



HAL
open science

Digital Twins and Healthcare: Quick Overview and Human-Centric Perspectives

Giacinto Barresi, Andrea Gaggioli, Federico Sternini, Alice Ravizza, Claudio Pacchierotti, Lorenzo de Michieli

► **To cite this version:**

Giacinto Barresi, Andrea Gaggioli, Federico Sternini, Alice Ravizza, Claudio Pacchierotti, et al.. Digital Twins and Healthcare: Quick Overview and Human-Centric Perspectives. *mHealth and Human-Centered Design Towards Enhanced Health, Care, and Well-being*, 120, Springer Nature, pp.57-78, 2023, *Studies in Big Data*, 10.1007/978-981-99-3989-3_4 . hal-04166907

HAL Id: hal-04166907

<https://inria.hal.science/hal-04166907>

Submitted on 20 Jul 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright

Digital Twins and Healthcare: Quick Overview and Human-Centric Perspectives

**Giacinto Barresi^{*1}, Andrea Gaggioli^{2,3}, Federico Sternini^{4,5}, Alice Ravizza⁴,
Claudio Pacchierotti⁶, Lorenzo De Michieli¹**

¹Rehab Technologies Lab, Istituto Italiano di Tecnologia (IIT), Genova, Italy

²Research Center in Communication Psychology, Università Cattolica del Sacro Cuore, Milan, Italy

³Applied Technology for Neuro-Psychology Lab, I.R.C.C.S. Istituto Auxologico Italiano, Milan, Italy

⁴USE-ME-D srl, I3P Politecnico di Torino, Torino, Italy

⁵PolitoBIOMed Lab, Politecnico di Torino, Torino, Italy

⁶CNRS, Univ Rennes, Inria, IRISA, Rennes, France

*Corresponding author: giacinto.barresi@iit.it

Abstract

Digital Twins constitute a class of innovative data-intensive network-based computing solutions based on real-time interactive simulations of physical systems – Physical Twins – in multiple domains, representing and predicting the states of complex systems (from bacteria to cities). However, the variety of Digital Twins proposed in literature makes difficult to shape a general definition for this class of computational tools (possibly merging with phygital systems). On the other hand, this is a sign of the versatility of Digital Twins, in both their own capability to solve heterogeneous problems in real world and to inspire novel approaches to handle the uncertainty in complex systems. Such advantages are also explored in fields like healthcare, especially considering domains of Digital Health and mHealth. Indeed, major efforts in research are pushing the methodological and technological boundaries of biomedical sciences, translational research, and precision medicine. Such efforts should be pursued for implementing Digital Twins helping, for instance, the human-centric optimization of the resources allocation in healthcare settings (hospitals, homes, and cities). This chapter will present the opportunity and the ethical issues of using these systems for foreseeing the future states of a person or a population (a need that certainly was highlighted during the COVID-19 pandemic) or a system including a medical device and its user.

Keywords: Digital Twin, Digital Health, mHealth, Phygital Twin, simulation, precision medicine, human-centric technology

1 Introduction

Emulating and simulating complex systems are computational strategies [1] for understanding phenomena that could difficultly be investigated through traditional approaches based on experiments. Emulating a system implies that a behavior is replicated without necessarily modeling its internal state. Simulations typically also include a model of the inner structure and functioning of a system: through its output, a simulation can be used for validating such an internal model. Following and transcending these approaches, recent technologies called Digital Twins have emerged over the past few years in multiple domains – from robotic manufacturing to precision medicine [2-6]. The versatility of these solutions is accompanied by the impressive efforts in exploring their capabilities of predicting future states of complex systems through a (possibly) bidirectional real-time data flow. Such features are enabled by pervasive sensor networks (as in Internet of Things, IoT), advanced visualization options (like the various extended reality items) and high-performance infrastructures (as the 5G/6G) alongside big data analytics solutions (supported by systems for Artificial Intelligence, AI) [7,8].

This promising approach is described in this chapter before focusing on its health-related applications [9]: indeed, major initiatives in research are facing the challenge of replicating biological systems – in particular, biological agents or their organs – or the systems that include them (a setting like a home, a hospital, a city). The goal of developing Digital Twins in biomedical domains is obviously the improvement of our ways to understand and manage health issues and healthcare services (especially in terms of sustainability), and it is still in its childhood, often in research laboratories.

However, major issues must be discussed to appropriately handle the development of these (sometime) futuristic solutions, in particular when current technologies (as in Internet of Medical Things – IoMT – and mobile Health – mHealth) seem ready to bring them to us for promoting a change in our behaviours for self-care. This chapter will dedicate a section to two human-centric sub-topics - specifically: the Phygital Twins as intuitive solutions to explore a phenomenon, the ethical issues in twinning procedures and results. These constitute examples of potential next steps in making this domain grow without ignoring the human requirements. These topics are just examples of the challenges that must be faced for developing these technologies that promise to revolutionize our healthcare approaches.

2 Digital Twins

The recent intensive exploration of Digital Twins as data-intensive network-based computational systems is surely supported by cutting-edge advances in several domains, including data collection (environmental and wearable sensors,

IoT systems), data processing (AI, systems for machine learning and deep learning, solutions for big data analytics), and data visualization with interactive features (virtual reality, various types of augmented reality and mixed reality, and, in general, the whole class of extended reality solutions). In general, Digital Twins exploit these solutions to manage the challenges (e.g., sustainability) of complex and unpredictable systems in real world, from cells to Smart Cities [10-17]. Considering its most typical definitions, a Digital Twin needs a real-time connection between a set of items in the real world and their counterparts in a virtual world, based on data about the first and their multimodal computational representations. Even if the common goal of the Digital Twins implementation is to monitor, predict, and manage uncertain conditions in complex systems [18], their heterogeneous applications and integration levels makes difficult to generally agree on one definition for this class of technologies. Furthermore, a Digital Twin can model a real item like a structural or functional component, an asset, a system, a process: such a variety of representational levels affects the definition of Digital Twins with additional multiplicity. An analysis of this concept history (including the 2012 NASA roadmap about information technology and processing with focus on modeling and simulation) is beyond the scope of this chapter and can be performed according to reviews like [19-23].

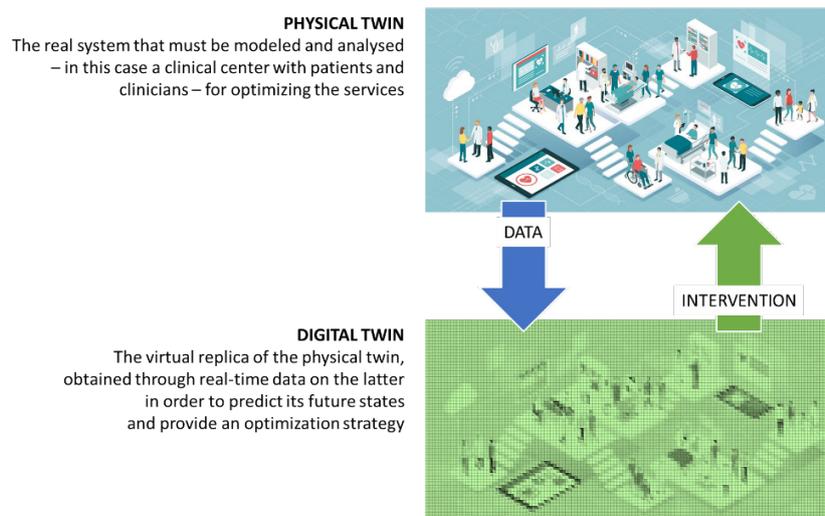


Figure 1. This illustration depicts the hypothetical case of a Digital Twin computationally replicating agents (mainly: patients, clinicians) and events within a hospital. Its objective is to help the experts formulate a strategy for optimizing the healthcare services within the Physical Twin.

