffing levels accordingly, optimize supply chain management, and improve patient outcomes. In the section on Digital Twins in Pandemic Response, we will present how digital twins have been used to detect and respond to pandemics and other public health emergencies. By creating virtual replicas of cities and other public spaces, healthcare professionals can simulate the spread of disease and test different intervention strategies, helping to prevent the spread of infectious diseases and reduce the impact of pandemics. In the section on Digital Twins in the Bio-Manufacturing and Pharmaceutical Industry, we will explore how digital twins have been used to improve the efficiency and effectiveness of the pharmaceutical industry. By creating virtual replicas of the manufacturing process, researchers can identify potential bottlenecks and other inefficiencies, and test new production strategies in a safe and controlled environment. Finally, in the section on Digital Twins in Machine Learning and Modeling, we will present how digital twins have been used in machine learning and modeling in healthcare. Digital twins are utilized for federated machine learning techniques, generating synthetic data, and system modeling in areas such as healthcare and disease prediction, and for creating decision support systems. However, these digital twin applications raise concerns around data privacy, security, and ethical considerations, which must be addressed before implementation. Therefore, we will also explain the security and ethical issues associated with the use of digital twins in healthcare. Finally, we will discuss the challenges and directions for future work in this field. Ultimately, we hope that this paper will provide a useful overview of the current state of technology in the context of the use of digital twins within the field of healthcare, and help to inform and inspire future research in this area. The rest of the paper is organized as follows. Section II presents several survey papers as related work of this paper. Section III prevents a review of the current methods and applications of digital twins in the healthcare field, focusing on the four key areas, and discusses the security and ethical issues in using digital twins. Section

IV discusses the future work and challenges. Finally, Section V concludes this paper.

Related Work

There have been several surveys conducted on the utilization of digital twins in the healthcare and other fields. Hassan et al. [5] reviewed the applications of the digital twin technology in the healthcare area, and indicated thatit has become increasingly important due to the COVID-19 pandemic. They reviewed current trends and functionality, and proposed a paradigm of digital twinning everything as a healthcare service, and discussed the challenges and insights for future research. Erol et al. [6] presented the important digital twin studies conducted in different branches of health, which could lead to new studies, and discussed about their predictions about what kind of developments these technologies may develop in the future. They indicated that in addition to the health field, detailed studies can be carried out on other areas such as aerospace, military, education, security systems, and on more specific application areas that have not been done yet in the field of health. Khan et al. [7] studied the characteristics of digital twins, communication technologies and tools utilized in the creation of digital twin models, reference models, standards, and the researcher's recent work in smart manufacturing and healthcare, and also discussed the challenges and open issues. Fuller et al. [8] presented a categorical review of publications relating to digital twins based on three research areas: manufacturing, healthcare and smart cities, they provided an assessment of the enabling technologies, challenges and open research for digital twins. Yang et al. [9] provided a survey of the major research and application areas of the use of digital twins in a variety of fields, especially in industry, smart cities, and smart health. The survey first presents the recent developments of digital twins, then summarizes the theoretical underpinnings of the technology, and finally concludes with specific developments in various application areas of digital twins. It also discusses the potential challenges that may arise in the future. Erol et al. [10] discussed the current works and future opportunities for applying digital twins in health, industrial, smart city management systems applications. Although some surveys have focused on the use of digital twins in different fields including healthcare, this paper will exclusively focus on the utilization of digital twins in the context of healthcare technologies. There have been several surveys conducted on the utilization of digital twins in various industries, including manufacturing and teaching [11-15]. These surveys have highlighted the potential for digital twins to improve productivity across different sectors, with some examples being in the construction industry [6,16]. For instance, digital twins have been used to improve construction processes, evaluate materials used in buildings, and enhance the safety of hoisting mechanisms used in pre-fabricated buildings [17-19]. In addition, digital twins have been utilized for post-earthquake evaluations of buildings and bridges [20,21]. Some surveys have focused on proposing frameworks and models to deploy digital twins as tools in industry or to improve edge Internet-of-Things (IoT) device-based networks [22-25].

Survey of Digital Twins in Healthcare

James [26] indicated that digital twin technology has the potential to transform healthcare in a variety of ways including enhancing the diagnosis and treatment of patients, optimizing preventive care, and enabling new strategies for hospital planning. The following section provides a comprehensive review of the applications of digital twins in healthcare. To facilitate the discussion, we categorize these applications into four areas: precision healthcare, pandemic response, bio-manufacturing and pharmaceutical industry, and machine learning and modeling. Each category represents a distinct area of application where digital twins have shown significant potential in improving patient care and advancing medical research.

