Evolution of digital twins in precision health applications: a scoping review study

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Evolution of digital twins in precision health applications: a scoping review study

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Abstract

An increasing amount of research is incorporating the concept of Digital twin (DT) in biomedical and health care applications. This scoping review aims to summarize existing research and identify gaps in the development and use of DTs in the health care domain. The focus of this study lies on summarizing: the different types of DTs, the techniques employed in DT development, the DT applications in health care, and the data resources used for creating DTs. We identified fifty studies, which mainly focused on creating organ- (n=15) and patient-specific twins (n=30). The research predominantly centers on cardiology, endocrinology, orthopedics, and infectious diseases. Only a few studies used real-world datasets for developing their DTs. However, there remain unresolved questions and promising directions that require further exploration. This review provides valuable reference material and insights for researchers on DTs in health care and highlights gaps and unmet needs in this field.

Introduction

Digital Twin (DT) is a novel approach in aiding decision-making to solve various real-world challenges and has attracted growing attention in both industry and research communities. The original use of the "twin" concept can be traced back to NASA's Apollo mission in the 1960s, where engineers created a "living model" to simulate spacecraft. In 2010, John Vickers introduced the term "digital twin", which consists of three components: a virtual system, a physical entity, and a bidirectional connection linking each other. While DTs have been widely studied in manufacturing, there is more and more interest in their applications in health care.

Recently, healthcare research has evolved from traditional reactive methods to proactive strategies [2–4]. Healthcare practitioners are trying to provide precision medicine, focusing on improving human health by evaluating individualized factors and acting on them [2]. The goal is to "target the right treatments to the right patients at the right time" [3]. Health digital twin, relying on artificial intelligence (AI) and machine learning (ML), is promising in this context. A health DT refers to the use of DT in health care, modeling patients, organs, pathophysiological systems, and/or other health-related entities (e.g., a hospital), to offer solutions in precision medicine, clinical trials, and public health.

DTs resemble other modeling techniques, such as microsimulation (MSM) and agent-based modeling (ABM). In health care, an MSM model simulates individual behaviors ("micro", e.g., at the patient or household level) to estimate population-level effects [1,2]. MSM has been used in various disease analyses (e.g., dementia [3] and oncology [4]). The National Cancer Institute (NCI)'s Cancer Intervention and Surveillance Modeling Network (CISNET) program has built MSM models to analyze cancer control interventions [5]. ABM, another simulation method, is focused on simulating the actions of targeted agents (e.g., patients) interacting with a specific environment. During the COVID-19 pandemic, ABM was used to model human activities and

virus transmissions for assessing the impact of public health interventions (e.g., social distancing and vaccination strategies). [6–8]

While MSM and ABM have a long history in health care applications, discussions surrounding DTs have surged more recently along with the advancement of AI/ML and the proliferation of big data. Several existing efforts have provided up-to-date perspectives on DTs in health care [9–11]. A few review papers were published to discuss specific disease applications, such as multiple sclerosis [12], cardiovascular disease [13], COVID-19 [14], and the immune system [15]. Nevertheless, the existing work has only focused on discussing DTs, MSM, and ABM, separately, without drawing similarities and distinctions across the three. In addition, DTs studies have emerged in health care, however, there is a lack of clarification of the difference among DTs, MSMs, and ABM, and the summarization of the DTs in health. In this scoping review work, first, we aimed to bridge this gap by providing a comprehensive and nuanced picture of health DT literature, highlighting the differences and overlaps across these modeling techniques. In addition, we conducted a comprehensive review of individual studies in DTs for healthcare applications.

Method

Search strategy and selection criteria

In this study, we performed a two-phase literature review: the first phase focused on evaluating existing review articles related to DTs, MSM, and ABM; the second phase assessed individual studies about health DTs. For both phases, we adhered to the same methodology following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which included a comprehensive literature search, a review of abstracts and full texts, and data extraction from selected articles.

In the first phase, we aimed to examine the definition, scope, and progress of DTs by extracting review papers that discussed relevant techniques and concepts, including DTs, MSM, and ABM. We collected peer-reviewed publications from mainstream databases, including IEEE Xplore (n = 36), ACM Digital Library (n = 4), Web of Science (n = 57), PubMed (n = 158), and Embase (n = 25), using the search query: Title: ("survey" OR "review" OR "overview" OR "summary") AND Abstract: ("digital twin*" OR "microsimulation" OR "agent-based simulation") AND ("healthcare" OR "health" OR "infection" OR "disease*") with filters limiting to studies published in the last decade (2013-2023). We then excluded papers that (1) were not review articles, (2) were not related to health care or medicine, or (3) were not written in English. A total of 25 review papers were included from 274 papers.

In the second phase, we focused on individual studies of DTs in health care, sourced from PubMed (n=611) and Embase (n=669). Our initial inclusion criteria specified studies that were (1) published within the past 10 years (2013–2023), (2) written in English, and (3) related to DTs in health care and biomedical applications (e.g., diagnosis, treatment, and drug discovery/development). We excluded studies that were (1) not peer-reviewed original research (e.g., pre-prints), (2) lacking full text, (3) commentaries, perspectives, or editorials, or (4) unrelated to the health care domain. After an initial screening of 940 papers, we discarded those that were not relevant (n=800) or did not meet our criteria (n=90), resulting in 50 papers selected for data extraction and final analysis.

