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Digital twin in healthcare: Recent updates and challenges

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Abstract

As simulation is playing an increasingly important role in medicine, providing the individual patient with a customised diagnosis and treatment is envisaged as part of future precision medicine. Such customisation will become possible through the emergence of digital twin (DT) technology. The objective of this article is to review the progress of prominent research on DT technology in medicine and discuss the potential applications and future opportunities as well as several challenges remaining in digital healthcare. A review of the literature was conducted using PubMed, Web of Science, Google Scholar, Scopus and related bibliographic resources, in which the following terms and their derivatives were considered during the search: DT, medicine and digital health virtual healthcare. Finally, analyses of the literature yielded 465 pertinent articles, of which we selected 22 for detailed review. We summarised the application examples of DT in medicine and analysed the applications in many fields of medicine. It revealed encouraging results that DT is being increasing applied in medicine. Results from this literature review indicated that DT healthcare, as a key fusion approach of future medicine, will bring the advantages of precision diagnose and personalised treatment into reality.

Keywords

Digital twin, healthcare, precision diagnose, personalised treatment, medicine

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Introduction

It is often said that ‘there is no disease, there is the patient’. Compared with other disciplines, medicine has inherent uncertainty, which makes medical practice challenging. Conventional drug therapy has many limitations such as medication ineffectiveness and the concept of personalised medicine has proved to play an important role in the healthcare sector.[1–3] Over the past few decades, more and more attention is being paid to precision medicine, which has been described as an emerging approach for disease treatment and prevention that considers variability in the genes, environment and lifestyle among individual people.[4] Some previous studies have used digital technology to construct a virtual physiological human body, with the vision of translating computational physiology into clinical practice, and have achieved certain progress.[5,6] The development of the technologies of big data, cloud computing, virtual-reality and the internet of things (IoT) has laid a technical foundation for the application of digital twin (DT) and thus provided clinicians and researchers with a more detailed dimension with which to study the occurrence and development of diseases and to conduct more precise diagnoses and treatments.

In recent years, the concept of DT is attracting more and more attention from researchers and engineers. With the continuous DT research by both industry and academia, however, the boundaries between DT and other related concepts have become increasingly blurred. The preliminary meaning of the DT included the physical product, virtual product and their connections.[7] The rapid development of communication technology, sensor technology, big data analysis, the IoT and simulation technology has led to the

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exponential growth of research on DTs.[8,9] Then, DT was redefined as a digital replication of living or non-living physical entities, which opened the gateway to using the DT for humans, such as in the field of health and well-being.[10] As a moving concept, DT is a virtual copy of the human organs, tissues, cells or micro-environment that constantly adjusts to variations in the online data and can predict the future of the corresponding counterpart.[11,12] However, the DT is more than just a digital model that is connected with a real-life twin through various emerging technologies. It is a living, intelligent and evolving model which can optimise the processes and continuously predicts future statuses (e.g. defects, damages and failures) through the closed-loop optimisation between DT and surrounding environment.[13] Generally speaking, the technologies required for DT can be divided into two categories, one is a statistical model driven by data, and the other is a mechanical model that integrates multi-scale knowledge and data.[14,15] The numerical model is used to calculate the structural performance while the analytical model is used for structural analysis. The artificial intelligence (AI) model, trained with the samples and numerical data, obtains the real-time structural performance from real-time sensor data.[16,17]

The DT is revolutionising industry and been used by many major companies to increase efficiency and spot problems.[18] Healthcare can be another domain where DT can be applied.[19] In an application perspective, DT can treat patients as virtualised standalone assets that can be further used in environments and situations involving multiple related strategic assets of healthcare organisations.[20] The DT has great application potential to patients or hospitals to improve treatment and diagnostics.[21] The objective of this study is to make a review of the progress on DT technology in medicine and discuss the potential applications and future opportunities as well as several challenges remaining in digital healthcare.

Method

Study design

This study aimed to review the technology in medicine and discuss the potential applications and future opportunities as well as several challenges remaining in digital healthcare. It was conducted through the academic databases PubMed, Web of Science, Google Scholar, Scopus and related bibliographic resources in which the following terms and their derivatives were considered during the search: DT, medicine, digital health and virtual healthcare. There are some important concepts and technologies in the previous research that laid the foundation for the construction of DT, such as virtual physiological human. However, as a fusion of various technologies, DT is an expansion and enrichment of previous researches. Therefore, only applications of DT technology in medicine are selected and presented, followed by a brief discussion of the advantages and limitations involved in such applications. We began the review with an overview of DT technology in the main databases. Then we continued by examining the models that meet medical characteristics and the applications of DT technology in medicine. Finally, we concluded the review by discussing the current limitations and directions for future work.

Eligibility criteria

The studies included in the review were in line with the following criteria: (1) articles in English; (2) building models of patients through DT-related technologies and (3) achieving assistance in diagnosis or personalised treatment through DT technology. However, studies that met any of the following criteria were excluded: (1) duplicated; (2) irrelevant articles; (3) proposed ideas or frameworks but not been applied yet; (4) not based on DT or medicine; (5) absence of technological support of DT during the establishment of models; (6) articles published only in the form of conference abstracts; (7) articles with the type of proposal, protocol, letter, conference or viewpoint and (8) some independent digital technologies are applied to assist diagnosis and treatment without the integration of DT technologies.