However, Fuller et al. [24] proficiently handled the task of describing Digital Twins (Fig. 1) and their applied domains, as discussed in [25]. The authors

highlighted how a Digital Twin is not a mere offline digital model that simulates a physical object (the Physical Twin). It must also be highlighted how a Digital Twin cannot be reduced to a digital shadow, which depicts a physical object and automatically adjusts its structure to it, while the Physical Twin can just be manually modified. According to the authors, a virtual system replicating a physical system should be fully labeled as a Digital Twin if it changes automatically replicate and influence the conditions of its Physical Twin. In such a case, we can acknowledge the bidirectional flow of data between digital and physical items of the twinning process [26]. Moreover, [27] considers the Digital Twin as an adaptive virtual model emulating the behavior of a physical system according to real-time data.

Through these features, the Digital Twin can be “played” by humans with specific expertise and decision-making roles (e.g., managers, engineers, designers) as an interactive simulation enabling the prediction of future issues in the real world based on past and current states and behaviors of the Physical Twin. This can lead to improve and optimize the physical system through interventions on policies and decision-making processes of experts evaluating the Digital Twin. According to literature analyzed in [28], it is possible to define a taxonomy of Digital Twins based on the features frequently occurring in most papers on this topic. For instance: the Physical Twin usually exists before someone creates its Digital Twin; the (raw and processed) data are bidirectionally exchanged between the twins and analysed; each item and its counterpart tend to be synchronized, identical, and physically bound; the Digital Twin can also interface two machines or a human and a machine (human-machine interaction, HMI). Anyway, the ongoing outburst of novel DT-based concepts keep defying these categories: this is the case of the “Digital Triplet” [29,30], an AI layer dedicated to assist the human decision-making according to the DT output.

Among the recurring features retrieved in literature, bidirectionality in digital twinning (i.e., the process generating a Digital Twin and its relationship with its physical counterpart) does not constitute an obvious characteristic because a consensus on its definition does not seem concluded. Although many papers refer to “automated bidirectionality”, the feedback from Digital Twin to Physical Twin is often based on updating a designer or a manager with information to improve the Physical Twin according to predictions made by playing the Digital Twin during the product life cycle. This is highlighted by observing how a Digital Twin can be defined by its main scope [31]: (i) monitoring the conditions and the features of a Physical Twin, (ii) replicating the future patterns of the Physical Twin states, (iii) establishing direct interactions with a Physical Twin based on a cyber-physical system (in this case, we can talk about “operational Digital Twins”). The latter case could happen, even without any human intervention, through a Physical Twin enriched by actuated components that respond to automatic decisions based on parameters for optimizing the replicated system according to the replica-based predictions [32]. Obviously, such an automated bidirectionality is a feature with high requirements, scaling with the Physical Twin complexity and depending on ubiquitous infrastructures and high-performance telecommunication protocols [31]

for managing uncertain conditions in the computationally modeled real settings [33]. Additionally, they need advanced machine learning and deep learning systems to discover or to implement the optimal ways to modify the Physical Twin [34].

Such processes are actively explored in intelligent manufacturing solutions like [35] and, in order to make Digital Twins closer to real-world, [36] in cyber-physical twins. This term emphasizes the environmental influence on the physical object and the feedback from the digital world to the real world. The authors proposed this new type of twins to improve the product development processes, which can be empowered beyond the advantages offered by Digital Twins [37] to make simulated experiments with virtual prototypes. Within this context, an interesting approach is based on the opportunity to program machines through Digital Twins experienced (even in teleoperation conditions) by the expert as the user of intuitive virtual reality interfaces [38]. Such a scenario discloses the potential of these advanced interactive simulations in robotics and human-robot interaction (HRI) [39]. However, there are unexplored ways to make this process more intuitive for the expert [40]. This could become viable by connecting a Digital Twin with a physical replica of the robot constituting part of the Physical Twin (this topic will be treated in the penultimate section of this chapter, within the sub-section on “Phygital Twins”) [25]. We can consider this as a result of a trend making physical and virtual items converge [41], especially in case the first are based on an embodied AI like a robot.

Interestingly, the main challenges of Digital Twins in HRI [42] can depend on the difficulty of representing the human component within the human-robot system. Such a barrier becomes even more challenging if we face the complexity of the human health and of the healthcare systems, as next section will discuss.

3 Healthcare Applications

The healthcare applications of Digital Twins constitute further challenges for this innovative technology. Indeed, fully modeling human beings (even organs or cells) is certainly beyond the technical capabilities of any device that can be developed nowadays. It is difficult to envision if and when a comprehensive Digital Twin of any living organism can be implemented (especially considering how cognitive-behavioural processes cannot be excluded from the domain of biological systems). However, it is possible to proceed through a pragmatic approach for devising interactive models able to assist the problem-solving procedures in specific subdomains, circumscribing issues that constitute constraints to our actions in understanding and improving the health conditions of a person for implementing precision medicine strategies [11,43,44]. Nonetheless, Digital Twins can be exploited in healthcare for modeling not only human beings but any system, process, and product [45] in order to optimize workflows and to improve clinical performance and health outcomes with minimal risk. Even the experiences of patients, doctors, and other stakeholders can become a target, ameliorating the healthcare services management as well.

Considering these scenarios, next sub-sections will propose exemplary applications of Digital Twins to healthcare, with special attention to the ones of mHealth as framework that remarks the opportunity of collecting data and offering feedback ubiquitously, especially to the patients. These examples constitute preliminary explorations in this field: they offer promising prototypes that can contribute to investigate and improve human health.

3.1 Digital Twins for Health

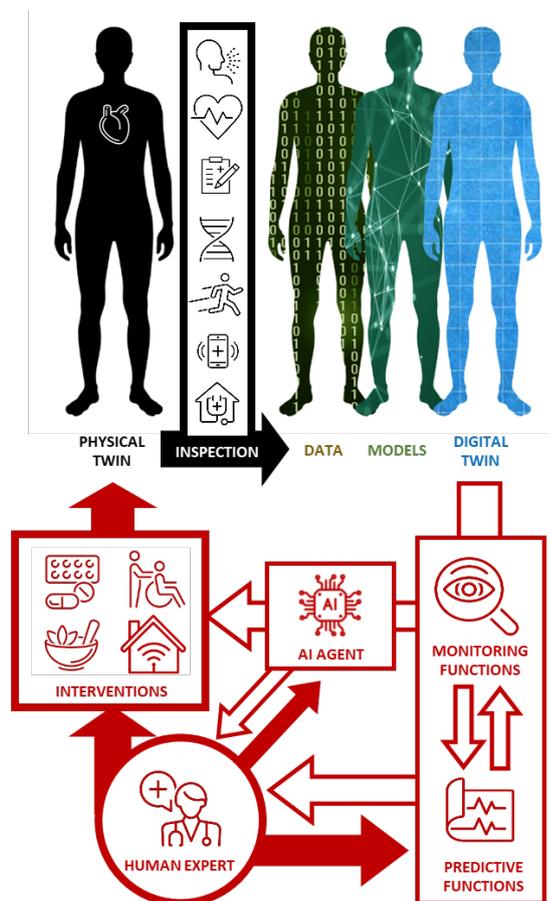


Figure 2. A representation of the potential steps in Digital Twin generation and exploitation. The latter can be performed by AI systems and/or a human expert (e.g., clinician, researcher). It is also necessary to make the interventions automatic through digital feedback or mechatronic actuation (technically, these AI systems can be part of the Digital Twin itself within a cyber-physical system). However, human experts should always check the decisions implemented by the AI.

Fig. 2 represents a typical perspective of Digital Twin applications for biomedical research and healthcare: as introduced above, digital human modeling [46] is a real challenge for the current technological constraints. In order to collect information on the patients' conditions and journey, wearable devices and IoT systems provided data should be combined with the ones derived from clinical procedures so as to approach the real-time replication of the individual. The study in [47], focused on the creation of a "perioperative Human Digital Twin", lists different types of data that can be exploited for accomplishing this task:

- clinical electronic documentation,
- results of laboratory tests (including genotyping) and bioimaging,
- psychological tests (with special attention to stress and mood),
- patient-reported outcomes,
- medication consumption,
- remote patient monitoring.
- data from wearable devices for health tracking,
- exposomic data (from pollution to diet and urban safety),
- social media (e.g., text mining through Natural Language Processing),
- technology use habits (from smartphones to refrigerator),
- GPS (e.g., time spent on the gym and on the ice-cream store),

The authors [47] also discussed a set of requirements for generating Human Digital Twin that could display just information with high relevance for clinical decision-making. These Human Digital Twins should be based on features (partially discussed in terms of ethical issues in the third section of this chapter too) like:

- seamless integration into the clinical activities described into the actual workflow (without being unobtrusive and difficult to use);
- being widely available and affordable;
- interoperability between different systems for clinicians and patients;
- large evidence basis for the validation of their output (that should work as digital biomarkers and as recommendations for treatments);
- iterative processing for continuous learning to refine models of individuals and populations during the individual treatments;
- capability to accommodate all available source-independent data;
- reliable automated solutions for dealing with missing information;
- ability to mitigate biases inherently present in clinical data;
- standards of data security and privacy.

