Chapter

Digital Twins for Health: Opportunities, Barriers and a Path Forward

Patrizio Armeni, Irem Polat, Leonardo Maria De Rossi, Lorenzo Diaferia, Giacomo Visioli, Severino Meregalli and Anna Gatti

Abstract

The concept of precision medicine involves tailoring medical interventions to each patient's specific needs, considering factors such as their genetic makeup, lifestyle, environment and response to therapies. The emergence of digital twin (DT) technology is anticipated to enable such customization. The healthcare field is, thus, increasingly exploring the use of digital twins (DTs), benefiting from successful proof of concept demonstrated in various industries. If their full potential is realized, DTs have the capability to revolutionize connected care and reshape the management of lifestyle, health, wellness and chronic diseases in the future. However, the realization of DTs' full potential in healthcare is currently impeded by technical, regulatory and ethical challenges. In this chapter, we map the current applications of DTs in healthcare, with a primary focus on precision medicine. We also explore their potential applications in clinical trial design and hospital operations. We identify the key enablers of DTs in healthcare and discuss the opportunities and barriers that foster or hinder their larger and faster diffusion. By providing a comprehensive view of the current landscape, opportunities and challenges, we aim to contribute to DTs' ongoing development and help policymakers facilitate the growth of DTs' application in healthcare.

Keywords: human digital twins, precision medicine, DT of the eye, clinical trials, hospital operations management

1. Introduction

Digital twins (DTs) are currently implemented in various sectors such as smart cities, manufacturing, construction, automotive and aerospace. Successful proof of concept in various industries and the growing accessibility of technological devices capable of gathering patient data facilitate an emerging utilization of DTs in the healthcare field [1]. DTs present significant potential, particularly in the realm of precision medicine [2]. In this context, DTs offer the capability to simulate personalized treatment approaches, providing a visual representation of the potential outcomes of therapies and the progression of diseases for each individual patient [3]. Furthermore, the healthcare sector has already witnessed successful implementations of DTs, particularly in areas like predictive maintenance and performance enhancement of medical devices, as well as the optimization of hospital management systems.

While DTs have demonstrated significant success in various fields, it is important to acknowledge that DTs developed for healthcare differ significantly from those designed for industrial applications. Healthcare DTs face unique challenges and requirements due to the complexity and sensitivity of medical data, and there are several important points to consider. For instance, human DTs indeed rely heavily on the integration of artificial intelligence (AI) applications, and these applications often utilize sensitive medical data. Given the sensitive nature of medical data, ensuring the proper handling and protection of this information becomes crucial [4].

Unlike other industrial applications, health DTs have unique characteristics that require a dedicated examination. This review encompasses an evaluation of the technologies used in health DTs, the specific areas of application within healthcare, and the barriers that exist in both the research field and the market for these technologies. By conducting this comprehensive analysis, a deeper understanding can be gained regarding the potential benefits, challenges and opportunities associated with health DTs in healthcare settings.

This chapter contributes to the DTs in healthcare literature as follows:

- We introduce a comprehensive background and recent advances of DTs in healthcare covering multiple areas of healthcare.

- We provide a comprehensive summary of enabling technologies and possible data sources in DTs in healthcare, assessing their benefits and drawbacks.

- We summarize DT applications in healthcare (precision medicine, clinical trials design and hospital operations) from the literature. As a case study, we present a comprehensive review focused on DTs of the eye and how they differ from creating DTs of other organs.

- Finally, we discuss limitations and open issues. We engage in a discussion on potential strategies to address these challenges and overcome the barriers they pose.

2. Background: concept of DTs in healthcare

A Digital Twin (DT) serves as a reflection of the real world, offering a way to simulate, predict and enhance physical manufacturing systems and procedures [5]. In the realm of healthcare, DTs can be described as virtual representations, also known as "digital twins," of patients, their anatomical structure and medical devices. These twins are created using a combination of multimodal patient data, population data and real-time updates on patient and environmental variables [6, 7]. Additionally, when it comes to healthcare facilities, a DT of a hospital environment can also be included within the scope. Overall, in the healthcare field, DTs offer various benefits, covering diverse areas such as enhancing diagnostics, treatment and care, assisting in medical pathway planning, as well as supporting hospital organization and management, and facilitating medical or asset resource allocation.

The concept of human DTs comprises three essential components: the physical object, the virtual object and the digital thread. The author [8] summarizes these three components as follows: (1) The physical object can be a patient, a medical device, a wearable device, an external factor (e.g., social behavior, weather, air quality, or even government policies influencing patient health), or a system consisting of more of these objects (e.g., a hospital). (2) The virtual object is the medical device model, wearable device model, digital person model, external factor model and digital system models. (3) The digital thread is healthcare data, including real-time data detected from medical and wearable devices or external factors, simulation data from digital models, historical health data and electronic health records (EHRs) from healthcare institutions, and service data from platforms that enable the communication between the physical and virtual objects and spaces.

The physical object in DT applications primarily comprises physical patients and devices such as medical instruments, auxiliary equipment and wearable sensors that are connected to actual individuals. Various medical detection and scanning instruments, as well as wearable devices, are utilized to collect dynamic and static multi-source data related to physical humans. This data is then transmitted in real-time to a virtual space and is processed to finally return to the physical objects as real-time instructions and commands (**Figure 1**). This interplay between the physical twin (PT) and virtual twin (VT) enables seamless interaction and data exchange for improved healthcare outcomes [8]. Thus, to enable the continuous development of DTs, the co-evolution of both PTs and VTs is essential. A reliable data link facilitates the mapping between the PT and VT, enabling their synchronized development in both the physical and virtual environments. This enables real-time data analysis and continuous monitoring of the PT's condition, allowing for instance the early detection or crisis warning of potential health issues [9].

