Digital Twins for Precision Healthcare

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Abstract Precision healthcare is an emerging concept that will see technology-driven digital transformation of the health service. It enables customised patient outcomes via the development of novel, targeted medical approaches with a focus on intelligent, data-centric smart healthcare models. Currently, precision healthcare is seen as a challenging model to apply due to the complexity of the healthcare ecosystem, which is a multi-level and multifaceted environment with high real-time interactions among disciplines, practitioners, patients and discrete computer systems. Digital Twins (DT) pairs individual physical artefacts with digital models reflecting their status in real-time. Creating a live-model for healthcare services introduces new opportunities for patient care including better risk assessment and evaluation without disturbing daily activities. In this article, to address design and management in this complexity, we examine recent work in Digital Twins (DT) to investigate the goals of precision healthcare at a patient and healthcare system levels. We further discuss the role of DT to achieve precision healthcare, proposed frameworks, the value of active participation and continuous monitoring, and the cyber-security challenges and ethical implications for this emerging paradigm.

Keywords Digital healthcare · Smart healthcare · Real-time model · Cyber-physical systems · Ethics

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1 Introduction

Traditionally, the healthcare system was reactive by design. It supported patients after they became symptomatic with the disease rather than providing preventative care. This has changed over time, with the ambitious definition of health as the state of complete wellbeing including the physical, mental, social aspects on top of the biomedical one [1]. The evolving concept of healthcare deviated from focusing solely on the illness towards primary healthcare and health promotion [2]. Healthcare became a multi-level multifaceted complex.

In addition to the change in defining what is 'health', the complexity in healthcare resulted from the interaction of different factors such as the specialities in medicine, communication channels, the health system, and the context in which all of these operate. This complexity has undermined the adoption of digitally-enabled innovations in healthcare and often led to resistance in adaptation or failure in application [3].

The emergence of evidence-based medicine helped to 'regulate' the clinical decision process by healthcare professionals to achieve optimal treatment. In principle, this requires regular development and updates to clinical guidelines based on research findings. However, the guidelines could not replace the human factor in terms of the physicians' experience, and the patients' input [4]. Additionally, patients' needs are often complex and require a personalised management plan, think about chronic conditions and co-morbidities.

Recent years have witnessed a surge in digital health technologies but their adoption into clinical practice is comparatively slow. While there is a profound shift in the way individuals participate in health matters, the transformative benefits of the technological innovations remain to be realised. Therefore, better understanding is needed on how new healthcare technologies meet the needs between patients and healthcare practitioners and how this leverages the quality of care [5, 6].

The concept of Digital Twins (DT) has emerged to enable modelling and the fusion of individual physical artefacts with digital models reflecting their status in real-time. Healthcare, one of the fastest-growing sectors, due to its system complexity has a need to model its services and resources to improve the quality of care, services and patients' outcomes [7].

In this article, the challenges and the role of digital technologies in healthcare are discussed alongside the concept of DT technology in precision healthcare. We discuss the key transformational technologies and examine recent work in proposed DT frameworks. We further discuss the role of DT to improve the delivery of precision health. We cover the cyber-security challenges afterwards. The last part of the article deals with the ethical implications for this emerging paradigm.

2 Defining Precision Healthcare and Digital Twins

2.1 The Cost of Healthcare and Its Challenges

The healthcare lifecycle, a continuum originating at birth and ending at death, is a highly complex ecosystem converged of multiple disciplines which makes it incredibly difficult to view healthcare as a single domain. Globally, there are several approaches to healthcare, some are driven by the private sector (e.g. Switzerland, USA), others include the UK's National Health Service, the social insurance-based system of France, Netherlands and Germany and there is also the Canadian provincial government health insurance.

In the USA, it is widely acknowledged that healthcare costs, at almost 18% GDP in 2011 and forecasted to rise to 20% by 2020, in their current form are unsustainable. Challenging areas include preventative care, increased dependency for the chronically ill for whom coordination is deemed essential for health and function, and excessive use of medication [8]. Medical errors are the third leading cause of death [9], therefore, strategies are required to design safer systems to mitigate the frequency, visibility and consequence of these errors. Canada's health-care expenditure represents 11.3% of its GDP. The data reported by the Canadian Institute for Health Information shows that in 2016, 16.5% of the population was in the age group of 65 and older with the highest spending of 44.8% on the health expenditure [10]. Within the EU member states, Germany has the highest healthcare expenditure equivalent to 11.3% GDP, but this varies across member states based on a number of factors ranging from disease burden, system priorities and costs. A significant portion of the health expenditure is spent on curative and rehabilitative care while other major categories are health-related long-term care followed by prevention and public health [11]. In the UK, the healthcare expenditure is at 9.6% GDP according to the latest available information from the Office for National Statistics (ONS) with 96% of the government spending related to curative or rehabilitative, health-related long-term and preventative care [12].