Digital Twins in Precision Healthcare

Precision healthcare can be defined as an approach to healthcare that takes into account the variability in a patient's genetics, lifestyle, and environment when prescribing a treatment [27]. Currently, digital twins are being used to advance precision healthcare by leveraging genetic or molecular markers to identify specific diagnoses and corresponding treatments [28]. This represents a significant departure from the traditional approach of one-size-fits-all treatment based on the average person, and enables more personalized and effective treatment options for individual patients.

Digital Twins for Elderly Care and Patients: One area where the use of digital twins as a means of administering precision healthcare has been effective is in the care for the elderly [29]. Leveraging the capabilities of cloud technology and IoT devices, Liu et al. proposed a novel cloud framework, ClouDTH that leverages the digital twin of a patient to actively monitor and manage their health-related information [30]. As part of their evaluation of ClouDTH, they conducted a case study of their framework, which included a notification system that alerts patients to take their medication based on their vital signs. Digital twins can also be used to detect when elderly people are in a stage of pre-frailty, in order to restore their health before they become frail [31]. As rates of frailty increase due to longer work hours and stress, detecting pre-frailty with digital twins can be crucial in preventing conditions from worsening. Additionally, elderly people can use digital twins to personalize their nutritional approach [32]. Furthermore, studies have explored the use of digital twins to revolutionize the management of obesity and its comorbidity, helping patients avoid major complications as

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Ghatti S, et al., Arch Clin Biomed Res 2023
DOI:10.26502/acbr.50170352

they age [33]. The field of disease detection and prediction has also seen the use of digital twins. For instance, one application of digital twins involves predicting the treatment response of patients with sepsis within the first 24 hours of diagnosis. This is achieved by constructing a digital model that utilizes graph structures to represent the causal relationship between organ systems and treatments used. Techniques such as agent-based modeling, discrete-event simulation, and Bayesian networks are then employed to predict how medication will affect the organ systems [34]. Another example involves using IoT-enabled medical devices to detect and monitor respiratory sounds in patients, with the aim of identifying respiratory diseases. These devices, such as chest-wearable and mobile devices, can be combined to create a digital twin that allows for personalized healthcare [35]. Digital twins have also proven to be valuable predictive tools in oncology, the study of cancer. Numerous studies have utilized digital twins to better understand cancer progression and treatment outcomes [36-39]. Digital twins have also been utilized in modeling cancer treatments [40]. For example, research has used modeling technologies and virtual reality to create a digital twin of a radiotherapy system to evaluate its reliability and usability for users [41]. Overall, the use of digital twins in the cancer disease detection and prediction shows great potential in improving patient outcomes and advancing medical research. One area of recent research has been in using digital twins for the purpose of detecting breast cancer in patients. Specifically, by monitoring and modelling the patient's bio-heat model, breast cancer can be diagnosed non-invasively [42]. Researchers have combined machine learning-based digital twins with other technologies to develop new diagnostic and treatment tools. For example, a framework for visualizing and predicting cancer diagnosis using artificial intelligence and a human digital twin has been developed using augmented reality [43]. Additionally, research has been conducted on the use of Deep Q Networks and digital twins to optimize treatment steps for head and neck cancer patients based on patient data, such as age and tumor grade [44]. These Deep Q Networks were trained to provide a decision-making tool for planning a three-step treatment program for patients with head and neck cancer. Digital twins have also been studied in the field of cardiology to provide precision healthcare [45-47]. Cardiology, the study of the heart and its diseases, can benefit greatly from digital twins. For example, Corral-Accreo et al. conducted a survey of the possible uses of digital twins in healthcare and emphasized the potential of computational models to boost cardiovascular research [48]. One application of digital twins in cardiology is the prediction of hypertension. A proof-ofconcept model was built using data from 47 patients to create a mathematical model of blood circulation, which can be used as a digital twin to predict hypertension [49]. Additionally, digital twins have been used to model the electro-mechanical components of the heart, with a two-step process to build a personalized low-fidelity model for a patient followed by finetuning it to a higher fidelity [50]. Another application of digital twins in cardiology is the development of a digital twin of a heart to predict the proper treatment for a patient, whether that involves a non-invasive procedure or medication plan [51]. Digital twins of human cells have also been studied [52,53] with applications in precision healthcare [54]. For instance, one research direction has explored building digital twins at a cellular level and using the metabolic changes modeled in the digital twins to investigate cancer [55]. Digital twins have been used to detect signs of dementia without conducting interviews. Kobayashi et al. [56] proposed a system that digitally transforms a subject's behavior using installed communication robots, ambient sensors, and wearable devices to configure the subject's digital twins. They confirmed that with high accuracy that the system successfully detected cognitive and life function disorders from daily life. Ferdous et al. tested the assumption that smartwatches with digital twin technology could monitor physical health aspects of dementia patients, benefiting home-based care [57]. Digital twins can also identify ways to treat diseases. Through multilayer modules, where several types of molecules are mapped on the protein-protein interaction (PPI) network, scientists can identify what problems in genes, proteins, and cells are causing the patient's disease and treat them accordingly [58]. Additionally, a digital twin model of human head vibrations and blood flow has been used to predict the severity of carotid stenosis [59]. The model was trained using computer vision on input videos of the patient's face to build the combined head vibration/ blood flow model, allowing for the prediction of the severity of carotid stenosis. Digital twins have also been employed to track and monitor the prevalence of diseases by utilizing patient data. For instance, a digital twin of a building was utilized to monitor the internal conditions of the building, such as temperature and humidity, along with survey responses from occupants to track and monitor the prevalence of sick building syndrome within the occupants of the building [60]. Digital twins have been employed in the healthcare industry to provide better care for patients with ongoing medical conditions [61]. One example of this is the use of digital twins in the treatment of Multiple Sclerosis, a disease that affects the brain and spinal cord by triggering the immune system to attack these areas [62]. While treatments for this disease focus on speeding up recovery from attacks and reducing negative impacts on the patient, Voigt et al. proposed using digital twins to actively track and monitor patient data with the goal of preventing the progression of the disease [63]. By continuously collecting medical data over the course of a year, rather than only during a patient's periodic clinic visits, digital twins can aid in early detection of changes in a patient's health status and enable doctors to respond more quickly. Digital twins have also been researched for the treatment and diagnosis of other spine and bone related