Overall, the largest set of individual data (potentially compatible with information from novel sources) we can afford according to the current limitations in information processing should be used for facing challenges like managing a viral infection [48], monitoring and anticipating the life course of an individual [49], predicting the therapeutic outcomes for developing novel pharmacological treatments [50], improving our own methodologies in biomedical research [51] –

indeed, Digital Twins can be used by healthcare services and in scientific investigations as well. Another example can be based on the need of predicting the response to treatments during the first 24 hours of sepsis [52] through the advanced computational implementation of mathematical models and algorithms for replicating events across multiple functional stages of major systems in the human body (cardiovascular system, neurologic system, renal system, respiratory system, gastrointestinal system, blood system) and their inflammatory responses. Relevant biomarkers are visualized for enabling the medical doctors to take decisions on next interventions according to the patient's expected responses, predicted according to the Digital Twins output.

Any Digital Twin of patients and their biological systems (from a cell to the person as a whole) can be exploited in different ways. Achieving a Digital Patient [53] is a strategy explored in multiple medical domains. It can focus on the heterogeneous effects and issues of a specific disease, as in the cases discussed by Voigt et al. [54], on Multiple Sclerosis, demonstrating the multiple types of data that Digital Twins can be applied in this domain in various ways. For instance, they can work as individualized innovative disease management solutions for helping people with multiple sclerosis to cope with the quite unpredictable progression of this disease, hitting different sensory, cognitive, and motor functions. AI techniques for the analysis of disease parameters – e.g., medical procedures, clinical and preclinical outcomes, biomarkers, patient-related data, information on the individual life circumstances and plans, multi-omics – can generate a Digital Twin can be coupled with the patient's characteristics. Such a virtual replica can help the clinicians handling large and complex datasets as coherent predictive information on degenerative diseases, contributing to a personalized healthcare plan. Such an approach may lead to standardized procedures for achieving individual clinical pathways, even supporting the clinician-patient communication to facilitate a shared decision-making process.

Digital Patients can also be adopted for appropriately improve highly critical procedures like surgeries [55,56]. In such a domain, the Digital Twin of a patient can be used for helping a physician or a team of doctors during activities like planning an operation or getting practice about a procedure on a specific individual (beyond the effectiveness of any simulator for the training of medical residents). The review in [57] discussed, for instance, the potential role of Digital Twins in improving the procedures for arthroscopic surgery education through the integration of diagnostic data, bioimaging, surgical practice, and intraoperative data. This would enable surgical skills training, preoperative planning, and novel databases of surgical simulations. The predictive capabilities of Digital Twins can also be employed for anticipating the consequences of surgeries. For example, the authors of [58] considered post-hepatectomy portal hypertension as a major cause of liver failure leading to death. This defines the need of accurately predicting such a complication for each patient. Thus, they proposed and tested (on a cohort of 47

patients undergoing major hepatectomy) a mathematical model implemented as a Digital Twin-like solution predicting the portocaval gradient at the end of the liver resection. The authors demonstrated that their Digital Twin prototype can inform the physicians for modifying the currently adopted algorithms for surgical decision-making.

Considering general medical decision-making, [59] discusses another aspect of the potential applications of Digital Twins in health domains: improving the workflow efficiency in a large medical procedural suite of Electronic Health Record systems. In such contexts, many processes could become erroneous, impairing the individual capability (and increasing the frustration of the medical doctors) to manage and optimize the workflow in real-time. The authors proposed a Digital Twin of the procedural suite enabling the process of making data-driven decisions, providing gastroenterology outpatient centers with long-term improvements.

Another example of medical optimization can be based on approaching the domains of Health Technology Assessment (HTA) and medical devices usability engineering. Indeed, Digital Twins could also be advantageous for virtually representing and assessing a medical device before planning and performing its clinical trials. This strategy could work for mitigating any predictable risk before the trials themselves. In [60], the authors address and discuss this, specifically referring to the development of endoscopic medical devices for minimally invasive screening and intervention. After facing ethical and safety considerations about in vivo animal studies and clinical trials for the evaluation of these systems, the authors propose the computational digital modeling of biological tissues and processes, medical devices, and their interactions in order to provide a set of cost-effective solutions for accelerating the evaluation of endoscopic devices and minimizing most risks in these procedures.

According to their observations, the development of a Digital Twin including the human gastrointestinal tract requires the reconstruction of the complex intestinal geometry according to medical images and a multi-physics model replicating the in vivo systems and processes. Certainly, the complexity in these items represent most current criticalities in the adoption of Digital Twin in healthcare, and they can be extended to the medical device personalization.

These examples certainly play a role within the organization of a healthcare center like a hospital. The complexity of these contexts additionally increases the burden of any Digital Twin that could be proposed for anticipating and managing the potential issues in a place inhabited by patients in heterogeneous conditions at different degrees of severity and by professionals operating on these critical situations. However, the impact of Digital Twin can surely be disruptive in improving the care processes, as in the trauma management cases discussed in [61] for introducing the opportunity of use intelligent agents in healthcare. The authors proposed innovation solutions for Digital Twins, integrating frameworks and approaches for modeling and design with computational agents.

They also foresaw a roadmap of research in this domain: investigating semantic models supporting agent reasoning about Digital Twins; pondering how agent-based Digital Twins could be helpful for devising and improving the future healthcare information architecture systems and standards; defining simulations to support the agent's decision-making. This certainly includes even the information retrieval and the data mining for the Decision Support System (DSS) in medical domains [62].

Thus, Digital Twins can optimize processes at different scales (e.g., replicating cybersecurity criticalities) [63], encompassing smart environments (from the Hospital 4.0 to a Smart City) as in IoMT settings [64] (including homes enriched by sensors and systems for ambient intelligence). They can even simulate apparently narrow problems like the pathways of patients [65] or surely widespread ones like the safety of elder people [66,67]. Even the vaccination centers during the COVID-19 pandemic emergency were analyzed to be represented by Digital Twins [68]. The reference to the pandemic is not casual: the stress experienced by the healthcare systems forced the scientific-technological community to propose novel ways for optimizing the allocation of resources among frail people at risk.

This situation pushed the need of presenting solutions of sustainable and resilient healthcare based on decentralized services supported by approaches like Telemedicine and Telerehabilitation (including robotic systems), Digital Health and services of Connected Care, especially for older adults [69-72]. This situation unveiled the need of considering the complexity of these phenomena within wider frameworks like the One Digital Health to shape future technological ecosystems [73], starting with Smart Cities designed (and modeled through Digital Twins) for sustaining health and well-being through cost-effective solutions for countering public emergencies too [74].

Noteworthy, these solutions do not necessarily require advanced and expensive systems. Even if major research efforts should be made to propose effective Digital Twins for health in terms of capability to perform real-time simulations, even the currently common device like a smartphone can become a medium for exploiting their potential.

Next sub-section will discuss this point, showing how mHealth can be an exemplary domain of application of Digital Twin technologies, especially considering the patients' journey.

3.2 An Exemplary Domain: mHealth

About mHealth, it is obviously possible to consider the mobile devices (and many wearable devices) as one of classes of information sources that may update a Digital Twin, monitoring the conditions of a patient (in order to inform the latter or

a clinician) or of a wider system (e.g., home, hospital, city). For example, the study in [75] proposed a Digital Twin prototype for analyzing the requirements (low latency, high reliability, high security levels) of telecommunication in a critical application of remote surgery supported by mobile networks.