For both phases, all papers underwent a two-person independent review process for the inclusion and exclusion; and conflicts were resolved by a third reviewer. The details and outcomes of both the Phase 1 and Phase 2 reviews, following the PRISMA guidelines, are illustrated in **Figure 1**.
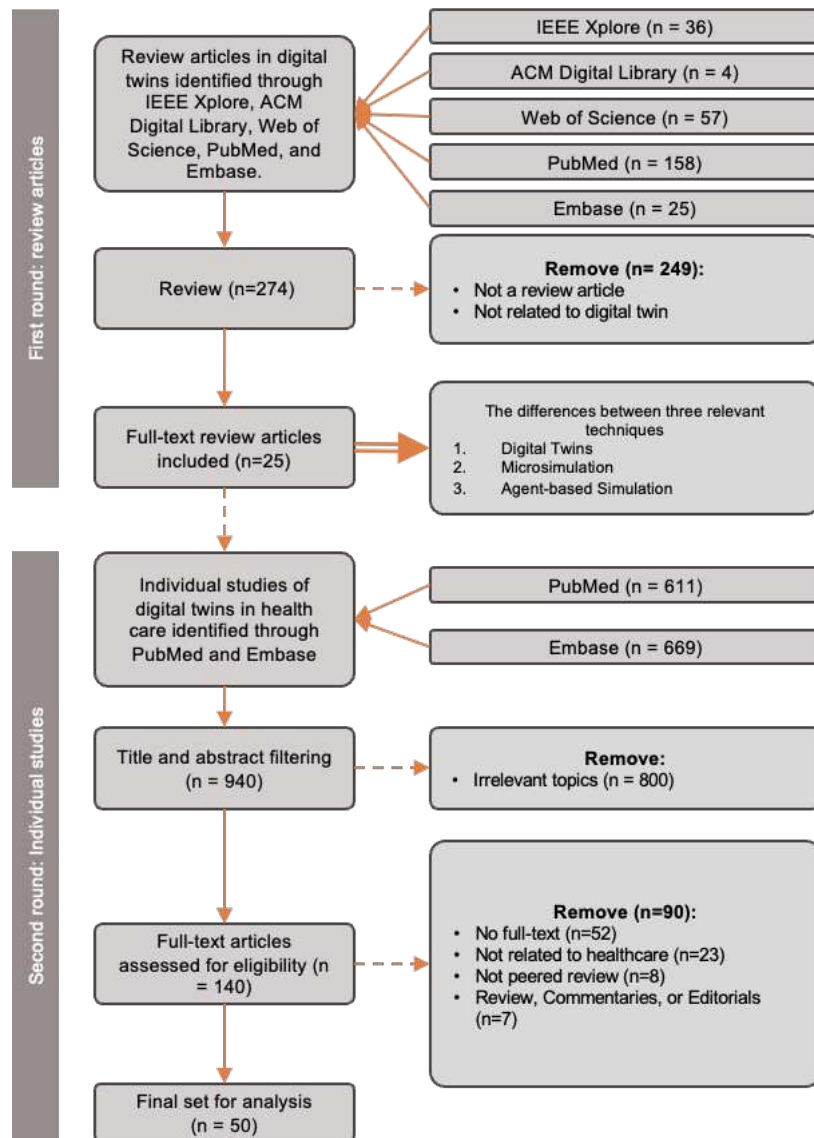
Figure 1. Flow diagram illustrating the process of study.

Results

We summarized the characteristics (**Figure 2**) of DTs, MSM, and ABM, based on 25 review articles. These three modeling approaches have distinct ways of analyzing data and serve different purposes during applications. DTs rely on AI/ML and visualization techniques to create personalized models of real-world objects with data connections. MSM mainly leverages existing statistics and conducts analysis and draws evidence at the population level, while ABM focuses on the behaviors of agents in specific environments. It is worth noting that the analytical methods used in MSM and ABM can also contribute to the development of DTs.
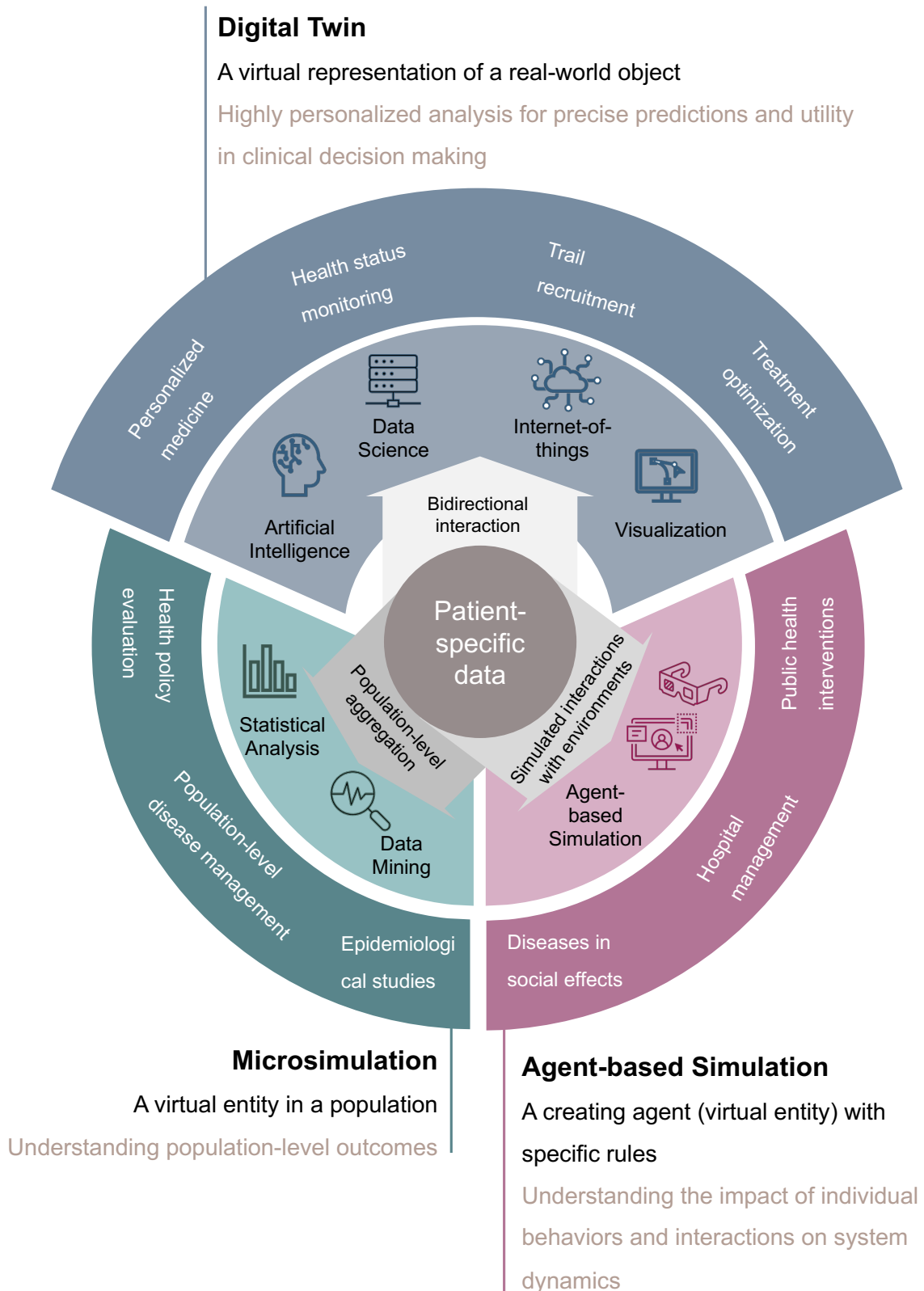
6

Figure 2. Differences among digital twins, microsimulation, and agent-based simulation in healthcare.

