Information Systems Frontiers (2025) 27:7–32
https://doi.org/10.1007/s10796-024-10536-4

A Conceptual Framework for Digital Twin in Healthcare: Evidence from a Systematic Meta-Review

Giulia Pellegrino[1] · **Massimiliano Gervasi**[2] · **Mario Angelelli**[3] · **Angelo Corallo**[4]

Accepted: 22 August 2024 / Published online: 12 September 2024

Abstract
Digital Twin (DT) technology monitors, simulates, optimizes, models, and predicts the behavior of physical entities. Healthcare is a significant domain where a DT can be functional for multiple purposes. However, these diverse uses of DTs need a clear understanding of both general and specific aspects that can affect their adoption and integration. This paper is a meta-review that leads to the development of a conceptual framework designed to support the high-level evaluation of DTs in healthcare. Using the PRISMA methodology, the meta-review synthesizes insights from 20 selected reviews out of 1,075 studies. Based on this comprehensive analysis, we extract the functional, technological, and operational aspects that characterize DTs in healthcare. Additionally, we examine the structural (e.g., hierarchical) relationships among these aspects to address the various complexity scales in digital health. The resulting framework can promote the effective design and implementation of DTs, offering a structured approach for their assessment.

Keywords Digital twin · Healthcare · Systematic literature review · Meta review · Conceptual framework

1 Introduction

Digital Twins (DTs) are used to simulate a variety of physical entities, with increasing levels of complexity, from consumer objects (Tao et al., 2019) to transport systems (Kušić et al., 2023), cities (Lehtola et al., 2022), ecosystems (Jianfeng et al., 2022), up to the human body (Dai et al., 2022). Physical entities can belong to various domains such as construction, education, business, transport, energy and electronics, human healthcare, sports, and networks and communications (Sun et al., 2022; Cellina et al., 2023).

Compared to others, the healthcare domain has an inherent uncertainty that makes medical practice and the development of accompanying technologies more challenging (Sun et al., 2023). At the global economic level, it is one of the fastest-growing sectors (Boyes & Watson, 2022; Gazerani, 2023; Segovia & Garcia-Alfaro, 2022), even though healthcare facilities represent complex systems whose management is subject to multiple types of constraints (Boyes & Watson, 2022; Gazerani, 2023). Therefore, DT-based strategies can provide a promising contribution to improving the efficiency of healthcare. Evidence suggests that the growing adoption of various information technologies can revolutionize healthcare systems (Kamel Boulos & Zhang, 2021). This evolution should be contextualized in the gradual transition of the medical industry from traditional to digital and then to information medicine, resulting in the current notion of smart medicine (Sun et al., 2023). A selection of the most performing characteristics is prompting a rapid evolution both in technical aspects and in care paradigms and processes (Barricelli et al., 2019; Tao et al., 2022a).

✉ Giulia Pellegrino
giulia.pellegrino1@unisalento.it

Massimiliano Gervasi
massimiliano.gervasi@unisalento.it

Mario Angelelli
mario.angelelli@unisalento.it

Angelo Corallo
angelo.corallo@unisalento.it

[1] Department of Engineering for Innovation, University of Salento, Lecce, Italy

[2] Lecce, Italy

[3] Department of Human and Social Sciences, University of Salento, Lecce, Italy

[4] Department of Experimental Medicine, University of Salento, Lecce, Italy

A lack of comprehensive definitions for DTs, both general and specific to the healthcare domain, is detected in the literature (Liu et al., 2022). Consequently, there is a need to define DT aspects to support design and analysis in the medical field (Coorey et al., 2022). Furthermore, several reference architectures exist, and, as a consequence, the need for their harmonization and standardization arises (Botín-Sanabria et al., 2022; Rossmann & Hertweck, 2022). This requirement has practical implications since the effectiveness of a medical DT implementation is influenced by the same constraints that affect the healthcare domain. They refer to privacy issues in managing personal data, different purposes that a DT can relate to (from diagnosis to monitoring, pre-, intra-, and post-operative support, up to medical training), and interaction and scale complexity in digital representations of human bodies and health status.

Driven by the need to define healthcare DTs and their key aspects, this work adopts a rigorous methodology to extract and analyze the main *dimensions* whose identification can support the proper design and implementation of a healthcare DT. The term *dimension* refers to a specific functionality, component, or aspect of the DT that should be addressed along with other dimensions to obtain a consistent view of the digital system. The concept of dimension is broad, and different dimensions encompass technological, functional, and operational aspects, among others. The adoption of a dimensional framework provides a means to introduce a dynamic and flexible approach that can be adapted to various contexts and specific needs, allowing for increasing granularity (through hierarchical structures) (Tao et al., 2022a) or modifying the dimensional framework when this proves inadequate or impractical (Angelelli et al., 2024).

In particular, this paper has two specific objectives: (1) characterize a DT in the healthcare domain, and (2) identify its dimensions to support design and analysis. We extract information for this investigation through a systematic literature meta-review, focusing on reviews in the scientific literature that examine at least one DT belonging to the healthcare domain.

The paper is organized as follows: in Section 2, we overview the background regarding DT definitions, first from a general perspective and then focusing on the healthcare domain. Section 3 formalizes the research questions and the adopted research methodology, describes its main phases, and compares it with other meta-reviews on DTs in the state-of-the-art. The results of the systematic meta-review and their analysis are reported in Section 4. Based on these findings, the proposal of a multi-dimensional framework is detailed in Section 5. The entire work is discussed in Section 6, followed by conclusions and research directions for future works (Section 7).

2 Theoretical Background

2.1 Digital Twin Definitions

The DT represents one of the most important advances in technology-related domains in the past 20 years (Barricelli et al., 2019; Grieves, 2022). The term *Digital Twin* was coined in 2010 by John Vickers of NASA (Grieves, 2022; Piascik et al., 2012) and it was first adopted in 2011 to digitally reproduce the structural behavior of an aircraft (Tuegel et al., 2011; Rathore et al., 2021). The concept of DT was already introduced by Michael Grieves of the University of Michigan in 2002 (Grieves, 2022). He asserted that:

> The digital twin is a set of virtual information constructs that completely describe a potential or actual physical artifact from the micro atomic level to the macro geometric level. At its best, all the information that can be obtained from inspection of a physical product can be obtained from its digital twin (Grieves & Vickers, 2017; Inamura, 2023).

Subsequently, Grieves (2014) defined digital twinning as a combination of the following three primary components: the *Physical Twin* (PT), the *Digital Twin*, and the *Digital Thread* (Grieves, 2014, 2022; Rathore et al., 2021). The *Physical twin* is a physical object that can be a product or a product lifecycle (Sharma et al., 2022), a system (Jianfeng et al., 2022), a model, or any other component, such as a robot (Inamura, 2023), car (Bednarz et al., 2024), electric turbine (Mahmoud et al., 2024), human being (Voigt et al., 2021), or hospital (Elkefi & Asan, 2022). Currently, it exists or will exist in the physical world. The *Digital Twin* is a virtual or digital counterpart that exists in the virtual or digital world (Grieves, 2019). It is also referred to as *Virtual Mirror* or *Virtual Replica* (Barricelli et al., 2019). Usually, DT modeling is mainly referred to as the physical entity, the virtual entity (Inamura, 2023), and the communication between virtual and physical space in terms of data and respective enabling sensors (Sharma et al., 2022; Jiang et al., 2021). Therefore, DTs are virtual replicas of physical objects or systems (Cellina et al., 2023), where the virtual replicas are algorithms that replicate the behavior of the corresponding physical counterparts and generate the same output under the same given input values (Rathore et al., 2021).

The Digital Thread is a data flow cycle that feeds data from a PT to its DT and returns information and processes from the DT to the PT (Grieves, 2014; Rathore et al., 2021; Singh & Willcox, 2021; Grieves, 2022). It represents a key feature of DT, which is the creation of dynamic bidirectional mapping (Kamel Boulos & Zhang, 2021). In fact, the term

Digital Thread is sometimes interpreted as synonymous with DT (see, e.g., Barricelli et al. 2019 and references therein). Other times it is seen as a framework that enables a connected data flow without explicitly referring, as seen above, to the bidirectionality of that flow (Barricelli et al., 2019). The concept of Digital Thread can also be extended to integrate different models into a single representation that is always available and up-to-date (Siedlak et al., 2018). The Digital Thread makes it possible to have *the right information in the right place at the right time*, even from heterogeneous sources. However, it lacks the potential inherent in the DT in terms of monitoring, maintaining, and optimizing the physical system (Barricelli et al., 2019), which motivates our interpretation of Digital Thread in our framework as one of the three components of the DT.

The lifecycles of the physical and digital twins do not have to coincide. The only requirement is that a twin's counterpart exists at some point in the twin's lifecycle (Grieves, 2000, 2014). This means a DT can exist before its physical counterpart is created and after the physical counterpart is gone (Grieves, 2022).

The definition of DT and the components reported above (Grieves, 2014; Grieves & Vickers, 2017) are not the only ones present in the literature, which causes confusion as to what a DT is Coorey et al. (2022); Grieves (2022); Liu et al. (2022). In fact, it is sometimes called Digital Avatars (Garner et al., 2016), Digital Masters (Biahmou et al., 2016), Digital Shadows/Snapshot (Kamel Boulos & Zhang, 2021), or Digital Model (Kritzinger et al., 2018; Inamura, 2023; Botín-Sanabria et al., 2022; Yao et al., 2023). A Digital Shadow lacks real-time communication between the virtual space and the real world, which is a characteristic of a DT. A Digital Model is completely devoid of real-time communications between physical and virtual space (Kritzinger et al., 2018; Inamura, 2023; Botín-Sanabria et al., 2022; Kamel Boulos & Zhang, 2021). A Digital Avatar is a combination of rules and data related to a particular user and her/his environment (Bertoa et al., 2020), while a Digital Master is a set of linked data records in a self-contained document that is used, in particular, in the industrial field (Biahmou et al., 2016; Hoffman & Joan-Arinyo, 1998). The DT is also described as a repository of information about the physical object represented. Information is populated into the DT and consumed by it. The digital DT could be queried by its users to use information (Grieves, 2022).

In 2022, the concept of the Intelligent Digital Twin (IDT) emerged. Unlike the traditional DT, the IDT can only be active and online, and goal-seeking is shared between it and its human users. The IDT is anticipatory; that is, it constantly performs simulations of its counterpart (Grieves, 2022). IDT has several definitions in the literature. For example, the view of the IDT exclusively as a data-driven entity (Gazerani, 2023; Lim et al., 2020) is opposite to the idea of the DT, which also has mechanistic and statistical modeling (Bjelland et al., 2022; Corral-Acero et al., 2020).

2.2 DT in Healthcare Domain

Nowadays, DTs applied in healthcare are a popular research trend, but successful implementations are rarely found (Tao et al., 2022a). In literature, the applications of DTs in healthcare are in an early stage (Armeni et al., 2022; Gazerani, 2023). DTs can be used in several areas of healthcare, such as precision medicine (Sun et al., 2023), personalized medicine (Cellina et al., 2023; Gazerani, 2023), clinical trial design, hospital facility management (Cheng et al., 2022; Gazerani, 2023), and medical education (Gazerani, 2023; Nagaraj et al., 2023), as well as medical devices or pharmaceutical development (Armeni et al., 2022; Gazerani, 2023). Precision medicine has the following two general objectives: providing therapies tailored to each patient and maximizing the effectiveness and efficiency of healthcare facilities (Bjelland et al., 2022; Corral-Acero et al., 2020). DTs allow the analysis of big data through Artificial Intelligence (AI) techniques and, therefore, prove functional to the first objective, i.e., the phenotyping of patients. This means visualizing the different stages of a disease for a specific patient and supporting therapeutic strategies in a personalized way (Bjelland et al., 2022; Lauzeral et al., 2019; Voigt et al., 2021). Healthcare organizations and facilities, such as hospitals, can also have their corresponding Digital Twin of Organizations (DTOs). DTOs are useful to plan, manage, coordinate, monitor, and optimize patient care interventions from a population and societal perspective, but also from a resource and cost perspective (Armeni et al., 2022; Barricelli et al., 2019; Kamel Boulos & Zhang, 2021). For example, in extreme cases, such as pandemics, DTOs can simulate different possible conditions and their corresponding potential solutions in virtual environments before implementing them in physical space (Armeni et al., 2022). In addition, a DT allows surgical procedures to be planned for a specific patient and their execution to be tested (Fuller et al., 2020) with the aim of optimizing it and managing better the post-operative phase (Aubert et al., 2021). A DT, in the healthcare domain, also has the following principal parts described in Section 2.1: PT, DT, and Digital Thread (Rathore et al., 2021). In this context, the PT can be represented not only by a healthcare organization (Kamel Boulos & Zhang, 2021) but also, for example, by a disease, such as multiple sclerosis (Falkowski et al., 2023), a particular organ (Chu et al., 2023), a system or an apparatus (Laubenbacher et al., 2022), or a patient (Karakra et al., 2019). The Digital Thread refers to the communication between PTs and DTs of health data collected from medical and wearable devices or external factors, simulation data from digital models, and historical health data contained in the electronic health records (EHRs) of healthcare institutions (Armeni et al., 2022; Liu et al., 2019). Therefore, a digital thread is a time data pipeline of a DT (Kamel Boulos & Zhang, 2021).

The definition of DT, even in the healthcare field, is not totally equable (Liu et al., 2022), as it depends on the PT represented. For example, the term DT is used by Aubert et al. (2021) to indicate a finite element model of a patient-specific tibia, while in Hernigou et al. (2021), it describes the identification of a customized axis of motion of the tibiotarsal joint.