Digital Twins can also work for providing the Physical Twin with feedback aiming at intervening for a positive change. However, there are peculiarities in Digital Twin for mHealth that derive from the capability of mobile systems to be personal and portable, following “everyone everywhere”. For instance, the research in [76] aimed at exploring the perceptions of a 3D Digital Twin representing the anatomy of a person through a mobile application designed for promoting a behavior change in terms of health and weight management. Thus, this type of mHealth apps can exploit Digital Twin technologies through the advantages of mobile systems - convenience, easy access, automatic progress monitoring for delivering solutions addressing issues of societal concern like the obesity increase. Literature has already remarked how avatars based on digital replicas – as the Digital Twins can be – of individuals can engage people in thinking about themselves and their difficulties, from emotion regulation to weight management. These virtual representations, experienced through mobile devices too [77-82], can be helpful for persuading the users in changing their behaviours in several contexts of daily life (thanks to the device portability). The authors in [76] moved their investigations from such a background to remark the importance of detailed and realistic depictions of one’s body as one of the main guidelines in this type of applications of Digital Twins. Indeed, they propose to focus upcoming research on the individual differences in anthropomorphism perception [83], a suggestion that can lead to advances in personalization and adaptive features of Digital Twins supported by mHealth apps for the patients. Extensive follow-up studies with large sample size would be necessary, anyway, for clarifying the impact of these solutions, possibly disclosing the opportunity of release further applications of these approaches for mitigating the effects of chronic diseases, improving the individual self-care attitude by providing the users with visual information on their current conditions and their potential change over time. Such a scenario could mitigate health risks through a persuasive and pervasive use of these technologies.

These applications probably tend to elicit the same processes underlying the effects of game-based solutions for health [84], based, for instance, on making the person aware of the consequences of their actions (feeling competent and “in charge”) and, possibly, sharing these information with other individuals. Obviously, proposing any gamification (adopting engaging game-like features in applications that are designed for scopes not including the leisure – e.g., exercise and education) feature could be premature without an adequate series of studies. It is not strange that this is envisioned even in applications using virtual reality settings and Digital Twins for construction safety training [85].

However, they could become one of the many components of a multi-faceted technological ecosystem for health [86] where each patient can experience the feeling of being involved in the care processes by making them aware of their conditions and of their options in decision-making through portable, personal, engaging solutions [47]. Such a scenario could exploit the data collected on a person to generate multiple Digital Twins, designed in specific ways for the well-being and the scopes of the user (patient, for self-care, or physician, for diagnostics), interconnecting them where it would be appropriate and useful.

Beyond these applications targeting individual users (even if groups engaging tasks through the same mHealth app including Digital Twins of each member can be envisioned), Digital Twins can be developed [87] for assisting the strategies of decentralization in healthcare systems (a remedy to their overload), especially exploiting wider networks including mobile systems, wearables, IoMT and smart environments. This approach would lead to an improvement of the healthcare system sustainability by spreading virtual replicas of the patients and of any person at risk (and everyone is at health risk even through a healthy aging process) who can find easy and acceptable the usage of a smartphone. However, the usability and the acceptance of Digital Twins can raise further issues that are introduced in next section.

4 Human-Centric Perspectives

The panorama of Digital Twin solutions for healthcare is certainly rich of different options for helping patients, clinicians, researchers, and anyone involved in this domain for ameliorating the health conditions of individuals and groups. Obviously, improvements can be made. Aside the technical enhancements of sensors capabilities, computational power, connection reliability and speed, there are aspects that must be addressed in order to be ready for the introduction of these technologies. Handling these issues requires a “human-centric” perspective that must lead any healthcare 4.0 system to appropriately serve its users [88,89]. In this domain, such a point of view is intrinsically based on approaches promoting the engagement of patients and stakeholders (especially in terms of collaboration), the growth in awareness of one’s health, the competitive advantage of systems like hospitals in terms of care and costs. Accordingly, a methodological and paradigmatic shift towards the centrality of the person can be helpful to envision how to improve the Digital Twin systems even before their most recent technical features will be implemented (possibly predicting the problems that could be generated by them). Next sections will present two examples of human-centric topics in this discussion.

The first one will focus on a potential strategy to improve the experience of the experts interacting with a Digital Twin by adding “phygital” features to it. This focus on Digital Twin users (e.g., clinicians, researchers) is quite advantageous for

involving them in the decision-making processes, considering the complexity of handling a virtual system that can affect the real one. The proposed solution can be seen as an insight offered to “twinning designers” that could be inspired to further exploit the convergent technologies supporting the Digital Twins for easing the interaction of the experts with the virtual models of health-related systems.

The second one will be dedicated to the ethical issues raised by Digital Twins as “tentative” replicas of human beings or of systems bringing sensitive data on individuals and groups. These issues must be managed far before the introduction of novel technologies into the market and in any real use context. Such a perspective is definitely human-centric: it pays attention to problems that could be generated by the introduction of novel technologies, enabling actions and situations that could not have been expected by the developers or by any stakeholders.

4.1 Beyond Digital Twins: Phygital Twins

A recent opinion paper proposed the term of “Phygital Twins” in neuroergonomics (the discipline that, according to neuroscientific methods, investigates and improves the interactions between a person and the other elements of a system) applied to HRI design [25]. This neologism – previously used in [90] to label an IoT setup collecting data to depict an environment in precision agriculture applications – refers to the opportunity of blending physical and real dimensions in “phygital” spaces and interactions [91,92], possibly as extensions of Tactile User Interfaces (TUIs) within a general trend of virtuality-reality confluence [41] that involves healthcare too [93]. Interestingly, such a trend matches the expectations underlying the most recent ways to define the metaverse, a digital world possibly encompassing and intertwining cyber-physical systems and Digital Twins with their connection with the real world [94].

In operative terms, Fig. 3 depicts an example of Phygital Twin based on [25]. In this case, the Physical Twin is based on a system including an exoskeleton and its user. Such a system can be fully replicated by a Digital Twin that does not enable any physical interaction or by a Phygital Twin, which replicates just certain components of its real counterpart as digital objects. The other components are replicated by physical objects. Overall, the digital and physical replicas are integrated within an extended reality model. In this model, the physical objects are constituted by instances of the same product (it could be any kind of physical system, certainly not only robots) in the Physical Twin. Both digital and phygital settings are experienced by a remote expert through a headset for mixed reality. In this example, such a setup enables a live visualization of anomalies in the right shoulder muscles of the wearable robot user.

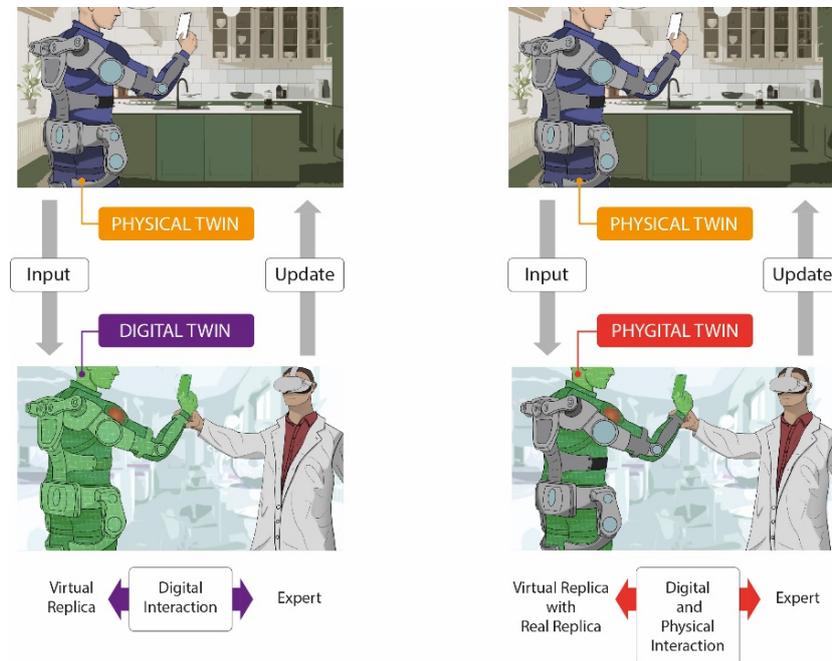


Figure 3. On the top of the image - adapted from [25] we show a human-exoskeleton system within a use context. This Physical Twin is connected to the bottom twins. Left: a Digital Twin (in green) - this is a virtual replica of the system on top. Right: a Phygital Twin - a “holographic” replica of the device user on a mannequin “wearing” a second exoskeleton into a laboratory. The smartphone held by the user is employed to collect data and to interact with the exoskeleton and with the remote expert assessing the situation for improving the device settings.