Latest data published by the United Nations Department of Economic and Social Affairs show that the global population is ageing with the number of older people set to double to reach 2.1 billion by 2050, overtaking the adolescents and youths. In addition, of the 67 countries surveyed, data indicates that more older people live independently compared to 1990 [13]. Specifically, in the UK by 2040, it is estimated that one in seven people will be aged over 75 [14]. With greater longevity comes increased demand on the healthcare system and increase in complexity of care due to long-term and chronic disease. It is estimated that nearly 50% of all medical resources globally will be used by the elderly [13] with the health threats of those 75 years of age and over attributed to chronic illnesses, respiratory disease, Alzheimer's disease including other forms of dementia, diabetes and heart disease [11]. In 2015 across the European Union 1.2 million people across EU died prematurely that could have been avoided through more effective healthcare [11], with 86% of all deaths in Europe attributed to chronic diseases, and 80%

of those affecting elderly over the age of 65 [14]. Duration, treatability, added complications, prevalence and weakened immune system are some of the facets of chronic diseases, which if combined with independent living within the community create complex medical needs across multiple healthcare disciplines. The World Health Organisation reported that chronic disease threat is increasing, it needs to be better understood and acted upon. Comprehensive and integrated government-led action incorporating existing scientific knowledge is required to overcome this threat [15]. In the UK, the government recognises the importance of technology and innovation in healthcare to transform patients' care with an ambitious vision of Healthtech [16].

2.2 The Role of Digital Technologies in Healthcare

The relentless proliferation of innovations in disruptive digital technologies such as 5G, Edge Computing, Human Augmentation, Artificial Intelligence, Digital Twin combined with big data and substantial computational power will have a significant impact on society over the next decade and offer opportunities to create new digital ecosystems [17, 18]. The arrival of IPv6 and 5G networks could mean that over 50 billion Internet of Things (IoT) devices will be connected by 2020 [19, 20] many of which are medical devices and on-body sensors. IoT enabled Medical Cyber-physical Systems (mCPS), pave the way for the next generation of digital transformation in healthcare. Instead of relying on infrequent visits to hospitals, patients' health monitoring could be used in real-time to empower individuals, facilitate early detection, or manage plans for chronic conditions. Wearable health sensors anticipate a $650 million global market share by 2020 which should save $200 billion in healthcare cost over the next 25 years [21]. Furthermore, assistive technologies, life-critical networked medical devices [22] and an increase in real-time data collection create a unique opportunity to enable healthcare professionals to deliver more convenient and accurate healthcare service including remote operations. Smart IoT services will continue to revolutionise how healthcare is delivered and how we manage our health [5, 7, 14, 23, 24]. Technology will help managing large datasets, a key driver for research to improve the outcomes for disease prevention and early detection. The widespread and consistent adoption of disruptive technologies into healthcare fused with other smart sectors such as smart-homes and smart-mobility creates unprecedented opportunities to lower national healthcare spending and improve citizens wellbeing.

2.3 Towards Precision Healthcare

The term "digital health" includes a number of medical technologies, disruptive innovations and communication networks converged inseparably in providing healthcare services. Digital health has not been clearly defined in academic literature

[25] despite several attempts to provide a definition for it [26–28]. The World Health Organisation (WHO) defines digital health as "the use of digital, mobile and wireless technologies to support the achievement of health objectives", the term is used interchangeably in literature with mHealth, eHealth [29], virtual care, telehealth or telemedicine [5]. Despite advances in medical research and improved treatments, the increasing healthcare costs, rising life expectancy and shortage of health workers refocuses the efforts towards disease prevention. The estimated global shortage of health workers will be 12.9 million by 2035 [30]. Preventative medicine is an established field [31], aspects of the vision originate from the Human Genome Project which has enabled deeper understanding of medicine, the underlying disease mechanisms, environment-biology interactions and exploration of complex diseases including diabetes, heart disease, cancer, rare diseases, neurological or developmental disorders leading to personalised diagnosis and treatment [21, 32, 33]. Precision medicine is referred to by other terms including system medicine, P4 or computational system biomedicine. These terms all describe the idea of delivering targeted and the right treatment to the patient when it is required [6, 32–34] (Fig. 1).