DT models can be effectively employed to enhance the outcomes of diverse clinical procedures. By leveraging real-time data and processing capabilities, DT algorithms can provide accurate insights and predictions, thereby improving decision-making in

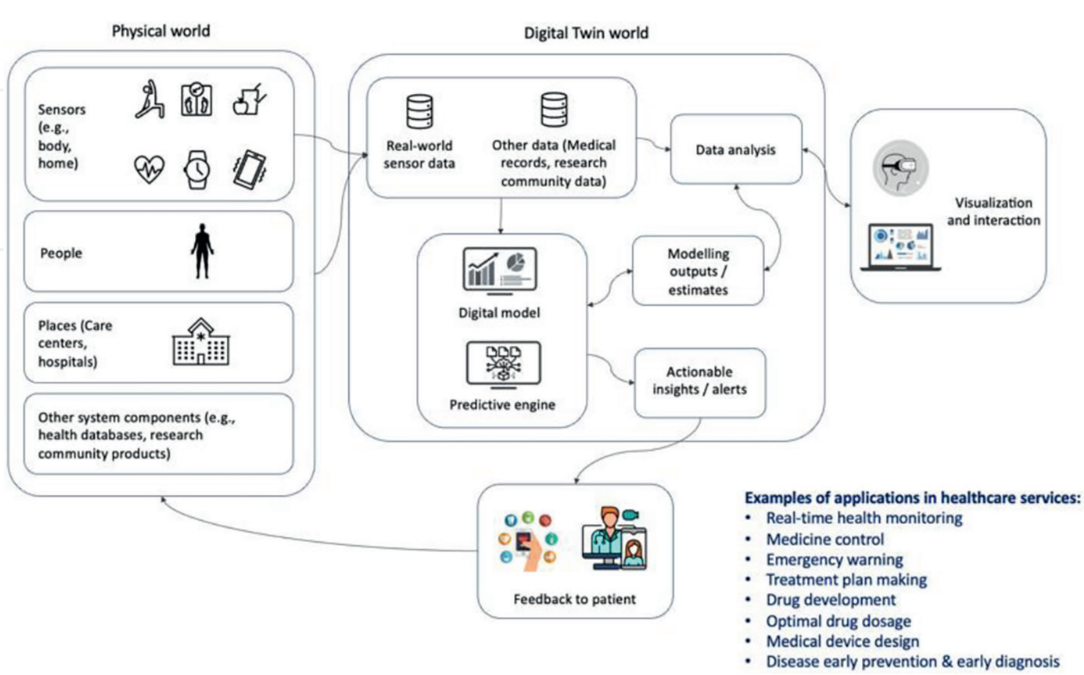

Figure 1.
High-level component view of a DT for precision medicine.

medical settings. Through the utilization of a vast dataset and AI-powered models, an ideal replica of the human body or specific body parts can be generated. This replication mimics human physiology and can provide potential answers to a wide range of clinical questions [10, 11]. Additionally, DTs can provide a secure environment for young practitioners, doctors and surgeons to practice, undergo training procedures and conduct tests on a virtual representation of the human body. This enables them to enhance their skills and expertise in a safe environment.

3. Health DT development: enabling technologies and data sources

The DT model allows for the continuous collection and accumulation of data throughout its entire lifecycle [12]. The accessibility of biomedical data has significantly increased due to various sources such as large biobanks, electronic health records, medical imaging, wearable devices, biosensors, as well as cost-effective genome and microbiome sequencing. This accessibility has played a crucial role in the development of health DT solutions [13]. Moreover, data gathered through personal digital devices, and patient-generated health data, such as patient-reported function or symptoms, physical markers, and demographic, and lifestyle data over time of an individual contribute to the development of more comprehensive DTs [9, 14, 15]. The integration of diverse data streams within health DTs allows for a broad understanding of an individual's health. This holistic view enables personalized healthcare interventions tailored to the specific needs of each individual.

In a health DT process, collected data from patients and the surrounding environment is transmitted and stored in real-time within the Internet of Things (IoT) cloud. Through the utilization of big data analytics and AI, valuable insights are extracted from the vast volume of data. This knowledge can be reused and enhanced over time. These insights then enable the creation of a VT, representing the PT's condition. Through this process, information regarding the PT's attributes, health status and other relevant data is fed back to the virtual models, enabling a two-way transmission of data. Thus, effective communication techniques that enable bi-directional data transmissions between the PT and VT are crucial for the success of this model. By constructing product models in the virtual space and facilitating the feedback of digital models to the physical space, a closed-loop process is achieved in the DT mode [9]. Finally, to comprehend and monitor the PT's status comprehensively, visualization tools are necessary. These tools allow for a visual representation of the PT's data, aiding in understanding and monitoring their condition.

The progress made in Digital Health technologies has made it possible to observe a rich amount of digital data and detailed aspects of people's behavior, the complex factors that influence behavior at any given moment, and how behavior changes over time within each person. This advancement relies on a range of devices such as smartphones, wearables, implantable sensors and ingestible sensors (like smart pills) to gather and analyze biological (e.g., blood glucose), physiological (e.g., heart rate and blood pressure) or behavioral data [16, 17]. Wearable sensors particularly enable healthcare professionals to gather real-time data outside of traditional clinical settings. The availability of affordable and noninvasive devices, such as smartwatches or bands, has rapidly increased. These wearable sensors are capable of accurately measuring various physiological metrics. By integrating data from these wearable devices with EHRs, it becomes possible to extract relevant information about a patient's underlying disease risk. This integration enables the creation of a personalized remote monitoring experience for patients and caregivers [13].