Results

A total of 465 papers were retrieved by our search and 22 of them met the inclusion criteria and were, therefore, included in the further analysis. The flowchart of the selection procedure is shown in Figure 1. Papers described only models or without applications were descripted in this review but excluded during eligibility screening and extraction. In general, the popularity of DT research in medicine has risen globally at an accelerating rate. There was a particularly sharp rise around 2010. The analysis of country distribution of DT publications in medicine reveals that the three countries having published the highest number of articles are the United States (35%), China (11%) and the United Kingdom (15%). Other countries like Australia (7%), Japan (5%), Canada (5%), Italy (6%) and Korea (4%) also contributed to the research in this field.

Figure 2 compares the time distributions of DT research in the medical field among the three main countries.

DT models

Model construction is the core of basic research on DT in medicine, combining human anatomy and digital technology through image processing, digital collection processing, mathematical modelling and other technologies. Researchers digitally process two-dimensional (2D) cross-sectional images of the human body and use three-dimensional (3D) reconstruction

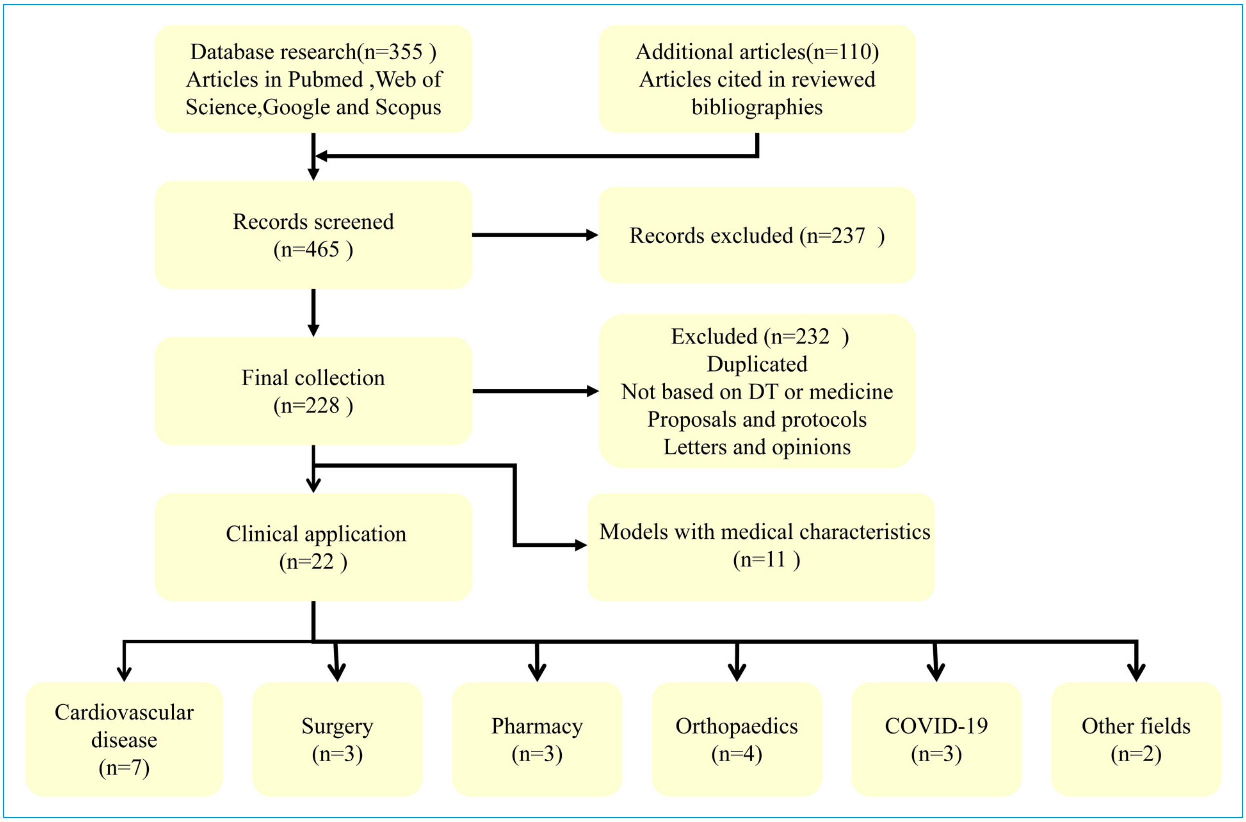

Figure 1. Flow diagram illustrating the screening process for papers in this study.

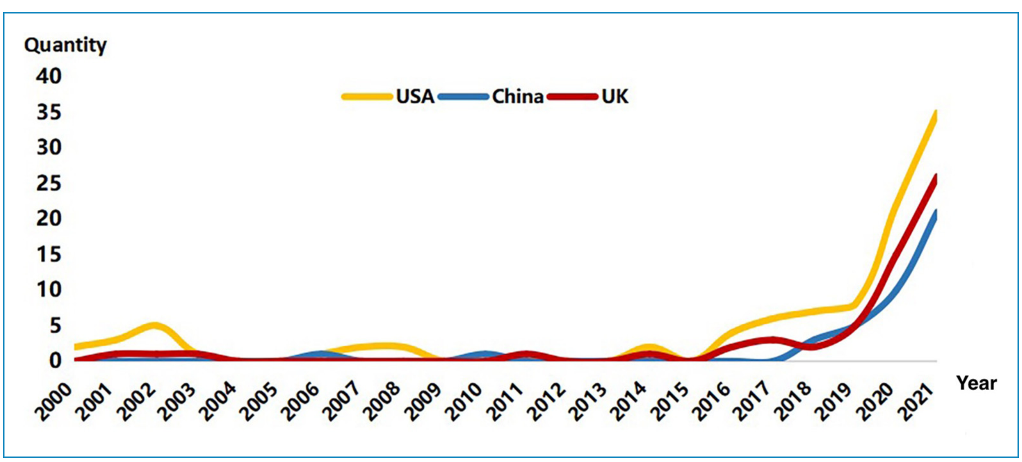

Figure 2. Comparison of studies on digital twin technology conducted in the United States, the United Kingdom, and China in the past 20 years.