2.4 A Digital Twin for Precision Healthcare

The concept of precision healthcare draws upon the experiences of other smart sectors. For example in engineering, aircraft engine's health is monitored in real-time by a quantum of sensors, actuators and controllers to prevent failures and

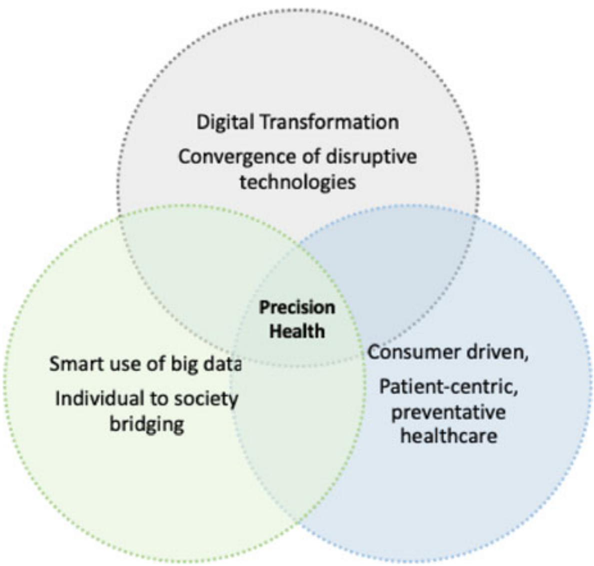

Fig. 1 Physical-Data-Cyber Converged domains driving precision health

repairs are forecasted using "Digital Twins" (DT) [35]. In the manufacturing sector, Industry 4.0 converges the physical and cyber domains through interconnectivity of Cyber-Physical Systems (CPS) to provide a virtual representation of the manufacturing lifecycle [36]. Additionally, gathering information to pinpoint anomaly or deviation from the norm using Artificial Intelligence is a mature concept used in the field of cybersecurity and implemented within anomaly-based intrusion detection systems. Digital Twining, a converged paradigm of cyber-physical-data domains, reflects on the physical artefacts within a virtual, computer-based representation of itself with data passed to it in real-time. The National Aeronautics and Space Administration (NASA) suggests "a Digital Twin is an integrated multi-physics, multiscale, probabilistic simulation of an as-built vehicle or system that uses the best available physical models, sensor updates, fleet history, etc., to mirror the life of its corresponding flying twin" [37]. In engineering, such dynamic computer models are instrumental in predictive analysis, like when to carry out maintenance or when modelling real-world engineering artefacts. In healthcare, the concept of the DT, a "virtual patient", is the same as in engineering. Adopting and adapting this novel engineering practice will elevate healthcare to a different level in disease prevention, early detection of disease, enhancement of patient care, wellbeing and lower the cost of national healthcare. In principle these concepts can be analysed and parallels found in analogy with practice applied in engineering and cyber security of "normal behaviour", "anomalous behaviour", "predictive maintenance", "automation" and "optimisation" [21, 38] (Fig. 2).

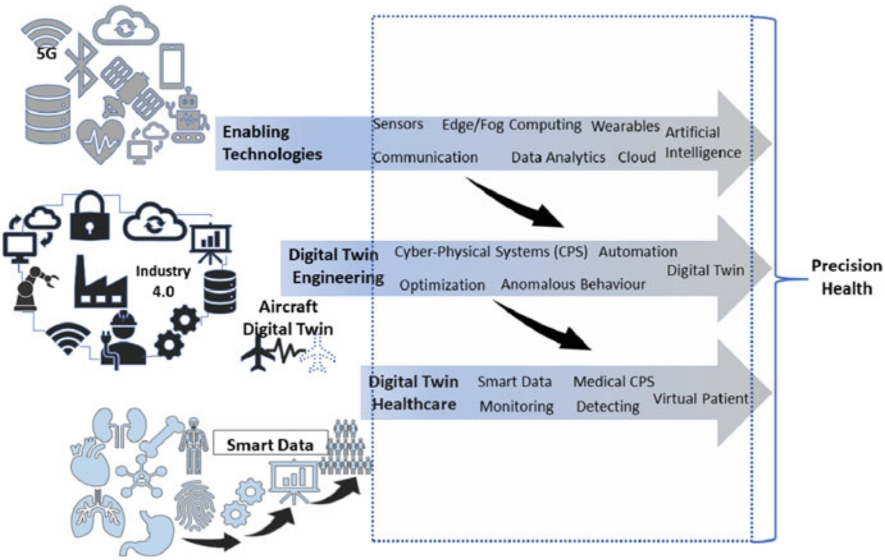

Fig. 2 The role of smart sectors and enabling technologies in delivering precision health