In the Phase 2 review, we conducted a detailed analysis of the existing studies on health DTs, summarizing their types, foundational techniques, applications, and datasets:

Types of DTs in Health care

As shown in **Figure 3**, current research on DTs in health care can be categorized into five classifications based on the physical entity they represent: organ-based (30%), physiological system-based (4%), patient-based (60%), procedure-based (4%), and miscellaneous (2%).
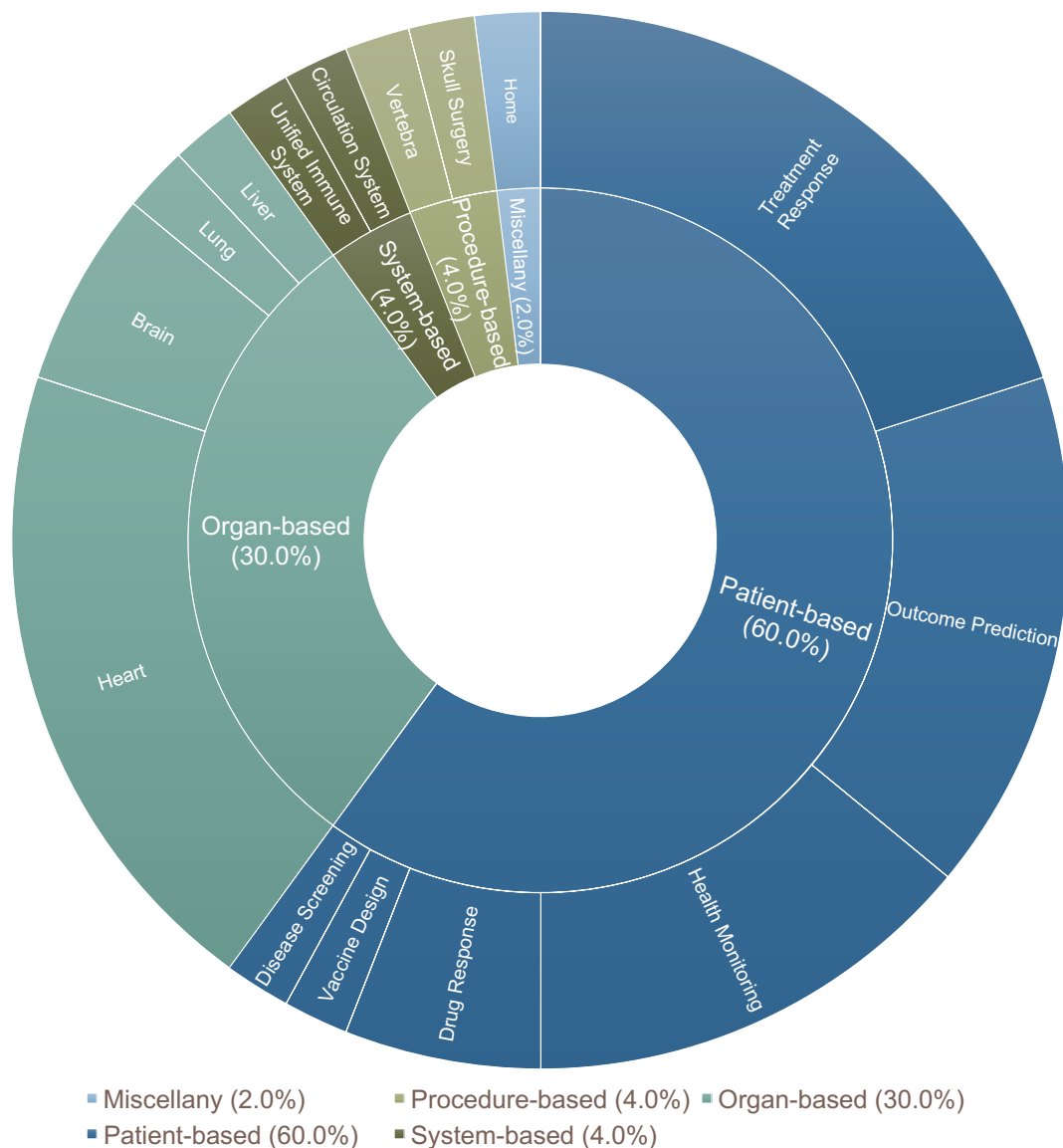
Figure 3. Types of current health digital twins.

Health DTs for modeling specific organs were commonly used for improving health monitoring and treatment regimen optimization. In this classification, the majority of studies [16–25] developed DTs of the heart (n=10), with fewer studies targeting the brain [26–28] (n=3), liver [29] (n=1), and lungs [30] (n=1).

In DT application for physiological systems, Golse et al. [31] created a DT to mimic the overall circulation system to estimate patients' preoperative conditions and predict postoperative hemodynamic status. Similarly, Maleki et al. [32] built a DT model of the immune system to inform clinical decisions.

Patient-level DTs replicate individual patients and are primarily focused on utilizing patient-DTs to support decision-making on therapeutics and interventions, including optimizing treatment strategies [33–38], predicting chemotherapy responses [39], and evaluating dietary interventions [40–43]. Another application focus is patient health and outcomes predictions using DTs, such as the onset of disease-specific brain atrophy [44], the spread of COVID-19 [45], the risk of vertebral fracture[46], the occurrence of metastases [47], the progression of diabetic retinopathy and cataracts [48], the auxiliary diagnosis of sepsis [49], and long-term health management (e.g., life-course risk of multimorbidity) [50]. Additionally, there is a growing interest in creating patient DTs for health and vital sign monitoring, such as tracking and forecasting glucose [51–54], blood velocity and pressures [55,56], and body mass [57]. Being distinct from organ or physiological system-based DTs, patient-based DTs do not model an organ or physiological system directly. Nevertheless, patient-based DTs adopt a more comprehensive view of the human body and the surrounding environment, allowing for the simulation of physiological systems or organs as part of the patient-based DTs. A smaller segment of research was focused on building patient-based DTs for drug development, such as drug reactions [58,59] and diffusion [60]. In addition, using data from actual human leukocyte antigen (HLA) haplotypes of ~22,000 individuals, Malone et al. [61] employed a DT-type simulation to design vaccines for preventing COVID-19.

Two studies focused on procedure-based DTs, such as Ahmadian et al. [62] simulated the cement injection process of the vertebra in a DT to predict vertebral compression fractures. Shu et al. [63] proposed a DT framework, called Twin-S, to simulate skull surgery procedures. We also identified miscellaneous DTs beyond organs, physiological systems, patients, or procedures. Fahim et al. [64] constructed a home-based DT to monitor the daily activities of the elderly.