Moreover, DT models also rely on biomarkers that cannot be directly measured or require invasive procedures. These biomarkers play a crucial role in various applications, such as precision cardiology. In precision cardiology, the integration of cardiovascular imaging with computational fluid dynamics enables the noninvasive assessment of flow patterns and the computation of diagnostic metrics. This approach is particularly useful for conditions like coronary artery disease, aortic aneurysms, valve prostheses and stent design, providing valuable insights without the need for invasive procedures [18].

Despite these advancements in the healthcare field, there are several challenges (technical limitations, ethical considerations and financial constraints) that hinder data acquisition for building DTs and unfolding their full potential. Unlike industries like automotive, where sensors are readily available and integrated into the assets, humans do not naturally possess embedded sensors [3, 19]. Still, humans mostly rely on periodic medical examinations to gather data about their health; thus, the intermittent data collection method poses limitations in maintaining real-time and continuous updates for human DTs. The seamless connection between humans and their DTs cannot be guaranteed yet [4].

The implementation of DTs encompasses a wide range of technologies. These include the IoT, 5G networks, cloud and edge computing, extended reality (XR), simulation tools, visualization tools, and AI and machine learning (ML) models. Additionally, the integration of technologies such as federated learning (FL) and blockchain is rising to address security, transparency and privacy-related issues. These technologies coupled with the availability of diverse and accurate create exciting opportunities for the use of DTs in healthcare [3, 12, 19, 20].

3.1 Internet of Things

Enhanced IoT sensors and devices refer to internet-connected sensors and devices that have the capability to be integrated into ordinary objects or attached to the human body, such as wearable devices. These advanced sensors and devices enable data collection, communication and interaction with the surrounding environment, thereby enhancing connectivity and enabling a wide range of applications and services [21]. The integration of IoT into medical systems holds immense potential for driving the future of DTs in healthcare. Rather than relying solely on visits to hospitals, real-time health monitoring of patients enabled by IoT devices can empower individuals, allow early detection of health issues, and facilitate effective management of chronic conditions. This shift toward continuous monitoring and personalized healthcare plans has the potential to significantly improve patient outcomes and enhance overall healthcare delivery [22].

The decreasing cost and increasing accessibility of IoT devices have facilitated the rise of connectivity. However, challenges remain in achieving real-time monitoring, particularly due to factors like power outages, software errors and ongoing deployment issues. These challenges pose significant obstacles to the overall objective of establishing seamless connectivity. For instance, one of the challenges is the reliance on a single sensor to provide data for AI algorithms. If there is a dysfunction or failure in the sensor, it can hinder the success of a specific process. Achieving complete connectivity and redundancy in data collection is crucial to mitigate the impact of such failures.

3.2 5G network

The high transmission rate of the 5G network enables the collection of sensor data at a rate that satisfies the demands of big data analysis and advanced forms of AI in DT systems [23]. Thus, the adoption of 5G networks in DT applications has the potential to enhance ongoing operations through continuous monitoring of physical systems in real time. Despite this clear potential, DTs adoption within 5G networks remains relatively new [24].

3.3 Artificial intelligence

AI is revolutionizing healthcare by employing a widely applied combination of highly complex algorithms that emulate human cognitive functions across various applications and sectors. This transformative technology, including techniques like deep learning (DL) and ML, can be extensively applied to diverse healthcare data types [11, 22]. Multimodal AI models have the potential to integrate data from multiple sources, such as biosensors, genetic information, epigenetic markers, proteomic data, microbiome profiles, metabolomic measurements, medical imaging, textual data, clinical records, social determinants of health and environmental data [13].

DT applications leverage AI technologies and techniques, and software analytics to create and maintain a dynamic, real-time digital representation of a physical object. Currently, AI-powered DTs of human biological systems or organs play a significant role in diagnosing existing medical conditions and forecasting potential future health issues. This is accomplished by analyzing aggregated data and medical histories associated with individuals [25]. Furthermore, AI is crucial in designing DTs of organs by leveraging physiological data to generate 3D images. A notable example is the development of a DT model by Siemens Healthineers, which utilized a vast database comprising over 250 million annotated images, reports and operational data. By harnessing AI capabilities, this DT model enables the creation of digital heart designs based on patient-specific data, considering factors such as size, ejection fraction, muscle contraction and other relevant conditions unique to each patient. This AI-driven approach facilitates personalized and precise modeling of organs, contributing to advancements in healthcare diagnostics and treatment planning [26].

One of the major challenges DTs faces is particularly regarding privacy concerns. The collection and storage of large volumes of data in a centralized repository raise significant privacy concerns and increase the risk of data breaches. Solely removing patient identifiers from the data is not sufficient to address these concerns since there is a possibility of reconstructing the original data even without the identifiers. FL offers a potential solution to this issue by enabling the utilization of the combined power of individual data modalities without the need to centralize the data [27].

3.4 Federated learning

FL aims to address data governance and privacy concerns by enabling collaborative training of algorithms without sharing the actual data. FL allows institutions to gain insights collectively, such as through a consensus model, while keeping patient data within the institution. The ML process takes place locally at each participating institution, with only model characteristics (such as parameters and gradients) being transferred. Recent research has demonstrated that FL-trained models can achieve performance levels similar to those trained on centralized datasets and outperform models that only have access to isolated data from individual institutions [27, 28].

FL has the capacity to facilitate large-scale precision medicine, resulting in models that provide unbiased decisions, accurately represent an individual's physiology, and account for rare diseases, all while addressing governance and privacy concerns. However, the implementation of FL still requires careful technical considerations (including data heterogeneity, traceability and explainability issues) to ensure optimal algorithm performance without compromising safety or patient privacy [28].