3 Key Enabling Technologies

3.1 *Gartner's Hype Cycle*

Five key trends and a number of dominating technologies emerged in the 2018 Gartner's Hype Cycle all of which are expected to be significant market disruptors. Although some of these are on-the-rise such as 5G, others including AI reached a peak with wider adoption expected within 2–5 years. The period of maturity has been estimated as 5–10 years for Smart Robots, Smart Workspaces, Edge Computing, Digital Twins, Biochips and IoT Platforms [18, 39]. However, frameworks will be required to create the foundation to apply these within the healthcare sector.

3.2 *Transformational Technologies and Associated Applications*

The healthcare industry is undergoing a rapid digital transformation but one of the key challenges of solving the highly complex healthcare ecosystem remains the real-time interaction and convergence of the cyber, physical and natural domains. An effective way to model this challenge is through the concept of DT. Within the current trend of digitalisation, automation, application of AI and big data, Industry 4.0 has paved the way for a systematic integration of IoT and CPS converging physical objects and digital technology to develop and maintain products' lifecycle from design to implementations using the concept of DT [36, 40, 41]. The concept of product lifecycle from marketing models' perspective, dates back to 1967, to the development of a product lifecycle for ethical drugs, which was greatly facilitated by the availability of the relevant data records, whilst the stages of the process were inspired by the biological lifecycle of introduction, growth, maturity and decline [42]. At present, despite utilising modelling, the different data streams still remain isolated and fragmented, therefore meaningless to the smart manufacturing industry. The aim of the current research is to shift the paradigm from focusing on the physical products to their virtual models to solve the problem of fusing the various big datasets across the different stages of the product lifecycle [41]. The exploitation of recent and emerging technologies integrates the physical objects, the virtual models and the data in real-time to create a twin representation of the physical product in a digital space. For example, DT has been applied in Industry 4.0 as virtual factories for as part of the asset management lifecycle [43], production system or IoT lifecycle [44–47]. Likewise, in the aviation industry to build high-fidelity flight models [35], to simulate aerothermal model predictions [48], to detect and monitor aircraft structure damage [49], predictive maintenance and failures.

Findings from the emerging literature, based on their description of the digital health ecosystem, agree on a common ground that the digital healthcare ecosystem is a subset of larger digital ecosystems [25, 50, 51] and a core component of smart cities [52, 53] forming a complex growing network of fragile [54] Cyber-Physical-Natural (CPN) systems centred around people. Digital ecosystems create dynamic digital communities of shared infrastructures, resources and knowledge that with associated applications can define and deliver a set of healthcare services and interactions. Despite the volumes of data that healthcare applications produce and depend on, the datasets remain isolated, significant data artefacts duplicated, with number of providers maintaining multiple Patient Health Records with inefficient sharing practices, lack of motivation to collaborate hindering early detection of diseases or management of chronic illnesses with continued drain on the healthcare resources, thus the quantum of healthcare data is meaningless and does not realise the aims and benefits of precision healthcare [50]. Data collected from IoT connected CPS creates an unprecedented wealth of information but to achieve the true potential of the data, research was that cross-smart sector transferable solutions should emerge from individual smart sectors [55]. For example, combining data for beds planning, with staff rotas and patient flow aided by AI could help manage the inconsistency between demand and capacity in hospitals [7] whilst extending the model to add data from GPs to provide early detection of an epidemic or integrating major incidents data from smart transport could help manage emergency care more proactively and efficiently [56]. Additionally, combining data from Medical Cyber-Physical Systems (mCPS), wearable technology, medical records and external behaviour captured using tracking across smart spaces [14, 24] could revolutionise care of the elderly in the community or those with chronic illnesses.