The definition is also declined in terms of the functionalities and services offered. For example, Lauzeral et al. (2019) report that: "*The Digital Twin merges complex biophysical modeling and advanced real-time simulation techniques with data assimilation and analysis for decision support*" (also see Bjelland et al. 2022). It is also said that the concept of DT in healthcare extends the definition derived from the industrial world (Tao et al., 2018). We move from a DT that represents industrial physical systems in silico, guaranteeing the real-time connection between PT and DT, but used to optimize and control processes, to a DT seen as a virtual tool that dynamically integrates clinical data acquired from a specific individual with mechanistic and statistical models (Corral-Acero et al., 2020).

However, in comparison with the industrial world, some definitions show the difficulty for healthcare to establish and guarantee continuous and real-time communication between the physical part and the virtual counterpart and vice versa. Indeed, a DT is defined as a "*near-real-time digital image of a physical human being*" (Bjelland et al., 2022). In addition to the healthcare definition, there is also the definition of *Human Digital Twin*. The Human DT is defined as "*the replica of a human being from the physical world in the digital world*" Lin et al. (2022). With a data-oriented view, one of the definitions given to the *Health Digital Twins* is "*a new model of analyzing multi-factorial patient data to improve patient outcomes and population health*." A health DT is sometimes defined as a "*virtual representation of the patient*" (Venkatesh et al., 2022). In this paper, we define a Healthcare DT consisting of the three main components defined above, but also with dimensions derived from the study and analysis of the reviews (see Section 5). In the current healthcare domain, the PT often exists before its digital counterpart; however, it is not excluded that future advances in healthcare DTs could better adhere to the definition in Section 2.1 (Grieves, 2000, 2022), where it is only required that the physical and digital twins coexist at some points of their lifecycles.

3 Research Methodology

The research work is conducted in the form of a meta-review. The term *meta* means that the review landscape is examined (Schryen & Sperling, 2023). A meta-review is also called "*umbrella review*," "*overview of systematic reviews*," "*systematic review of systematic reviews*," or "*tertiary study*" (Thomson et al., 2010). It can be described as a type of study that integrates evidence from multiple (qualitative or quantitative) reviews into a single accessible and usable document (Becker & Oxman, 2008). A meta-review provides a concise but comprehensive synopsis of reviews on a specific topic, deftly addressing the perennial challenge of balancing in-depth coverage with focused specificity (Grant & Booth, 2009). This study also adopts the systematic literature review (SLR) methodology with the aim of conducting a systematic assessment of reviews on DTs. It is defined as a "*a systematic, explicit and reproducible method for identifying, evaluating and synthesizing the existing body of completed and recorded work produced by researchers, scholars, and practitioners*" (Fink, 2019). A significant and robust overview of the general characteristics of reviews is provided in Tables 1 and 2. They provide a synthetic perspective of the analyzed reviews, including the query (or search terms) used, the consulted DBs, the keywords, the type of review, and the number of papers analyzed in each review. The division into two tables serves to quickly provide an idea about the content. Table 1 encloses all papers that analyze only DTs from the medical domain, while Table 2 includes cross-domain reviews.

3.1 State of the Art

A systematic and rigorous approach is also adopted in the study of previous works. Several queries are made in the *Scopus* (www.scopus.com) and *Web of Science* (WOS - www.webofknowledge.com) databases, the same ones used for the extraction of the papers analyzed in the present work. The keyword used is "*Digital Twin*," followed by "*Meta-review*," "*Meta-survey*," or "*Review of reviews*."

The query returns only 3 meta-reviews already present in the scientific literature. Two of them (Kuehner et al., 2021; Carvalho & da Silva, 2021) were published in 2021, and one in 2022 (Rossmann & Hertweck, 2022). Our study differs from these works in several aspects. First, none of the works are oriented to the healthcare domain, as they focus on the application of DTs to smart cities (Carvalho & da Silva, 2021), logistics and manufacturing fields (Kuehner et al., 2021), or the definition of a general-purpose architecture that is useful for the development of DTs, but not for their analysis (Rossmann & Hertweck, 2022). Then, our study encompasses more recent studies (up to 2023) to take into account new reviews that explore emerging aspects in the

Table 1 Systematic analysis of reviews in healthcare domain

REF.	QUERY or RESEARCH TERMS	DB	KEYWORDS	TYPE	n.DT
Cellina et al. (2023)	Digital twin & Drug development Digital twin & Healthcare Digital twin & Medicine Digital twin & Surgery Digital twin & Trasplant Human digital twin	Google Scholar	Artificial intelligence DHT Drug development Human digital twin Surgical planning Transplant	Narrative Review	6
Chu et al. (2023)			Artificial intelligence Diabetes management Diabetes mellitus Digital twin Virtual reality	Review	13
Gazerani (2023)			Artificial intelligence Cloud computing Deep learning Digital twins Intelligent digital twins Machine learning Migraine Patient-centric Personalized The Internet of Things	Review	5
Sun et al. (2023)	Digital health DT Medicine Virtual healthcare	Google Scholar Pubmed Scopus WoS	Digital twin Healthcare Precision diagnose Personalised treatment Medicine	Literature review	22
Armeni et al. (2022)			Clinical trials design; Convergence; Digital technologies; Digital twins; Hospital operations Personal health management; Precision medicine;	Critical Review	10
Bjelland et al. (2022)	"Digital AND twin AND (orthopedic OR orthopaedic) AND surgery"	IEEE Xplore PubMed ScienceDirect	Biomechanics Computational modeling Digital twin Haptic rendering Medical simulation	Systematic Literature Review	6

Table 1 continued

REF.	QUERY or RESEARCH TERMS	DB	KEYWORDS	TYPE	n.DT
Coorey et al. (2022)	“digital twin” AND “heart” “digital twin” AND “disease” “digital twin” AND “vascular” “digital twin” AND “vessel” “digital twin” AND “patient”	Compendex EMBASE Medline ProQuest Scopus		Mapping review	88
Elkefi and Asan (2022)	“digital twin” and “health”	IEEE Xplore PubMed ScienceDirect Scopus Web of Science	Digital health Digital twins Health care Health informatics Human factors Information management Literature synthesis Operational control Safety Scheduling and optimization Supply chain management Technology Well-being promotion	Rapid Literature Review	17
Van Willigen et al. (2022)			Digital twin Fetal cardiovascular system Mathematical models Perinatal life support system Review	Review study	0
Voigt et al. (2021)			Decision analysis Digital twin Medical care Multiple sclerosis Personalized medicine Precision medicine	Review	7

Table 2 Systematic analysis of cross-domain reviews

REF.	QUERY or RESEARCH TERMS	DB	KEYWORDS	TYPE	n.HDT/n.DT
Correia et al. (2023)	((“digital twin” OR “cyber-physical” OR “CPS” OR “digital model”) AND “data management” OR “data integration”OR “data repository” OR “data transformation” OR “data provenance” OR “data governance” OR “heterogeneous data” OR “data interoperability” OR “metadata management” OR “data storage” OR “data quality” OR “data enrichment” OR “data modeling”))	ACM Dig. Lib. IEEE Dig. Lib. Onepetro Science Direct Scopus Web of Science	Big data Data management Digital twin Systematic literature review	Systematic literature review	12/64
Falkowski et al. (2023)	Digital twin Digital twin education Digital twin industry Digital twin manufacturing Digital twin medicine Digital twin physiotherapy Digital twin robotics Digital twin robotics VR Digital twin surgery Digital twin treatment limited to 2017 and newer.	IEEE Xplore Google Scholar PubMed ResearchGate	Digital twin Exoskeletons Home rehabilitation Human-machine interaction IoT Motor therapy Remote treatment Robot-aided rehabilitation	Literature overview	12/64
Inamura (2023)			Behavior change Digital twin Human-robot interaction Virtual reality	Review	3/9
Yao et al. (2023)			Digitalization Digital twin Information technology Simulation Virtual modeling	Sistematic review	1/39
Botín-Sanabria et al. (2022)	“Digital twin ” in keywords , AND/OR in title. Publication range from 2017. Q1 and Q2 ranked journals	MDPI ProQuest Research Gate Science Direct	Digital twin Enabling technologies Literature review Smart city Smart mobility	Systematic Literature Review	6/18

Table 2 continued

REF.	QUERY or RESEARCH TERMS	DB	KEYWORDS	TYPE	n.HDT/n.DT
Sharma et al. (2022)			Autonomous systems Big data Digital Twin Internet of Things Machine learning	Review	2/45
Tao et al. (2022a)	TITLE ({digital twin} OR {digital twins} OR {Digital twin} OR {Digital twins} OR {Digital Twin} OR {DigitalTwins}) AND TITLE ({model} OR {models} OR {modeling} OR {modeling} OR {Model} OR {Models} OR {Modeling} OR {Modeling})	Scopus	Digital twin Digital twin model Digital twin modeling Enabling technologies Enabling tools	Systematic Literature Review	11/296
Kamel Boulos and Zhang (2021)			Digital twins Human digital twins Personalised medicine Precision medicine Precision public health	Overview	17/18
Rathore et al. (2021)	"Digital twin" AND ("Artificial intelligence" OR "Big data") "Digital twin" AND ("Automotive industry" OR "Transportation") "Digital twin" AND ("Energy" OR "Power sector") "Digital twin" AND ("Healthcare" OR "Fitness") "Digital twin" AND ("Industry" OR "Production" OR "Manifacturing") "Digital twin" AND ("Machine learning" OR "Deep learning") "Digital twin" AND ("Predictive analysis" OR "Maintenance")	ACM digital library Hindawi IEEE Xplore IGI-Global Scopus SpringerLink Taylor Francis online US patents database Wiley online library	Artificial intelligence Big data Digital twin Industry 4.0. Machine learning	Sistematic literature review	14/137
Barricelli et al. (2019)	"digital twin artificial intelligence" "digital twin model"	Google Scholar	Artificial intelligence Digital twin Human-Computer interaction Internet of Things Machine learning Sensor systems	Survey	17/75

HDT: Healthcare Digital Twin

evolving context of healthcare DTs. Finally, our work fills the gap related to the integration of different dimension types, as previous works mainly address specific aspects (e.g., functionalities) or concentrate on bibliometric characteristics of the reviews (Kuehner et al., 2021) in favor of a comprehensive management perspective. This last point adheres with the aforementioned goal of the present work, which is the combination of technological, operational, functional, and analytical aspects of DTs in healthcare.

3.2 Objective and Research Question

The research question guiding the development of this work is:

What are sufficient and necessary dimensions for the analysis of a DT belonging to the healthcare domain and to support its design?

The concept of *dimension*, as outlined in Section 1, serves to identify a scalable and dynamic framework. In more detail, a dimension can be seen as an element that supports the description of the identified application (Enders & Hoßbach, 2019). By contributing to its description, it consequently enables its analysis and provides support for the design phase (Wu et al., 2021).

In the literature, various works have proposed and utilized dimensional frameworks, such as the five-dimensional model by Wu et al. (2021), which includes the physical entity (PE), the virtual entity (VE), the services' module (Ss), the digital twin data module (DD), and the connection module (CN). Another example is given by the six dimensions of DT Applications in Enders and Hoßbach (2019), which comprise the industrial sector, purpose, physical reference object, completeness, creation time, and connection. Additionally, the "*Dimensions of a Digital Twin model*" by Tao et al. (2022a) includes: physical entity, virtual model, connection, data, and service.

Despite these valuable contributions, the current state of the literature does not provide a comprehensive view. Reviews typically focus either on the technological dimensions or the functional dimensions of DTs (Shen et al., 2024). The present work aims to be as comprehensive as possible by focusing on the technological, functional, and operational aspects of DTs in the healthcare domain. Additionally, it highlights that existing frameworks in the literature are rarely tailored to the specific domain under consideration. With these premises, we can specify the approaches carried out in this meta-review to address this work's objectives and the research question: (i) providing a systematic analysis of reviews (referred to as a *meta-review*) on Digital Twins (DTs) with a primary focus on the healthcare domain; (ii) identifying dimensions of DTs that can serve as a clear, complete, and comprehensive framework to support a rigorous approach to the design and analysis of DTs in the healthcare domain. This framework is aimed at both academia and industry.

3.3 Search Process

This meta-review adopts the SLR approach by Bell et al. (2022) as a starting point to characterize the dimensions of a DT in the healthcare domain. This choice guarantees that the work follows a solid methodology with a systematic selection and analysis of the articles (Snyder, 2019). Furthermore, the SRL process is reproducible, transparent, and includes a sample with all relevant and appropriate studies (Hansen et al., 2022).

The process follows the widely used PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology for literature retrieval and screening (Jing et al., 2023; Kumar et al., 2022). The four phases of the procedure that we followed in agreement with the PRISMA requirements are presented in Fig. 1. The search process is detailed in the following sub-phases: (i) searching criteria; (ii) paper selection; (iii) paper assessment.

3.3.1 Searching Criteria

The papers' search is carried out through two major scientific databases: *Scopus* and WoS.

The query performed on Scopus searches exclusively for the term *"Digital Twin"* in the fields *Title, Keywords and Abstract*. Filters limiting the document type to *Review* and the language to *English* are applied. The search *query* performed on *Scopus* is provided below:

Query: TITLE-ABS-KEY ("Digital Twin") AND (LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (LANGUAGE , "English")).