technology to establish an intuitive 3D shape of the human body, allowing visualisation of the body structure.[22] The Blue Brain Project, for example, began in 2005 as a collaboration between EPFL (Ecole Polytechnique Fédérale de Lausanne) and International Business Machines and aims to model the neocortical column.[23] Schütt et al.[24] developed a DT of the Dynamic Colon Model that considered media viscosity, and peristaltic wave speed. It provided new insights for dissolution testing beyond established pharmacopoeial methods.

Modelling includes mechanics modelling, mechanical network modelling and statistical modelling. Establishing an appropriate mechanical model would make it possible to theoretically study the mass transmission of the human body and electrophysiological problems coupled with mechanics. The mechanics models can predict the emergency behaviour of biological systems in the fields of health and disease because they combine the interaction of biological components of the system. Mechanical network models usually take the form of a coupled system of ordinary differential equations, which are solved to discover how the molecular concentration evolves with time when molecules interact and respond to network inputs. Statistical models are complementary tools with which to verify the mechanics models by finding mechanistic explanations of inductive inference. Similarly, data from mechanics models need to be scrutinised quantitatively for validation.[24,25] To acquire and integrate real-time data or signals from a connected bioreactor, sensors including traditional sensors and newer sensors such as spectroscopic sensors are used in process analytical technology.[26] In a whole-cell project, specific types of cell and organism were modelled to better understand the molecular basis of diseases.[27]

Therefore, faster solving surrogates of these models may be developed in the form of machine learning models to solve problems in real-time.[28] It can help accelerate development and improve the quality of modelling by allowing modular development and linkages that account for interactions between various sub-processes. However, the need for further validation and the lack of clinical interpretability have limited the achievements of DT technologies.[29] When used on patients from different countries or centres, the models may need recalibration and the quality of datasets may need validation before they are integrated in clinical decision making. In realising clinical translation, model synergy can be used to increase clinical interpretability, verify the versatility of results, promote effective research results and testing methods and accelerate the integration of new technologies and clinical practice.[14]

Clinical application of the DT

Assisted by improvements in engineering technology, the medical industry has gradually transitioned from traditional medicine to digital medicine and then to information medicine, resulting in today's concept of smart medicine, which satisfies the individual's preventive and personalised medical needs to a greater extent. The purpose of building a DT diagnosis and treatment system is to realise precision medicine. The core of precision medicine is personalisation such that the treatment is patient centric by using AI or other cutting-edge technologies to accurately locate the cause of a patient's disease. The clinical applications of DT are shown in Table 1.

Cardiovascular disease. The application of the DT to the cardiovascular system includes the establishment of DT heart models and the precise treatment of cardiovascular disease. Models can be used to accurately determine the most valuable diagnostic basis and reliably infer biomarkers through non-invasive procedures. The key to DT-guided diagnosis is the personalised construction of the model. This approach has been adopted for the computation of pressure drops in flow obstruction and has proved to be more accurate than following clinical guidelines.[48] Philips developed a personalised DT model based on unique computed tomography (CT) images of the heart obtained before the surgical procedure.[49] The Philips HeartNavigator tool combines CT images in a single image of the patient's heart anatomy and provides real-time 3D insight into the positioning of devices during surgery, which can simplify the prior procedure planning and help a surgeon to select the best device. Nelson et al.[31] introduced the HeartFlow Analysis technology that enables more comprehensive evaluation of coronary artery disease by providing functional information and improves the patient's outcome. As a non-invasive electrocardiographic imaging system, the Acorys Mapping system combined a biopotential amplifier and a high-density sensor with innovative image and signal processing technologies to provide electrical activity in the surface of the heart in a completely non-invasive way.[33]

A DT can simulate dosage effects or the device response before a specific treatment and thus indicate whether the medical device or treatment is appropriate for patients and improve the treatment of patients with different causes of disease. After transcatheter aortic value implantation, FEops' HEARTguide was used to predict the device–patient interactions.[50] FEops' cutting-edge technology transforms cardiac images into DTs to improve and expand personalised management for patients with structural heart disease.[30] Combining DTs with AI-enabled anatomical analyses generates data-driven insights aspiring to enhance and improve structural heart disease management along the entire patient pathway, spanning from patient selection, procedure planning, periprocedural guidance to patient follow up. Cardiac resynchronisation therapy (CRT) is widely used for patients with prolonged QRS duration, but there remain uncertainties in the decision making in the 'grey zone'.[32] Niederer et al.[51] used mechanical models to investigate the dependence of the CRT efficacy on cellular-scale mechanisms and organs and identify novel patient selection criteria. Such a model is used to identify the length dependence of tension as a regulator of CRT and predicts that a patient will respond less to CRT treatment if he or she has cellular-scale dyssynchronous electrical activation but effective length-dependent tension regulation. Another example is in the field of infarct-related ventricular tachycardia, where researchers use a DT to improve the ablation guidance through the accurate identification of patient-specific optimal targets before a clinical procedure.[52] Mazumder et al.[35] used a two-chambered heart, haemodynamic equations and pressure control mechanisms based on pressure reflexes to construct a DT body of the cardiovascular system. Synthetic physiological

Table 1. Representative applications of DT in medical fields.