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DOI:10.26502/acbr.50170352

medical conditions in patients beyond Multiple Sclerosis [64,65]. For instance, digital twins have been used to model a patient's vertebral column and predict fracture risk using a generative adversarial network called ReconGAN that is trained on quantitative micro-computed tomography images of the vertebral bones [66]. This digital twin is then used to predict the risk of vertebral fracture based on a patient's specific image data. In addition to modeling bones, digital twins have also been used to monitor patient behavior in treatment approaches, such as correcting the posture of those with Parkinson's disease, a neurodegenerative disease that can impair movement [67,68]. Another example is the use of digital twins to help individuals with Type 2 diabetes reverse their condition. By continuously collecting data on glucose levels, blood pressure, food intake, and other factors, a digital twin can be created to represent an individual's metabolism. Through a phone app, individuals can access recommendations for how much to eat, sleep, and exercise. They can also input what they eat and get real-time predictions on how their glucose levels will react based on their digital twin in order to reverse their diabetes [69]. In a study involving 19 females and 45 males with Type 2 diabetes who adhered to the Twin Precision Treatment Program, the program's digital twin helped the patients achieve low glycemic variability, as well as significant reductions in Body Mass Index (BMI) and blood pressure (BP) [70]. Digital twins have also been used for diagnosing and treating diseases by modeling a patient's colon and evaluating the effect of prescribed medication on the patient [71]. In addition to physical conditions, digital twins have also been researched as a tool to help individuals manage their mental health disorders, such as depression and stress [72]. One example is the digital twin of Mental Stress (DTMS) model [31], which uses IoT-based multi-modal sensing and machine learning techniques for mental stress prediction, with the goal of creating a digital replica of stress during the COVID-19 pandemic. The research achieved 98 percent accuracy for four widely used machine learning algorithms in predicting stress levels of human participants. The authors suggested that this model could replace in-person stress prediction and avoid the associated hassles.

Digital Twins for Surgeries: Digital twin technology has the potential to be a tool for surgeries in the future. Surgeons can create a digital twin of the patient they will operate on and practice the surgery beforehand, enabling them to detect any potential complications. This will allow surgeons to test new techniques or tools on the digital twin before using them on their patients, thereby reducing the risk of mistakes and complications [73]. Additionally, digital twins are being developed to facilitate remote surgeries, where patients can be operated on without the physical presence of the surgeon [74]. This work utilizes a robotic arm and a virtual reality system connected over a 4G network to create a digital twin of robotic surgeries. The ultimate goal is to gather data within the required network latency necessary to successfully facilitate remote surgeries. Surgical training can benefit from digital twins by enabling trainees to abstract away from real, risky operations and practice the task accurately [75]. In addition to aiding surgical procedures, digital twin technology can also enhance the training of medical residents before they become doctors [73]. In the field of arthroscopic surgery, traditional apprenticeship training has given way to simulation-based training, but the potential of expanding surgical simulations to digital twins remains unexplored. Bjelland et al. introduced an arthroscopic digital twin that utilizes patientspecific data and interactive surgical soft tissue simulation methods [76]. Another promising area of research involves using digital twins for coronary stenting, a process used to clear clogged arteries [77]. This study focuses on building patient-specific artery models through image-based approaches to conduct simulations of coronary stenting. Digital twin technology is also applicable for trauma management and associated surgical procedures [78]. The management of trauma comprises two critical phases: pre-hospital and operative phases. In the pre-hospital phase, the digital twin system would encompass the ambulance, Emergency Medical Technicians (EMT), patient, and location of the accident. In the operative phase, the digital twin system would include the patient, the physician, and the equipment used. By leveraging this technology, trauma patients can be treated efficiently in critical situations where every minute counts.