In WoS, the same term is used to search within the topic fields of each paper. Topic ensures that the term is searched within the fields: *Searches Title*, *Abstract*, *Author Keywords*, and *Keywords Plus*. Below is the query used to search on WoS:

Query: TS=("Digital Twin") AND DT==("REVIEW") AND LA==("ENGLISH").

The search was performed in October 2023. To not exclude potentially useful results, we preferred to use a more inclusive approach at the query level and then proceed to manual screening. For this purpose, the query does not contain any terms or filters related to the healthcare domain or the publication year, envisaging the selection of reviews with at least one DT related to the healthcare domain.

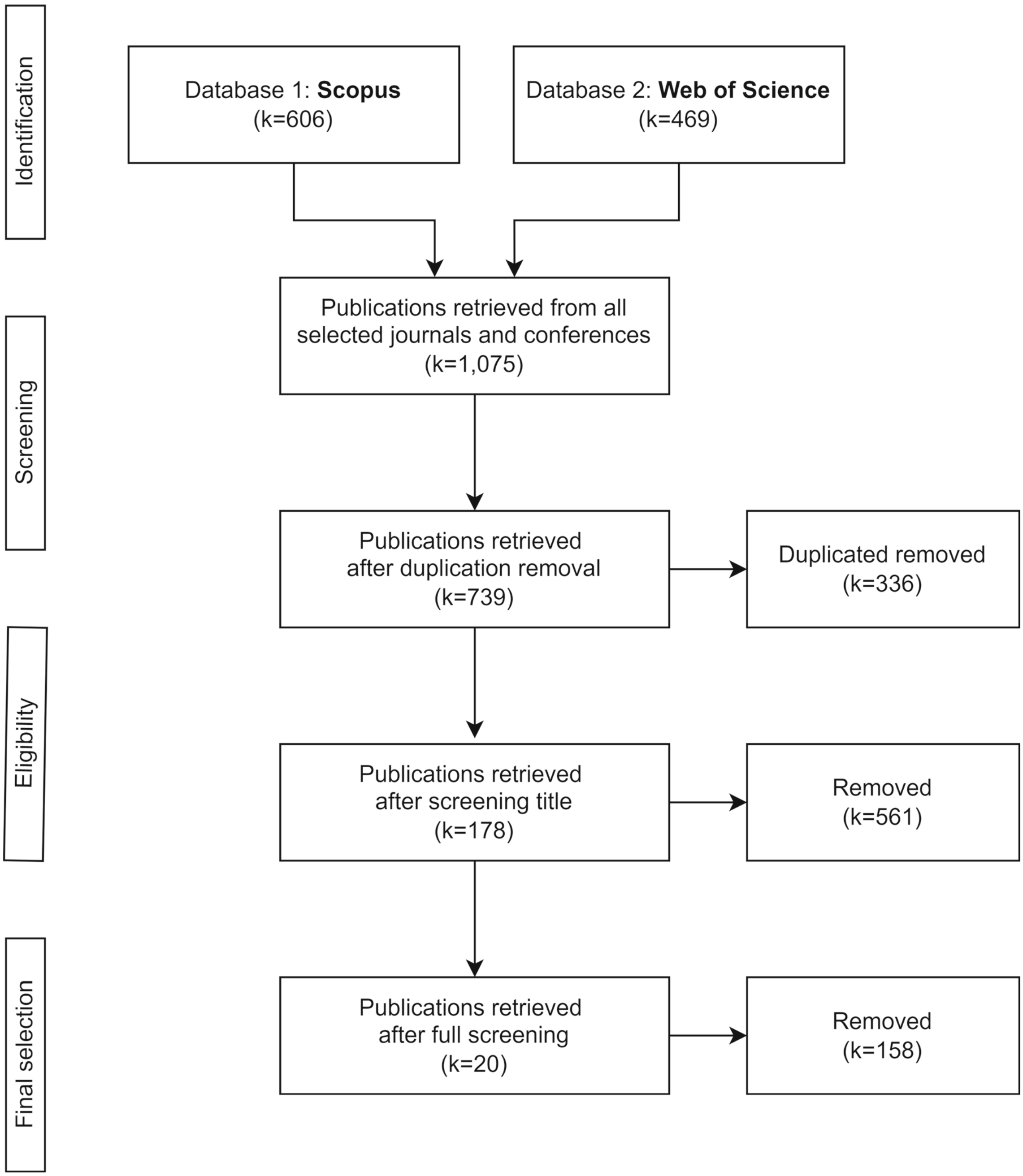

Fig. 1 PRISMA flow diagram of the paper selection process

3.3.2 Paper Selection

From the query of the databases described above, 606 results were obtained from *Scopus* and 469 from WoS. A total of 1,075 papers was found in the literature. In this result, duplicates were excluded using a Python script made by the authors. 178 papers were fully screened, and only 20 were included in this meta-review. The screening process is summarized in the PRISMA flowchart shown in Fig. 1.

Below, we specify the inclusion and exclusion criteria used to select the papers considered relevant:

- Explicit statement to be a review on DTs;
- Analysis of at least one DT related to the Healthcare domain.

The results of this selection are reported in Tables 1 and 2.

The screening based on title allowed the exclusion of papers explicitly focused on technologies other than DTs, or those not explicitly belonging to the healthcare domain. Specifically, starting with 178 articles obtained through selection by title, 108 were excluded because they do not analyze any DTs in healthcare, and 50 were excluded because they do not meet the criterion of being review articles or dedicated only a specific paragraph to literature review.

3.3.3 Paper Assessment

The selected papers were divided into two groups: (1) reviews studying DTs belonging exclusively to the healthcare domain ($k = 10$); (2) reviews studying DTs belonging to different domains ($k = 10$). Each group of reviews was initially analyzed using Tables 1 and 2. Both of them collect the following information: *Reference, Year of publication, Query or Research Terms* used, queried *Database, Keywords, and Type* of review conducted. They differ only in one field, i.e., the last column in Table 1, which shows only the DTs in the healthcare domain. Values in this field refer to the number of DTs analyzed; on the other hand, in Table 2 we report the number of DTs belonging to the healthcare domain over the total number of DTs analyzed in the considered review. After this analysis, the main characteristics of the DTs analyzed by each review are identified. These features are grouped into a set of Healthcare DT dimensions introduced in Table 3. In the third column (*Mapping*) of Table 3, there are the bibliographic references of the proposed dimension. The dimensions were extracted from both systematic and non-systematic reviews, encompassing the entire set of 20 articles considered in this work.

4 Findings

In this section, we present the detailed results of the analysis of the 20 selected papers. This section is followed by an analysis and discussion of the dimensions that have been extracted with reference to the characteristics of a DT.

Regarding the descriptive statistics (frequencies) reported in Tables 1 and 2, in some reviews, the authors do not indicate the number of DTs analyzed. This information is calculated from the analysis conducted on the respective reviews and reported in the SLR analysis phase (Cellina et al., 2023; Chu et al., 2023; Gazerani, 2023; Armeni et al., 2022; Voigt et al., 2021 in Table 1; Falkowski et al., 2023; Yao et al., 2023; Inamura, 2023 in Table 2). The number of analyzed articles is determined by counting only those discussed in the reviews, excluding those mentioned without detailed analysis.

In the healthcare domain, only two systematic reviews are identified: the *rapid literature review* by Elkefi and Asan (2022), which focuses on *managing healthcare systems*, and the SLR by Bjelland et al. (2022), which focuses on DTs for knee arthrosis. The work by Bjelland et al. (2022) analyzes 6 DTs, carrying out an in-depth analysis of the necessary enabling technologies for the realization of a DT to support arthroscopic surgery. Examination of this review shows that the healthcare field needs detailed analysis focusing on specific domains. This is also evident from the absence of general-purpose SLRs in healthcare. However, the absence of such studies in the healthcare context limits the definition of a standard for Healthcare DTs, as well as the specification and the analysis of their characteristics. This confirms the gap already identified and reported in our research question.

Although not systematic, the other reviews analyzed highlight several significant points. In Sun et al. (2023), an analysis of DTs is conducted, ranging from 2011 to 2022, both in the boundary of the research (DBs reported in Table 1), and directed at prototypes/products of DTs that have been identified on the websites of the proprietary companies. The analysis of the characteristics of the DTs in Sun et al. (2023) is business-oriented; in fact, in different clinical applications, such as "*Cardiovascular disease, Surgery, Pharmacy, Orthopedics, COVID-19 and Other Fields*," the authors analyze each DT according to their respective functionalities and characterize them according to the purposes and uses for which the DTs are intended. In Coorey et al. (2022), similarly to Sun et al. (2023), six specific websites are consulted in addition to certain databases for patent searching (Table 1). The websites are indicated in the "*Other data sources*" section of Coorey et al. (2022). When conducting a systematic review of DTs, this brings attention to the possibility of using, in addition to classic search engines, third-party sources to identify DTs and features that would otherwise make the analysis incomplete.

Among the reviews of DTs not only in the healthcare field, we also find several SLRs. The SLR of Rathore et al. (2021) includes research papers, patents, and web reports, analyzing sensors, analysis techniques (AI-Machine Learning), but also the standards to which DTs must or should comply, and the criteria for validation and success of a DT. It is emphasized that the number of DTs in the healthcare domain identified in this SLR is small compared to those in other domains. The SLR of Tao et al. (2022a) does not focus only on DTs in the healthcare domain. The analysis investigates DTs from multiple perspectives, from aspects of modeling to those of enabling technologies. Of particular interest is the contribution by Barricelli et al. (2019), which focuses on the various definitions of DTs in the literature and in which domains they are developed. It also focuses on the main characteristics that should be present in a DT, highlighting the difficulty in having all-inclusive models. It becomes evident that most of the DTs in the literature are focused specifically on certain aspects. It is also worth remarking the insight into the lifecycles of DTs, which can be of two types: (1) DTs defined in the design phase of its PT, which does not yet exist; in this case, the DT and its twin live together in continuous com-

Table 3 A multi-dimensional framework for the healthcare digital twin

DIMENSION	DESCRIPTION	REFERENCE
Domain	Field of application in which the PT exists or will exist.	Domain (Botín-Sanabria et al., 2022; Coorey et al., 2022; Correia et al., 2023; Sharma et al., 2022; Sun et al., 2023), (Gazerani, 2023)* Applications (Barricelli et al., 2019; Botín-Sanabria et al., 2022; Rathore et al., 2021; Yao et al., 2023) Field (Tao et al., 2022a)
Physical Twin	A PT is the entity that is replicated by a DT. It can be a Unit, a System, or a System-of-Systems (SoS).	Physical Twin (Botín-Sanabria et al., 2022; Elkefi & Asan, 2022; Gazerani, 2023; Sharma et al., 2022) Target of DT (Armeni et al., 2022; Inamura, 2023), (Kamel Boulos & Zhang, 2021)*, (Voigt et al., 2021)*
Team	All users, experts in the application domain, and required skills needed for the development and validation of the DT.	Team (Sun et al., 2023)
Sensors	The set of sensors and edge devices for collecting information from different sub-components of the physical asset.	Technology (Sharma et al., 2022) (Armeni et al., 2022)*, (Inamura, 2023)*, (Barricelli et al., 2019)* Sensors (Botín-Sanabria et al., 2022) Communication (Barricelli et al., 2019; Botín-Sanabria et al., 2022), (Kamel Boulos & Zhang, 2021)*
Data	All data collected by various IoT components and software, stored, historicized, manipulated, and pre-analyzed. They are necessary for the operation of the DT according to its functions and purposes.	Data Sources (Armeni et al., 2022)* Raw Data (Sharma et al., 2022; Correia et al., 2023; Falkowski et al., 2023) (Voigt et al., 2021)* Data Collection (Sharma et al., 2022; Correia et al., 2023), (Chu et al., 2023)*, (Voigt et al., 2021)*, (Bjelland et al., 2022)*, (Yao et al., 2023)* Data Storage (Armeni et al., 2022)*, (Coorey et al., 2022)*, (Bjelland et al., 2022)*, (Inamura, 2023)*
Modeling	Architectural, technological modeling, and analytical aspects enabling DT functionality.	AI, BDA, ML (Sharma et al., 2022; Rathore et al., 2021; Botín-Sanabria et al., 2022) (Armeni et al., 2022)*, (Barricelli et al., 2019)*, (Kamel Boulos & Zhang, 2021)*, (Chu et al., 2023)* Model and Modeling (Van Willigen et al., 2022; Bjelland et al., 2022; Coorey et al., 2022; Tao et al., 2022a; Sharma et al., 2022; Barricelli et al., 2019), (Bjelland et al., 2022)*, (Voigt et al., 2021)*, (Coorey et al., 2022)*, (Yao et al., 2023)*, (Barricelli et al., 2019)*, (Van Willigen et al., 2022)* Computing (Botín-Sanabria et al., 2022; Correia et al., 2023; Armeni et al., 2022; Yao et al., 2023)
Functions	The ability of a DT to respond to specific needs, making certain services available to users (e.g., simulation, monitoring, optimization, testing, *etc.*).	Functions (Armeni et al., 2022; Barricelli et al., 2019; Botín-Sanabria et al., 2022; Cellina et al., 2023; Coorey et al., 2022; Correia et al., 2023; Elkefi & Asan, 2022; Falkowski et al., 2023; Gazerani, 2023; Sun et al., 2023; Tao et al., 2022a; Voigt et al., 2021; Yao et al., 2023) (Bjelland et al., 2022)*, (Rathore et al., 2021)*
User interaction	The set of techniques and technologies that make interaction with a DT possible and, thus, allow access to its functions.	Feedback (Bjelland et al., 2022), (Chu et al., 2023)*, (Inamura, 2023)*, (Voigt et al., 2021)* Technology (Armeni et al., 2022)*, (Bjelland et al., 2022)*
Hierarchy	Hierarchical levels of DTs, from the unit level up to Systems-of-Systems (SoS).	Hierarchy (Chu et al., 2023; Tao et al., 2022a; Yao et al., 2023), (Kamel Boulos & Zhang, 2021)*
Status and Maturity	Status characterizes DTs from theoretical models to business DTs. Maturity refers to each status and measures its performance.	Status (Botín-Sanabria et al., 2022; Coorey et al., 2022), (Kamel Boulos & Zhang, 2021)*, (Sharma et al., 2022)* Evaluation Index (Yao et al., 2023)

Table 3 continued

DIMENSION	DESCRIPTION	REFERENCE
Limitations	Model limitations as a function of modeling design choices and impacting DT functionality and user interaction.	Limitations, Challanges and Future Trend (Armeni et al., 2022; Barricelli et al., 2019; Bjelland et al., 2022; Botín-Sanabria et al., 2022; Coorey et al., 2022; Correia et al., 2023; Chu et al., 2023; Inamura, 2023; Kamel Boulos & Zhang, 2021; Rathore et al., 2021; Sharma et al., 2022; Voigt et al., 2021; Yao et al., 2023)

The symbol "*" indicates the dimensions that have been described in the reviews. Dimensions without the symbol are used to analyze papers in the reviews. The descriptions reported in the table are the result of the author's elaboration and are not intended as precise quotations from the original sources

munication and interaction. (2) DTs created when the PT has already been operational for some time; in this case, the DT must be connected to the PT, and the two continue their lives in perfect interaction (Barricelli et al., 2019).