Year	Team	Applications of DT in medical field	The characteristics of DTs in medical field
2011	Niederer et al.[30]	Using mechanical models to investigate the dependence of the CRT efficacy on cellular-scale mechanisms and organs	It was used to predict that a patient will respond less to CRT treatment and identify novel patient selection criteria
2017	Cone Health team[31]	The HeartFlow Analysis combined the information of CT, AI, cloud computing and computational physiology	The non-invasive diagnostic test helped physicians identify the impact that blockages have on blood flow to the heart
2018	Prakosa et al.[32]	They used DT technology in the field of infarct-related ventricular tachycardia	It improved the ablation guidance through the identification of patient-specific optimal targets before a clinical procedure
2018	The Philips[33]	The Philips HeartNavigator tool combines CT images in a single image of the patient's heart anatomy	It provided real-time 3D insight into the positioning of devices during surgery, which can simplify the prior procedure planning
2019	Chakshu et al.[34]	They built a DT model coupled with blood flow and head vibration to develop diagnostic tools	Comparing the in vivo vibration against the virtual data to detect the severity of carotid stenosis from a video of a human face
2019	Mazumder et al.[35]	A DT body was built through dynamic equations and pressure control mechanisms based on pressure reflexes	It can generate large amounts of data on blood pressure and blood flow changes
2020	Suzuki et al.[36]	They obtained a rupture risk model through multivariate logistic regression through CT images	The model considered multi-dimensional parameters and listed age, length and pressure loss coefficient as risk factors
2020	Mussomeli et al.[37]	Takeda Pharmaceuticals switched to DT technology in production to offer transformative therapies around the world	DT models could shorten pharmaceutical processes and allow realistic input–output predictions of biochemical reactions
2020	Erol et al.[38]	Atos and Siemens worked with the pharmaceutical industry to establish DT models supported by the IoT, AI and many other advanced technologies	It improved the manufacturing process using physical DT models, which were created to overcome difficulties in terms of efficiency and production
2020	Grosman et al.[39]	Generating a DT that personalised system settings during the study phase to assess the system use and glycemic outcomes	It was the first demonstration that DT can successfully preform the insulin pump therapy with automation and personalisation
2020	Croatti et al.[40]	They integrated agents and multi-agent system technologies together with DT on trauma patients	It is the first application of agent-based DT on severe traumas and realised personalised management
2020	Subramanian et al.[41]	They built a DT that integrated scientific information and clinical source information	It helped drug research, bio-markers identification, test development, screening and clinical trial optimisation
2021	Golse et al.[42]	They built a model of entire blood circulation which is automatically calibrated based on patients	The DT model was demonstrated to predict post-operative portal hypertension through estimated hepatic flow rate
2021	He et al.[43]	Constructing a DT of the lumbar spine based on AI,	They built a shape-performance integrated DT body

(continued)

Table 1. Continued.

Year	Team	Applications of DT in medical field	The characteristics of DTs in medical field
		data analytics, motion capture system, IK method and FEM	to predict the biomechanical properties of real lumbar spine
2021	Zohdi[41,44]	Zohdi built a framework-combined DT and machine learning based on a genomic algorithm and coupled with simplified equations for the relationship between the particles and the fluid	It was used to ascertain the placement and flow rates of multiple ventilation units, so as to optimal ventilation systems
2021	Pilati et al.[40]	They developed a DT system for the vaccination process and tested it in a clinic	It allowed a real-time simulation and creates a dynamic vaccination centre, thus improving the efficiency of vaccination
2022	Aubert et al.[45]	They created a DT with the help of 3D X-ray images of patient to simulate the scenarios of bone healing	The risk of recurrent fractures was assessed by applying the maximum load during gait
2022	Hernigou et al.[46]	They built a DT model based on CT and AI technology and improved the accuracy of the model to identify the orientation and evaluated the compensation of the axis of subtalar joints	They minimised the inaccuracy of manual selection of anatomical landmarks by imaging systems
2022	Laybenbacher et al.[47]	They outlined a roadmap for building a DT for immune system in four stages	It would help to change the nature of biomedical research and accelerate the clinical translation of basic research
2022	Cydar[37]	They harnessed the latest in cloud GPU computing, computer vision and machine learning technology	It advanced surgical visualisation and decision making in theatre, and across the surgical pathway
2022	FEops[30]	They transformed cardiac images into DT and combined with AI-enabled anatomical analyses to generate data-driven insights	It provided physicians with unique digital tools to treat the right patients with the right technology at the right time
2022	Corify Care[33]	The mapping system combined hardware together with innovative image and signal processing technologies	It was used for the beat-to-beat, multi-chamber and 3Dmapping of cardiac activity

3D: three-dimensional; AI: artificial intelligence; CRT: Cardiac resynchronisation therapy; CT: computed tomography; DT: digital twin; FEM: finite element method; GPU: graphics processing unit; IK: inverse kinematics; IoT: internet of things.

data such as photoplethysmogram (PPG) was generated from healthy and atherosclerosis models, which can generate large amounts of data on blood pressure and blood flow changes.