3.5 Immersive technologies (XR)

The emergence of immersive technologies in both industrial and consumer electronics has introduced innovative possibilities for DTs. These technologies offer new paradigms that can enhance the visualization and interaction capabilities of DTs, and enable highly realistic simulations. The combination of DTs and immersive technologies has primarily been utilized in the manufacturing domain [29], and there is emerging evidence of its potential use cases in healthcare as well. Some use cases of VR in conjunction with DTs offers a safe and immersive platform for training, enhancing skills, and refining medical techniques, remote operations, and remote collaborations, for instance, in surgeries [30]. This integration allows clinicians to practice complex procedures in a virtual environment. For instance, [31] developed a novel DT prototype that facilitates remote surgeries by integrating a robotic arm and a VR system connected over a 4G mobile network. By testing the prototype, the authors were able to analyze communication and cybersecurity requirements within their DT system. Moreover, medical education benefits significantly from this advancement, as healthcare professionals can gain hands-on experience by practicing treatments and procedures on virtual patients before performing them on real individuals.

3.6 Cloud and edge computing

DTs rely on a substantial volume of data, requiring high computing power to enable clinicians to extract real-time patient information. However, the storage and computing capabilities required for DTs often surpass what is currently available in healthcare centers [32]. Thus, many healthcare centers outsource their healthcare data and monitoring services to different locations, such as the edge or the cloud.

The deployment decision of twins in healthcare is primarily influenced by two key factors: available computing power and latency. In a typical Cloud Computing (CC) setup, data storage and computation are carried out within a centralized system. Cloud deployment provides greater computing power but higher latency due to its remote nature [10, 33]. As the number of IoT devices, mobile services, and the size of data continue to grow rapidly, it becomes imperative to alleviate the computational burden on the operating station or cloud. As an alternative, Edge Computing (EC) enables the network to conduct computation or process data at the extreme edges of the network, closer to the data source, rather than relying on centralized or distributed nodes in the core of the network [10]. EC offers limited computing power compared to CC but also benefits from low latency as it is in close proximity to devices. In the healthcare domain, EC comes into play when time is critical when dealing with emergencies such as ischemic heart disease (IHD) or stroke, as it improves efficiency by reducing data circulation and providing faster data processing [34]. In 2019, [34] developed Cardio Twin, a platform designed as a DT of the human heart. The purpose of this DT platform is to detect, prevent and mitigate the risk of heart disease. Cardio Twin runs on the edge devices like smartphones and connects with external sensors through Bluetooth communication to gather biosignals and collects data from other sources like medical records. In turn, this data is processed to detect and help in case the real twin is suffering an IHD or a stroke.

The integration of AI and ML algorithms with EC will significantly contribute to the progress of various applications, including healthcare and industries. A novel concept called Edge Machine Learning enables smart devices to perform local processing utilizing ML and DL algorithms. While edge devices can still transmit data to the cloud, processing data locally offers several advantages. It allows for data screening before sending it to the cloud and facilitates real-time data processing and response [10].

Finally, an integrated cloud-edge computing framework will support the advancement of healthcare DTs by ensuring the availability of low-latency and high-capacity storage solutions. A cloud-edge computing arrangement enables time-sensitive tasks to be accomplished at the network's edge. Tasks that require heavy computation or storage and cannot be executed at the edge are transferred to the cloud [9]. Ultimately, it is crucial for an effective DT framework to establish mechanisms that guarantee security and privacy, ensure highly reliable communications and reduce latency [35]. The decision to deploy DTs involves a careful balance, considering the aforementioned characteristics [33].

3.7 Blockchain

Recent advancements in DTs could pose specific challenges (e.g., privacy and security) in data sharing, storage and access in the healthcare sector [36]. Blockchain technology could address them by storing a patient's medical history records in a secure, transparent, trustworthy and timely manner [37]. This ensures that healthcare providers and professionals have access to reliable and up-to-date information whenever needed. Having access to such comprehensive and timely data enables healthcare providers to make informed decisions and consider appropriate courses of action in the event of any future complications or medical concerns [38]. Despite the benefits of blockchain-enabled systems, one of the challenges they face is high latency caused by complex consensus mechanisms. This latency can hinder the system's efficiency in meeting DTs' low latency requirements. To overcome this challenge, novel optimization schemes are necessary [9].

4. Current applications of DTs in healthcare

In this section, we explore various examples of DT applications that have made significant advancements in facilitating the use of DTs in multiple healthcare domains. The primary objective of this section is to demonstrate the deployment of DTs in precision medicine and their role in supporting medical decision-making. Additionally, we introduce a detailed review of developing a DT of the eye. To provide a comprehensive overview of DTs in healthcare, we also present our findings on the utilization of DTs in clinical trial design and optimizing hospital operations.

4.1 Precision medicine and medical decision-making support

Precision medicine can be defined as an approach to target the right treatments to the right patients at the right time [39]. The broad goal of precision medicine is to deliver customized therapies to individual patients, aiming to optimize both the effectiveness of treatments and the overall efficiency of our healthcare system (e.g., to prevent disease, improve survival and extend health span) [18, 40]. However, the original concept of precision medicine has faced criticism for its heavy emphasis on genomics and its limited focus on addressing clinical management challenges [40]. Additionally, a significant barrier to achieving precision medicine is the lack of consistent treatment response among patients with the same disease. This discrepancy primarily results from the substantial complexity of the underlying condition, which can involve complex interactions among thousands of genes that vary across individuals with the same diagnosis. As a result, the concept is evolving and expanding to incorporate a broader range of data, including lifestyle factors, environmental influences and biological information, moving away from a solely gene-centric perspective [41].

Precision medicine necessitates not only improved and more comprehensive data but also advancements in computer capabilities to analyze, integrate and leverage this data, ultimately constructing a DT of an individual patient. In this context, DTs have the potential to facilitate the prediction of illnesses by analyzing the personal history of an individual's real twin and considering its current state, including factors such as location, time and activity. By leveraging the data collected from the real twin, DTs can simulate and predict the potential impact of different treatments on these patients, a shift from the "one-size-fits-all" treatments to tailor-made treatments [26]. This capability enables DTs to provide valuable insights into personalized treatment approaches, enabling them to make informed decisions and optimize patient care [18, 26]. An important challenge lies in integrating this data with healthcare organizations while ensuring the security and confidentiality of sensitive information [18].