In Table 2, there is only one 0 in the *n. DT* column. In fact, the review of the corresponding record does not identify any model in the literature that meets the requirements deemed necessary for a DT of a fetus in a Perinatal Life Support System (Van Willigen et al., 2022). At the same time, however, it defines the technical and functional requirements for the DT of a fetus. For the sake of completeness, they have been reported in Table 3.

5 A Multi-dimensional Framework for the Healthcare Digital Twin

In this section, we present 11 dimensions identified from the analysis and detailed in Table 3. Table 4 shows the frequency of each dimension in the analyzed articles. Table 4 is divided into two parts. The upper section includes reviews focused exclusively on the healthcare domain, while the lower section features those that are cross-domain. It is evident that all the chosen dimensions have already been used within the specific domain. They are related to each other, and all of them are functional to the design and analysis of DTs. Figure 2 represents the relationships and interactions among the dimensions, also aligning with the conceptualization of a DT made by Grieves (2014).

Figure 2 provides a diagrammatic representation of our multi-dimensional framework. This view specifies the integrative approach that moved our research, starting from the scientific literature. In particular, the three primary components of Grieves (2014) are highlighted in the boxes with double-line borders: the *Physical Twin*, the *Digital Twin*, and the *Digital Thread*. Our interpretation of the Digital Thread as a flow of data between the physical and virtual entities can be linked to Ackoff's model (Ackoff, 1989). Indeed, the information extracted from data collected by sensors in its raw form, after gathering and processing, is transformed into knowledge and wisdom, supporting actions that directly interact with the physical entity. In this context, the digital thread can be interpreted as an application of the big data value chain related to digital twins. This facilitates the association with aspects related, for example, to the adoption of data architectures tailored to the objectives and functionalities of DTs. Furthermore, it allows for representing the uncertainty factors that characterize the data flow, its cyclicity, and the value generation process from data (Gervasi et al., 2023a, b) that can be directly utilized by the physical entity.

For the sake of methodological completeness, it is worth noting that we exclude from the proposed multi-dimensional model aspects or attributes of bibliometric nature, such as *Year* (Sun et al., 2023; Coorey et al., 2022; Correia et al., 2023), *Reference (Company, Journal)/Scientific Venue, Institution Type* (Armeni et al., 2022; Correia et al., 2023), *Description* (Armeni et al., 2022; Barricelli et al., 2019); *Authors, First author Country/Country* (Coorey et al., 2022; Correia et al., 2023), *First author affiliations, Article type* (Coorey et al., 2022), *Research concept* (Coorey et al., 2022), *Key findings* (Elkefi & Asan, 2022). Furthermore, we also exclude from the model dimension the *Digital Asset* (Barricelli et al., 2019; Sharma et al., 2022) (also called *Virtual, mirror, replica*) as in fact corresponding to the same DT (Sharma et al., 2022).

At this point, we analyze the dimensions proposed in the multi-framework in detail. First, each dimension is introduced in its general purpose and, then, contextualized in the healthcare domain.

5.1 Domain - Physical Twin - Team

The Domain, PT, and Team dimensions are necessary to identify the perimeter of the DT in terms of model requirements, reference area, and interacting agents. The **Physical Twin** dimension represents the physical entity, and it has already been defined and made explicit in the introductory sections.

The **Domain** dimension of a DT refers to application areas or fields (Botín-Sanabria et al., 2022; Tao et al., 2022a). The Domain can contain information about the hierarchical

Table 4 Frequency analysis showing the various dimensions present or absent in literature

	Domain	Physichal Entity	Team	Sensors	Data	Modeling	Functions	User Interaction	Hierarchy Level	Status - Maturity	Limitations
Cellina et al. (2023)							•				
Chu et al. (2023)					•	•		•	•		•
Gazerani (2023)	•	•					•				
Sun et al. (2023)	•		•				•				
Armeni et al. (2022)		•		•	•	•	•	•			•
Bjelland et al. (2022)					•	•	•	•			•
Coorey et al. (2022)	•				•	•	•			•	•
Elkefi and Asan (2022)		•					•				
Van Willigen et al. (2022)						•					
Voigt et al. (2021)		•			•	•	•	•			•
Correia et al. (2023)	•				•	•	•				•
Falkowski et al. (2023)					•						
Inamura (2023)		•		•	•		•	•			•
Yao et al. (2023)	•				•	•	•		•	•	•
Botín-Sanabria et al. (2022)	•	•		•		•	•			•	•
Sharma et al. (2022)	•	•		•	•	•				•	•
Tao et al. (2022a)	•					•	•		•		
Kamel Boulos and Zhang (2021)		•		•		•			•	•	•
Rathore et al. (2021)	•					•	•				•
Barricelli et al. (2019)	•			•		•	•				•

• indicates occurrence and ‘ ’ indicates absence

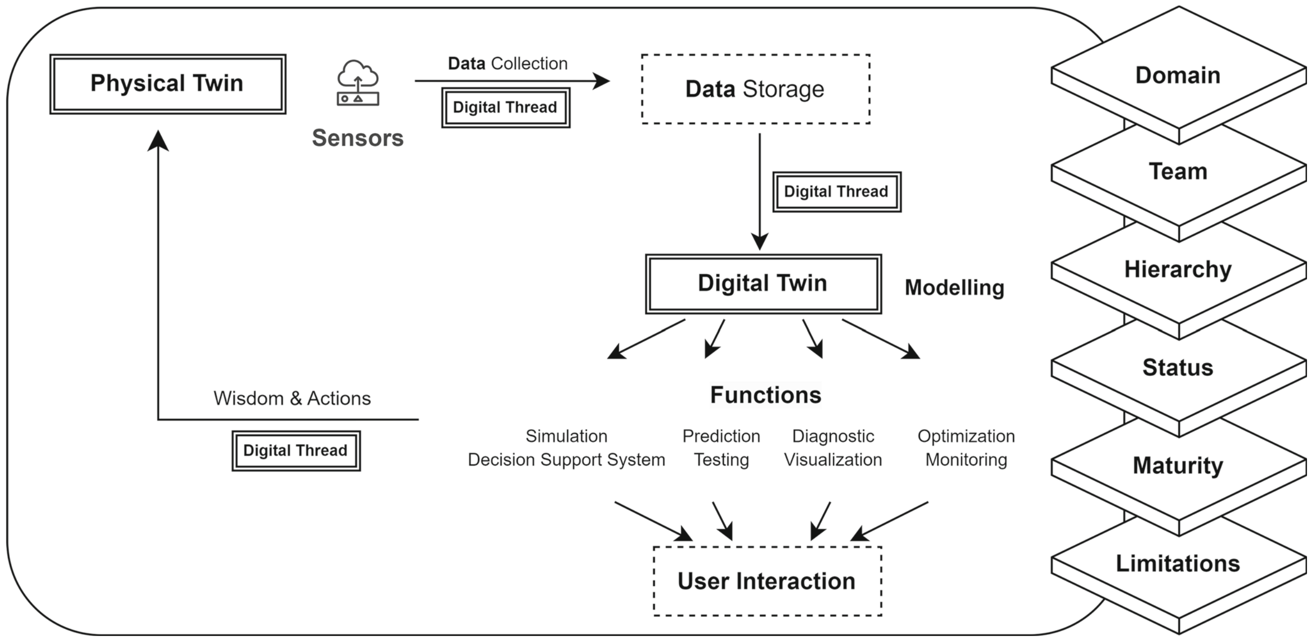

Fig. 2 DT architecture, relationships, and interactions among the 11 dimensions highlighted in bold

nature, if it is specified that the Domain is a sub-domain of a more complex system (Sharma et al., 2022; Correia et al., 2023) or a System-of-Systems (SoS). Finally, the Domain may be referred to as a specific use case, and thus, indirectly focused on the functionality of the DT (Barricelli et al., 2019; Botín-Sanabria et al., 2022; Rathore et al., 2021; Yao et al., 2023; Sharma et al., 2022). Indeed, in the healthcare domain, we identify both generic domains, such as *Healthcare Domain* or *Medical Domain* (Coorey et al., 2022; Sun et al., 2023; Gazerani, 2023), and focused on specific clinical application (Sun et al., 2023), such as cardiovascular disease (Coorey et al., 2022), or smart cities and healthcare (Coorey et al., 2022).

The **Team** dimension refers to the group of experts with multiple (specific or transversal) skills (Sun et al., 2022; Barricelli et al., 2019), who participate in the design, prototyping, implementation, and maintenance phases of the DT. This dimension is only considered in one review among those analyzed (Table 4). However, we consider it important to propose this dimension also in the light of a social, technical, and collaborative DT design (Zhu et al., 2011).

5.2 Data and Sensors

The **Data** dimension represents the fundamental layer between the *Physical Space System* and the *Virtual Space System*, as shown in relation to data management, by the "*Five-components DT architecture*" of Correia et al. (2023), in which data is captured, transformed, and utilized.

In the medical field, the work of Gazerani (2023) refers to the DT both as a *Data Generator* (e.g., "*the simulation of patients' conditions and therapeutic responses and multi-scale modeling from cells to the whole body*") and as a *Data Source* to be combined with other data sources in order to extract more knowledge through AI and ML techniques. For these reasons, in DTs, the classic *big data value chain* (Kriksciuniene et al., 2015; Curry, 2016; Gervasi et al., 2023b, a) should be revised to accommodate the need for the constant interaction between physical and virtual spaces.

In Table 3, the Data dimension is decomposed into four sub-dimensions that emerged from the analysis: (1) *Data Sources*, (2) *Raw Data*, (3) *Data Collection*, and (4) *Data Storage*. Clearly, each of these aspects can be considered within the broader perimeter data management, analyzed by the SLR in Correia et al. (2023), as can be seen from the corresponding search query used by the authors and shown in Table 2.

The data should be associated with the respective acquisition techniques, and, thus, with the respective ETL (Extract, Transform, Load) and data quality processes (Correia et al., 2023). Data collection is a key aspect of DTs to be investigated. The techniques for acquiring and integrating the multi-sources of a DT should guarantee the heterogeneity of the data (Chu et al., 2023). In addition, closely related to data collection and *transmission technology*, there are the aspects of virtual and physical model updates (Yao et al., 2023). They depend on the synchronization property of the model, the presence of static or continuously updated data (Sharma et al., 2022; Kamel Boulos & Zhang, 2021) associated with a *high-dimensional data-decoding* (Barricelli et al., 2019). We exclude from this dimension the data analysis modeling, such as machine or deep learning techniques, which are included in the Modeling dimension (Section 5.3).

The **Sensors** dimension relates to the respective sensors used in the DTs and allows the acquisition and transition of the data between the PT and the DT. This dimension is fundamental to both the design of the model and its functionality. Indeed, the sensors contribute to enabling the DT online or offline (Botín-Sanabria et al., 2022), calibrating the update rate (Kamel Boulos & Zhang, 2021; Barricelli et al., 2019), and achieving continuous communication between the digital and physical parts (Grieves, 2022). It is remarkable that in the healthcare domain, online DTs are almost completely absent (Table 4), even at the theoretical status, and this seems to be related to the lack of such enabling sensors (Bjelland et al., 2022).

5.3 Modeling

As can be seen in Coorey et al. (2022), the **Modeling** dimension, has a dual nature: the first is linked to design and architectural aspects leading to the modeling of the physical object; the second is related to the enabling aspects, the properties, and the desired functionalities of the model, such as technological aspects (Yao et al., 2023; Sharma et al., 2022; Barricelli et al., 2019; Bjelland et al., 2022), computational aspects (Botín-Sanabria et al., 2022; Correia et al., 2023; Armeni et al., 2022; Yao et al., 2023), and AI and ML techniques (Sharma et al., 2022; Rathore et al., 2021; Botín-Sanabria et al., 2022; Tao et al., 2022a; Bjelland et al., 2022). As can be seen in Table 4, these aspects are directly or indirectly addressed in every review analyzed in this work.