Surgery. The idea of using the DT in the surgical field is to create a patient model for multi-disciplinary teams to plan a surgery and verify the anatomy and thus avoid inadvertent damage to structures.[34] A number of surgical specialties evaluated patient-specific simulation, including neurosurgery, vascular surgery and interventional radiology. As an example, the use of the DT in treating cardiovascular disease is growing and there is an emerging interest in the application of AI in vascular surgery.[36,53] The virtual model established using DT technology can used to develop diagnostic tools. Chakshu et al.[42] proposed a semi-active DT model coupled with blood flow and head vibration to detect the severity of carotid stenosis from a video of a human face. They compared the in vivo vibration against the virtual data to find the best fit between the virtual and in vivo data. Intracranial aneurysms may cause stroke and thrombosis and there may be immediate death in severe cases. Suzuki et al.[54] considered clinical, morphological and haemodynamic parameters and used computational fluid dynamics to calculate haemodynamic parameters from CT images. They obtained a rupture risk model through multivariate logistic regression and listed age, longer length, location at a bifurcation, lower pressure, loss coefficient and presence of a bleb as risk factors.

Owing to the extremely high risk of surgery, doctors usually use shunts to guide the blood flow away from the aneurysm sac. This method is less invasive, but the procedure is more complicated because the implant may cause additional damage to the artery. Sim&Cure adopted 3D rotational angiography to create a 3D model of an aneurysm and surrounding vessels before surgery, with the model being presented to the surgeon to complete the simulation and help choose points defining the ideal end position and the size of implants.[55] As a surgical-augmented intelligence company, Cydar's Intelligent Maps applied the latest in cloud graphics processing unit computing, computer vision and machine learning technology to advance surgical visualisation and decision making across the surgical pathway.[37] Golse et al. built a mathematical model of the entire blood circulation, which is automatically calibrated from patient characteristics. They demonstrated that a DT model could correctly predict post-operative portal hypertension, using estimated hepatic flow rate as input data.[38] Combined simulation with virtual-reality platforms, DT can be used to teach foundational technical skills in various surgical specialties and improve the surgical training of residents and provide a realistic account of the performance at the same time.[43,56]

Pharmacy. The medicine used in treatment should be personalised as human bodies and physiology are different. DT models created using genetic code can reveal changes in the performance of the body and provide researchers a more cost-effective opportunity to evaluate new compounds with a more accurate result. Takeda Pharmaceuticals has switched to DT technology in production to offer transformative therapies around the world. The creation of DT models can shorten pharmaceutical processes and allow realistic input–output predictions of biochemical reactions.[45] Additionally, Atos and Siemens worked with the pharmaceutical industry to improve the manufacturing process using physical DT models, which were created to overcome difficulties in terms of efficiency and production.[46]

In the phase of operation, DT can constantly provide real-time process control and optimisation information in order to support the product development and risk analysis.[44] Subramanian proposed a top-down approach for creating a DT that integrated information from scientific and clinical sources to help drug discovery and research, biomarkers identification, test development, screening and clinical trial optimisation.[41] The DT models have been shown to work well and are supported by the IoT, AI and many other advanced technologies.

Orthopaedics. With the development of numerical simulation and worn devices, the use of a DT for the real-time monitoring and analysis of the lumbar spine has become a highly promising cutting-edge technology in the biomechanical field. In applying the DT in the field of orthopaedics, it is important to develop physics-based experimental models and data-driven numerical models, which have the advantages of low cost and high integrity. Croatti et al. discussed the integration of DTs with agents and multi-agent systems technologies in healthcare and presented a first case study about the application of agent-based DT to the management of severe traumas.[40]

Our team firstly tried the application of DT in the human lumbar spine. Through the collection of customised information on the lumbar spine bones of a specific experimenter, we built a shape-performance integrated DT body for the prediction of the biomechanical properties of a real lumbar spine for different human postures.[57] The real-time motion posture and spatial position of the human body were obtained using human-motion-capture technology. The lumbar posture of the corresponding human body was calculated using a wearable virtual-reality device and a small volume of sensor data. Using the information of the inverse kinematics system and adopting the FE method and Gaussian process regression, a DT body of the lumbar spine was established, so as to realise various motion postures of the human body. In addition, the biomechanical properties of the lumbar spine were evaluated and predicted in real-time. Using the proxy model, the mechanical properties of the DT of the lumbar spine were dynamically calculated for real-time monitoring and prediction. Finally, a 3D virtual-reality system was developed using Unity3D software to record the real-time biomechanical performance of the lumbar spine during the movement of the body, which provided a new and effective method of warning and real-time planning in the field of orthopaedic treatments, especially in spinal rehabilitation.