In the medical and clinical fields, there is a growing interest and increasing availability of prototypes in the development of DTs in the precision medicine scope. The author in [42] proposed a framework for DT of patients, where a DT representing a patient exhibiting symptoms of a specific disease is created in unlimited copies, replicating the network models of all relevant molecular, phenotypic and environmental factors associated with the disease's mechanisms. Subsequent simulations are conducted using various drugs to determine the optimal treatment strategy.

DT technology is also encouraging to mimic human organs. The human heart [43], brain [44] and liver [45] are some examples of research areas within the DT scope. The Living Heart (Dassault Systèmes) project presented in [43] is a pioneering initiative in the field of organ DTs. This research project introduced a proof-of-concept simulator for reproducing cardiac excitation and contraction in the human heart. By utilizing human computer tomography and magnetic resonance images, the researchers successfully developed a comprehensive model of the entire heart, including all four chambers interconnected by four valves, incorporating various aspects of its functionality, such as blood flow dynamics, mechanical behavior and electrical impulses. This model integrated a human heart simulator, enabling the exploration of various clinical parameters and facilitating device design and treatment planning for cardiac diseases and dysfunctions. Another study in [45] describes the development of a DT of the liver with the aim of enhancing our understanding of liver disease and its correlation with drug toxicity, which is a leading cause of drug failures in clinical settings.

Moreover, several studies have been conducted with the aim of enhancing our comprehension or control of specific conditions or diseases and the care process [21]. The author [3] discusses the DTs design for the management of multiple sclerosis, a chronic autoimmune and degenerative disease that affects the central nervous system.

DTs have emerged as a promising tool in the field of multiple sclerosis (MS) and are particularly well-suited for MS due to the complex and heterogeneous nature of the disease, the multitude of treatment options available, and the need for comprehensive data integration and analysis. By integrating big data analysis and ML techniques, DTs can provide a comprehensive visualization of the disease progression and enable more informed therapeutic decisions (e.g., enhancing disease characterization, predicting disease course and conducting deep clinical phenotyping of individuals). Another application is trauma management, where effective management of trauma is highly critical in time-sensitive medical conditions. The author [46] introduced an initial case study that focuses on utilizing agent-based DTs for the management of severe traumas. This includes the prehospital phase, where physicians provide initial aid to patients and transfer them to the hospital emergency department, as well as the operative phase, where the trauma team provides necessary care in the hospital emergency setting. While the implementation of such systems is still in progress, a prototype has been developed to showcase the potential of this approach. In the case of elderly management, [8] introduced a framework called CloudDTH for managing the healthcare of elderly individuals. The framework specifically addresses the challenges related to real-time monitoring and accurate crisis warnings in healthcare services for elderly patients. Finally, the application of DTs extends to diabetes management as well. The author [47] introduced the DT model employed in diabetes management tracks various aspects such as nutrition, sleep patterns and changes in physical activity. DT model continuously monitors important health parameters for diabetes management including patients' blood sugar levels, liver function, weight and more. Ongoing clinical trials have indicated that providing daily precision nutrition guidance, which relies on a continuous glucose monitoring system (CGM), food intake data and ML algorithms, can offer substantial benefits to individuals diagnosed with type 2 diabetes.

4.2 Case study: Developing a DT of the eye

While significant efforts have been invested in the development of DTs for various human organs, including the heart, brain and liver, the field of ophthalmology currently lacks any such prototype or application, and this could be explained by several factors.

The main reason can be found in the peculiarity of the eye compared to other organs. For example, creating a DT of the heart can be, in certain respects, less complex than creating one for the eye. This is largely due to the differences in the scale and nature of the functional components involved in these two organs. One of the fundamental functions of the heart – the dynamics of blood flow – operates on a macroscopic level [18]. This involves the larger structures of the heart, including the chambers and valves, which are more easily accessible and observable. In contrast, the key functions of the eye involve microscopic structures that are more challenging to examine in detail and replicate digitally. Furthermore, the study and simulation of specific interventions in the heart, such as the functioning of a new valve, is inherently a macroscopic event. It does not necessitate an exploration of microscopic structures or phenomena. Therefore, the development of a DT for the heart can focus primarily on these larger, more observable elements, simplifying the task of creating a functionally representative model [6]. Additionally, the heart's relatively exposed location within the chest cavity makes it more accessible for detailed scanning and data collection, a critical step in creating a DT. This accessibility is less straightforward in the case of the eye, which is largely shielded within the orbital bones.

Overall, the eye is a composite organ, constituted of various distinct tissues, each with its own unique function and characteristics. These include the cornea, sclera, uvea and retina, with their microscopic structures. Each of these structures plays a crucial role in the overall function of the eye, and thus, any comprehensive digital representation of the eye must incorporate the intricate interactions between these tissues. AI has been instrumental in studying these separate structures (e.g., optical coherence tomography or topography), but it has yet to reach the level of sophistication required to integrate these diverse elements into a single, coherent model [48]. The vision process is a result of the harmonious functioning of all these diverse elements. As such, the development of a DT that would reproduce these intricate interactions could significantly advance research in ophthalmology with potential advantages spanning from precision medicine to education, diagnostics and medical research.