In this dimension, when a DT is analyzed, it is fundamental to survey all the architectural and design choices and the methods and techniques of analysis used in it. The complexity in defining a model and, thus, implementing a DT is evident, given the numerous design, architectural, and technological aspects that must be considered. The *modus operandi* for defining DT prototypes can be based on different design stages that must be coherent and comply with a set of protocols and best practices. An example can be found in Tao et al. (2022a), where authors list the following steps: (1) identification of the physical object and its modeling for the definition of the virtual object; (2) definition of the connection and real-time data exchange between the physical object and its virtual copy; (3) testing and validation; (4) definition of the functionalities and respective feedback modes of the outputs (Liu et al., 2019; Armeni et al., 2022).

The procedure just described is not suitable to be applied to the design and development of any DT. Indeed, the procedure starts from the assumption that the physical object to be modeled already exists and, therefore, the virtual object is created accordingly. As we have already seen in Section 1, the virtual entity could exist before the physical one (Grieves, 2000, 2022). The testing and validation phase (3) is fundamental in the design of a DT, as it tests and validates its functionality. In the literature, we find several references (Armeni et al., 2022; Sharma et al., 2022; Tao et al., 2022a). The validation and assessment of a DT's modeling requirements can be carried out through the identification of specific metrics, evaluation methods, analysis techniques (machine or deep learning), or human feedback (Sharma et al., 2022; Botín-Sanabria et al., 2022). An example is *evaluating a successful digital twin* phase in Rathore et al. (2021).

Finally, this dimension includes all the techniques belonging to *Big Data Analytics* (BDA). They allow the transformation of simple data (raw data) into information and knowledge and the interaction between the physical and the virtual entities (Sharma et al., 2022; Rathore et al., 2021; Botín-Sanabria et al., 2022). The analyzed reviews make reference to specific techniques, such as data fusion algorithms (Barricelli et al., 2019), embedded machine learning (Kamel Boulos & Zhang, 2021), and federated learning (Gazerani, 2023; Sharma et al., 2022).

5.4 Functions and User Interaction

From the results in Table 4, the dimension **Functions** seems to be the most used in the analyzed studies (18 out of 20 papers). Functions can be directly identified in the form of functional requirements or procedures (Voigt et al., 2021). Table 5 organizes the main functionalities mentioned above in terms of applications to healthcare DTs retrieved from the analyzed papers.

Depending on the modeling aspects, the Functions dimension reflects the purpose for which the DT is designed and should be as consistent as possible with the PT (Barricelli et al., 2019). Currently, DTs in the healthcare field have a reduced set of functions; indeed, they are not yet able to simulate the system to be represented in real-time, and they rely on, e.g., offline simulations (Bjelland et al., 2022). A DT that reproduces a certain condition of a patient (Gazerani, 2023) should allow not only the simulation of a surgical operation (Bjelland et al., 2022; Pellegrino et al., 2023a), but also the prediction of responses to certain therapeutic treatments (Gazerani, 2023), as well as the evolution of his/her health status (Voigt et al., 2021). Clinical decision support offered by DTs is becoming a priority for precision medicine (Correia et al., 2023; Armeni et al., 2022) and not limited to monitoring a patient or a disease (Rathore et al., 2021; Inamura, 2023; Van Willigen et al., 2022).

The functions of a DT are closely related to how users will be able to employ them and, thus, to the **User Interaction** dimension. While the functions can be seen as the output generators of a DT, visualization and interaction systems

Table 5 Functions of DTs in the analyzed reviews

Function	Reference
Simulation	Botín-Sanabria et al. (2022); Barricelli et al. (2019) Voigt et al. (2021); Yao et al. (2023) Chu et al. (2023); Bjelland et al. (2022) Rathore et al. (2021); Tao et al. (2022a) Correia et al. (2023); Gazerani (2023) Inamura (2023)
Testing	Barricelli et al. (2019)
Prediction	Barricelli et al. (2019); Voigt et al. (2021) Tao et al. (2022a); Yao et al. (2023) Correia et al. (2023); Rathore et al. (2021) Inamura (2023)
Decision support system	Voigt et al. (2021); Correia et al. (2023) Chu et al. (2023); Van Willigen et al. (2022) Armeni et al. (2022); Cellina et al. (2023)
Monitoring	Rathore et al. (2021); Tao et al. (2022a) Yao et al. (2023); Correia et al. (2023) Inamura (2023); Van Willigen et al. (2022) Voigt et al. (2021)
Optimization	Rathore et al. (2021); Tao et al. (2022a) Yao et al. (2023); Correia et al. (2023) Van Willigen et al. (2022); Armeni et al. (2022) Barricelli et al. (2019)
Visualization	Tao et al. (2022a); Voigt et al. (2021)
Diagnosis	Correia et al. (2023); Rathore et al. (2021) Voigt et al. (2021)

enhance their usability (Gazerani, 2023). When conducting a DT analysis, it is necessary to identify how information and interaction with the model can be accessed intuitively, even by non-technical end-users (Coorey et al., 2022; Barricelli et al., 2019). Information from the DT can be experienced through advanced technologies such as multi-dimensional holographic projections, 3D avatars, and eXtended Reality (XR) technologies (Sharma et al., 2022; Coorey et al., 2022). XR technologies offer immersive experiences that transform the sense of space and enhance interactions through interfaces, such as hand-tracking (Pellegrino et al., 2023b). Perceived benefits from such interfaces derive from a user-centered design and implementation (De Luca et al., 2023).

We conclude this section by noting that user interaction is constantly evolving, proposing new interacting models between humans, Virtual Reality (VR), and robotic devices, and laying the foundations for a new generation of DTs (Inamura, 2023).

5.5 Hierarchy

In the literature, DT systems are classified using a hierarchical structure consisting of the following a 3-level: (1) *unit-level*, (2) *system-level*, and (3) *System-of-Systems-level* (Yao et al., 2023; Yang et al., 2021). This structure is shown on the left in Fig. 4. In the healthcare domain, the complexity of the interactions and dependencies between different systems, apparatuses, organs, tissues, *etc*. has led to the rise of specific DTs and sub-DTs at these different hierarchical levels (Hirschvogel et al., 2019), but even at the molecular, cellular, and sub-cellular levels. The motivations leading to such DTs are manifold, from pharmacological experimentation (Kamel Boulos & Zhang, 2021; Chu et al., 2023) to modeling, for example, polymer melts (Baaden, 2022). According to Tao et al. (2022a), the DTs in the healthcare sphere and their hierarchical structures can be classified into the following two categories: (1) DTs oriented towards healthcare organizational systems and medical resources (Kamel Boulos & Zhang, 2021); (2) human-oriented DTs.

(1) *DT medical resource-oriented hierarchy*: this category includes DTOs (Kamel Boulos & Zhang, 2021; Armeni et al., 2022; Barricelli et al., 2019). The associated DTs can map the whole SoS into the *equipment level*. For example, referring to the magnetic resonance machine as the level of SoS, it could correspond to radiofrequency (RF) at the system level, while we have the DTs of the functional units of RF at the unit level, e.g., RF coil, RF generator, etc. (Tao et al., 2022a). Other levels could be added to the previous ones, such as the DT of an operation room (Patrone et al., 2020), a ward (Erol et al., 2020), an emergency room (Liu et al., 2023), or a hospital system (Armeni et al., 2022).

These categories of DTs enable healthcare institutions to allocate their resources in ways that increase efficiency, save costs, and avoid predictable crises (Armeni et al., 2022). They can also monitor the health of their equipment in terms of efficiency and maintenance. However, hierarchical levels of DTs have not been investigated in a structured manner in the medical resource-oriented sense (Tao et al., 2022a).

(2) *Human-oriented hierarchy*: in the human-oriented DTs, the human body system represents the SoS. Therefore, we have the system level in which we find the eight human body sub-systems (e.g., cardiovascular system or digestive system) and, finally, the unit level corresponding to the human organ level (e.g., heart), as shown in Fig. 3. In the healthcare domain, there are several examples of hierarchy structures with multiple levels. Modeling a population as an entity in its own right could be seen as a SoS, in which the system level is the human body. These could also be seen as a series of interacting DTs, defined as *Digital Twin Aggregates* (DTAs), which are a set of *Digital Twin Instances* (DTIs) belonging to different individuals, e.g., sets covering one family, population group, or whole population (Kamel Boulos & Zhang, 2021), as can be seen from Fig. 4. We can also identify DTs at the sub-organ level, such as the DTs of heart vessels (Tao et al., 2022a; Naplekov et al., 2018). In the literature, we find different hierarchies, in the healthcare field, depending on the domain and purpose of the DT, e.g., hierarchy *human body, organ, molecular*, in reference to the study of diabetes (Chu et al., 2023), and, as already seen, the hierarchies *molecular, cellular or sub-cellular* in reference to organelle/sub-organelle associated DTs (Kamel Boulos & Zhang, 2021).

For this reason, in Fig. 3, we provide a hierarchical system based on the results from the literature (Sharma et al., 2022; El Malki & Zdun, 2019; Malakuti & Grüner, 2018) to characterize DTs associated with the human body. Clearly, other levels could be added to the proposed hierarchical model. A formative approach should be taken into account to envisage increasingly complex models to better represent the physical entity and improve its understanding (Ozvoldik et al., 2021; Baaden, 2022).

More generally, hierarchy is a distinguished aspect of DTs since it acts as both a dimension and a structural property linking dimensions. Indeed, when multiple DTs interact as components of a larger DT, hierarchical relations may arise between dimensions that characterize individual DTs (e.g., data accessibility or domain comparability). This requires discriminating between the scale of the physical system modeled by a DT and the scale of dimensions representing single DTs. While the exploration of this aspect for healthcare DTs is beyond the scope of this work, we refer to Angelelli et al. (2024) for a model proposal to represent structural relations and uncertainty arising when multi-dimensional frameworks interact, with a special focus on interactions between human agents and technologies in data-driven initiatives.

5.6 Status and Maturity

In the **Status** dimension, we propose a classification of DTs into the following categories: (1) theoretical model (Sharma et al., 2022); (2) Proof of Concept (PoC) (Coorey et al., 2022); (3) prototype; (4) Minimum Viable Product (MVP); (5) business DT. Each of these categories could be associated with a *Technology Readiness Level* (TRL) (Salvador-Carulla et al., 2024) and a *Societal Readiness Level* (SRL) (see, e.g., Botín-Sanabria et al. 2022 and references therein). SRLs quantify the impacts that the DT has on society, as well as the impact on each end user. In relation to DTs, we sometimes use *levels of sophistication (or degrees of abstraction)* (Kamel Boulos & Zhang, 2021), which can be determined by the model's fidelity level, the frequency of their interactions with their PT, and functionality's efficiency (Arup, 2019; Kamel Boulos &

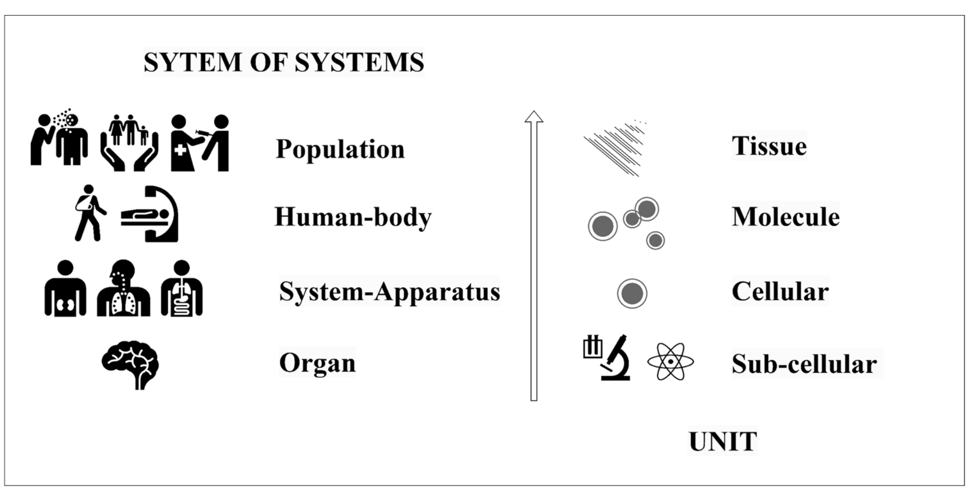

Fig. 3 Hierarchical system for the human-body domain

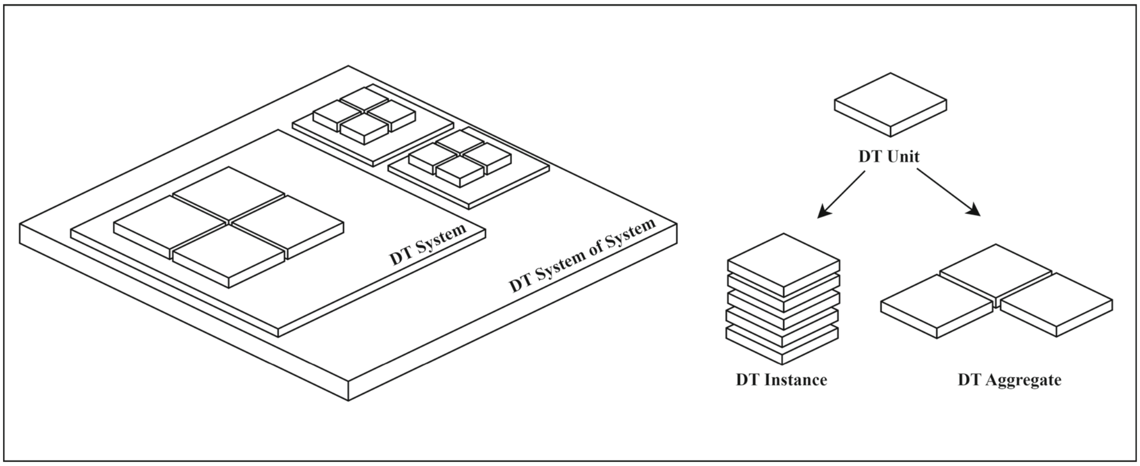

Fig. 4 3-dimensional hierarchical structure of DTs; DT unit, DT instance and DT aggregate

Zhang, 2021). Functionalities also allow a DT classification within the *Maturity Spectrum* of Botín-Sanabria et al. (2022).