However, we argue that it is the twin representation of the physical object in digital space aspect of Industry 4.0 and the aviation smart sectors that are of value to precision healthcare. Although the concept of DT is not new and emerged from other smart sectors, its application in healthcare is new and extremely ambitious. Healthcare by its very nature is patient-centric but relies on technology to deliver its services. DT creates a model that converges the patient's physical world with the various datasets in cyberspace in real-time in order to combine the patient-centric nature of healthcare and draw on the benefits of technology to better understand the patient risk and define interventions with applying precision approaches to improve health in the population context [32]. The key components of the DT are common to the smart sectors across multitude of environments:

IoT Platform the driving mechanism of the digitalised ecosystem, which connects the quantum of sensors, actuators and controller from CPS and facilitates network communication between the physical objects. 5G's ubiquitous infrastructure will be a significant driving force for its commercial rollout, which is expected to have a massive impact on society and business bringing about societal and economic opportunities for everyday connected objects and innovative applications across number of smart sectors including smart homes, smart transport, smart grids, smart workplace, smart health and others [57–59].

Edge Computing combining 5G with mobile edge technology, also in its infancy in terms of wide commercial rollout, could provide real-time collaborations, monitoring of patients or even remote surgery [59]. With the explosion of data, devices and interactions, cloud architecture on its own cannot handle the influx of information and processing of data far-removed from its source creating latency and performance issues. With the advancement of IoT driven CPS huge amounts of data will be generated continuously that must be stored, processed and responded securely and cognitively [19]. For example, medical devices are increasingly IoT enabled like Computed Tomography (CT) or medical therapeutic activities in the community and are capable of processing the data at the edge [60, 61].

Cloud That said, cloud technology is a fundamental building block for ubiquitous CPS and services in precision healthcare due to its fundamental characteristics of a distributed, on-demand, scalable and virtualised service. However, there are a few cloud storage platforms specific to healthcare that enable real-time monitoring of patients [24]. The concept of large-scale cloud storage integrated with edge computing and 5G network capabilities can be converged with large numbers of IoT enabled devices amongst themselves, across different smart sectors and also with human users, enabling large scale IoT design and deployment at different abstraction layers [62, 63].

Artificial Intelligence (AI) drives a paradigm shift in healthcare through a widely applied combination of a highly complex algorithm that aims to mimic human cognitive functions in a range of applications and smart sectors. AI, including Deep Learning and Machine Learning, can be applied to a wider range of healthcare data to process complex data structures and enable computers to collect knowledge, thus human intervention in building that knowledge is not required.

CPS the gradual integration of CPS technologies by Industry 4.0 has led the way to enable real-time monitoring of physical activities in virtual space through the networked connectivity of CPS [36] into other smart sectors including urban space in smart cities [64], smart grids [65], smart homes [66], smart workplaces [67], smart transport [68] and healthcare [22] forming safety-critical, intelligent networked systems. **mCPS** are critical connected medical devices that are used increasingly more in hospitals for the provision of quality patient care [22].

The emerging digitalised ecosystems in healthcare will require visionaries, new business strategies and support of innovative technical foundation that enable the physical-cyber-data domains converged and bridged with humans to shift the paradigm from conventional to precision healthcare.

4 Proposed DT Frameworks

Precision healthcare is seen as a significant challenge. To address the design and management of this complexity, we investigate recent works in DT to realize the goals of precision healthcare.

4.1 DT for Better Community Healthcare

The problems that continue to persist in healthcare are the absence of real-time interactions, lack of convergence between medical physical and information systems, absence of active participation and continuous interactive monitoring throughout the elderly person's lifecycle [24]. The panacea to these problems is presented in the concept of Digital Twin for Healthcare (DTH), a novel cloud-based framework for the care of elderly in the community. The study adopts NASA's definition of DT [37] and highlights the complexity of interactions between people, medical devices and the variety of institutions involved in providing healthcare services to elderly. It is argued that due to the current complexity of the healthcare system, introducing DT can achieve greater medical flexibility, reduced medical risk and cost through modelling and simulation with real scenarios, thus gaining better quality and efficiency in disease diagnosis, treatment and prediction. The key phase behind the proposed CloudDTH medical simulation approach is the physical to digital representation using advanced 3D modelling techniques, followed by inclusion of real-time data from external factors like weather, elderly patients' physiological data from wearable monitoring devices, patients' healthcare records and virtual data from digital models. The fused data is stored in the healthcare cloud service. Utilising modelling methods, a virtual model is constructed for fast simulations with use of machine learning algorithm for accuracy of crisis prediction. The study discusses number of DTH applications: an early crisis warning, real-time supervision and scheduling. As the CloudDTH receives real-time data it is put through the virtual model and optimised, the model produces warnings and the scheduling system is based on predictions of the combined data. The viability of CloudDT was tested with 2 volunteers simulating a normal and abnormal heart rate. The experimental process successfully distinguished between the volunteers' needs based on the DTH model and demonstrated the feasibility of individualised medicine using DTH. Furthermore, the crisis warning was simulated using virtual modelling and combined with the hospital scheduling showed promising results. The authors conclude that although most of the research and commercial efforts concentrate on platforms, business models, standard and Health IoT interoperability, DTH is an effective way to solve the physical and cyber convergence and interactions. Whilst [14] are looking at ways to augment traditional clinical health services using IoT devices to help detect early changes in the lives of the elderly in the community, [24] demonstrates that DTH with the knowledge extracted from the real-time data enables the delivery of precision healthcare.