To construct more sophisticated models, it would be first necessary to generate a static reproduction of a specific eye. This preliminary step entails the integration of images derived from both the anterior and posterior segments of the eye. The primary challenge for engineers in this endeavor is the synthesis of data originating from a multitude of sources. The construction of a comprehensive static model necessitates the utilization and interpretation of raw data and images from different technologies such as slit lamp imaging, topography, optical coherence tomography of the anterior and posterior segment, confocal microscopy, gonioscopy, echography, etc. The task of harmonizing such varied and extensive data sets would be the first challenge. Further, certain regions of the eye, such as the vitreous base, the extreme periphery of the fundus or the ciliary body, are difficult to capture with the imaging technology currently available. In these instances, AI could be employed to supplement the missing data. For example, in an eye with severe myopia, it is probable that its peripheral retina would be thinner and that retinal degenerations would be more frequent. AI algorithms could be developed to acknowledge these alterations and fill in the gaps in the data accordingly [49]. Consequently, the resulting static model, enhanced by AI, could offer a reliable and comprehensive representation of the eye. Another example is the use of confocal microscopy, an imaging tool that enables high-resolution imaging of the cornea, providing in vivo images of its structure. However, performing confocal microscopy across the entirety of the cornea - due to the enormous data requirements and time needed for comprehensive image acquisition – would be a challenge. Here, again, AI algorithms employing data from a set of representative samples obtained through confocal microscopy could predict the corneal structure in areas that were not directly imaged [50]. This method, combining direct imaging with intelligent prediction, could feasibly construct a complete, high-resolution model of the cornea.

Even though the creation of a DT of the eye would initially involve the development of a static model, the ultimate goal of this research field would not be limited to just an anatomical representation; it would be a functional replica capable of imitating both structural and functional attributes specific to an individual's eye. This could, in theory, enable the DT to react to treatments and surgeries much like their physical counterparts, offering interesting opportunities for the exploration and testing of therapies and surgical procedures. One potential application could be clinical trials for rare conditions, such as Retinitis pigmentosa. The rarity of such conditions often makes it challenging to conduct traditional clinical trials due to the lack of a large patient sample or ethical issues [51]. However, with the generation of multiple DTs reproducing the specifics of these rare diseases, it would become possible to test new treatments within a digital environment. This could significantly accelerate the process of therapy development. Moreover, the DT of the eye could be instrumental in the ethical training of young doctors, providing a realistic, risk-free environment for surgical practice. Trainees could refine their skills, reduce potential complications and increase their confidence before moving on to real-life surgeries on a specific eye and predict outcomes [52]. Finally, by accurately mirroring a patient's unique eye characteristics, the DT could simulate visual experiences, effectively predicting the individual's visual acuity and field [53]. This predictive capability could have vital applications in legal and rehabilitative contexts. In legal situations where visual capability is a determinant factor, such as in disability claims or determining fitness to drive, the DT could provide a comprehensive, objective measure of a person's visual function. It would serve as a reliable tool for accurately assessing visual impairment levels and substantiating legal claims. Furthermore, in the realm of visual rehabilitation, a DT could offer indispensable insights. By simulating a patient's visual experience, clinicians could tailor rehabilitative strategies to address specific visual deficits, enhancing the effectiveness of the rehabilitation process [54]. Finally, with the assistance of AI, a DT of the eye could integrate various biomarkers of ocular diseases such as diabetic retinopathy [55]. This would allow for the prediction of disease progression and treatment outcomes in a specific eye.

Despite being in the early stages, research into developing a DT of the eye holds considerable potential. The complexity of the task, involving extensive data integration and sophisticated computational methods, is substantial. However, given the far-reaching implications for individualized diagnostics, tailored treatment strategies and surgical training, the potential benefits underscore the value of continued research in this direction.

4.3 Other applications

4.3.1 Clinical trials design

The idea of incorporating virtual patients into the clinical trial design is an evolving concept [56]. DTs have the potential to enhance randomized controlled trials (RCTs) by reducing the number of subjects required to achieve the desired statistical power [57]. Current empirical trials have limitations because they often exclude patients with comorbidities or complex treatment regimens [18]. Additionally, clinical studies face delays in the enrollment phase, and some trials fail to meet overall enrollment goals. DTs have the potential to create unlimited virtual replicas of actual patients, enabling computational treatment with a wide range of drug combinations that can serve as the control group. This approach allows for the testing of early-stage drugs on DTs of real patients, accelerating clinical research, mitigating potential risks and reducing the need for costly trials to approve new therapies. By leveraging DT technology, the impact of hazardous drugs can be minimized, while the overall process of drug development and approval can be improved [2].

In comparative clinical trials, the use of a control group can sometimes raise ethical concerns, particularly when the treatment being tested has the potential to save lives, and the standard of care or placebo is not considered effective. Ethical issues can also arise when there are significant differences in the characteristics of the treatments being compared, such as safety concerns or invasive procedures compared to noninvasive ones. DTs have the potential to address these ethical issues by replacing placebo or standard-of-care patients with virtual counterparts that simulate the evolution of health states based on patients' characteristics. By doing so, DTs can provide a representative view of how an intervention may impact the VT, effectively creating a synthetic control group [2].

While virtual clinical trials have demonstrated significant potential and offer several advantages, they have not yet reached a stage where they can completely replace human trials [56]. There are several issues to be considered including ensuring the accuracy and reliability of the VT's simulation, addressing potential biases in the data used to create the DT, and maintaining transparency in how the DT is developed and utilized. Addressing these limitations in DTs in clinical trials could pave the way toward more targeted and efficient patient trials in the development of efficient drugs and medical devices.