Digital Twins as Active Monitoring Tools: In the field of healthcare and patient well-being, there is a need for active monitoring of patient data streams to ensure their safety and well-being. Digital twins have been found to be an ideal tool for this purpose [79]. In fact, digital twins have been researched and utilized as monitoring tools in various fields, including industrial personnel safety [80], motivating sedentary patients to exercise [81], and enhancing athletic training regimens [82]. One study created digital twins of workers in nuclear power plants to monitor their health and ensure safe and effective shifts [80]. For sedentary patients, digital twins were built using health devices and user interaction, along with motivational methods, to encourage exercise [81]. On the athletic side, an athlete's digital twin could be created with data about their lifestyle, such as diet, activity preferences, and sleep patterns. Based on the athlete's future food, sleep, and activity choices, the digital twin could predict their performance and advice on lifestyle changes to improve performance, thus helping athletes and trainers achieve their goals faster [82].

Digital Twins in Hospital/Clinic Management

The study in [83] studied the convergence of Medical Devices (MD) and Digital Twin (DT) technologies, and analysed whether invention convergence is a valid predictor of technological significance. The research is based on a

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DOI:10.26502/acbr.50170352

statistical analysis of patent data records, which reveals that convergent MD-DT inventions are more technologically significant compared to non-convergent inventions. The study suggests potential future directions for the information technology field.

Hospital Process Optimization: Digital twins are increasingly being used as a simulation tool to optimize the use of resources in hospitals and healthcare centers, particularly outside of emergency situations [84,85]. For instance, Karakra et al. [86] developed a digital twin to model a hospital's healthcare delivery systems and services. This model enables the hospital to evaluate the current state of their services and simulate changes to services without disrupting dayto- day operations, such as patient care. The use of digital twins in this way can help hospitals identify areas for improvement and optimize their use of resources, leading to more efficient and effective healthcare delivery. Digital twins have proven to be an effective tool in designing efficient vaccination clinics by monitoring and optimizing resource utilization. Near Field Communication (NFC) systems are used to track the time spent by patients at each step in the vaccination process, and the data is analyzed to identify inefficiencies in the system. With this information, clinic managers can propose and implement solutions to improve efficiency [87]. Pilat et al. [87] developed a simulation model of the vaccination process at a clinic in South Tyrol, which was used to test different configurations of resources. The most sustainable configuration was determined based on the number of patients that could be vaccinated every hour by a single nurse. Their model achieved the vaccination of 2164 patients in a 10-hour shift, with a process time of 25 minutes. Similar research has been conducted using IoT devices and artificial intelligence models to create digital twins of hospitals with real-time patient data to predict patient outcomes based on their healthcare data. This allows for better resource allocation, such as providing the correct treatment and resources like ventilators and medications at the right time to the right patient [88]. A case study of a digital twin integrated hospital showed a desired increase in hospital performance by reducing electricity consumption, avoiding facility faults, and reducing overall maintenance [89].

Equipment/Resource Management: As the use of IoT and data-driven devices in healthcare facilities continues to increase for smarter management purposes [90,91], there is growing interest in understanding how digital twins can be leveraged for better healthcare facility management. Preliminary research suggests that utilizing digital twins can facilitate effective decision-making and improve healthcare services [92,93]. A particular area of focus has been on utilizing digital twins to improve management in crisis areas of healthcare facilities, such as emergency departments. Research has been conducted to enable active monitoring and tracking of resources in emergency departments for more intelligent utilization of resources, as well as the ability to model and predict the department's capabilities in various "what-if" scenarios [94]. Similar work has been undertaken to model and simulate events to aid in better management of equipment and staffing decisions in intensive care units, specialized hospital treatment units designed to provide care to patients who are extremely ill [95]. One potential application of digital twins in healthcare is monitoring the health and condition of medical equipment used to combat Covid-19 in healthcare centers. For instance, digital twins can be used to model and monitor the performance of medical equipment, such as X-ray and CT scan machines, which are used for diagnosing Covid-19 infections. The objective is to optimize the use of each piece of equipment while accurately predicting maintenance needs [96]. Another area where digital twins have been utilized to combat and support the fight against Covid-19 is in resource delivery. For example, digital twins have been used to model the flight and delivery capabilities of unmanned aerial vehicles (UAVs) to test the feasibility of using UAVs for delivering medical supplies through simulation experiments [97]. The digital twins output the possible flight paths of the UAVs, which is used to determine whether using UAVs for delivering resources is a viable solution.