4.2 DT as Part of Intelligent Control and Emergency Planning in Hospitals

A crisis warning system was simulated with promising results by researchers proposing a concept of DTH [24]. Diversifying and evolving the application of DT in healthcare, an emergency unit performance evaluation of current state and major incident intelligent control is researched [56] using Discrete Event Simulation (DES) in the context of a major incident like substantial patients arrival related to an epidemic, as a result of natural disasters like tsunami, earthquake or due to terror attacks. Discrete Event Simulation is a widely researched field for healthcare modelling and although some studies present highly complex models [69] others are more generic and transferrable [70] for wider applicability.

The study highlights the innovative use of DES for modelling and decision-making functions of the framework for use by health-care professionals to enable scenario modelling based on real-time data to create a more efficient patient flow through the emergency unit, reduce patient stay, the demand on resources and increase the number of patients treated. The proposed DT-based modular framework consists of a modular model which is connected to a process analyser tool fed with data from the hospital information system and the patient arrivals forecast including data from the GP network alerts, crisis alerts, patient transfers information and utilisation of other hospital services.

The model was represented using the MedPRO UML-based modelling framework and implemented using the ROCKWELL Arena 14.5. The variables were extracted from the hospital information system, interviews with staff members and observations. The main focus of the study was the process view: patients' care in the emergency and the resources view the healthcare professionals' activities. The viability of the framework was demonstrated on a diverse set of scenarios with predefined key performance indicators. In their concluding remarks, the authors point to the innovative use of DT-based monitoring and control of the hospital emergency unit without disruption to services demonstrating aspects of precision healthcare delivery system through physical and cyber convergence.

4.3 DT as Part of Strategic Planning of Hospital Services

Whilst most DES applications relate to the discrete aspects of healthcare modelling such as clinics or emergency units [71], an innovative DES-base DT concept is proposed to assess and optimise the efficiency of the healthcare delivery systems and evaluate changes thus aid decision making related to staff scheduling, waiting time or appointment problems without disrupting the daily hospital activities [7]. The requirement to remain consistently efficient in the changing healthcare landscape and deal with the inconsistency between demand and capacity create significant challenges [7]. A key challenge highlighted in this study is the increasing demand for health services, therefore increased costs, and it is argued that these changes are due to the growing ageing population and increase in chronic illnesses. The study provided a general modular framework extendible to other healthcare services and simulated four key services for the proof of concepts. The model used the FlexSim HealthCare 3D simulation and modelling tool. To enable accurate and real-time simulation, the input of data was proposed from across hospital information systems, DES and IoT connected ubiquitous computing devices which could be used to track patient flow. The DT model is based on a hospital patient flow which enabled a variety of scenarios to be simulated including patient tracking from admission to discharge in real-time which enables the patient to receive the necessary medication, equipment or operating room at the right time. The framework's methodology feasibility was tested on number of different scenarios. The proof-of-concept shows that improvement of resource usage can be achieved through the concept of DT. Authors in their concluding remarks outlined further development of the proposed approach to handle more complex scenarios.

5 How Can Digital Twin Technology Improve the Delivery of Precision Healthcare

One of the global challenges in public health is the burden of chronic conditions in both developed and developing countries [72]. In medicine, these are a heterogeneous group of diseases characterised by their long duration, frequent recurrence and slow progression. As discussed earlier, the cost of managing chronic conditions, their co-morbidities and complications comprise a burden on health systems worldwide. Further, most of these conditions are subjects for extensive research in which risk factors and treatment options are explored, and this made them a promising aspect in medicine to invest new technologies and promote wellbeing. However, one of the major factors that undermined the use of technology in healthcare is the complexity of patient's needs [3]. This section will focus on managing chronic conditions at different levels and how DT could be hypothetically applied.