4.3.2 Optimization of hospital operations

Another significant application of DT technology lies in the optimization of the entire operations management of hospitals. At the healthcare facilities and at the individual department level, one approach to improving processes involves creating testable scenarios based on real-time data inputs within a DT system. These scenarios aim to enhance various aspects such as staff allocation, visitor and patient flow management, reducing waiting times, optimizing equipment and resource allocation, facilitating emergency vehicle access, and improving overall service-related operations [6, 46]. Notably, GE Healthcare and Siemens Healthineers have developed DTs specifically for hospital management optimization. DTs in digital process optimization in hospitals facilitate the optimization of digital processes by enabling predictive capabilities and capacity planning based on patient activity and demand. In this context, DTs can analyze historical data, current trends and other relevant factors to forecast patient flow and resource requirements accurately. Additionally, they allow for the execution of workflow simulations, enabling the testing and evaluation of various operational scenarios and layouts. This capability helps hospital administrators, and decision-makers assess the potential impact of different process changes or optimizations before implementing them in the physical environment [26].

5. Limitations and open issues

DT applications face several challenges and concerns that could impede the realization of their full potential. Especially, the multidisciplinary nature of designing and developing health DT systems presents a significant challenge. While collaboration across various fields of research can potentially lead to breakthroughs, it can also impede progress [1]. Indeed, DTs combine emerging technologies, such as AI, IoT, big data and XR, and each component brings its own socioethical issues and technical limitations to the implementation stage, resulting in a lack of standardization and, thus, slower outcomes [1, 58]. The absence of standardized practices impacts various aspects, including security, privacy, interactions, roles, contribution protocols, data transmission and synchronization between the VTs and PTs. The establishment of global standards would play a crucial role in accelerating the widespread adoption of DTs and making them a reality more quickly. By having universally accepted standards, organizations and industries can benefit from streamlined processes and interoperability, fostering a more efficient and effective utilization of DT technology [59]. Although DTs can show great performance in some tasks (e.g., predictive capability), DT capabilities could not be considered yet sufficient for therapy selection and preventive care [2].

5.1 Technical limitations

DTs are indeed a complex combination of emerging technologies, each with its own set of limitations. While DTs offer numerous benefits, it is important to acknowledge the challenges associated with the individual technologies involved. For instance, while the cost-effectiveness and ease of implementation of IoT devices have facilitated increased connectivity, it is important to recognize the persistent challenges associated with their use. Issues such as power outages, software errors and ongoing deployment errors continue to pose obstacles. In the healthcare domain, these challenges become particularly critical, as the disconnection of sensors that provide data to health AI algorithms can significantly impact the objective of real-time monitoring [1]. When taking into account the advancements in AI technology, the full potential of ML in healthcare is hindered by the underutilization of existing medical data, primarily due to data silos and privacy concerns that limit access to this valuable information. Without access to an ample amount of data, ML faces obstacles in effectively transitioning from research to clinical practice [28]. For instance, training an AI-based tumor detector poses challenges due to the need for a vast database covering diverse anatomies, pathologies and input data types. However, obtaining such data is difficult as health data is highly sensitive and subject to stringent regulations. Even if data anonymization is employed, it is increasingly recognized that removing identifiable information alone may not adequately protect privacy. Additionally, the process of collecting, curating and maintaining a high-quality dataset requires significant time, effort and financial investment. As a result, these data sets possess substantial business value, leading to a decreased likelihood of their free sharing. Data collectors tend to maintain strict control over the data they have gathered, retaining fine-grained ownership and access rights. Another challenge refers to VR technology, where issues related to the VR interaction design, networking optimization and optimized hardware controls need to be addressed [30].

5.1.1 Data diversity and multisourcing

The progress of AI-integrated DTs heavily depends on data fusion, which entails integrating diverse information from multiple sources. However, one of the significant challenges for human DTs is the heterogeneity and operational complexity of EHRs and healthcare information systems. For instance, dealing with different health data sources such as EHR data and imaging reports, creates inefficiency in data coding and sharing [7].

5.1.2 Data bias

A crucial concern revolves around building DT technology on data sets that contain biased patterns. Since DT technology focuses on identifying patterns, training algorithms with flawed data can amplify and perpetuate those biases. Unfortunately, many existing data sets contain biases based on factors such as race, gender or other demographics. Utilizing these data sets without appropriate correction can perpetuate and amplify these biases, leading to DTs making suboptimal or inappropriate recommendations, particularly for individuals who do not align with the “ideal” demographic profile. It is essential that DT designers address this concern to ensure that DT systems do not inadvertently reinforce existing biases present in the data, which could have negative implications for decision-making and outcomes [19].

5.1.3 Overconfidence in data and models

The consequences of bad data, flawed analysis and subsequent inaccurate representation are magnified due to the trust placed in these models. It is crucial to remain cautious about the overreliance on data and ensure robust data validation and analysis methods to mitigate the risks associated with overconfidence in the results produced by DT models [58].

5.2 Socioethical issues

5.2.1 Security and privacy

The primary socioethical risk that stands out is the violation of security and privacy. The ethical concern surrounding healthcare organizations, insurance companies or any other entities possessing a persistent and detailed record of an individual's biological, genetic, physical and lifestyle information over an extended period is a troubling issue with significant implications. The protection of DT systems from unauthorized access, misuse, modification or disclosure presents a significant challenge, similar to any other information system. Given that DT systems handle large volumes of sensitive and personal data, they become attractive targets for threat actors and cyber-attacks. Moreover, the integration of IoT devices and sensors further complicates the implementation of adequate security measures, as traditional security controls may not be well-suited for these components.

Furthermore, processing personal user data within DT systems introduces regulatory risks. Compliance with privacy regulations such as the General Data Protection Regulation (GDPR) in Europe or relevant national data protection laws becomes mandatory, which adds further complexity when designing DT systems and imposes additional challenges [18]. The future objective should be to prioritize the privacy of the data utilized in DT applications [1, 8, 58].