Core Models of Health Digital Twins

The existing research employed both complex AI/ML techniques (58%) and simple statistical/mathematical models (36%) to build DTs (**Figure 4-a**). For instance, Lal et al. (2020) [33] utilized Bayesian networks as the core of a DT to simulate treatment responses for sepsis patients. Malone et al. (2020) proposed a DT framework with variations of Support Vector Machines [61] for COVID-19 vaccine design. Recurrent neural networks (RNN) [18,37,52,64] and generative adversarial networks (GAN) [45,51,55] were utilized for DT development in the analysis of complex data like sequential data (e.g., sensor readings and vital signs). When dealing with medical images, convolutional neural networks (CNN) [26,27,49] and GAN [23,46,62] are frequently used. Batch et al. (2022) [47] integrated RNN and CNN to develop a cancer DT for metastasis detection based on information extracted from a sequence of patients' past structured radiology reports. Additionally, reinforcement learning has been applied to optimize therapeutic regimens, including parameter adjustments for implantable cardioverter defibrillators [21] and treatment strategies for cancers like oropharyngeal squamous cell carcinoma [35].
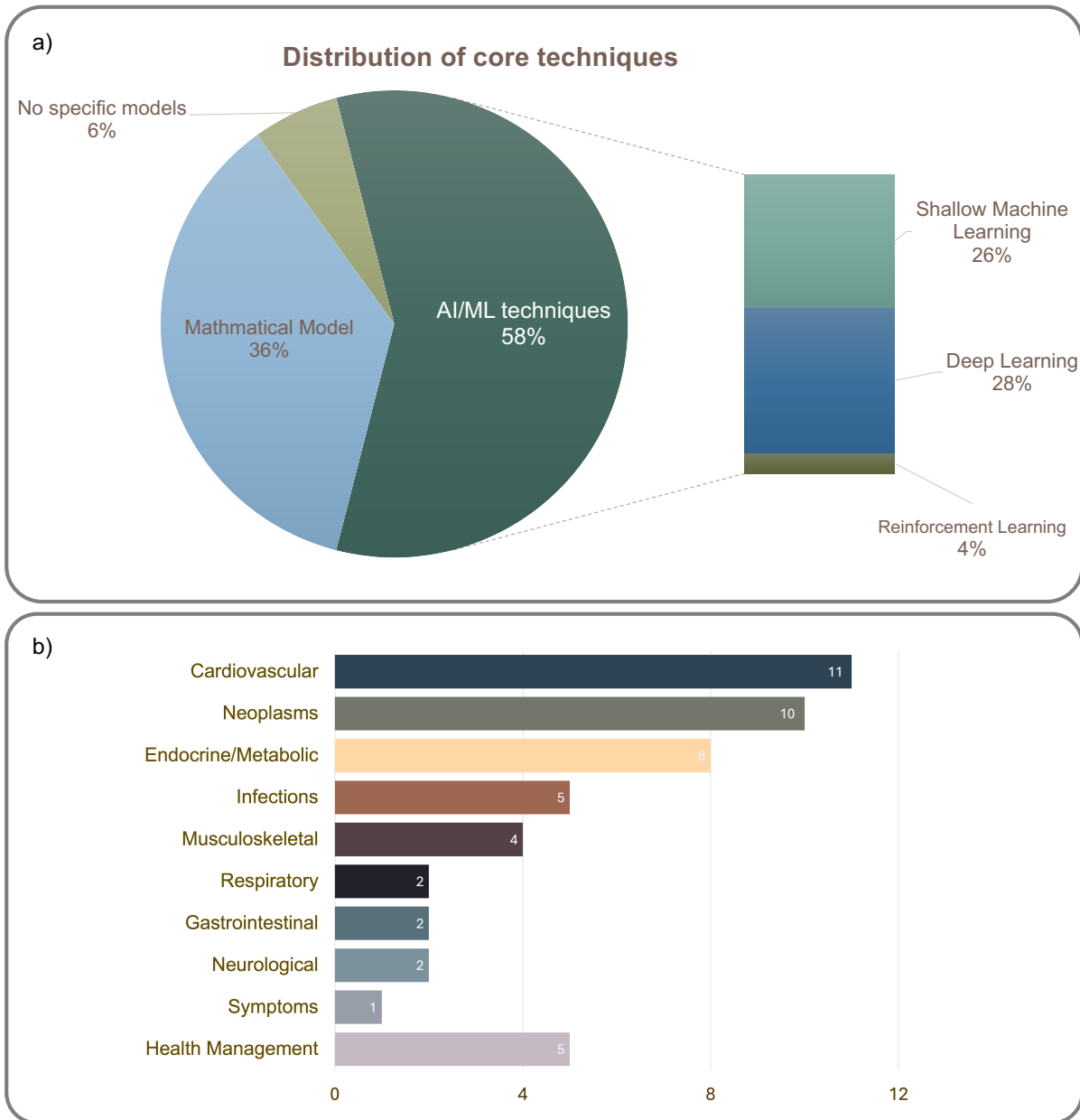
Figure 4. Techniques and applications of health digital twins. a) Core techniques to create health digital twins. b) Distributions of health digital twins in disease application domains.

Mathematical models often leverage prior knowledge (e.g., equations of cell model and tissue propagation) and/or existing statistics to create DTs. For example, Goodwina et al. [54] proposed a metabolic DT framework based on a probabilistic model to optimize insulin dosing by simulating the blood glucose trajectories. Galappaththige et al. [22] developed a cell model and tissue propagation equations to establish patient-specific cardiac electrophysiological models. Gillette et al. [16,17] employed a reaction-eikonal model to create high-fidelity cardiac

DTs that simulate ventricular electrophysiology. Wu et al. [39] combined magnetic resonance imaging (MRI) data with biologically based mathematical models to generate patient-specific DTs for predicting and assessing treatment responses (e.g., chemotherapy). Qi et al. [38] created virtual patients by incorporating realistic baseline tumor burdens, anatomical lesion distributions, non-target progression rates, and site-specific response dynamics. Azzolin et al. [25] used a statistical shape model to generate detailed personalized computational models of human atria. Cappon et al. [53] developed personalized DTs using patient physiology for glucose concentration simulations.

Disease Applications of Health DTs

We categorized existing studies using the Phecode [65] category to summarize the applications of DTs across different disease domains as shown in **Figure 4-b.** The most applications of health DTs are in cardiovascular medicine [16,17,19–25], such as extracranial carotid artery disease [56] and aortic aneurysms [18]. Neoplasms are the second largest application domain, with DTs modeling different cancers and associated conditions, such as lung [38], brain [26–28], breast [39], colorectal [66], metastatic cancers [47], and cancer-induced pain [60]. Eight studies focused on chronic conditions, such as diabetes (Type 2 [40–42,48,52] and Type 1 diabetes [51,53,54]). Some researchers applied health DTs to study infectious diseases [33,49], for example, developing the COVID-19 vaccine [45,61].

About 22% of the studies belong to various other disease domains. In the musculoskeletal domain, DTs were used to improve skull surgery procedures [63] and fracture management [34,46]. Two studies developed DTs for selecting treatments for respiratory conditions including pneumonia [37] and neonatal respiratory failure [30]. In gastroenterology, DTs were used for predicting the progression of Crohn's disease [36] and portal hypertension [31]. DTs were also applied to predict the onset of brain atrophy [44] and validate treatments [32] for multiple sclerosis. Bahrami et al. (2022) [58] employed a physics-based DT to propose tailored therapy for chronic

pain management. In addition to specific disease domains, DTs were also developed for broad health management applications, such as diet and healthy aging [43,50,55,57,64].