Differently from the case of the Digital Twin, the expert interacting with the Phygital Twin can influence the model and test its future states through intuitive physical interactions with haptic feedback offered by a real exoskeleton. Importantly, the case presented in Fig. 3 shows the exoskeleton user interacting with a mobile phone, enabling (beyond any data collection of their conditions) a communication with the remote expert. Through this channel, the exoskeleton user can provide or negate the informed consent to receive any update of the wearable robot software based on the Phygital Twin predictions and the expert decisions.

Overall, the physical components of the Phygital Twin would facilitate the assessment and the management of the Physical Twin, and they would replicate their counterparts with higher reliability than any digital model because they are constituted by the same items. Further computer-generated objects and settings may also be integrated in the visual scene in a virtual environment fully surrounding the user. Furthermore, another phone can help the remote expert to interact with the

Phygital Twin without a fully immersive scenario, especially for focusing on specific details on the individual conditions. About the latter, the paper in [25] focused on neuroergonomics in HRI contexts with exemplary cases akin to Phygital Twins in fields like bionic prosthetics [95,96] and rehabilitation technologies [97], envisioning the generation of quantifiable indices of healthy and pathological conditions or response to treatments: digital biomarkers [98] becoming a “phygital biomarker” thanks to the informational components based on physical interactions that can be exploited by a clinician for evaluating the individual conditions [69]. Interestingly, novel frameworks considering dual Digital Twins representing patients and clinicians within a telerehabilitation setting already provides scenarios that can take advantage of this approach [72].

However, the “twinning design” concept proposed by [25] is potentially not limited to human-centered robot design and neuroergonomic evaluation into a “metalaboratory” (a hybrid context where virtual and real items can be manipulated to influence each other) that surely has a great potential for biomedical research and healthcare. Indeed, any item that (before and after its deployment) can be physically replicated and integrated within a Phygital Twin may constitute part of the implementation of this paradigm. This may be the case of an assistive or rehabilitative device, or a home environment as a whole, especially for testing the appropriateness of introducing IoT devices [70] in terms of individual reactions (detected through data collected by means of distal and wearable sensors). Obviously, this would require a certain level of actuation in the Physical Twin, but this could become an important option for easing the activity of a remote clinician or researcher desiring to modify the surroundings of a frail person in order to evaluate their conditions or for anticipating the interventions to be adopted when certain symptoms initiate to occur [69]. Certainly, this approach can be used for evaluating medical devices too, especially (as in the example) robotic systems. It would also be interesting to predict the learning performance of health tech users and clinical trainees, but it is important to not let the enthusiasm for modeling exceed in computationally depicting and, hazardously, de-personalizing any human being. Such a situation would be detrimental in terms of human-centric design: involving people and considering holistically their setting would not be enough to counter any fall in catching the value of the person represented by a software-based model. This last point leads to the next sub-section, dedicated to ethical issues in twinning processes and their results.

4.2 Ethical Issues in Twinning for Health

The technologies supporting these paradigms surely have limitations: replicating live processes in ecologically valid contexts surely brings a the computational burden, preceded by the connectivity issues generated by the effort of approaching real-time conditions. However, Digital Twins also raise a series of questions that must be faced for introducing them in real contexts, pondering topics like technology acceptance [99]. Ethical issues are certainly among the problems that

should be considered before planning the development of any technological solution in order to make it truly human-centric, especially when we consider situations requiring quick decision-making processes as in several healthcare procedures [61] and, in general, most precision medicine scenarios that are considered by HTA [100].

Accordingly, the authors of [101] proposed an “ethical map” of the potential ethical issues that Digital Twin could generate. According to this map, there could be sources of ethical issues in data collection (hypercollection, data quality, and unorthodox use of data), data management (ownership and accessibility of data, brokerage, hacking), data analysis (biased algorithms, biased training data set), information use (disease decontextualization, epistemic injustice, overdiagnosis). These items can lead to heterogeneous issues, encompassing the distortion of the physician’s diagnosis or the distortion of the patient’s body image, and even detrimental effects on the doctor-patient relationship. Further issues can affect the privacy and the consent in data authoring, representation, storage, and use: the standardization of these aspects should aim at assuring that only authorized people can access and edit personal information on patients. Even the definitions of concepts like normality, enhancement, and extension of human beings must be pondered. These themes cross domains encompassing engineering and philosophy[102].

For instance, [103] discusses how the requests of personalized medicine of fine grained information on individuals can be supported by the exploitation of Digital Twins to assess the emerging data-driven healthcare practices, even pondering their implications for therapy, preventive care, and human augmentation. However, representing the physiological state and the habits of a person over time leads to the need of reflecting on what we consider a therapeutic intervention or an enhancement procedure: while these technologies emerge, we must carefully define the risks on these aspects, pointing at the concept of normality (difficultly depicted through quantitative parameters in most cases). Thinking about these issues is a premise to weight the societal impact of Digital Twins alongside other criticalities as in the domains of transparency and privacy in data usage.

On the other hand, [104] highlights the concrete challenges posed by Digital Twins in terms of interactions between people and their virtual counterparts before discussing how a digital item may replicate a person. The author interestingly analyzes the peculiarities of Digital Twins, remarking their dynamic quality in co-adapting with their Physical Twins. The focus on human beings, especially about their health and value, is particularly demonstrated by the attention in depicting the relationships between physical and simulated worlds as bidirectional activities: representation and control. This is especially important for clarifying how the Digital Twins can be depicted as a way to influence the people and the organizations they model through their predictive power, generating potential concerns (in particular considering the possibility of having an embodied replica that could be perceived as an extension of the original body). The author discusses how Digital

Twins do not fundamentally threaten the individual integrity, and their challenges are affordable. However, it could be critically important to consider the opportunity for a person to have control over their simulated representation. This implies the need of a dynamic consent (mimicking the dynamic quality of twinning itself), enabling a person to approve to be represented by a Digital Twin, even selecting if this is allowed for therapy or for health prediction. However, if a person does not have control over their Digital Twin (or they are not aware of it), this could become an illegitimate representation, approaching the perception of a shift towards an inappropriate surveillance. Even if this latter aspect can be countered by solutions of privacy-by-design and value-sensitive design typically discussed in contexts of IoT and ambient intelligence [70] and in the ubiquitous and pervasive scenarios of IoMT and mHealth [105], it is definitely important to consider their potential impact to define a responsible way to deal with any emergent technology enabling novel paradigms of modeling and interaction. Interestingly, the proposal in [104] to employ embodied machines for enabling the person to have a true interaction with their computational model matches the user-centered proposal of the aforementioned Phyigital Twins of the previous sub-section: this way, a solution proposed for easing an expert (e.g., clinician, researcher, designer, manager) in the fruition of a technological representation can help solving a morally sensitive issue for a patient. These are among the conditions that, according to the author, can make a Digital Twin an ethically justifiable form of human (and human health) representation. It would be wise to discuss them within the dialectics about the factors facilitating or restraining the adoption of twinning procedures [106].

As suggested above, the human-centric role of these issues is based on the opportunity to anticipate potential problems (possibly through design guidelines and standardization policies) for the human capabilities and dignity while even pondering the opportunities offered by innovations that never cease to create innovative frameworks from the confluence of different technologies [107].