5.2.2 Change of structures and roles in organizations

DT stakeholders have raised concerns about the risks associated with institutional changes related to DTs, even if they may seem minor initially. One significant concern relates to the question of diagnostic responsibility once a DT becomes involved in the diagnostic process. If the real-life physician remains the primary diagnostician, what happens if they override the AI-based component of a DT? Similarly, what happens if a wrong diagnosis is made based on the data from the DT? To address these concerns, some stakeholders are now limiting the influence of DTs: while a DT can provide valuable insights into different intervention scenarios, the decision-making process remains in the hands of the human physician. These issues gain importance as computers become increasingly intelligent, while policies and regulations struggle to keep up [58].

5.2.3 Lack of trust in DT systems

There is still a prevailing lack of confidence among doctors when it comes to relying on AI algorithms and big data for decision-making in real-world problems. The primary reason behind this skepticism is the absence of clear and comprehensible explanations to support the predictions made by these systems: To what extent can we rely on the predictions made by ML models, and how accurate are these models? [59, 60]. Second, DTs are seen as flawed due to their reliance on devices to transfer data. This poses a significant gap in the reliability of DT since these devices can experience crashes or disconnections for various reasons [59]. A recent study investigating the incorporation of AI systems in hospital settings reveals that numerous physicians maintain a skeptical attitude toward AI due to the significant risks associated with possible misdiagnoses and inappropriate treatment [60]. Therefore, establishing trust and confidence in the concept of DT as a whole necessitates the establishment of standards, raising awareness and advancing technologies, all of which require significant effort and time [59].

5.2.4 Inequality and injustice in terms of accessibility to technology

The utilization of DT technology can contribute to inequality and other forms of injustice. Certainly, since it is a relatively new technology, not everyone may have access to it or be covered by health insurance that includes DT services. This can further widen existing socioeconomic disparities.

5.2.5 Human enhancement and good gene pool

The potential for predicting lifespan could be based on a combination of genetic makeup and lifestyle information found in someone's DT. By analyzing data from DTs, it may be possible to identify clusters of people with different life expectancies and distinguish those prone to leading long and healthy lives from others. This medically relevant distinction can be built upon existing statistical patterns in the population of DTs. If certain lifestyle factors associated with long life are discovered, efforts can be made to encourage more people to adopt those healthier habits using various incentives. The question arises as to whether this life extension or betterment achieved through such means should be considered therapy or enhancement [61]. While the debate regarding the distinction between therapy and enhancement is ongoing, there is currently no consensus regarding the intended purpose of DTs [62]. A clearer understanding of the differentiation between therapy and enhancement in the context of DT is likely to emerge as DT applications mature and receive broader attention and engagement from the scientific community, policymakers and regulators.

6. Conclusions

DTs in healthcare represent a promising and (to some extent) revolutionary convergence of advanced technologies such as AI, IoT, Big Data and VR to create applications that can benefit human health and health systems' efficiency. They have transformative potential across various dimensions of healthcare, from diagnostics and therapy planning to medical education and clinical trial design. Their inherent capabilities to deliver personalized, predictive and dynamic models of individual patients could vastly improve health outcomes, and their ability to reproduce complex systems and to exploit the available informative set bears the potential to create much-needed efficiencies for both healthcare providers and technology producers. DTs provide exciting possibilities in diagnostics and therapy planning, through which physicians can visualize and understand a patient's health state in real time, enabling personalized and timely interventions. Medical education stands to benefit significantly from DTs, providing immersive, realistic training without the risks associated with training on real patients. Furthermore, DTs can contribute substantially to clinical trials, addressing issues such as ethical concerns, participant selection and trial design. They also hold the promise to optimize hospital operations and service delivery, thereby further enhancing the quality of healthcare and optimizing the use of healthcare resources.

However, DTs are not devoid of challenges. On the technical side, the integration of multiple technologies, most of which were not initially developed to work in integration, and the need for synchronized operation presents a formidable challenge. The quality of data that forms the basis of DTs, including potential bias, overconfidence in models, and diversity of data sources, are just some of the current limitations of DTs that need to be critically assessed to ensure accuracy and reliability. Moreover, the socioethical implications of DTs are complex. Issues surrounding security and privacy, changes in structures and roles within healthcare institutions and in clinical decision-making, trust in DT systems and accessibility inequalities necessitate rigorous examination and appropriate policy responses. These concerns become especially pertinent given the sensitive and personal nature of the data involved in DTs, which makes them attractive targets for cyber threats and raises ethical considerations. The advent of DTs also brings up intriguing discussions on the subject of human health enhancement, as DTs may eventually facilitate personalized health optimization strategies. However, this must be cautiously approached, ensuring it does not foster (or even boost) inequality or violate ethical principles.

We believe that healthcare institutions must proactively navigate these challenges, considering both the technical complexities and the broader socioethical implications. Developing global standards for DT technology, fostering trust and understanding among medical practitioners, and ensuring adherence to security and privacy regulations will be essential steps toward realizing the full potential of DTs. Future efforts should be directed toward advancing the technology, promoting its understanding among key stakeholders, and establishing robust policies that strike a balance between leveraging the immense potential of DTs and addressing the associated challenges. A holistic and ad-hoc approach that integrates technical advancement, regulatory compliance and ethical considerations will be key to unlocking the vast potential of DTs for global healthcare improvements.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Patrizio Armeni[1*], Irem Polat[2], Leonardo Maria De Rossi[3], Lorenzo Diaferia[3], Giacomo Visioli[4], Severino Meregalli[3] and Anna Gatti[2]

1 LIFT Lab and CERGAS, Claudio Demattè Research Division and GHNP Division, SDA Bocconi School of Management, Milano, Italy

2 LIFT Lab, Claudio Demattè Research Division and GHNP Division, SDA Bocconi School of Management, Milano, Italy

3 LIFT Lab and DEVO Lab, Claudio Demattè Research Division and GHNP Division, SDA Bocconi School of Management, Milano, Italy

4 Sense Organs Department, Sapienza – University of Rome, Rome, Italy

*Address all correspondence to: patrizio.armeni@unibocconi.it

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