<u>**Data Sources**</u>

Data for constructing DTs comes from three primary sources: data from prior clinical studies (58%), real-world data, including electronic health records (EHRs) (22%), and simulation-generated data (20%). Clinical study data include both clinical trial data [30,32,39,51,52,59,60] and data gathered from observational cohorts [20,36,38,40,42,44,49]. This category covers various types of data, such as structured clinical variables (e.g., conditions and treatments) [31,33,43], imaging data (e.g., CT scans [57], specimens [46], and 3D images [23,34]), and sensory readings [16,17,25]. Among these, only very few datasets (6 datasets used by 5 studies) are publicly accessible (**Table 1**).

Real-world data are the data relating to patients' health status collected during routine care, including EHRs and administrative insurance claims data [26,28,37,47,56,61]. Nine real-world datasets (used by six studies) are publicly accessible (**Table 1**), with the remaining five studies using private data. Some studies use simulated data for testing the DT models across various disease and application domains, including cardiovascular [18,19,21,22], type 1 diabetes [53], vertebroplasty procedures [62], and 3D skull structure [63]. While these simulated data are useful for developing and validating the DT models, they may fall short of creating comprehensive DTs that represent real-world patients and health care settings.

Discussion

In this review, we elucidated the differences among DTs, MSMs, and ABMs. We then reviewed n=50 existing DT studies in health care and summarized the studies based on the DT types, foundational techniques, applications, and datasets. We identified five types of health DTs, including patient-based DTs (n = 30), organ-based DTs (n = 15), physiological

system-based DTs (n=2), procedure-based (n=2), and miscellaneous (n = 1). Most organ-based DTs were designed for forecasting treatment response, while patient-based DTs are primarily used for health monitoring. Regarding foundational techniques of DTs, our review identified 29 studies that employed AI/ML techniques and 18 studies that adopted mathematical models in developing DTs. From the view of applications, most DTs are designed for cardiovascular medicine, Neoplasms, chronic conditions, and infectious diseases. Clinical study data, real-world data, and simulated data have all been used for DT development. Overall, our review shows that AI-based DTs have demonstrated an emerging trend as more and more large-scale datasets, especially large collections of real-world EHR data, have become increasingly available, and computational power has dramatically increased, given the rising capability of Graphics Processing Units (GPUs) and deep neural networks.

Admittedly, there seems to be a clout-chasing phenomenon in a few of the existing studies because of the hot trend of DTs. Some research [22,53,58] focused more on developing modeling approaches using simulated data rather than proposing a true DT, i.e., linking the virtual model to real-world entities. Although the authors claimed that these methods have the potential to develop health DTs using real-world data, they neglected to explain to what extent their studies could be associated with the DT development process. For instance, a study merely developed models for metastatic disease detection based on radiology reports of three separate organs but did not explain how their models can contribute to creating a DT. [47] Being able to predict outcomes (or any future events or changes in the system) is a basic need of DTs, but these alone should not be called DTs. Furthermore, some authors may have inaccurately described their studies as creating DTs, when they should have been classified under other simulation techniques. For example, Lin et al. (2023) [66] claimed to have created patient DTs of 5,417,699 Taiwanese individuals to simulate the effectiveness of colorectal cancer screening as an intervention, rather than conducting true randomized controlled trials. This study seems to be more aligned with the definition of microsimulation models; indeed the

authors cited microsimulation as DT, stating, "*the concept of the digital twin was realized in the realm of cancer prevention and screening by the parallel universe approach, which has already been used in a micro-simulation scenario for the development of CISNET (Cancer Intervention and Surveillance Modeling Network)*" [66]. However, it remains unclear whether those virtual patients do correspond to actual patients in the real world or were just generated using simulation parameters derived from the real-world population, leading to the misclassification of their CISNET microsimulation models as "digital twins".

In addition to the misuse of the terminology, several other issues that need to be carefully considered in creating health DTs, are not adequately addressed in prior research. First, model fairness and bias have not been considered in existing health DT studies [67,68]. Health DTs, corresponding individuals in the real world, should serve everyone fairly, regardless of their socioeconomic status, and should not exacerbate existing health disparities and inequalities. DT developers should assess the potential biases of data used to train the models, as well as the bias that is introduced by the modeling approaches. Bias mitigation would be conducted for identified bias before the health DT application [67]. Furthermore, health DTs rely heavily on the quality and completeness of real-world data from real-world individuals for both model creation and linkage to real-world entities. Lin et al suggested data completeness can generally improve model effectiveness, emphasizing the importance of data quality [69,70]. Another important gap in existing DT research is explainability and transparency; stakeholders often lack insight into how the DT works, leading to concerns about the trustworthiness of the models. Integrating tools that facilitate technical scrutiny of an algorithm's behavior and its uncertainties is essential and should become a standard practice in algorithm development [71]. Researchers and developers also need to make the DT workflow and models transparent, creating "*white-box*" rather than "*black-box*" systems. Last but not least, it is important to note that currently almost all existing studies are focused on the development of DT modeling approaches. There are still no real-world implementations of health DTs, and no study has been able to make a live connection to continuously achieve the

bidirectional data exchange as defined in true DTs, i.e., DTs inform health choices or actions and the individuals' data feedback to the models with updated information or improvement to the models. To address these research gaps and unmet needs in health DTs, the involvement of all stakeholders, with consideration of human-AI teaming,[72] is critically needed in the development and co-creation of the health DTs.

Looking ahead, there is a promising future in research focused on developing and implementing health DTs, particularly given the recent rapid evolution in large foundation models, especially in large language models (LLMs) such as ChatGPT and GPT-4. These foundation models have impressive abilities to adapt to various downstream tasks, a desired goal of DTs. Discussions of foundation models for DTs have started in the general domain [73,74]; nevertheless, more research and development work is very much needed, especially for health DTs[74]. From the application standpoint, real-world applications of utilizing DTs, especially for ongoing care and monitoring of chronic diseases, are greatly needed. Other novel uses of health DTs should also be a focus of future research. Furthermore, more and more studies are utilizing deep learning techniques to build up health DT systems. As deep learning models often lack interpretability, a possible solution would be integrating deep learning techniques with prior domain knowledge to improve transparency, in addition to the line of explainability research [75]. Besides, most current studies have built DTs based on data from a single source. The next-generation DTs should incorporate multimodal data (e.g., structured fields from medical records, free-text reports and physician notes, imaging, genomics, and environmental factors) to comprehensively model an entity. The rising interest and ability of multimodal foundation models that can leverage data from multiple modalities might be a critical advancement for building health DTs. Finally, as mentioned above, addressing bias and fairness remains a primary concern, with researchers urged to assess and mitigate potential biases of current health DT techniques.