There is a lack of systematic evaluation theories and methods for DT models in the literature; from the analysis conducted in this meta-review, we identify only two proposed evaluation indexes (Yao et al., 2023; Zhang & Tao, 2021; Yao et al., 2023; Tao et al., 2022b). One of them is based on the maturity of DTs in terms of: (1) effectiveness, (2) generality, (3) efficiency, (4) intuitiveness, (5) connectivity, (6) integrity, (7) flexibility, (8) model intelligence. The evaluation criteria for DTs in the healthcare domain are multiple and often oriented towards: *safety, effectiveness, patient-centered care, timeliness, equity, and efficiency* (Committee on Quality of HealthCare in America, 2001; Gazerani, 2023).

Finally, it is clarified that one should not confuse the status of a DT, as specified above, with the maturity of the DT, which is proper for each status. These aspects deserve in-depth studies that are beyond the scope of this work; however, in the next sections, we briefly discuss some opportunities to adapt measurement methods for the assessment of maturity and user interactions.

5.7 Limitations

Limitations of a DT constitute a dimension because awareness of the model limitations emphasizes its reduced capabilities or functionality (Botín-Sanabria et al., 2022; Sharma et al., 2022). The limitations help to create a comprehensive description of the DT and facilitate the subsequent evolution of the prototype. We also stress that there is no clear distinction between *Limitations* and *Challanges* in the literature.

We map the different limitations identified from the analysis in Table 6. However, the specification of this dimension in the actual analysis of a healthcare DT should be case-based, which means that further subdimensions beyond the ones in Table 6 could arise.

6 Discussion

The analysis carried out in the previous sections points out some aspects of practical interest for the architectural design of Healthcare DTs and, in particular, for their interoperability in a multi-purpose healthcare setting. These aspects are reflected in the dimensions constituting the multidimensional framework detailed in Section 5.

The dimensional structure of the proposed framework promotes a set of criteria constituting a model through which DTs can be investigated, in practice, starting from their preliminary design phase. This framework adheres to the definition of a conceptual structure that may enhance the formalization of good practices and standards, platforms, and tools supporting the prototyping of DTs (Botín-Sanabria et al., 2022; Corallo et al., 2021).

Such generality is a strength of the framework, which should provide a shared high-level structure among different types of DTs without introducing *a priori* obstructions in their interoperability. This is in line with evidence collected from the literature; for example, the definition of the *Time flow for DT* by Falkowski et al. (2023), who focused on multiple sclerosis, is not limited to this application domain.

The description and examples provided for each dimension are intended to specialize and highlight those aspects that should necessarily emerge from an exhaustive and complete analysis of one or more DTs in the healthcare perimeter. In this regard, the *Modeling* and *Functional* aspects of DTs are of special interest due to the significant dependence on the specific use cases or sub-domains, as discussed in Sections 5.3 and 5.4, respectively. The selection of possible

Table 6 Challenges and limitations of DTs in analyzed reviews

LIMITATION/CHALLENGE	REFERENCES
Ethical/Social impact	Armeni et al. (2022); Barricelli et al. (2019) Bjelland et al. (2022); Botín-Sanabria et al. (2022) Coorey et al. (2022); Chu et al. (2023) Kamel Boulos and Zhang (2021); Inamura (2023) Voigt et al. (2021)
Governance and regulatory	Armeni et al. (2022); Barricelli et al. (2019) Coorey et al. (2022); Botín-Sanabria et al. (2022) Sharma et al. (2022)
Technical limitations	Armeni et al. (2022); Barricelli et al. (2019) Botín-Sanabria et al. (2022); Coorey et al. (2022) Correia et al. (2023); Chu et al. (2023) Kamel Boulos and Zhang (2021); Inamura (2023) Rathore et al. (2021); Sharma et al. (2022) Voigt et al. (2021)
Privacy	Barricelli et al. (2019); Botín-Sanabria et al. (2022) Coorey et al. (2022); Chu et al. (2023) Rathore et al. (2021); Voigt et al. (2021)
Financial resource	Barricelli et al. (2019); Botín-Sanabria et al. (2022) Sharma et al. (2022)
Security and cybersecurity	Chu et al. (2023); Barricelli et al. (2019) Rathore et al. (2021); Sharma et al. (2022) Voigt et al. (2021)

architectures, techniques, and methods associated with a DT could pave the way to different research directions within specific application domains.

One of the issues that emerged in Section 5.5 is the need to define multiple hierarchical levels, as is partly proposed. A major application of this dimension is the multi-scale modeling of components of the human-body. The potential occurrence of multiple DTs that replicate biological systems interacting at different scales (from genomics to tissutal, up to organs or systems) configures the hierarchical structure as a conceptual framework for a SoS, in which each sub-system has a distinguished complexity level. We stress that the need to prompt healthcare DT interoperability at multiple scales may increase over time along with other technological capabilities related, for example, to multimodal spectroscopy, organs-on-chip, new imaging techniques, and integration with omic data supporting personalized medicine. These technological advances require structures that can enable communication and orchestration of multiple DTs. This concept is also related to the *composite DT* notion defined as the composition of two or more DTs (Kamel Boulos & Zhang, 2021). We emphasize that the composition is not limited to DTs belonging to the same hierarchical level, but the interaction between DTs belonging to different levels of hierarchy must be ensured. In fact, the combination of three types of DT related to *processes, products, and performance* (referred to as *digital thread*) enables the simulation and modeling of a complex system capable of increasing the fidelity of the system (Elkefi & Asan, 2022).

Another strategy that can increase the performance of the model and its fidelity is the creation of copies of the same DT. In the literature, we find different types of DT: *Digital Twin Prototype* (DTP), *Digital Twin Instance*, and *Digital Twin Aggregate* (Grieves, 2022). We have already mentioned DTAs in Section 5.5. The DTI are identical copies of a DT, all of which refer to the same PT (Fig. 4). Such copies can be used, for example, in multiple hypothesis testing or comparison, counterfactual reasoning (Pearl et al., 2016; Pearl, 2001), and simulations (Kamel Boulos & Zhang, 2021). The potential benefits of a hierarchical structure in terms of information transferred among multiple scales (through model-based simulations or data-driven approaches) extend the notion of DT composition already mentioned in Section 5.5. The hierarchical structures of DTs' composition fit well into the description of complexity and pathways linking different scales in biological and human systems. This benefit integrates efficiency advantages in having multiple DTs of the same entity (e.g., timing and cost earnings by comparing different parameter settings and simulating the system's behavior in different contexts) (Sharma et al., 2022).

The interaction between different DTs is closely related to the data-sharing modes, which in turn depend on the types of IoT sensors used and the synchronization modes adopted (Sharma et al., 2022; Jiang et al., 2021). In this direction, a standardization of fitness criteria among multiple DTs based on model similarities and protocol compatibility would facilitate the respective interaction among DTs (Coorey et al., 2022). Multiple DTs within a complex system, such as the human body, need to exchange and synchronize information. This requires advancements in software-to-software interoperability to seamlessly integrate virtual entities and PTs (Coorey et al., 2022). Additionally, novel models for data management among different DTs could redefine the traditional big data value chain, as detailed in Section 5.2. Each DT in the composite DT can be understood as both a *data generator* (data product) and a *data source* that must meet the requirements of quality and interoperability within federated governance (Gervasi et al., 2023a). Collaboration among academia, industry, and health institutions will be crucial for identifying and adopting standardized practices, ensuring interoperability of diverse DTs in compliance with relevant legislation, as well as meeting security and privacy standards (Coorey et al., 2022).

The final observation in Section 5.5 entails a connection with other dimensions, in particular Team, Data, User Interaction, and Maturity. Hierarchy within a digital system often involves structural relationships that link individual DTs. To effectively manage these relationships, it is essential to assess resource accessibility, including the team's capabilities and the availability of necessary data. Additionally, evaluating the compatibility of interacting systems is crucial. This includes considering how users interact with the DT, the maturity level of the DT, and the system's overall management capabilities. Findings have highlighted the potential for adapting structural conditions when evaluating the compatibility of various dimensions, particularly when data, technological components, and human agents interact (Angelelli et al., 2024). Robust multivariate techniques, such as partial least squares structural equation modeling (Hair et al., 2017), may be adapted for exploring the complex relationships between determinants of technology adoption (Edo et al., 2023). In this regard, existing measurement tools (Venkatesh et al., 2003; Corallo et al., 2023) can be employed to refine the proposed dimensional framework and integrate it with contextual factors that might influence the use of healthcare digital technologies.

In summary, the dimensional framework we have proposed is associated with a multiplicity of interpretations that could be attributed to such dimensions, which, in turn, generate relations among them. This multiplicity is observed in other dimensions besides Hierarchy, e.g., Modeling: *model construction*, *model assembly*, *model fusion*, *model verification*, *model modification*, and *model management* (Tao et al., 2022a). Of particular interest are the aspects related to *model fusion* and, hence, to the different interactions among several DT models up to the architectures enabling the DTs of DTs. Such a multiplicity may be seen both as a source of uncertainty and a resource (Angelelli et al., 2024), as it allows refining or updating DT's characteristics, as well as model requirements, enabling technologies, and maturity levels.

6.1 Strenghts and Limitations of this Work

This review has as its strength the systematic and rigorous methodology adopted. Readers of a meta-review can obtain a unique and up-to-date synthesis (Lim et al., 2022) of reviews that answer a specific research question. It encapsulates critical insights through the process of reinterpretation and reorganization of the knowledge extracted from the set of articles analyzed (Fan et al., 2022). In fact, the results and analyses are organized in a synthetic view for practical purposes and accompanied by bibliographical references. An analysis of reviews of the DT technology oriented to the healthcare domain is provided for the first time, investigating its various conceptualizations and dimensions. A multi-dimensional framework for the design and analysis of healthcare DTs is proposed starting from robust premises extracted from the literature study through an analytic process, finally providing a comprehensive guideline for both the research and industrial communities interested in DTs technology.

The weaknesses of this literature meta-review include the limited number of queried databases and systematic literature reviews (SLRs) available on DTs. This lack of available literature led us to include non-systematic reviews in order to gain a more representative view of the current state of healthcare DTs.

In some cases, this led us to integrate the required information (e.g., number of analyzed DTs) by extracting it from individual reviews and to include features proposed but not used in the DTs' analysis within the papers. The limited number of reviews entirely focused on the healthcare domain suggested extending the search to reviews that analyze at least one DT in this specific domain. Despite this limitation, the relaxation of such a search criterion resulted in the proposal of a multi-dimensional framework that may support the design and analysis of DTs beyond the healthcare domain. However, this extension should not be defined as the result of a rigorous and methodical study, since reviews that did not contain a specific use case (healthcare) for at least one of the DTs analyzed within it were excluded. The use of the document-type filter within the search query may have resulted in the exclusion of results that were not categorized as reviews in the databases.

7 Conclusion and Future Works

The proposed multi-dimensional framework aims to guide the analysis of DTs and support their modeling and design phases. The focus of our analysis on the healthcare domain brings out the need for the identification and adoption of a unified framework in a DT definition, as asserted by Botín-Sanabria et al. (2022) and Rossmann and Hertweck (2022).

The intrinsic complexity that resides in the definition of a human-body DT is inherited from the complexity of the human-body itself, whose modeling requires, as we have seen, systems of DTs organized into hierarchical levels that interact and work in synergy. The 11 dimensions identified in Table 3 encode the importance of specific aspects, such as a clear definition of the hierarchical levels where a DT must be embedded and interactions with other DTs can be structured and analyzed.

The Data dimension implies the need for a new Big Data Value Chain capable of abstracting and managing the continuous data flow between physical and virtual entities. The virtual entity exists if it has a set of data related to it such that it can be represented. Thus, lack of completeness, quality, or constant updating of data may produce incorrect modeling of the physical entity.

The Status dimension indirectly encodes a first classification of DT types. Such a classification does not refer to performance, which is better captured by the Maturity dimension. Indeed, the comparability of a theoretical DT model and an implemented DT is not guaranteed along one or more dimensions; hence, they could represent incomparable digital entities without one being the preliminary version of the other. The joint analysis of DTs should take into account the occurrence of structural relations or their absence (incompatibility) among them, which can be encompassed in the hierarchical structures among composite DTs (Fig. 4). Complementing the notion of DT instance could help track the DT's dynamics in terms of updates along its main dimensions. The analysis of the remaining dimensions, such as Modeling, Functions, Sensors, and User Interaction, emphasizes how a general-purpose analysis could lead to non-operational results, although they may have explanatory power.