Subsequently, several other studies have constructed DTs based on orthopaedic surgical models to provide quantitative and valuable information for clinical decision making and to evaluate reasonable parameters such as mechanical strength and interfragmentary strain to quantify the risk of recurrent fractures.[47,58,59] Aubert et al.[47] created a DT using post-operative 3D X-ray images of the patient, from which 4 stabilisation methods and 3 bone healing conditions resulted in a simulation of 12 scenarios from the DT. The risk of recurrent fractures was assessed by applying the maximum load during gait to assess mechanical strength, stress distribution, interfragmentary strain and fragment kinematics. Hernigou et al. built a patient model based on CT, AI and DT technology, which minimises the inaccuracy of manual selection of anatomical landmarks by imaging systems, and improved the accuracy of the model.[59] They identified the orientation and evaluated the compensation of the axis of subtalar joints.

COVID-19. The COVID-19 pandemic has generated enormous interest in the modelling and simulation of infectious diseases. A coronavirus spreads through person-to-person contact via respiratory droplets, especially when an infected patient coughs or sneezes. Zohdi built a rapidly computable respiratory emission model and developed a combined DT and machine learning framework with which to optimise ventilation systems.[60,61] The framework is based on a genomic algorithm and coupled with simplified equations for the relationship between the particles and the fluid to ascertain the placement and flow rates of multiple ventilation units, so as to optimally sequester particles that are released from patients who are coughing or sneezing.

During the pandemic, it has been necessary to find a way to vaccinate more people in a shorter time period, especially when healthcare workers are scarce. Pilati et al.[39] developed a DT system for the vaccination process and tested it in a clinic. The system allows a real-time simulation of patients and creates a dynamic vaccination centre. The virtual model can be run to find problems and address them in the real system, thus improving the efficiency of vaccination.

Other fields of application. The use of the DT in medicine is mainly focused on the personal health management, especially for the elderly. For example, Gkouskou et al.[62] described the virtual DT for precision nutrition, combining the information extracted from the genome with immunity, longitudinal and biological variables. Such a model can improve dietary choices and provide highly individualised lifestyle recommendations. It may revolutionise the management of obesity and its comorbidities, and provide a pillar for healthy ageing. Moreover, Laybenbacher et al.[63] outlined a roadmap for building an immune DT to capture key features of the immune system, which was to structure in four stages: specification, model constructions, personalisation and continued improvement. It would help to change the nature of biomedical research and accelerate the clinical translation of basic research.

In an artificial pancreas model for patients with type-1 diabetes, mathematical models of the human glucose metabolism and data algorithms that simulate insulin delivery have been customised as a patient-specific DT model, which continuously calculates the insulin requirement and regulates the blood insulin concentration.[64,65] For example, Grosman et al. used the run-in data from system users to generate a DT that personalised system settings during the study phase.[66] The result showed that personalised auto mode reduced the mean of sensor glucose. It is the first demonstration that DT can successfully preform the insulin pump therapy with automation and personalisation.

Discussion

The main finding of this review is that DT has achieved initial applications in medicine, such as cardiovascular disease, orthopaedics, surgery, pharmacy, etc. Using this new technology successfully helped solve several problems, such as real-time monitoring, dynamic analysis and precise treatment for diseases, which were difficult to deal with traditional methods. DT has the advantages of FE methods, such as non-invasiveness, controllability, repeatability, etc. At the same time, it can obtain the real-time health data of patients through wearable devices or sensors to perform real-time analysis, so as to continuously monitor and prevent the development or further deterioration of medical conditions. Further, DT makes it possible to select a more precise treatment options for the individual patient by using computer algorithm-based methods and principles in bioinformatics. It can also enable patients to exercise a greater degree of autonomy and achieve equitable treatment for patients irrespective of race or gender. The DT technology can be used both in patient healthcare and in hospital management. Using DT, scenarios can be predicted and evaluated in the virtual environment for scheduling and implementation in the real environment, which will reduce risk and save costs. It can also transmit information of treatment methods and drugs to the DT models for validation, which can optimise treatment options and ultimately enable early diagnosis or prevention of disease.

However, the effectiveness of the technology largely depends to a large extent on the accuracy of simulation. Current methods for validation are mainly based on comparison with cadaveric data or previous studies, which lack individualised assessment and accurate validation. There are several technical hurdles to creating high-fidelity models, including the multi-scale and multi-physics nature of the models, the difficulty in linking sub-process models across scales and physics, and the scarcity of experimental data. How to solve the gap between the results calculated by the DT and the real situation is another difficulty for DT. For example, the risks which were not predicted or estimated during the modelling for a surgery, while this risk occurred when the surgery was performed. There are also socio-ethical risks in DT healthcare. Privacy, seems to be the most important socio-ethical risk, is the main reason why DT may be disadvantageous. To some extent, DT healthcare faces legal and economic problems. The government and international legislatures should conduct strict supervision and establish standards that are valid and feasible for their own countries or regions. For example, service providers ought to seek explicit informed consent from the users and convey their plans for the secondary use of the entrusted data to relevant parties transparently. At the same time, more investment is needed to support the development of DTs. Obviously, a person's DT can cause discrimination or interference with the real person, which may cause trouble to his work and life. Furthermore, the high cost of DT healthcare may lead to inequality and injustice and thus widen the existing socio-economical gap.[67] Due to the promise of DT for personalised healthcare is built on extensive health-related data and the data of the sensor is transmitted to the cloud through the 5G network, so that the safety system during the operation of DT is crucial. Besides, real-time data collection will increase the accuracy of the simulation, some invasive examinations also increase the risk of the technology itself.