Our study is subject to several limitations. First, we excluded non-English studies and reports. Second, given that the current scope review is focused on DTs, we reviewed solely review-type articles discussing MSM and ABM, without diving into the individual studies and details of those techniques. Future investigations should comprehensively explore DTs and relevant techniques within specific application domains.

In conclusion, this scoping review offers valuable reference information and perspectives for researchers who are interested in DT techniques and applications in health care, while also highlighting the gaps and future research directions in this field.

Data availability

No new or unpublished data is included within the study.

References

1. Rutter, C. M., Zaslavsky, A. M. & Feuer, E. J. Dynamic microsimulation models for health outcomes: a review. *Med. Decis. Making* **31**, 10–18 (2011).

2. Abraham, J. M. Using microsimulation models to inform U.s. health policy making. *Health Serv. Res.* **48**, 686–695 (2013).

3. Dallora, A. L., Eivazzadeh, S., Mendes, E., Berglund, J. & Anderberg, P. Machine learning and microsimulation techniques on the prognosis of dementia: A systematic literature review. *PLoS One* **12**, e0179804 (2017).

4. Bespalov, A., Barchuk, A., Auvinen, A. & Nevalainen, J. Cancer screening simulation models: a state of the art review. *BMC Med. Inform. Decis. Mak.* **21**, 359 (2021).

5. Çağlayan, Ç. *et al.* Microsimulation modeling in oncology. *JCO Clin. Cancer Inform.* 1–11 (2018).

6. Gozzi, N. *et al.* Estimating the impact of COVID-19 vaccine inequities: a modeling study. *Nat. Commun.* **14**, (2023).

7. Hladish, T. J. *et al.* Evaluating targeted COVID-19 vaccination strategies with agent-based modeling. *medRxiv* (2023) doi:10.1101/2023.03.09.23285319.

8. Kumaresan, V. *et al.* Fitting and validation of an agent-based model for COVID-19 case forecasting in workplaces and universities. *PLoS One* **18**, e0283517 (2023).

9. Armeni, P. *et al.* Digital Twins in Healthcare: Is It the Beginning of a New Era of Evidence-Based Medicine? A Critical Review. *J Pers Med* **12**, (2022).

10. Elkefi, S. & Asan, O. Digital Twins for Managing Health Care Systems: Rapid Literature Review. *J. Med. Internet Res.* **24**, e37641 (2022).

11. Sun, T., He, X. & Li, Z. Digital twin in healthcare: Recent updates and challenges. *Digit Health* **9**, 20552076221149652 (2023).

12. Voigt, I. *et al.* Digital Twins for Multiple Sclerosis. *Front. Immunol.* **12**, 669811 (2021).

13. Coorey, G. *et al.* The health digital twin to tackle cardiovascular disease-a review of an emerging interdisciplinary field. *NPJ Digit Med* **5**, 126 (2022).

14. Luo, Y., Wunderink, R. G. & Lloyd-Jones, D. Proactive vs Reactive Machine Learning in Health Care: Lessons From the COVID-19 Pandemic. *JAMA* **327**, 623–624 (2022).

15. Laubenbacher, R. *et al.* Building digital twins of the human immune system: toward a roadmap. *npj Digital Medicine* **5**, 1–5 (2022).

16. Gillette, K. *et al.* Automated Framework for the Inclusion of a His-Purkinje System in Cardiac Digital Twins of Ventricular Electrophysiology. *Ann. Biomed. Eng.* **49**, 3143–3153 (2021).

17. Gillette, K. *et al.* A Framework for the generation of digital twins of cardiac electrophysiology from clinical 12-leads ECGs. *Med. Image Anal.* **71**, 102080 (2021).

18. Chakshu, N. K., Sazonov, I. & Nithiarasu, P. Towards enabling a cardiovascular digital twin for human systemic circulation using inverse analysis. *Biomech. Model. Mechanobiol.* **20**, 449–465 (2021).

19. Camps, J. *et al.* Inference of ventricular activation properties from non-invasive electrocardiography. *Med. Image Anal.* **73**, 102143 (2021).

20. Jung, A., Gsell, M. A. F., Augustin, C. M. & Plank, G. An Integrated Workflow for Building Digital Twins of Cardiac Electromechanics-A Multi-Fidelity Approach for Personalising Active Mechanics. *Mathematics (Basel)* **10**, 823 (2022).

21. Lai, M., Yang, H., Gu, J., Chen, X. & Jiang, Z. Digital-twin-based Online Parameter Personalization for Implantable Cardiac Defibrillators. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2022**, 3007–3010 (2022).

22. Galappaththige, S., Gray, R. A., Costa, C. M., Niederer, S. & Pathmanathan, P. Credibility assessment of patient-specific computational modeling using patient-specific cardiac modeling as an exemplar. *PLoS Comput. Biol.* **18**, e1010541 (2022).

23. Xing, X. *et al.* HDL: Hybrid deep learning for the synthesis of myocardial velocity maps in digital twins for cardiac analysis. *IEEE J. Biomed. Health Inform.* **27**, 5134–5142 (2023).

24. Strocchi, M. *et al.* Cell to whole organ global sensitivity analysis on a four-chamber heart electromechanics model using Gaussian processes emulators. *PLoS Comput. Biol.* **19**, e1011257 (2023).

25. Azzolin, L. *et al.* AugmentA: Patient-specific augmented atrial model generation tool. *Comput. Med. Imaging Graph.* **108**, 102265 (2023).

26. Wan, Z., Dong, Y., Yu, Z., Lv, H. & Lv, Z. Semi-Supervised Support Vector Machine for Digital Twins Based Brain Image Fusion. *Front. Neurosci.* **15**, 705323 (2021).

27. Wang, J., Qiao, L., Lv, H. & Lv, Z. Deep Transfer Learning-Based Multi-Modal Digital Twins for Enhancement and Diagnostic Analysis of Brain MRI Image. *IEEE/ACM Trans. Comput. Biol. Bioinform.* **20**, 2407–2419 (2023).

28. Sarris, A. L., Sidiropoulos, E., Paraskevopoulos, E. & Bamidis, P. Towards a Digital Twin in Human Brain: Brain Tumor Detection Using K-Means. *Stud. Health Technol. Inform.* **302**, 1052–1056 (2023).

29. Lauzeral, N. *et al.* A model order reduction approach to create patient-specific mechanical models of human liver in computational medicine applications. *Comput. Methods Programs Biomed.* **170**, 95–106 (2019).

30. Förster, K. M. *et al.* In silico numerical simulation of ventilator settings during high-frequency ventilation in preterm infants. *Pediatr. Pulmonol.* **56**, 3839–3846 (2021).