5 Conclusion

The advantages of emulating and simulating complex systems are certainly obvious: it is possible to investigate a digital model representing a complex system by imitating its behavior and its inner structure. The most recent data-intensive network-based computing solutions are enabling a further revolution through the Digital Twins: real-time replicas of physical systems that can be analysed in their current and future states in order to influence them (according to the decisions of humans or intelligent agents or, synergistically, both). Digital Twins definitely represent a revolution in exploring the potential confluence of a variety of solutions for data collection and analysis, computational modeling, and interaction design for practical scopes. Surely, they can ease our way to handle complexities from the scale of tissues to the one of cities. Obviously, the promises of Digital Twins need further investigations, especially pondering their human-centric aspects.

This is especially true when we consider the applications of Digital Twins in healthcare domains – for instance: understanding the potential paths of a disease progression in individuals for adapting a therapy or for evaluating and optimizing the allocation of resources across a community during a pandemic particularly hitting the elderly population, assessing and improving the control of robotic medical devices according to the data collected from users with disabilities. Replicating organs, individuals, medical devices, or even a hospital can be successful examples of a strategy that needs novel sources of data and channel of intervention for refining its contribution to the frameworks enabling precision medicine and connected care.

In particular, mHealth offers unique opportunities for developing Digital Twins of mobile users and of the systems within they act. This approach aims at predicting and managing the system conditions through personal data and interventions that can be, respectively, gathered and provided ubiquitously, literally following the person and interacting with the surrounding devices. In particular, it discusses the personal use of an implementation of a Digital Twin as the avatar of a mobile user, specifically a patient who can find the visualization of the simulacrum as a solution to elicit attitude and proactivity for self-care.

This chapter presented introductory perspectives on this kind of scenarios as an overview of opportunities and critical aspects that must be handled to fully benefit from these novel technological solutions even before their actual development and access to the market. Easing the work of clinical experts in interacting with an intuitive Phygital Twin and facing the ethical issues intrinsically tied to the twinning process and its results are just two examples of human-centric aspects that must be pondered in this domain. Through these exemplary (critical and purposeful) perspectives, Digital Twins can also work as an interface with our well-being, the medical devices, and the healthcare services.

References

1. McGregor I The relationship between simulation and emulation. In: Proceedings of the Winter Simulation Conference, 2002. IEEE, pp 1683-1688
2. Hsu Y, Chiu J-M, Liu JS Digital twins for industry 4.0 and beyond. In: 2019 IEEE International Conference on Industrial Engineering and Engineering Management (IEEM), 2019. IEEE, pp 526-530
3. Bagaria N, Laamarti F, Badawi HF, Albraikan A, Martinez Velazquez RA, El Saddik A (2020) Health 4.0: Digital twins for health and well-being. In: Connected Health in Smart Cities. Springer, pp 143-152
4. Phanden RK, Sharma P, Dubey A (2021) A review on simulation in digital twin for aerospace, manufacturing and robotics. Materials today: proceedings 38:174-178

5. Juarez MG, Botti VJ, Giret AS (2021) Digital Twins: Review and Challenges. *Journal of Computing and Information Science in Engineering* 21 (3)
6. Ritto T, Rochinha F (2021) Digital twin, physics-based model, and machine learning applied to damage detection in structures. *Mechanical Systems and Signal Processing* 155:107614
7. Allam Z, Bibri SE, Jones DS, Chabaud D, Moreno C (2022) Unpacking the '15-Minute City' via 6G, IoT, and Digital Twins: Towards a New Narrative for Increasing Urban Efficiency, Resilience, and Sustainability. *Sensors* 22 (4):1369
8. Jiang J, Tobia M, Lawther R, Branchaud D, Bednarz T (2020) Double vision: Digital twin applications within extended reality. In: *ACM SIGGRAPH 2020 Appy Hour*. pp 1-2
9. Coorey G, Figtree GA, Fletcher DF, Redfern J (2021) The health digital twin: advancing precision cardiovascular medicine. *Nature Reviews Cardiology* 18 (12):803-804
10. Li X, Liu H, Wang W, Zheng Y, Lv H, Lv Z (2022) Big data analysis of the internet of things in the digital twins of smart city based on deep learning. *Future Generation Computer Systems* 128:167-177
11. Ahmadi-Assalemi G, Al-Khateeb H, Maple C, Epiphaniou G, Alhaboby ZA, Alkaabi S, Alhaboby D (2020) Digital twins for precision healthcare. In: *Cyber defence in the age of AI, Smart societies and augmented humanity*. Springer, pp 133-158
12. Evjemo LD, Gjerstad T, Grøtli EI, Sziebig G (2020) Trends in smart manufacturing: Role of humans and industrial robots in smart factories. *Current Robotics Reports* 1 (2):35-41
13. Yang D, Karimi HR, Kaynak O, Yin S (2021) Developments of digital twin technologies in industrial, smart city and healthcare sectors: a survey. *Complex Engineering Systems* 1 (1):3
14. Guo J, Lv Z (2022) Application of Digital Twins in multiple fields. *Multimedia Tools and Applications*:1-27
15. Qiu C, Zhou S, Liu Z, Gao Q, Tan J (2019) Digital assembly technology based on augmented reality and digital twins: a review. *Virtual Reality & Intelligent Hardware* 1 (6):597-610
16. Jeršov S, Tepljakov A Digital twins in extended reality for control system applications. In: *2020 43rd International Conference on Telecommunications and Signal Processing (TSP)*, 2020. IEEE, pp 274-279
17. Madhavan S, Beckman RA, McCoy MD, Pishvaian MJ, Brody JR, Macklin P (2021) Envisioning the future of precision oncology trials. *Nature Cancer* 2 (1):9-11
18. Grieves M, Vickers J (2017) Digital twin: Mitigating unpredictable, undesirable emergent behavior in complex systems. In: *Transdisciplinary perspectives on complex systems*. Springer, pp 85-113
19. Shafto M, Conroy M, Doyle R, Glaessgen E, Kemp C, LeMoigne J, Wang L (2012) Modeling, simulation, information technology & processing roadmap. *National Aeronautics and Space Administration* 32 (2012):1-38

20. Jones D, Snider C, Nassechi A, Yon J, Hicks B (2020) Characterising the Digital Twin: A systematic literature review. *CIRP Journal of Manufacturing Science and Technology* 29:36-52
21. Singh M, Fuenmayor E, Hinchy EP, Qiao Y, Murray N, Devine D (2021) Digital twin: origin to future. *Applied System Innovation* 4 (2):36
22. Kuehner KJ, Scheer R, Strassburger S (2021) Digital Twin: Finding Common Ground—A Meta-Review. *Procedia CIRP* 104:1227-1232
23. Rossmann A, Hertweck D Digital Twins: A Meta-Review on Their Conceptualization, Application, and Reference Architecture.
24. Fuller A, Fan Z, Day C, Barlow C (2020) Digital twin: Enabling technologies, challenges and open research. *IEEE access* 8:108952-108971
25. Barresi G, Pacchierotti C, Laffranchi M, De Michieli L (2022) Beyond Digital Twins: Phyigital Twins for Neuroergonomics in Human-Robot Interaction. *Frontiers in Neurobotics*:138
26. 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
27. Semeraro C, Lezoche M, Panetto H, Dassisti M (2021) Digital twin paradigm: A systematic literature review. *Computers in Industry* 130:103469
28. Van der Valk H, Haße H, Möller F, Arbter M, Henning J-L, Otto B A Taxonomy of Digital Twins. In: *AMCIS, 2020*.
29. Gichane MM, Byiringiro JB, Chesang AK, Nyaga PM, Langat RK, Smajic H, Kiiru CW (2020) Digital triplet approach for real-time monitoring and control of an elevator security system. *Designs* 4 (2):9
30. Umeda Y, Ota J, Kojima F, Saito M, Matsuzawa H, Sukekawa T, Takeuchi A, Makida K, Shirafuji S (2019) Development of an education program for digital manufacturing system engineers based on ‘Digital Triplet’ concept. *Procedia manufacturing* 31:363-369
31. Khan LU, Saad W, Niyato D, Han Z, Hong CS (2022) Digital-Twin-Enabled 6G: Vision, architectural trends, and future directions. *IEEE Communications Magazine* 60 (1):74-80
32. Liu Y, Ong S, Nee A (2022) State-of-the-art survey on digital twin implementations. *Advances in Manufacturing*:1-23
33. Barricelli BR, Casiraghi E, Fogli D (2019) A survey on digital twin: Definitions, characteristics, applications, and design implications. *IEEE access* 7:167653-167671
34. Groshev M, Guimarães C, Martín-Pérez J, de la Oliva A (2021) Toward intelligent cyber-physical systems: Digital twin meets artificial intelligence. *IEEE Communications Magazine* 59 (8):14-20
35. Wang T, Li J, Deng Y, Wang C, Snoussi H, Tao F (2021) Digital twin for human-machine interaction with convolutional neural network. *International Journal of Computer Integrated Manufacturing* 34 (7-8):888-897
36. Czwick C, Anderl R (2020) Cyber-physical twins-definition, conception and benefit. *Procedia CIRP* 90:584-588