These considerations should prompt the research for shared and harmonized protocols addressing normative and ethical, as well as architectural and modeling criteria. They also emphasize the general-purpose characteristics that such protocols should have. Specifically, appropriate rankings of evaluation criteria regarding the DTs' maturity should be explored even in terms of comparable status and conditions, enhancing the interoperability of DTs among different hierarchical levels.

The proposed research directions aim to investigate these aspects within a specific class of DTs. The lack of a representative sample of DTs becomes a limitation of the current research. However, this work could guide DT analyses by creating a common knowledge structure among distinct application domains and promoting the identification of comprehensive and exhaustive benchmarks for the healthcare domain, including compliance with ethical regulations related to the protection of individuals' rights and data sovereignty.

Acknowledgements MA, MG, and AC are members of the Centre for Applied Mathematics and Physics for Industry (CAMPI) at the University of Salento. GP and AC are members of the Nano and Digital Technologies for Precision Medicine (Na.Di.M.) at the University of Salento.

Author Contributions All the authors contributed to the study's conception and design. MA and MG contributed to the methodology and validation. GP contributed to data collection, software, and analysis. The first draft of the manuscript was written by MA, MG, and GP. AC supervised the work. All authors commented on previous versions of the manuscript, read, and approved the final manuscript.

Funding Open access funding provided by Università del Salento within the CRUI-CARE Agreement. The authors did not receive support from any organization for the submitted work.

Availability of data and material The data used in this research are publicly available.

Declarations

Ethics Approval and Consent to Participate Not applicable, because this article does not contain any studies with human participants or animals performed by any of the authors.

Consent for Publication Not applicable, because this article does not contain any individual person's data.

Competing Interests The authors have no competing interests to declare that are relevant to the content of this article.

References

Ackoff, R. (1989). From data to wisdom. *Journal of Applied System Analysis, 16*, 3–9.

Angelelli, M., Gervasi, M., & Ciavolino, E. (2024). Representations of epistemic uncertainty and awareness in data-driven strategies. *Soft Computing*. https://doi.org/10.1007/s00500-024-09661-8

Armeni, P., Polat, I., De Rossi, L. M., Diaferia, L., Meregalli, S., & Gatti, A. (2022). Digital twins in healthcare: Is it the beginning of a new era of evidence-based medicine? a critical review. *Journal of Personalized Medicine, 12*(8), 1255.

Arup (2019). Digital twin: Towards a meaningful framework. *Technical report, Arup, London, England*.

Aubert, K., Germaneau, A., Rochette, M., Ye, W., Severyns, M., Billot, M., Rigoard, P., & Vendeuvre, T. (2021). Development of digital twins to optimize trauma surgery and postoperative management.

a case study focusing on tibial plateau fracture. *Frontiers in Bioengineering and Biotechnology,9*, 722275.
Baaden, M. (2022). Deep inside molecules — digital twins at the nanoscale. *Virtual Reality & Intelligent Hardware,4*(4), 324–341. Virtual-reality and intelligent hardware in digital twins A).
Barricelli, B. R., Casiraghi, E., & Fogli, D. (2019). A survey on digital twin: Definitions, characteristics, applications, and design implications. *IEEE access, 7*, 167653–167671.
Becker, L. A., & Oxman, A. D. (2008). 22 overviews of reviews.
Bednarz, T., Baier, A., & Paprocka, I. (2024). A framework for communicating and building a digital twin model of the electric car. *Applied Sciences, 14*(5), 1776.
Bell, E., Bryman, A., & Harley, B. (2022). *Business research methods*. Oxford University Press.
Bertoa, M. F., Moreno, N., Perez-Vereda, A., Bandera, D., Álvarez-Palomo, J. M., & Canal, C. (2020). Digital avatars: Promoting independent living for older adults. *Wireless Communications and Mobile Computing, 2020*, 1–11.
Biahmou, A., Emmer, C., Pfouga, A., & Stjepandić, J. (2016). Digital master as an enabler for industry 4.0. In *Transdisciplinary engineering: Crossing boundaries* (pp. 672–681). IOS Press.
Bjelland, Ø., Rasheed, B., Schaathun, H. G., Pedersen, M. D., Steinert, M., Hellevik, A. I., & Bye, R. T. (2022). Toward a digital twin for arthroscopic knee surgery: A systematic review. *IEEE Access, 10*, 45029–45052.
Botín-Sanabria, D. M., Mihaita, A.-S., Peimbert-García, R. E., Ramírez-Moreno, M. A., Ramírez-Mendoza, R. A., & Lozoya-Santos, J. d. J. (2022). Digital twin technology challenges and applications: A comprehensive review. *Remote Sensing,14*(6), 1335.
Boyes, H., & Watson, T. (2022). Digital twins: An analysis framework and open issues. *Computers in Industry, 143*, 103763.
Carvalho, R., & da Silva, A. R. (2021). Sustainability requirements of digital twin-based systems: A meta systematic literature review. *Applied Sciences, 11*(12), 5519.
Cellina, M., Cè, M., Alì, M., Irmici, G., Ibba, S., Caloro, E., Fazzini, D., Oliva, G., & Papa, S. (2023). Digital twins: The new frontier for personalized medicine? *Applied Sciences, 13*(13), 7940.
Cheng, W., Lian, W., & Tian, J. (2022). Building the hospital intelligent twins for all-scenario intelligence health care. *Digital Health, 8*, 20552076221107896.
Chu, Y., Li, S., Tang, J., & Wu, H. (2023). The potential of the medical digital twin in diabetes management: A review. *Frontiers in Medicine,10*.
Committee on Quality of HealthCare in America, a. (2001). *Crossing the quality chasm: A new health system for the 21st century*. National Academies Press.
Coorey, G., Figtree, G. A., Fletcher, D. F., Snelson, V. J., Vernon, S. T., Winlaw, D., Grieve, S. M., McEwan, A., Yang, J. Y. H., Qian, P., et al. (2022). The health digital twin to tackle cardiovascular disease—a review of an emerging interdisciplinary field. *NPJ digital medicine, 5*(1), 126.
Corallo, A., Crespino, A. M., Del Vecchio, V., Gervasi, M., Lazoi, M., & Marra, M. (2023). Evaluating maturity level of big data management and analytics in industrial companies. *Technological Forecasting and Social Change, 196*, 122826.
Corallo, A., Del Vecchio, V., Lezzi, M., & Morciano, P. (2021). Shop floor digital twin in smart manufacturing: A systematic literature review. *Sustainability, 13*(23), 12987.
Corral-Acero, J., Margara, F., Marciniak, M., Rodero, C., Loncaric, F., Feng, Y., Gilbert, A., Fernandes, J. F., Bukhari, H. A., Wajdan, A., et al. (2020). The 'digital twin'to enable the vision of precision cardiology. *European Heart Journal, 41*(48), 4556–4564.
Correia, J. B., Abel, M., & Becker, K. (2023). Data management in digital twins: A systematic literature review. *Knowledge and Information Systems, 65*(8), 3165–3196.
Curry, E. (2016). The big data value chain: Definitions, concepts, and theoretical approaches. *New Horizons for a Data-Driven Economy: A Roadmap for Usage and Exploitation of Big Data in Europe* (pp. 29–37).
Dai, Y., Wang, J., & Gao, S. (2022). Advanced electronics and artificial intelligence: Must-have technologies toward human body digital twins. *Advanced Intelligent Systems, 4*(7), 2100263.
De Luca, V., Pellegrino, G., & De Paolis, L. T. (2023). The impact of usability and learnability on presence factors in a vr human body navigator. In *International conference on extended reality* (pp. 378–396). Springer.
Edo, O. C., Ang, D., Etu, E.-E., Tenebe, I., Edo, S., & Diekola, O. A. (2023). Why do healthcare workers adopt digital health technologies-A cross-sectional study integrating the TAM and UTAUT model in a developing economy. *International Journal of Information Management Data Insights, 3*(2), 100186.
El Malki, A., & Zdun, U. (2019). Guiding architectural decision making on service mesh based microservice architectures. In *Software architecture: 13th European conference, ECSA 2019, Paris, France, September 9–13, 2019, proceedings 13* (pp. 3–19). Springer.
Elkefi, S., & Asan, O. (2022). Digital twins for managing health care systems: Rapid literature review. *Journal of Medical Internet Research, 24*(8), e37641.
Enders, M. R., & Hoßbach, N. (2019). Dimensions of digital twin applications-a literature review. In *Proceedings of the 25th Americas conference on information systems, Cancun: Mexico* (pp. 1–10).
Erol, T., Mendi, A. F., & Doğan, D. (2020). The digital twin revolution in healthcare. In *2020 4th international symposium on multidisciplinary studies and innovative technologies (ISMSIT)* (pp. 1–7). IEEE.
Falkowski, P., Osiak, T., Wilk, J., Prokopiuk, N., Leczkowski, B., Pilat, Z., & Rzymkowski, C. (2023). Study on the applicability of digital twins for home remote motor rehabilitation. *Sensors, 23*(2), 911.
Fan, D., Breslin, D., Callahan, J. L., & Iszatt-White, M. (2022). Advancing literature review methodology through rigour, generativity, scope and transparency. *International Journal of Management Reviews, 24*(2), 171–180.
Fink, A. (2019). *Conducting research literature reviews: From the internet to paper*. Sage publications.
Fuller, A., Fan, Z., Day, C., & Barlow, C. (2020). Digital twin: Enabling technologies, challenges and open research. *IEEE Access, 8*, 108952–108971.
Garner, T. A., Powell, W. A., & Carr, V. (2016). Virtual carers for the elderly: A case study review of ethical responsibilities. *Digital health, 2*, 2055207616681173.
Gazerani, P. (2023). Intelligent digital twins for personalized migraine care. *Journal of Personalized Medicine, 13*(8), 1255.
Gervasi, M., Totaro, N. G., Fornaio, A., & Caivano, D. (2023a). Big data value graph: Enhancing security and generating new value from big data. In F. Buccafurri, E. Ferrari, & G. Lax (Eds.), *Proceedings of the Italian conference on cyber security (ITASEC 2023)* (Vol. 3488). CEUR-WS, Bari.
Gervasi, M., Totaro, N. G., Specchia, G., & Latino, M. E. (2023b). Unveiling the roots of big data project failure: A critical analysis of the distinguishing features and uncertainties in evaluating big data potential value. In *Proceedings of the 2nd Italian conference on big data and data science (ITADATA 2023)* (Vol. 3606). CEUR-WS, Naples.
Grant, M. J., & Booth, A. (2009). A typology of reviews: An analysis of 14 review types and associated methodologies. *Health information & libraries journal, 26*(2), 91–108.
Grieves, M. W. (2019). Virtually intelligent product systems: digital and physical twins. In *Complex systems engineering: theory and*

practice (pp. 175–200). American Institute of Aeronautics and Astronautics, Inc.

Grieves, M., & Vickers, J. (2017). Digital twin: Mitigating unpredictable, undesirable emergent behavior in complex systems. *Transdisciplinary perspectives on complex systems: New findings and approaches* (pp. 85–113).

Grieves, M. W. (2000). *Business is war: An investigation into metaphor use in Internet and non-Internet IPOs*. Weatherhead School of Management: Case Western Reserve University.

Grieves, M. (2014). Digital twin: Manufacturing excellence through virtual factory replication. *White paper, 1*(2014), 1–7.

Grieves, M. (2022). Intelligent digital twins and the development and management of complex systems. *Digital Twin, 2*(8), 8.

Hair, J. F., Hult, G. T. M., Ringle, C., & Sarstedt, M. (2017). *A primer on partial least squares structural equation modeling (PLS-SEM)* (2nd ed.). SAGE Publications.

Hansen, C., Steinmetz, H., & Block, J. (2022). How to conduct a meta-analysis in eight steps: A practical guide.

Hernigou, P., Olejnik, R., Safar, A., Martinov, S., Hernigou, J., & Ferre, B. (2021). Digital twins, artificial intelligence, and machine learning technology to identify a real personalized motion axis of the tibiotalar joint for robotics in total ankle arthroplasty. *International Orthopaedics, 45*, 2209–2217.

Hirschvogel, M., Jagschies, L., Maier, A., Wildhirt, S. M., & Gee, M. W. (2019). An in silico twin for epicardial augmentation of the failing heart. *International journal for numerical methods in biomedical engineering, 35*(10), e3233.

Hoffman, C. M., & Joan-Arinyo, R. (1998). Cad and the product master model. *Computer-Aided Design, 30*(11), 905–918.

Inamura, T. (2023). Digital twin of experience for human-robot collaboration through virtual reality. *International Journal of Automation Technology, 17*(3), 284–291.

Jianfeng, L., Luyao, X., Hao, Z., & Mengying, X. (2022). Research and application of manufacturing enterprise digital twin ecosystem. *Computer Integrated Manufacturing System, 28*(8), 2273.

Jiang, Y., Yin, S., Li, K., Luo, H., & Kaynak, O. (2021). Industrial applications of digital twins. *Philosophical Transactions of the Royal Society A, 379*(2207), 20200360.

Jing, Y., Wang, C., Chen, Y., Wang, H., Yu, T., & Shadiev, R. (2023). Bibliometric mapping techniques in educational technology research: A systematic literature review. *Education and Information Technologies* (pp. 1–29).

Kamel Boulos, M. N., & Zhang, P. (2021). Digital twins: From personalised medicine to precision public health. *Journal of personalized medicine, 11*(8), 745.