31. Golse, N. *et al.* Predicting the risk of post-hepatectomy portal hypertension using a digital twin: A clinical proof of concept. *J. Hepatol.* **74**, 661–669 (2021).

32. Maleki, A. *et al.* Moving forward through the in silico modeling of multiple sclerosis: Treatment layer implementation and validation. *Comput. Struct. Biotechnol. J.* **21**, 3081–3090 (2023).

33. Lal, A. *et al.* Development and Verification of a Digital Twin Patient Model to Predict Specific Treatment Response During the First 24 Hours of Sepsis. *Crit Care Explor* **2**, e0249 (2020).

34. Aubert, K. *et al.* Development of Digital Twins to Optimize Trauma Surgery and Postoperative Management. A Case Study Focusing on Tibial Plateau Fracture. *Front Bioeng Biotechnol* **9**, 722275 (2021).

35. Tardini, E. *et al.* Optimal Treatment Selection in Sequential Systemic and Locoregional Therapy of Oropharyngeal Squamous Carcinomas: Deep Q-Learning With a Patient-Physician Digital Twin Dyad. *J. Med. Internet Res.* **24**, e29455 (2022).

36. Venkatapurapu, S. P. *et al.* A Computational Platform Integrating a Mechanistic Model of Crohn's Disease for Predicting Temporal Progression of Mucosal Damage and Healing. *Adv. Ther.* **39**, 3225–3247 (2022).

37. Chakshu, N. K. & Nithiarasu, P. An AI based digital-twin for prioritising pneumonia patient treatment. *Proc. Inst. Mech. Eng. H* **236**, 1662–1674 (2022).

38. Qi, T. & Cao, Y. Virtual clinical trials: A tool for predicting patients who may benefit from treatment beyond progression with pembrolizumab in non-small cell lung cancer. *CPT Pharmacometrics Syst Pharmacol* **12**, 236–249 (2023).

39. Wu, C. *et al.* MRI-Based Digital Models Forecast Patient-Specific Treatment Responses to Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer. *Cancer Res.* **82**, 3394–3404 (2022).

40. Shamanna, P. *et al.* Reducing HbA1c in Type 2 Diabetes Using Digital Twin Technology-Enabled Precision Nutrition: A Retrospective Analysis. *Diabetes Ther.* **11**, 2703–2714 (2020).

41. Shamanna, P. *et al.* Retrospective study of glycemic variability, BMI, and blood pressure in diabetes patients in the Digital Twin Precision Treatment Program. *Sci. Rep.* **11**, 1–9 (2021).

42. Shamanna, P. *et al.* Type 2 diabetes reversal with digital twin technology-enabled precision nutrition and staging of reversal: a retrospective cohort study. *Clin Diabetes Endocrinol* **7**, 21 (2021).

43. Silfvergren, O. *et al.* Digital twin predicting diet response before and after long-term fasting. *PLoS Comput. Biol.* **18**, e1010469 (2022).

44. Cen, S., Gebregziabher, M., Moazami, S., Azevedo, C. J. & Pelletier, D. Toward precision medicine using a "digital twin" approach: modeling the onset of

disease-specific brain atrophy in individuals with multiple sclerosis. *Sci. Rep.* **13**, 1–14 (2023).

45. Quilodrán-Casas, C. *et al.* Digital twins based on bidirectional LSTM and GAN for modelling the COVID-19 pandemic. *Neurocomputing* **470**, 11–28 (2022).

46. Ahmadian, H. *et al.* Toward an artificial intelligence-assisted framework for reconstructing the digital twin of vertebra and predicting its fracture response. *Int. j. numer. method. biomed. eng.* **38**, e3601 (2022).

47. Batch, K. E. *et al.* Developing a Cancer Digital Twin: Supervised Metastases Detection From Consecutive Structured Radiology Reports. *Front Artif Intell* **5**, 826402 (2022).

48. Batagov, A. *et al.* Generalized metabolic flux analysis framework provides mechanism-based predictions of ophthalmic complications in type 2 diabetes patients. *Health Inf Sci Syst* **11**, 18 (2023).

49. Lv, Z., Guo, J. & Lv, H. Deep Learning-Empowered Clinical Big Data Analytics in Healthcare Digital Twins. *IEEE/ACM Trans. Comput. Biol. Bioinform.* **PP**, (2023).

50. Milne-Ives, M. *et al.* Life Course Digital Twins-Intelligent Monitoring for Early and Continuous Intervention and Prevention (LifeTIME): Proposal for a Retrospective Cohort Study. *JMIR Res. Protoc.* **11**, e35738 (2022).

51. Zhu, T., Li, K., Herrero, P. & Georgiou, P. GluGAN: Generating Personalized Glucose Time Series Using Generative Adversarial Networks. *IEEE J Biomed Health Inform* **27**, 5122–5133 (2023).

52. Thamotharan, P. *et al.* Human Digital Twin for Personalized Elderly Type 2 Diabetes Management. *J. Clin. Med. Res.* **12**, (2023).

53. Cappon, G., Vettoretti, M., Sparacino, G., Favero, S. D. & Facchinetti, A. ReplayBG: A Digital Twin-Based Methodology to Identify a Personalized Model From Type 1 Diabetes Data and Simulate Glucose Concentrations to Assess Alternative Therapies. *IEEE Trans. Biomed. Eng.* **70**, 3227–3238 (2023).

54. Goodwin, G. C. *et al.* A systematic stochastic design strategy achieving an optimal tradeoff between peak BGL and probability of hypoglycaemic events for individuals having type 1 diabetes mellitus. *Biomed. Signal Process. Control* **57**, 101813 (2020).

55. Barbiero, P., Viñas Torné, R. & Lió, P. Graph Representation Forecasting of Patient's Medical Conditions: Toward a Digital Twin. *Front. Genet.* **12**, 652907 (2021).

56. Dubs, L. *et al.* Assessment of extracranial carotid artery disease using digital twins - A pilot study. *Neuroimage Clin* **38**, 103435 (2023).

57. Geissler, F. *et al.* Personalized computed tomography - Automated estimation of height and weight of a simulated digital twin using a 3D camera and artificial intelligence. *Rofo* **193**, 437–445 (2021).

58. Bahrami, F., Rossi, R. M. & Defraeye, T. Predicting transdermal fentanyl delivery using physics-based simulations for tailored therapy based on the age. *Drug Deliv.* **29**, 950–969 (2022).

59. Susilo, M. E. *et al.* Systems-based digital twins to help characterize clinical dose-response and propose predictive biomarkers in a Phase I study of bispecific antibody, mosunetuzumab, in NHL. *Clin. Transl. Sci.* **16**, 1134–1148 (2023).

60. Bahrami, F., Rossi, R. M., De Nys, K. & Defraeye, T. An individualized digital twin of a patient for transdermal fentanyl therapy for chronic pain management. *Drug Deliv. Transl. Res.* **13**, 2272–2285 (2023).