Digital Twins in Pandemic Response

Digital twins have been used for Covid-19 and pandemic detection. Pang et al. [98] proposed a collaborative city digital twin based on federated learning to allow multiple city digital twins to share their local strategies and status in a timely manner. The federated learning provides a global model that is trained in multiple iterations until it gains correlations between various response plans and infection trends. This allows the collaborative city digital twin to obtain knowledge and patterns from multiple digital twins, establish a global view for city crisis management and improve each city digital twin without violating privacy rules. Burgos and Ivanov [98] studied the impact of the COVID-19 pandemic on food retail supply chains and their resilience using a discrete-event simulation model based on real-life pandemic scenarios encountered in Germany, with the help of anyLogistix digital supply chain twin. The results suggest that food retail supply chain resilience during the pandemic is affected by the pandemic intensity and associated lockdown/shutdown governmental measures, inventory-ordering dynamics, and customer behaviours. The authors proposed several practical implementation guidelines to improve supply chain resilience, and indicated the importance of digital twins. Quilodr´an-Casas et al. [99] introduced two digital twins of a SEIRS model which can predict complex dynamics at lower computational overhead. They compared one digital twin based on a data-corrected Bidirectional Long Short-Term Memory network with another digital twin based on a

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DOI:10.26502/acbr.50170352

predictive Generative Adversarial Network. The predictions from these digital twins are accurate. Pilati et al. [100] created a digital twin to optimize the vaccination process to achieve a sustainable and dynamic vaccination center. Schmidt et al. [101] proposed using digital twins to improve manufacturing capacity for COVID-19 vaccines. They introduced a digital twin of the pDNA to mRNA process, with multisensory PAT used for process monitoring. It could be used for process optimization and manufacturing operations. Security threats must be considered when applying digit twins to healthcare. For this purpose, Azzaoui et al. [102] proposed a Blockchain-based secure digital twin framework for a smart healthy city. They discussed as a case study the current COVID-19 pandemic and argue on the use of digital twins to control the situation, prevent future cases, and personalize the treatment. Cecconi et al. [103] proposed strategies to monitor and correct indoor air conditions by application a digital twin to the building management system. It enables real-time data collection and corrective actions. A soft digital twin coupled with an IoT network measure CO2 emissions and particulate matter pollutants while balancing ventilation rates and comfort. A particulate matter sensor verifies the influence of increased ventilation on outdoor pollutants. Alrashe et al. [104] indicted that in countries such as Pakistan, which has a large population and struggles with social distancing, data shows the efficacy of social distancing measures in preventing the spread of COVID-19, and digital twin technology can be deployed to provide essential services and facilities. The authors highlighted a few areas where digital twins can be created/deployed to provide services and essential facilities to citizens. Benedictis et al. [105] focused on the application of digital twin technology for virus containment in the workplace through social distancing. They presented a classification of digital twin applications and a generalized architecture, and also introduced a real-life industrial case study developed by Hitachi called CanTwin. Kotecha et al. [106] indicated the need for a functional modeling-based representation of digital twinning architectures, specifically for product digital twins. They reviewed existing digital twin architectures and frameworks and identified gaps that need to be addressed, and proposed a functional modeling-based digital twin architecture representation approach to address the identified gaps. They illustrated the approach through an example of a COVID- 19 testing breathalyzer kiosk. Barat et al. [107] developed a configurable, fine-grained agent-based digital twin, of a diverse and heterogeneous area such as a city to address the tradeoffs between individual health and safety, and socio-economic progress. The model is used to simulate various scenarios to predict the spread of the virus, understand the effectiveness of candidate interventions, and predict the consequences of intervention strategies that could lead to trade-offs between public health, citizen comfort, and the economy. Chen et al. [108] combined the digital twin technology with the blockchain and deep learning algorithms to improve the information security and prediction accuracy of epidemic prevention and control in smart cities, specifically for the COVID-2019 epidemic. The '15-minute city' concept is emerging as a potent urban regeneration model in post-pandemic cities. Allam et al. [109] argued that the '15-minute city' concept can value-add from Smart City network technologies in particular through digital twins, IoT, and 6G. The data gathered by these technologies, and processed via machine learning techniques, can unveil new patterns to understand the characteristics of urban fabrics.

Digital Twins in Bio-Manufacturing and Pharmaceutical Industry

Bio-manufacturing refers to the process of producing a product using biological systems that have been engineered or are operating outside of their natural context [110]. The pharmaceutical industry is an extensive field that includes the exploration, advancement, and production of drugs and medications [111]. In the following, we discuss the applications of digital twins in these two areas.