37. Haag S, Anderl R (2018) Digital twin–Proof of concept. *Manufacturing letters* 15:64-66
38. Burghardt A, Szybicki D, Gierlak P, Kurc K, Pietruś P, Cygan R (2020) Programming of industrial robots using virtual reality and digital twins. *Applied Sciences* 10 (2):486
39. Pairet È, Ardón P, Liu X, Lopes J, Hastie H, Lohan KS A digital twin for human-robot interaction. In: 2019 14th ACM/IEEE International Conference on Human-Robot Interaction (HRI), 2019. IEEE, pp 372-372
40. Ravichandar H, Polydoros AS, Chernova S, Billard A (2020) Recent advances in robot learning from demonstration. *Annual Review of Control, Robotics, and Autonomous Systems* 3:297-330
41. Tao F, Zhang M (2017) Digital twin shop-floor: a new shop-floor paradigm towards smart manufacturing. *Ieee Access* 5:20418-20427
42. Malik AA, Bilberg A (2018) Digital twins of human robot collaboration in a production setting. *Procedia manufacturing* 17:278-285
43. Fagherazzi G (2020) Deep digital phenotyping and digital twins for precision health: time to dig deeper. *Journal of Medical Internet Research* 22 (3):e16770
44. Booyse W, Wilke DN, Heyns S (2020) Deep digital twins for detection, diagnostics and prognostics. *Mechanical Systems and Signal Processing* 140:106612
45. Elkefi S, Asan O (2022) Digital Twins for Managing Health Care Systems: Rapid Literature Review. *Journal of Medical Internet Research* 24 (8):e37641
46. Paul G, Abele ND, Kluth K (2021) A review and qualitative meta-analysis of digital human modeling and cyber-physical-systems in Ergonomics 4.0. *IIEE Transactions on Occupational Ergonomics and Human Factors*:1-13
47. Lonsdale H, Gray GM, Ahumada LM, Yates HM, Varughese A, Rehman MA (2022) The Perioperative Human Digital Twin. *Anesthesia & Analgesia* 134 (4):885-892
48. Laubenbacher R, Sluka JP, Glazier JA (2021) Using digital twins in viral infection. *Science* 371 (6534):1105-1106
49. Milne-Ives M, Fraser LK, Khan A, Walker D, van Velthoven MH, May J, Wolfe I, Harding T, Meinert E (2022) Life Course Digital Twins–Intelligent Monitoring for Early and Continuous Intervention and Prevention (LifeTIME): Proposal for a Retrospective Cohort Study. *JMIR Research Protocols* 11 (5):e35738
50. Subramanian K (2020) Digital twin for drug discovery and development—The virtual liver. *Journal of the Indian Institute of Science* 100 (4):653-662
51. Schwartz SM, Wildenhaus K, Bucher A, Byrd B (2020) Digital twins and the emerging science of self: Implications for digital health experience design and “small” data. *Frontiers in Computer Science* 2:31
52. Lal A, Li G, Cubro E, Chalmers S, Li H, Herasevich V, Dong Y, Pickering BW, Kilickaya O, Gajic O (2020) Development and verification of a digital twin patient model to predict specific treatment response during the first 24 hours of sepsis. *Critical care explorations* 2 (11)

53. Erol T, Mendi AF, Doğan D The digital twin revolution in healthcare. In: 2020 4th International Symposium on Multidisciplinary Studies and Innovative Technologies (ISMSIT), 2020. IEEE, pp 1-7
54. Voigt I, Inojosa H, Dillenseger A, Haase R, Akgün K, Ziemssen T (2021) Digital twins for multiple sclerosis. *Frontiers in immunology* 12:1556
55. Ahmed H, Devoto L (2021) The potential of a digital twin in surgery. *Surgical Innovation* 28 (4):509-510
56. Tai Y, Zhang L, Li Q, Zhu C, Chang V, Rodrigues JJ, Guizani M (2022) Digital Twin-enabled IoMT System for Surgical Simulation using rAC-GAN. *IEEE Internet of Things Journal*
57. Bjelland Ø, Rasheed B, Schaathun HG, Pedersen MD, Steinert M, Hellevik AI, Bye RT (2022) Towards a Digital Twin for Arthroscopic Knee Surgery: A Systematic Review. *IEEE Access*
58. Golse N, Joly F, Combari P, Lewin M, Nicolas Q, Audebert C, Samuel D, Allard M-A, Cunha AS, Castaing D (2021) Predicting the risk of post-hepatectomy portal hypertension using a digital twin: A clinical proof of concept. *Journal of Hepatology* 74 (3):661-669
59. Garbey M, Joerger G, Furr S (2022) Application of Digital Twin and Heuristic Computer Reasoning to Workflow Management: Gastroenterology Outpatient Centers Study. *medRxiv*
60. Kalozoumis PG, Marino M, Carniel EL, Iakovidis DK (2022) Towards the Development of a Digital Twin for Endoscopic Medical Device Testing. In: *Digital Twins for Digital Transformation: Innovation in Industry*. Springer, pp 113-145
61. Croatti A, Gabellini M, Montagna S, Ricci A (2020) On the integration of agents and digital twins in healthcare. *Journal of Medical Systems* 44 (9):1-8
62. Patrone C, Galli G, Revetria R (2019) A state of the art of digital twin and simulation supported by data mining in the healthcare sector. *Advancing Technology Industrialization Through Intelligent Software Methodologies, Tools and Techniques*:605-615
63. Faleiro R, Pan L, Pokhrel SR, Doss R Digital Twin for Cybersecurity: Towards Enhancing Cyber Resilience. In: *International Conference on Broadband Communications, Networks and Systems, 2021*. Springer, pp 57-76
64. Cicirelli F, Guerrieri A, Mastroianni C, Vinci A (2021) Emerging Internet of Things Solutions and Technologies. *Electronics* 2021, 10, 1928. s Note: MDPI stays neutral with regard to jurisdictional claims in published ...
65. Karakra A, Fontanili F, Lamine E, Lamothe J HospiT'Win: a predictive simulation-based digital twin for patients pathways in hospital. In: 2019 IEEE EMBS international conference on biomedical & health informatics (BHI), 2019. IEEE, pp 1-4
66. Zhao Z, Shen L, Yang C, Wu W, Zhang M, Huang GQ (2021) IoT and digital twin enabled smart tracking for safety management. *Computers & Operations Research* 128:105183