61. Malone, B. *et al.* Artificial intelligence predicts the immunogenic landscape of SARS-CoV-2 leading to universal blueprints for vaccine designs. *Sci. Rep.* **10**, 1–14 (2020).

62. Ahmadian, H. *et al.* A digital twin for simulating the vertebroplasty procedure and its impact on mechanical stability of vertebra in cancer patients. *Int. j. numer. method. biomed. eng.* **38**, e3600 (2022).

63. Shu, H. *et al.* Twin-S: a digital twin for skull base surgery. *Int. J. Comput. Assist. Radiol. Surg.* **18**, 1077–1084 (2023).

64. Fahim, M., Sharma, V., Hunter, R. & Duong, T. Q. Healthy Aging: A Deep Meta-Class Sequence Model to Integrate Intelligence in Digital Twin. *IEEE Journal of Translational Engineering in Health and Medicine* **11**, 330–340 (2023).

65. Bastarache, L. Using Phecodes for Research with the Electronic Health Record: From PheWAS to PheRS. *Annu Rev Biomed Data Sci* **4**, 1–19 (2021).

66. Lin, T.-Y. *et al.* Assessing overdiagnosis of fecal immunological test screening for colorectal cancer with a digital twin approach. *npj Digital Medicine* **6**, 1–8 (2023).

67. Huang, Y. *et al.* A scoping review of fair machine learning techniques when using real-world data. *J. Biomed. Inform.* 104622 (2024).

68. Xu, J. *et al.* Algorithmic fairness in computational medicine. *EBioMedicine* **84**, 104250 (2022).

69. Lin, K. J. *et al.* Out-of-system Care and Recording of Patient Characteristics Critical for Comparative Effectiveness Research. *Epidemiology* **29**, 356–363 (2018).

70. Lin, K. J. *et al.* Identifying Patients With High Data Completeness to Improve Validity of Comparative Effectiveness Research in Electronic Health Records Data. *Clin. Pharmacol. Ther.* **103**, 899–905 (2018).

71. Lo Piano, S. Ethical principles in machine learning and artificial intelligence: cases from the field and possible ways forward. *Humanities and Social Sciences Communications* **7**, 1–7 (2020).

72. Committee on Human-System Integration Research Topics for the 711th Human Performance Wing of the Air Force Research Laboratory, Board on Human-Systems Integration, Division of Behavioral and Social Sciences and Education & National Academies of Sciences, Engineering, and Medicine. *Human-AI Teaming*. (National Academies Press, Washington, D.C., 2022).

73. Li, S., Yang, Q., Xing, J., Chen, W. & Zou, R. A foundation model for building digital twins: A case study of a chiller. *Buildings* **12**, 1079 (2022).

74. Karunakaran, M., Venkatachalam, C., Mahesh, T. R., Krishnan, B. & Nagaraj, S. Chapter 5 Machine learning for twinning the human body. in *Digital Transformation in Healthcare 5.0* 105–130 (De Gruyter, 2024).

75. Payrovnaziri, S. N. *et al.* Explainable artificial intelligence models using real-world electronic health record data: a systematic scoping review. *J. Am. Med. Inform. Assoc.* **27**, 1173–1185 (2020).

Figure Legends

Figure 1. Flow diagram illustrating the process of study.

Figure 2. Differences among digital twins, microsimulation, and agent-based simulation in healthcare.

Figure 3. Types of current health digital twins.

Figure 4. Techniques and applications of health digital twins. a) Core techniques to create health digital twins. b) Distributions of health digital twins in disease application domains.

Author Contributions

Y.H. and J.B. contributed to conceptualization. Y.H. searched the electronic databases and conducted reference list checking. Y.H., R.W., and L.S. performed screening, study selection, and data extraction. Y.H. and H.D. performed data synthesis and contributed to writing—the original draft. J.X., J.G., Y.G., and J.B. performed writing—review, and editing. J.B. supervised the study. All authors approved the manuscript for publication and agreed to be accountable for all aspects of the work.

Competing Interests

The authors declare no competing interests.

Table 1. Publicly accessible datasets for health digital twin research.

Data Source	Name	Description	Link
Clinical Studies	Human Connectome Project (HCP)	A public research data includes a series of studies that focus on the connections within the human brain.	https://www.humanconnectome.org/
	Alzheimer's Disease Neuroimaging Initiative (ADNI)	A longitudinal multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD).	https://adni.loni.usc.edu/
	OhioT1DM dataset	A dataset to facilitate research in blood glucose level prediction. It contains 12 individuals with type 1 diabetes.	http://smarthealth.cs.ohio.edu/OhioT1DM-dataset.html
	Center for Advanced Studies in Adaptive Systems (CASAS) dataset	This dataset consists of real-world sensor data collected from smart home environments.	https://casas.wsu.edu/
	Single heart failure patient with atrial fibrillation	This dataset includes detailed clinical data from a 78-year-old female heart failure patient with atrial fibrillation.	https://zenodo.org/records/7405335
	Human Hepatic Glucose Metabolism	This dataset comprises experimental data on glycogenolysis and glycogen synthesis extracted from various studies.	https://doi.org/10.1371/journal.pcbi.1002577.s001

Real-world Data	Medical Information Mart for Intensive Care -III (MIMIC-III)	A large database contains health-related data associated with over forty thousand patients who stayed in ICU.	https://physionet.org/content/mimiciii/1.4/
	eICU Collaborative Research Database	A large multi-center critical care database contains health data from ICU patients.	https://eicu-crd.mit.edu/
	Whole Brain Atlas	This dataset provides anatomical and functional imaging data of the human brain.	https://www.med.harvard.edu/aanlib/
	Global Initiative on Sharing All Influenza Data (GISAID)	This dataset contains genomic sequences and related clinical and epidemiological data for various influenza viruses and coronaviruses.	https://gisaid.org/
	National Child Development Study (NCDS)	This dataset contains longitudinal data on the lives of individuals born in a single week in 1958 in Great Britain, encompassing a wide range of information.	https://ncds.info/
	Clinical Practice Research Datalink (CPRD)	CPRD contains real-time UK population health data, for epidemiological and pharmacoepidemiological research.	https://www.cprd.com/data
	Cerner Real-World Data (CRWD)	The dataset is a de-identified big data source of multicenter electronic health records.	https://www.oracle.com/health/population-health/real-world-data/
	National Health and Nutrition Examination Survey (NHANES)	This dataset provides comprehensive health and nutritional data from a nationally	https://www.cdc.gov/nchs/nhanes/index.htm

		representative sample of the U.S. population	
	Brain MRI Image dataset from Kaggle	It contains brain MRI Images for brain tumor detection, collected from Google Images.	https://www.kaggle.com/datasets/navoneel/brain-mri-images-for-brain-tumor-detection