DT in future medicine

The number of studies on the application of DTs in the field medicine will increase with the exploration of the DT and advances of the technologies of the IoT, big data and AI. According to a Health Market report, global spending on the IoT in the field of healthcare is expected to reach USD 188.2 billion by 2025 with a growth rate of 21.0% and national health expenditures will reach 1795 per capita with a growth rate of 1.50% from 2012.[68] Ideally, the DT is a solution for precision medicine, which requires the integrating and processing of a large volume of the data. The IoT provides technical supports for the overall perception of the physical entity through data collection methods such as 2D codes, data acquisition cards and sensors. They are necessary for real-time data collecting, and then feedback on the processed data to optimise the models and regulate the operation through communication technology. It is envisaged that individuals will have their own DTs. Combining the DT of medical equipment and the DT of medical auxiliary equipment will provide a new platform and new experimental method for personal health management and healthcare services. Furthermore, adopting DTs and big data processing, simulations can be performed using high-resolution models of patients to find accurate treatment targets and suitable drugs or treatment methods for patients in realising precision medical treatment. Finally, establishing DTs at hospitals or in departments of hospitals allows the efficient management of medical resources and the planning of demand-oriented medical activities. Figure 3 depicts the application process of DTs in medicine and considers future possibilities.

Health monitoring. Generally, chronic diseases have the characteristics of a long duration, high incidence rate and large variety and are difficult to cure. Meanwhile, seniors have weak bodies and poor memories and do not have enough knowledge or information about the medical treatment. Hence, seniors need more care and community medical services, which can be effective solutions for real-time monitoring, medical guidance and crisis warnings. The healthcare service platform can build a DT model based on the physiological parameters of seniors and obtain the real-time health data of seniors using wearable devices and mobile phones. Possible abnormal conditions can then be calculated and analysed in a timely manner to realise crisis warnings. Integrating DT can better support the care of chronic diseases, such as dementia, thus ensuring greater precision and personalisation.[69] It will also be possible to transmit information of treatment methods and drugs to the model for verification in optimising the treatment plan and finally realise the early diagnosis or prevention of diseases in seniors.[70] The DT will track an individual's life journey, using data collected by wearable sensors and the lifestyle registered by the individual for the transition from clinical medicine to preventive medicine.

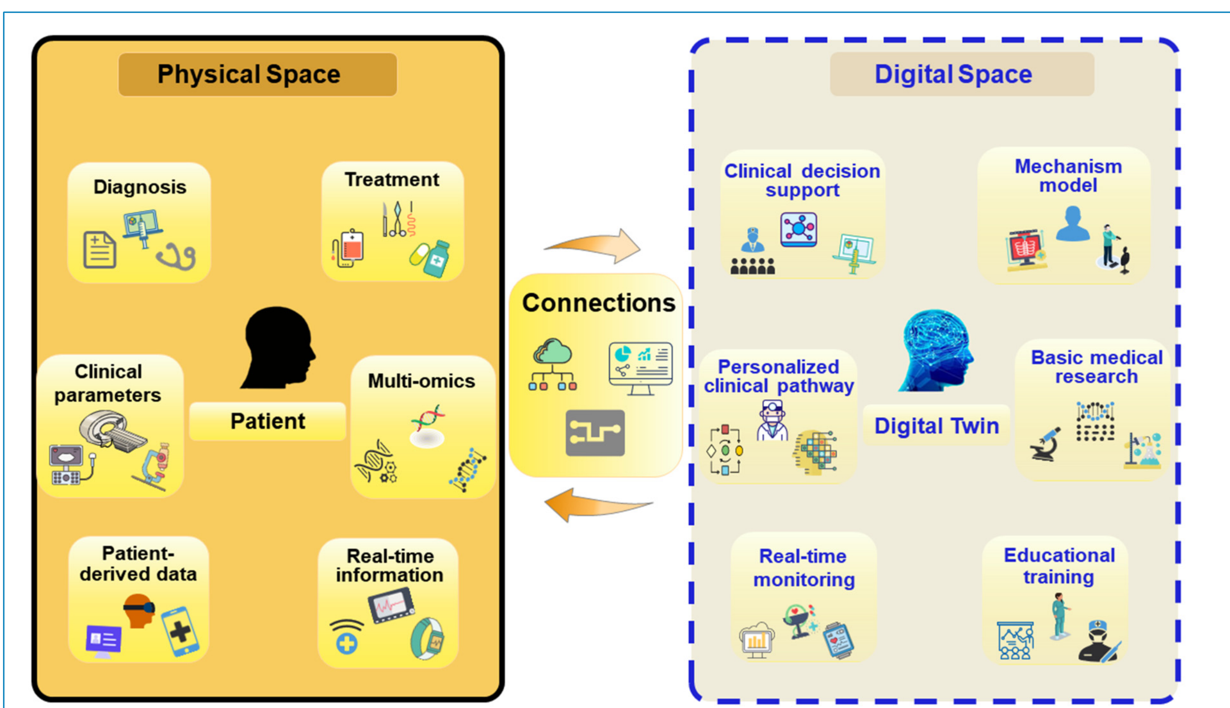

Figure 3. Application and prospects of digital twin technology in the medical field.