67. Liu Y, Zhang L, Yang Y, Zhou L, Ren L, Wang F, Liu R, Pang Z, Deen MJ (2019) A novel cloud-based framework for the elderly healthcare services using digital twin. *IEEE access* 7:49088-49101
68. Pilati F, Tronconi R, Nollo G, Heragu SS, Zerzer F (2021) Digital twin of COVID-19 mass vaccination centers. *Sustainability* 13 (13):7396
69. Barresi G, Zenzeri J, Tessadori J, Laffranchi M, Semprini M, Michieli LD (2022) Neuro-Gerontechnologies: Applications and Opportunities. In: *Internet of Things for Human-Centered Design*. Springer, pp 123-153
70. Petrushin A, Freddolini M, Barresi G, Bustreo M, Laffranchi M, Bue AD, Michieli LD (2022) IoT-Powered Monitoring Systems for Geriatric Healthcare: Overview. *Internet of Things for Human-Centered Design*:99-122
71. Ackerman MJ, Filart R, Burgess LP, Lee I, Poropatich RK (2010) Developing next-generation telehealth tools and technologies: patients, systems, and data perspectives. *Telemedicine and e-Health* 16 (1):93-95
72. Tröbinger M, Costinescu A, Xing H, Elsner J, Hu T, Naceri A, Figueredo L, Jensen E, Burschka D, Haddadin S A Dual Doctor-Patient Twin Paradigm for Transparent Remote Examination, Diagnosis, and Rehabilitation. In: *2021 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS), 2021*. IEEE, pp 2933-2940
73. Benis A, Tamburis O, Chronaki C, Moen A (2021) One digital health: a unified framework for future health ecosystems. *Journal of Medical Internet Research* 23 (2):e22189
74. Rodríguez-Aguilar R, Marmolejo-Saucedo J-A (2020) Conceptual framework of Digital Health Public Emergency System: digital twins and multiparadigm simulation. *EAI endorsed transactions on pervasive health and technology* 6 (21):e3-e3
75. Laaki H, Miche Y, Tammi K (2019) Prototyping a digital twin for real time remote control over mobile networks: Application of remote surgery. *Ieee Access* 7:20325-20336
76. Taylor L, Dibb B (2022) Exploring users and non-users views of the Digital Twin on a mHealth app: a Thematic, qualitative approach. *Cogent Psychology* 9 (1):2079802
77. Behm-Morawitz E (2013) Mirrored selves: The influence of self-presence in a virtual world on health, appearance, and well-being. *Computers in human Behavior* 29 (1):119-128
78. Fox J, Bailenson JN, Tricase L (2013) The embodiment of sexualized virtual selves: The Proteus effect and experiences of self-objectification via avatars. *Computers in Human Behavior* 29 (3):930-938
79. Wrzesien M, Rodríguez A, Rey B, Alcañiz M, Baños RM, Vara MD (2015) How the physical similarity of avatars can influence the learning of emotion regulation strategies in teenagers. *Computers in Human Behavior* 43:101-111
80. Horne M, Hill A, Murells T, Ugail H, Chinnadorai R, Hardy M (2020) Using avatars in weight management settings: A systematic review. *Internet interventions* 19:100295

81. Kim Y, Sundar SS (2012) Visualizing ideal self vs. actual self through avatars: Impact on preventive health outcomes. *Computers in Human Behavior* 28 (4):1356-1364
82. Matsangidou M, Otkhmezuri B, Ang CS, Avraamides M, Riva G, Gaggioli A, Iosif D, Karekla M (2022) “Now i can see me” designing a multi-user virtual reality remote psychotherapy for body weight and shape concerns. *Human-Computer Interaction* 37 (4):314-340
83. Blut M, Wang C, Wunderlich NV, Brock C (2021) Understanding anthropomorphism in service provision: a meta-analysis of physical robots, chatbots, and other AI. *Journal of the Academy of Marketing Science* 49 (4):632-658
84. Godfrey SB, Barresi G (2022) Video Games for Positive Aging: Playfully Engaging Older Adults. In: *Internet of Things for Human-Centered Design*. Springer, pp 375-404
85. Harichandran A, Johansen KW, Jacobsen EL, Teizer J A conceptual framework for construction safety training using dynamic virtual reality games and digital twins. In: *ISARC. Proceedings of the International Symposium on Automation and Robotics in Construction, 2021*. IAARC Publications, pp 621-628
86. El Saddik A, Badawi H, Velazquez RAM, Laamarti F, Diaz RG, Bagaria N, Arteaga-Falconi JS (2019) Dtwins: a digital twins ecosystem for health and well-being. *IEEE COMSOC MMTTC Commun Front* 14:39-43
87. Choukou M-A (2021) Sustainability of mHealth solutions for healthcare system strengthening. In: *Digital Health*. Elsevier, pp 171-189
88. Corti L, Afferni P, Bertolaso M (2020) Healthcare 4.0 and human-centric approach. *MEDIC*,
89. Afferni P, Merone M, Soda P Hospital 4.0 and its innovation in methodologies and technologies. In: *2018 IEEE 31st International Symposium on Computer-Based Medical Systems (CBMS), 2018*. IEEE, pp 333-338
90. Sarangi S, Choudhury SB, Jain P, Bhatt PV, Ramanath S, Sharma R, Srinivasu P Development and deployment of a scalable IoT Framework for digital farming applications. In: *2018 IEEE Global Humanitarian Technology Conference (GHTC), 2018*. IEEE, pp 1-2
91. Gaggioli A (2017) Phygital spaces: When atoms meet bits. *Cyberpsychology, Behavior, and Social Networking* 20 (12):774-774
92. Soloviov E, Danilov A (2020) The beginning of phygital world. *South Asian J Eng Technol* 10
93. Gregory D (2022) *Healthcare Goes Digital: Designing for the Convergence of the Digital and Physical Environment—Implications for Design Professionals*. SAGE Publications Sage CA: Los Angeles, CA,
94. Yoon K, Kim S-K, Jeong SP, Choi J-H Interfacing Cyber and Physical Worlds: Introduction to IEEE 2888 Standards. In: *2021 IEEE International Conference on Intelligent Reality (ICIR), 2021*. IEEE, pp 49-50
95. Frossard L, Lloyd D (2021) The future of bionic limbs. *Research Features* 134:74-77

96. Chen D, Ottikkutti S, Tahmasebi KN A Mechatronics-twin Framework based on Stewart Platform for Effective Exploration of Operational Behaviors of Prosthetic Sockets with Amputees. In: BIODEVICES-16th International Conference on Biomedical Electronics and Devices;, 2022.
97. Pizzolato C, Saxby DJ, Palipana D, Diamond LE, Barrett RS, Teng YD, Lloyd DG (2019) Neuromusculoskeletal modeling-based prostheses for recovery after spinal cord injury. *Frontiers in Neurorobotics*:97
98. Wright JM, Regele OB, Kourtis LC, Pszenny SM, Sirkar R, Kovalchick C, Jones GB (2017) Evolution of the digital biomarker ecosystem. *Digital Medicine* 3 (4):154
99. Kwok PK, Yan M, Qu T, Lau HY (2021) User acceptance of virtual reality technology for practicing digital twin-based crisis management. *International Journal of Computer Integrated Manufacturing* 34 (7-8):874-887
100. Leo CG, Tumolo MR, Sabina S, Colella R, Recchia V, Ponzini G, Fotiadis DI, Bodini A, Mincarone P (2022) Health Technology Assessment for In Silico Medicine: Social, Ethical and Legal Aspects. *International Journal of Environmental Research and Public Health* 19 (3):1510
101. Huang P-h, Kim K-h, Schermer M (2022) Ethical Issues of Digital Twins for Personalized Health Care Service: Preliminary Mapping Study. *Journal of Medical Internet Research* 24 (1):e33081
102. Nyholm S (2021) Should a medical digital twin be viewed as an extension of the patient's body? *Journal of Medical Ethics* 47 (6):401-402
103. Bruynseels K, Santoni de Sio F, Van den Hoven J (2018) Digital twins in health care: ethical implications of an emerging engineering paradigm. *Frontiers in genetics*:31
104. Braun M (2021) Represent me: please! towards an ethics of digital twins in medicine. *Journal of Medical Ethics* 47 (6):394-400
105. Nurgalieva L, O'Callaghan D, Doherty G (2020) Security and privacy of mHealth applications: a scoping review. *IEEE Access* 8:104247-104268
106. Perno M, Hvam L, Haug A Enablers and barriers to the implementation of digital twins in the process industry: a systematic literature review. In: 2020 IEEE International Conference on Industrial Engineering and Engineering Management (IEEM), 2020. IEEE, pp 959-964
107. Yi C, Park S, Yang C, Jiang F, Ding Z, Zhu J, Liu J (2022) Muscular Human Cybertwin for Internet of Everything: A Pilot Study. *IEEE Transactions on Industrial Informatics*