Medical Devices/Vaccine Manufacturing: When digital twin technology was first introduced, it was mainly used in the context of simulating manufacturing and industrial processes [112]. Recently, digital twins have been used to optimize the benefits of human operators involved in the manufacturing process, with examples listed in [113-116]. The focus of the digital twin research has been on optimizing manufacturing processes using the data modeling and monitoring capabilities of digital twins. One example of this is the use of digital twins to speed up the manufacturing of mRNA-Based Covid-19 Vaccines. The research focused on increasing manufacturing capacity, reducing the number of batch failures, speeding up the validation processes, and optimizing the utilization of sparse chemicals within the vaccine manufacturing process [101]. Another area of research investigates how digital twins can be used to create re-configurable and more sustainable manufacturing processes [117]. This research is particularly relevant in the manufacturing of medical equipment, which experienced a surge in demand due to the Covid-19 pandemic [118].

Supply Chain Management: Digital twins have been used to evaluate supply chain practices in the pharmaceutical industry. In one study, a digital twin was constructed using simulators and data analytical tools, and it was used to examine supply chain methods in the pharmaceutical industry [119]. The research found that the Stock-Security policy, which involves overestimating stock to ensure delivery of pharmaceutical products, was the best stocking policy for the industry. Another example of the use of digital twins in supply chain management is related to the production of N95 medical masks during the Covid-19 pandemic [120]. In this case, digital twins were used to simulate supply chain dynamics, with the output being the supply of N95 medical masks. The research found that an emergency decision cost and profit model with a fully shared supplier mode is more effective than a partially shared supplier mode. The fully shared supplier mode is a strategy for overcoming interruptions in the supply chain that involves full sharing with the supplier, while the partially shared supplier mode does not fully share the strategy. The research also found that a capacity repair strategy performs significantly better than the traditional strategy. This example highlights the potential for digital twins to optimize supply chain management in times of crisis. Digital twins also have been becoming increasingly useful in the field of e-health, where they can be utilized to design and develop software more effectively [121]. By creating digitaltwins of a patient, the user group, and the software itself, it is possible to improve the design and publication of software for use in e-health.

Digital Twins in Machine Learning and Modeling

Machine Learning: In recent years, there has been an increasing use of federated machine learning techniques, a decentralized approach to machine learning where the data used for the model is not on a centralized platform but on each individual device to preserve user privacy [122]. Digital twins have been researched as a tool for federated learning in the healthcare space, where a majority of collected data is private information [123]. By routing a patient's data in the digital twin service to an anomaly detection model in the cloudlet, anomalies can be detected. The local parameters of the anomaly detection model are then sent to the hospital cloud server to be exchanged with other anomaly detection models using a grouping approach that enhances the accuracy of local anomaly detection models. Apart from federated learning, digital twins have also been utilized in more traditional learning architectures, such as deep learning, to predict and analyze patients' cardiac states [124]. In one study, the authors proposed a hybrid deep learning (HDL) network designed for synthetic three-directional CINE multi-slice myocardial velocity mapping (3Dir MVM) data. The HDL algorithm can be implemented in real-world digital twins for myocardial velocity mapping data simulation. This research may involve both traditional deep learning architectures and edge devices, which operate on the boundaries of wireless networks and transfer traffic into a network, to further improve patient outcomes [125,126].

Data Generation: Digital twins are also used to generate synthetic data for training machine learning models that diagnose and predict diseases. A digital twin of the cardiovascular system was used to generate synthetic Photoplethysmogram (PPG) data with varying blood pressure and blood flow parameters, for the purpose of training machine learning models [127]. Digital twins have also been used to aid in the generation of knowledge for AI-based image segmentation. One application of this is using digital twins in combination with lightweight deep learning for the segmentation, detection, and tracking of stem cell images, resulting in more accurate and clearer image contours and higher accuracy than traditional phase contrast imaging [128]. Furthermore, research has shown that digital twins trained with Semi-Supervised Support Vector Machines (S3VMs) can significantly improve brain image segmentation and fusion, outperforming other state-of-the-art models such as Long Short-Term Memory (LSTM), Convolutional Neural Network (CNN), Recurrent Neural Network (RNN), and others [129].