It is envisaged that individuals will have a full-lifecycle DT body, where data are collected from birth to form a virtual twin, which will grow with the child and serve as a life-long health record or medical experiment object. Medical institutions can obtain data of the human body in various perceptual ways with the real-time connection of data being the basis of a full-lifecycle DT body, which will ensure the accuracy of the DT model. People can obtain information of their physical condition in a timely manner to predict the occurrence of risk and adjust their diet or schedule appropriately. Therefore, using the DT body and epidemiological big data, the medical system can perform the real-time monitoring of the patient's health status and predict the risk of disease that may occur at any time for that person. Furthermore, suggestions regarding the lifestyle and prevention methods for the individual can be given in a timely manner.

Precise diagnosis. The DT patient can be well developed using multi-source data, which can be collected using various medical scanning and wearable instruments, such as the instruments of CT, magnetic resonance imaging, emission CT and colour ultrasound. There are also biochemical data from routine blood tests, urine tests and tests of enzymes to simulate the micro-environment and basic vital signs, making the virtual patient more accurate. The ideal DT model should integrate all data of patients and all types of pathogenesis, to form multi-layer modules.[71] Data of different types can be connected through the mapping of the relationship between the different types of modules, such as messenger RNAs and proteins.[72] Additionally, network tools can link interactions between cells from different types of tissue model, thereby creating a realistically complex DT patient.[73] However, DT patients cannot be restricted to being molecular profiles. We should also consider environmental factors when it comes to a patient with severe asthma, who must avoid allergens. In addition, there are historical data, medical records, health prediction data, surgical simulation data and virtual drug test data. The collected data must be complete and made suitable for analysis in modelling and decision making. Therefore, using the DT of the human body, the medical system can predict an individual's immune response to infection or injury, which could make a precise diagnosis of disease and be lifesaving in many ways.

Precise treatment. When a person is attacked by a disease, the specialists do not need to have face-to-face consultations with the patient. Just remote visual consultations with the help of data and models are required to determine the cause of the disease or prevent it. Before an operation, a DT can assist in the drawing up of a surgical procedure plan and the surgeon can use a virtual display to evaluate the operation plan on the virtual human body. The surgeon can trial an operational process from multiple angles and for multiple modules to verify safety and feasibility and make improvements to the operational process until they are satisfied. During the operation, the DT can broaden the surgical perspective, warn of the danger of blind spots, predict hidden bleeding, and help prepare or respond to an action according to circumstance. Additionally, the DT can be used as a reference to verify the anatomy and avoid unnecessary damage to structures. Furthermore, including virtual data at the molecular cell level in conducting virtual experiments and clinical trials of drugs can greatly shorten the development period of drugs and reduce the side effects of drugs on the human body. In summary, the DT can help in realising personalised medicine including targeted intervention before the disease worsens and in performing accurate predictions, accurate detections and precise treatments.

As an example, the DT plays a vital role when precision medical methods are adopted to treat malignant tumours.[74] Using computer algorithm-based methods and the principles of bioinformatics, it is possible to choose treatment options that are more effective for malignant tumours according to the DT model of the individual patient, thereby improving the survival rate and quality of the patient's life. The patient's genotype data can be put into the calculation model for predicting the effect of anti-cancer drugs, with the model outputting the patient's sensitivity to single or multiple drugs and helping doctors to determine the most suitable therapeutic drugs for a cancer patient. All the above can help realise the precise treatment of cancer patients.

In hospitals, resource management and clinical departments can use DTs to address the lack of resources in healthcare, especially that during the COVID-19 pandemic. As an example, the radiology department of Mater Private Hospital created a DT to make various predictions and test many scenarios. Using the information provided by the DT, the hospital adjusted the planning and organisation for its radiology department and thus reduced the waiting time of patients and improved the efficiency of the hospital. The DT will be widely used in other departments of the hospital. As an example, the doctor's visit time can be adjusted according to the flow of outpatients, and the occurrence of failures can be predicted according to the DT of the equipment and repaired in a timely manner to reduce the error rate and the loss of the hospital. In addition, the virtual human body can be used to train medical staff and thus improve medical skills, the treatment success rate and the teaching level of the hospital.

Strengths

This review was conducted to introduce the DT technology and summarise its applications in medicine. It will help in identifying the strengths and limitations of DT in medicine. It also showed the potential and opportunities of this technology to further application in all the medical fields.

Future studies could include these aspects to expand this literature review or make more attempts of DT in medicine based on the existing researches.

Limitations

The search in this review was restricted to English articles only, which might result in the omission of some publications. Also, we restricted the search to articles that included the terms *digital twin, healthcare* or respective Medical Subject Heading terms. Some relevant papers which did not explicitly use these terms but dealt with relevant topics might be ignored. In addition, the application of DT in medicine is currently in the preliminary stage, and most of them are application attempts. So there is a lack of randomised controlled trials for quality assessment.

Conclusion

In this review, we studied the DT technology and the applications of DT in medicine. We concluded that DT will be more widely used in the medical field to solve the problems, such as real-time monitoring, dynamic analysis and precise treatment for diseases, which cannot be fully explained by traditional methods. It can model the perception and action of any relevant facility in the medical environment, coupling the observable state of the DT with the state of the physical entity (PE). Although, DT technology has technical and ethical problems in the medical field that need to be solved urgently, the progress is encouraging. The use of DT in medicine is not only limited to the diagnosis and treatment of diseases, but can also be used for the prediction of health and disease states, which provide a quantitative understanding of health and disease. DT healthcare, as a key fusion approach of future medicine, will realise precise medicine and bring the advantages of personalised treatment to reality.

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