The management of chronic conditions is a continuum, it starts at the prevention stage when a risk factor is identified, the pre-diagnosis, the diagnosis and the management stage [73]. The self-management of chronic conditions is an evidence-based approach in healthcare. It implies the involvement of patients in their own care and relies on developing skills, utilising psychological resources, in addition to pharmacological treatment and regular follow up with healthcare practitioners [74]. The management of chronic conditions is complex, at an individual level, healthcare professional and health system levels.

At an individual level, the genetic component is one of the biological determinants of health, which is where precision healthcare mostly relies upon. However, managing chronic conditions is far more complex and it also includes the psychosocial aspects which can vary hugely between individuals [75]. Hence, despite having the same condition, different people have different self-management plans based on the bio-psycho-social aspects of their lives. Thus, the ideal situation in employing DT to improve precision healthcare is to consider these variables, with the acknowledgement that psychological and social aspects, such as lifestyle choices are not easy to measure or monitor.

At a healthcare professional level, the development of evidence-based medicine [4], the adoption of clinical guidelines and the international classification of diseases [76] had brought a relatively common ground of communication among healthcare professionals. However, to provide a personalised care plan the involvement of both patients and healthcare professionals are crucial to feeding into the digitalised form. This could be achieved by maintaining a ‘doctor-patient’ relationship that is built on trust and informed decisions [77]. This is to encourage patients to share feedback on their own health experiences and their preferences in managing their conditions. For example, if patient x and patient y both have diabetes, and both attend the same clinic, if patient x do not trust the healthcare professional and do not give feedback on the management plan compared to patient y, then the digital twin for patient y will be more personalised and responds to this patient’s need.

At a system level, taking into consideration the promises given in precision healthcare and using DT to customise patient care by technology-enabled approaches [38], the journey of a patient with a chronic condition and/or comorbidities through the healthcare system could be transformed. DT could showcase the specific journey for the patient within the healthcare services. This could be achieved through simulating the ideal system navigation, referrals and resource management. It is worth thinking of the implications of precision health and DT application to two established approaches in healthcare, these are ‘chronic diseases management’ and ‘acute case management’ programs.

Chronic disease management programs target chronic conditions that are prevalent, with a high cost to manage, and have evidence-based guidelines to follow. National programs for chronic disease management existed in the United States, Austria, Denmark, England, Finland, France, Germany, Italy, Netherlands, and Poland, while regional or private initiatives were also adopted in England, France, Italy, Spain, and Sweden [78]. Hence, these programs are widely implemented, and they rely on modifying the health outcomes by coaching and managing the patients’ lifestyle, for example with patients having diabetes, asthma or chronic heart diseases [79, 80]. Disease management programs require a closed-loop of communications among the patients, the treating physician and the disease management nurse. They also require a flow of clinical, behavioural and self-monitoring data within the loop. In such case, precision health and DT could be promising to build a healthcare model where the evidence-based guidelines are embedded in a system that is also encoding the patients’ self-monitoring data, behavioural data in addition to the factors discussed under the individual level above.

Accordingly, the best theoretical scenario to apply DT in chronic disease management programs would be a patient with a chronic condition navigating within this healthcare model where the treating physician can have a holistic view that includes clinical and evidence-based information that could be further customised based on each patient's journey. The disease management nurse could be automated and customised to send tailored reminders, educational tips and responses not only to the self-monitoring data but also to the captured behavioural data. Such a model would potentially improve the clinical management outcomes and quality of life of patients with chronic conditions, and potentially avoid complications and their cost upon the system.

Some potential challenges to this application in disease management programs could be related to the variables in real-time that would deviate from the digitalised process [38]. A deviation from a physician side could emerge when the physicians' experience takes over the automated guidelines. From the patient's side, this could be influenced by the patient's complex needs [3] which might influence real-time behaviours, feelings, adherence to the set targets and the utilization of healthcare services.