System Modeling: One area of digital twin application is data modeling, ranging from modeling joint angles in patients while they walk [130] to detecting human poses using inertial sensors [131]. Other areas of research include modeling an entire human being through their digital twin [33,132] and even modeling the health of all citizens within a city [133]. For the purposes of this section, two types of data models have been focused on: mechanistic models and machine learning models. Mechanistic models are generated by creating causal mechanisms through observation of the variables of interest, and are often used to model biological systems [134]. Machine learning models, on the other hand, are trained to learn patterns across a large set of data. Digital twins have also been utilized to model biological systems [135]. One example is the utilization of digital twins as mechanistic models to model the human heart using electrophysiology and physics mechanics [136]. Another example is the utilization of digital twins for modeling the primary visual cortex of mice [137]. Specifically, the digital twin combined large-scale photon imaging and deep learning neural network models to model and output the sequence of various neurons that are activated in the visual cortex of a mouse when given visual input [137]. In an effort to take modelling these systems a step further, An et al. made three-dimensional bioprinting a reality by using these biological digital twins in combination with big data [138]. Outside of biological system-based models, digital twins have also been used as machine learning-based models to model the progression of cognitive diseases such as Alzheimer's disease, a cognitive disease that causes loss of cognitive functions over time due to atrophy of the brain [139,140]. Machine learningbased digital twin models have also been used to model the progression of cancer, both in pediatric cases [141] and adult cases [142] with prostate cancer. They have also been used to accurately detect and diagnose heart disease [143] using electrocardiogram (ECG) readings. Digital twin-based models have been utilized not only for modeling and representing clinical data but also as sources to use data mining techniques [144]. The application of digital twins and data mining techniques have been investigated for creating decision support systems [145]. Another area of research has been using digital twins as a hybrid model, which is a model that is both mechanistic and

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machine learningbased. One example of this is utilizing a mechanistic model to simulate a patient's blood pressure over time and then feeding this data into a machine learning model to calculate a patient's 5-year risk of stroke [146].

Security in Digital Twins

The availability of digital twins naturally raises several privacy concerns. The government will need to create protections for citizens who have digital twins to ensure that their data will not be misused. Specific protections that a government can implement include data privacy and transparency of data usage [147]. Beyond the potential for companies to use data for malicious intent, there is also the risk of companies' databases being hacked and sensitive information being stolen. Therefore, it is crucial that companies who collect data for digital twins establish strong security systems to prevent breaches [148]. Additionally, digital twins in the healthcare field, particularly in the fields of neurology and psychiatry, will deal with highly sensitive information. It is imperative that this information is treated in the most secure and ethical way possible [149]. In the following, we present the security technologies.

BlockChain Technologies: One area of interest is the use of blockchain technology in combination with the data monitoring capabilities of digital twins to improve pandemic response. Ye et al. developed a novel framework based on the experiences of healthcare facilities in the United Kingdom to support pandemic response using blockchain technology and digital twins [150]. Lu et al. investigated the integration of patient health information records and hospital resource flow (such as hospital equipment and available medications) into a digital twin, with the information being secured by the blockchain, to optimize decision-making on resource deployments [150]. Similarly, research has been conducted to create a rapid alerting system for pandemic responses that utilizes artificial intelligence, blockchain technology, and the data monitoring capabilities of digital twins [151]. Sahal et al. used the blockchain to secure sensor readings of patients, such as body temperature, which are used to construct the digital twins as part of an alerting system that could be used to notify users about possible exposure to COVID- 19 or other diseases in the future [152]. A recent project has investigated the integration of the blockchain technology with digital twins in healthcare to enhance the security of patient information [153]. To achieve this goal, the researchers developed a framework that employs a mathematical model to organize and accumulate patient data. The system creates a digital twin for each patient that interacts with the digital twins of hospital resources, such as ventilators, while ensuring that all access to the patient's health data is secured by the blockchain [153]. This approach increases transparency, improves interoperability between different healthcare systems and the accuracy of the patient's health status.

Artificial Intelligence Approaches: An example of this type of work involved using a Code Bidirectional Encoder Representation from Transformers (CodeBERT) based neural network model to read and analyze the written source code of a digital twin software. The goal was to identify and remove any code that could introduce security vulnerabilities into the software [154]. The digital twin in this instance represents the health information of a patient, and the output of the software is a more secure version of the digital twin. Similarly, another study utilized a deep neural network to recognize search words or keywords that could compromise the security of patients' data when querying a digital twin-based AI system that was used for treating lung cancer [155]. The ultimate objective of this system is to ensure the privacy of patients' data. In another example, a convolutional neural network-based framework was developed to differentiate between spoofed and authentic biometric authentication samples [156]. This framework was designed to protect against unauthorized attempts to access e-health cloud data, thereby safeguarding the privacy and security of user data.

Privacy Preserving Database: There has been a recent surge in the development of frameworks that leverage cloud computing and digital twins to improve healthcare services [157]. However, the issue of data privacy and security has yet to be adequately addressed in many of these frameworks. This is the very problem that the PSim-DTH (Privacy preserving Similarity Query Scheme for Digital Twin-based Healthcare services) aims to resolve [157]. The PSim-DTH scheme is based on a partition-based tree that indexes healthcare data and uses matrix encryption to create a privacy-preserving partition-based similarity query algorithm. This scheme is specifically designed for accessing healthcare data in a privacy-preserving manner whenever an external vendor queries the data through a healthcare center's data center. By utilizing PSim-DTH, healthcare providers can ensure that the privacy and security of their patients' data are maintained while still enabling authorized organizations, such as other healthcare providers, to access the information stored in the digital twins of the patients.