Karakra, A., Fontanili, F., Lamine, E., & Lamothe, J. (2019). Hospit'win: A predictive simulation-based digital twin for patients pathways in hospital. In *2019 IEEE EMBS international conference on biomedical & health informatics (BHI)* (pp. 1–4). IEEE.

Kriksciuniene, D., Sakalauskas, V., & Kriksciunas, B. (2015). Process optimization and monitoring along big data value chain. In W. Abramowicz (Ed.), *Business Information Systems Workshos, BIS 2015*, volume 228 of *Lecture Notes in Business Information Processing* (pp. 75–86). Springer International Publishing.

Kritzinger, W., Karner, M., Traar, G., Henjes, J., & Sihn, W. (2018). Digital twin in manufacturing: A categorical literature review and classification. *Ifac-PapersOnline, 51*(11), 1016–1022.

Kuehner, K. J., Scheer, R., & Strassburger, S. (2021). Digital twin: Finding common ground–a meta-review. *Procedia CIRP, 104*, 1227–1232.

Kumar, S., Sahoo, S., Lim, W. M., Kraus, S., & Bamel, U. (2022). Fuzzy-set qualitative comparative analysis (fsqca) in business and management research: A contemporary overview. *Technological Forecasting and Social Change, 178*, 121599.

Kušić, K., Schumann, R., & Ivanjko, E. (2023). A digital twin in transportation: Real-time synergy of traffic data streams and simulation for virtualizing motorway dynamics. *Advanced Engineering Informatics, 55*, 101858.

Laubenbacher, R., Niarakis, A., Helikar, T., An, G., Shapiro, B., Malik-Sheriff, R. S., Sego, T., Knapp, A., Macklin, P., & Glazier, J. A. (2022). Building digital twins of the human immune system: Toward a roadmap. *NPJ digital medicine, 5*(1), 64.

Lauzeral, N., Borzacchiello, D., Kugler, M., George, D., Rémond, Y., Hostettler, A., & Chinesta, F. (2019). A model order reduction approach to create patient-specific mechanical models of human liver in computational medicine applications. *Computer Methods and Programs in Biomedicine, 170*, 95–106.

Lehtola, V. V., Koeva, M., Elberink, S. O., Raposo, P., Virtanen, J.-P., Vahdatikhaki, F., & Borsci, S. (2022). Digital twin of a city: Review of technology serving city needs. *International Journal of Applied Earth Observation and Geoinformation, 114*, 102915.

Lim, W. M., Kumar, S., & Ali, F. (2022). Advancing knowledge through literature reviews: 'What','why', and 'how to contribute'. *The Service Industries Journal, 42*(7–8), 481–513.

Lim, K. Y. H., Zheng, P., & Chen, C.-H. (2020). A state-of-the-art survey of digital twin: Techniques, engineering product lifecycle management and business innovation perspectives. *Journal of Intelligent Manufacturing, 31*(6), 1313–1337.

Lin, Y., Chen, L., Ali, A., Nugent, C., Ian, C., Li, R., Gao, D., Wang, H., Wang, Y., & Ning, H. (2022). Human digital twin: A survey. arXiv preprint arXiv:2212.05937

Liu, Y., Moyaux, T., Bouleux, G., & Cheutet, V. (2023). An agent-based architecture of the digital twin for an emergency department. *Sustainability, 15*(4), 3412.

Liu, Y., Ong, S., & Nee, A. (2022). State-of-the-art survey on digital twin implementations. *Advances in Manufacturing, 10*(1), 1–23.

Liu, Y., Zhang, L., Yang, Y., Zhou, L., Ren, L., Wang, F., Liu, R., Pang, Z., & Deen, M. J. (2019). A novel cloud-based framework for the elderly healthcare services using digital twin. *IEEE Access, 7*, 49088–49101.

Mahmoud, M., Semeraro, C., Abdelkareem, M. A., & Olabi, A. G. (2024). Designing and prototyping the architecture of a digital twin for wind turbine. *International Journal of Thermofluids, 22*, 100622.

Malakuti, S., & Grüner, S. (2018). Architectural aspects of digital twins in iiot systems. In *Proceedings of the 12th European conference on software architecture: Companion proceedings* (pp. 1–2).

Nagaraj, D., Khandelwal, P., Steyaert, S., & Gevaert, O. (2023). Augmenting digital twins with federated learning in medicine. *The Lancet Digital Health, 5*(5), e251–e253.

Naplekov, I., Zheleznikov, I., Pashchenko, D., Kobysheva, P., Moskvitina, A., Mustafin, R., Gnutikova, M., Mullagalieva, A., & Uzlov, P. (2018). Methods of computational modeling of coronary heart vessels for its digital twin. In *MATEC Web of Conferences* (Vol. 172, p. 01009). EDP Sciences.

Ozvoldik, K., Stockner, T., Rammner, B., & Krieger, E. (2021). Assembly of biomolecular gigastructures and visualization with the vulkan graphics api. *Journal of Chemical Information and Modeling, 61*(10), 5293–5303. PMID: 34528431.

Patrone, C., Lattuada, M., Galli, G., & Revetria, R. (2020). The role of internet of things and digital twin in healthcare digitalization process. In *Transactions on engineering technologies: world congress on engineering and computer science 2018 26* (pp. 30–37). Springer.

Pearl, J., Glymour, M., & Jewell, N. P. (2016). *Causal Inference in Statistics: A Primer*. John Wiley and Sons Ltd.

Pearl, J. (2001). Causal inference in the health sciences: A conceptual introduction. *Health Services and Outcomes Research Methodology, 2*, 189–220.

Pellegrino, G., Barba, M. C., D'Errico, G., Küçükkara, M. Y., & De Paolis, L. T. (2023a). Extended reality & artificial intelligence-based

surgical training: A review of reviews. In *International Conference on Extended Reality* (pp. 345–355). Springer.
Pellegrino, G., d'Errico, G., De Luca, V., Barba, M. C., & De Paolis, L. T. (2023b). Hand tracking for xr-based apraxia assessment: A preliminary study. In *Nordic-Baltic conference on biomedical engineering and medical physics* (pp. 362–369). Springer.
Piascik, B., Vickers, J., Lowry, D., Scotti, S., Stewart, J., & Calomino, A. (2012). Materials, structures, mechanical systems, and manufacturing roadmap. *NASA TA* (pp. 12–2).
Rathore, M. M., Shah, S. A., Shukla, D., Bentafat, E., & Bakiras, S. (2021). The role of ai, machine learning, and big data in digital twinning: A systematic literature review, challenges, and opportunities. *IEEE Access, 9*, 32030–32052.
Rossmann, A., & Hertweck, D. (2022). Digital twins: a meta-review on their conceptualization, application, and reference architecture. In *Proceedings of the 55th Hawaii International Conference on System Sciences (HICSS 2022), 4-7 January 2022, virtual event/Maui* (pp. 4518–4527). University of Hawai'i at Manoa.
Salvador-Carulla, L., Woods, C., de Miquel, C., & Lukersmith, S. (2024). Adaptation of the technology readiness levels for impact assessment in implementation sciences: The trl-is checklist. *Heliyon*.
Schryen, G., & Sperling, M. (2023). Literature reviews in operations research: A new taxonomy and a meta review. *Computers & Operations Research, 157*, 106269.
Segovia, M., & Garcia-Alfaro, J. (2022). Design, modeling and implementation of digital twins. *Sensors, 22*(14), 5396.
Sharma, A., Kosasih, E., Zhang, J., Brintrup, A., & Calinescu, A. (2022). Digital twins: State of the art theory and practice, challenges, and open research questions. *Journal of Industrial Information Integration, 30*, 100383.
Shen, M.-d., Chen, S.-b., & Ding, X.-d. (2024). The effectiveness of digital twins in promoting precision health across the entire population: A systematic review. *NPJ Digital Medicine,7*(1), 145.
Siedlak, D. J., Pinon, O. J., Schlais, P. R., Schmidt, T. M., & Mavris, D. N. (2018). A digital thread approach to support manufacturing-influenced conceptual aircraft design. *Research in Engineering Design, 29*, 285–308.
Singh, V., & Willcox, K. E. (2021). Decision-making under uncertainty for a digital thread-enabled design process. *Journal of Mechanical Design, 143*(9), 091707.
Snyder, H. (2019). Literature review as a research methodology: An overview and guidelines. *Journal of Business Research, 104*, 333–339.
Sun, T., He, X., & Li, Z. (2023). Digital twin in healthcare: Recent updates and challenges. *Digital Health, 9*, 20552076221149652.
Sun, T., He, X., Song, X., Shu, L., & Li, Z. (2022). The digital twin in medicine: A key to the future of healthcare? *Frontiers in Medicine, 9*, 907066.
Tao, F., Sui, F., Liu, A., Qi, Q., Zhang, M., Song, B., Guo, Z., Lu, S. C.-Y., & Nee, A. Y. (2019). Digital twin-driven product design framework. *International Journal of Production Research,57*(12), 3935–3953.
Tao, F., Cheng, J., Qi, Q., Zhang, M., Zhang, H., & Sui, F. (2018). Digital twin-driven product design, manufacturing and service with big data. *The International Journal of Advanced Manufacturing Technology, 94*, 3563–3576.
Tao, F., Xiao, B., Qi, Q., Cheng, J., & Ji, P. (2022a). Digital twin modeling. *Journal of Manufacturing Systems, 64*, 372–389.
Tao, F., Zhang, C.-Y., Qi, Q., & Zhang, H. (2022b). Digital twin maturity model. *Computer Integrated Manufacturing Systems, 28*(5), 1267–1281.
Thomson, D., Russell, K., Becker, L., Klassen, T., & Hartling, L. (2010). The evolution of a new publication type: Steps and challenges of producing overviews of reviews. *Research synthesis methods, 1*(3–4), 198–211.
Tuegel, E. J., Ingraffea, A. R., Eason, T. G., & Spottswood, S. M. (2011). Reengineering aircraft structural life prediction using a digital twin. *International Journal of Aerospace Engineering,2011*.
Van Willigen, B. G., Huberts, W., van de Vosse, F. N., et al. (2022). A review study of fetal circulatory models to develop a digital twin of a fetus in a perinatal life support system. *Frontiers in Pediatrics, 10*, 915846.
Venkatesh, V., Morris, M. G., Davis, G. B., & Davis, F. D. (2003). User acceptance of information technology: Toward a unified view. *MIS quarterly* (pp. 425–478).
Venkatesh, K. P., Raza, M. M., & Kvedar, J. C. (2022). Health digital twins as tools for precision medicine: Considerations for computation, implementation, and regulation. *NPJ digital medicine, 5*(1), 150.
Voigt, I., Inojosa, H., Dillenseger, A., Haase, R., Akgün, K., & Ziemssen, T. (2021). Digital twins for multiple sclerosis. *Frontiers in Immunology, 12*, 669811.
Wu, C., Zhou, Y., Pessôa, M. V. P., Peng, Q., & Tan, R. (2021). Conceptual digital twin modeling based on an integrated five-dimensional framework and triz function model. *Journal of Manufacturing Systems, 58*, 79–93.
Yang, F., Wu, T., Liao, R., Jiang, J., Chen, T., & Gao, B. (2021). Application and implementation method of digital twin in electric equipment. *High Voltage Engineering, 47*(05), 1505–1521.
Yao, J.-F., Yang, Y., Wang, X.-C., & Zhang, X.-P. (2023). Systematic review of digital twin technology and applications. *Visual Computing for Industry, Biomedicine, and Art, 6*(1), 10.
Zhang, C., & Tao, F. (2021). Evaluation index system for digital twin model. *Computer Integrated Manufacturing System, 27*(8), 2171–2186.
Zhu, L., Barricelli, B. R., & Iacob, C. (2011). A meta-design model for creative distributed collaborative design. *International Journal of Distributed Systems and Technologies (IJDST), 2*(4), 1–16.

Giulia Pellegrino is a Ph.D. student at the University of Salento. Her research activities are conducted in collaboration with the Na.Di.M. (Nano and Digital Technologies for Precision Medicine) laboratory. Her current research interests focus on the analysis and development of eXtended Reality (XR) applications for surgery and Digital Twins for healthcare. She received her master's degree in Computer Engineering. In her thesis work, she combined optimal control techniques with Virtual Reality (VR) applied to the assessment and rehabilitation of neurological disorders.

Massimiliano Gervasi is a Senior Consultant at Deloitte Consulting S.r.l. S.B. in Lecce, Italy. He received a Ph.D. in Complex Systems Engineering from the University of Salento, where his research focused on big data, formal models, and methods for creating and measuring value extracted from data. His current research interests include the big data maturity model, data management, data quality, data architecture, and processes for creating and capturing business value within big data strategies.

Mario Angelelli is a research fellow and adjunct professor at the Department of Human and Social Sciences of the University of Salento. He received his Ph.D. in Theoretical Physics at the University of Salento, focusing on formal methods for the study of complex systems. His current research concentrates on structural equation modeling and uncertainty modeling in Psychometry, combining statistical, order-theoretic, and information-theoretic approaches for representing ambiguity, epistemic uncertainty, and cyber-risk perception. He is a member of SIS (Italian Statistical Society) and INdAM (National Institute of Higher Mathematics).

Angelo Corallo is an associate professor at the Department of Experimental Medicine, University of Salento. His research interests are related to technologies, methodologies, and organizational models supporting the New Product Development process in complex industries and knowledge management and collaborative working environments. Since 2000, he has been the coordinator of several European and Italian research projects.