Ethical Issues of Digital Twins

When creating digital twins of physical entities, especially if those entities are human beings or related to human beings, ethical concerns arise. For the purposes of our discussion, ethics can be defined as the branch of philosophy concerned with what is morally good and morally wrong [158]. Privacy is a significant concern when it comes to digital twins, but there are also worries that they may exacerbate societal divisions. If everyone's physical and mental strengths and weaknesses are available as data points for public analysis, it could lead to discrimination. Additionally, it is unlikely that digital twins will be accessible to poorer segments of the population until it becomes inexpensive to implement. This means that wealthier segments of society will be able to enhance their lives with digital twins while poorer segments will not have access to this technology [147]. Digital twin models rely on complex algorithms, but algorithms and datasets have the potential to be biased. Society tends to place trust in data-driven findings without considering the possibility that the results could be biased. For instance, an algorithm could erroneously link a particular ethnicity to heart disease without considering the average income levels of each ethnicity [159]. Therefore, it is crucial that digital twin studies are carefully evaluated to avoid discrimination.

Future Work and Challenges

Although there has been a significant amount of work and research on integrating digital twins in healthcare, there are still many challenges ahead. We will now present a few of these challenges.

Efficient Computing

One of the primary challenges in utilizing digital twins in the healthcare area is the vast amount of data that is generated. Digital twins require a large amount of data to perform effectively, which could require high storage, processing and bandwidth capacities, and hence generate efficiency issues. In order for digital twins to be usable in healthcare systems, efficient storage and computing systems must be developed to manage and process the vast amounts of data. As data continues to grow exponentially, there is a growing need for advanced computing power to be able to handle the computational load of digital twin systems. Cloud computing can provide scalable and flexible computing resources, which can allow for more efficient and cost-effective digital twin systems. Further, emerging systems such as edge computing has shown great promise in addressing the issues of computing efficiency. Edge computing enables processing data closer to where it is generated, thus reducing the amount of data needed to be transferred, and decreasing latency.

Privacy

Another critical challenge in the integration of digital twins in healthcare is privacy. Healthcare data is among the most sensitive data, and the unauthorized disclosure of this data can have severe results. Therefore, it is important that a system built upon digital twins ensures that patient privacy is maintained, and the system is secure. As explained above, blockchain technology has been considered as a means of protecting data security and privacy. Also, the use of federated learning, which trains machine learning models in a decentralized manner, can also be utilized to ensuring data privacy while still being able to build a global machine learning model from all the data. Techniques for data security and privacy that can be employed here also include differential privacy, multiparty differential privacy, homomorphic encryption, multiparty computation, data and model poisoning detection in federated learning.

Integration

Furthermore, the interoperability of digital twins with existing healthcare systems is another challenge that needs to be addressed. Digital twins will need to communicate and integrate with existing devices and systems such as electronic health record (EHR) systems in order to provide seamless and efficient healthcare. This integration will require the standardization of data formats and communication protocols between different systems.

Regulations

Moreover, the development of ethical guidelines and regulations for the use of digital twins in healthcare is important to ensure that patient rights and privacy are protected. This includes the development of standards for data security, data sharing, and informed consent for patients.

Involvement of Stakeholders and Training

In addition, the development of digital twin tools for healthcare need the involvement of the stakeholders such as healthcare providers, patients, policymakers, governments and etc. to input their requirements and feedback, so that the digital twin tools will have high usability in practice. Finally, the education and training of healthcare professionals and patients on the use and interpretation of digital twin data is crucial for the successful adoption of this technology. Healthcare professionals need to be able to understand and use digital twin data to provide personalized and effective care to patients. On the other hand, patients will need to be trained on the use of digital twins. In summary, while there has been significant progress in the integration of digital twins in healthcare, there are still many challenges that need to be addressed in order for this technology to become widely adopted and beneficial for patients and the society.

Conclusion

The application of digital twins for healthcare has the potential to revolutionize the way we approach healthcare and patient care. The current work being conducted in the field showcases the its promises in assisting precision healthcare, hospital/clinic management, and pandemic response, and the operation of machine learning and modeling. However, there are still significant challenges that need to be addressed in order to fully realize the potential of digital twins in healthcare. These challenges include efficient computing, privacy and security, interoperability, ethical guidelines and regulations, and stakeholder involvement and training of the professionals and patients. Further research and development work is necessary to overcome these and other challenges to bring digital twins to fruition as a practical tool in the healthcare area.

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DOI:10.26502/acbr.50170352

Acknowledgements

This research was supported in part by U.S. NSF grants NSF- 2206522, NSF-1827674, NSF-1822965, Microsoft Research Faculty Fellowship 8300751, and the Commonwealth Cyber Initiative (CCI), an investment in the advancement of cyber research, innovation and workforce development. For more information about CCI, visit cyberinitiative.org.

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