Another approach is 'acute case management', it deals with acute and expensive cases such as oncology and severe accidents [81]. Applying precision health and DT to acute case management is similar in principle to the application in disease management, however, case management requires many urgent diagnostics and procedures, in addition to costly treatments. To decide the diagnostics to perform, and which procedures and treatment to follow is not simply based on guidelines. It is determined by a complex matrix of guidelines alongside the individual's specific data, such as susceptibility, genetics, or tolerance. Precision health and digital twinning could have a positive impact on this complicated healthcare model, to create a DT for the patient and simulate the best possible care plan which is being promised mainly in oncological research [82]. This would also have an impact on the system navigation and efficient resource management, and most importantly all save time and of unnecessary efforts and trials for such acute or severe cases. Potential challenges to this application could be related to which degree the digital twin could be precise when applying the best care plan on the ground.

A final factor to consider in employing DT in healthcare is the context in which the healthcare professionals and the health system operate, for example, the consideration of minorities, marginalised groups and stereotyping. Examples include the misdiagnosis of mental health illness and misunderstanding of people from ethnic minorities [83]. Accordingly, the design of a DT should consider all of the factors above and avoid exacerbating existing stereotyping and creating a systematically discriminatory process.

6 Why Is It Important to Have an Early Threat Model for DT

6.1 To Facilitate Security-by-Design (SbD) for DT Frameworks

The myriad of connected devices and sensors that exist and are used in solutions across the smart healthcare ecosystem and in other smart sectors, as presented in Fig. 3, could increase the data collection capabilities and the level of automation helped by Artificial Intelligence for precision healthcare [59]. DT represent one of the many concepts of technology-driven digital transformations that are gaining momentum. However, injecting intelligence into old technology, retrofitting machines with sensors to collect data and badge them as smart or collecting and processing large datasets using existing software under the umbrella of cognitive solutions are poor designs that are set to fail. Such practice introduces serious security gaps and a poor approach to cybersecurity. Evidence indicates that the natural desire for cutting-edge technology solutions, cost control, new attractive features are prioritised and security is an after-thought rather than integral to

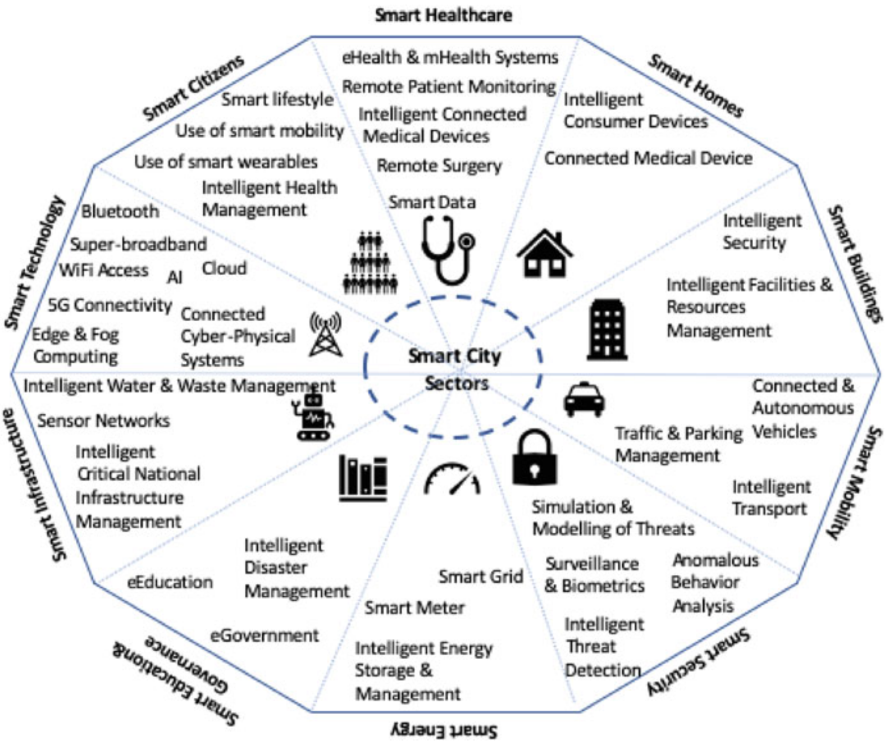

Fig. 3 Smart City sectors impacted by cybersecurity challenges

the framework design [7]. While this paradigm is not specific to the smart healthcare sector [84] there is little evidence of cross-organisational information security sharing, coordination and cybersecurity collaboration [85]. Although DT-based practices in civil engineering provide a good conceptual framework [36], the ubiquitous proliferation of DT across smart sectors from manufacturing to precision healthcare has many complexities introduced by IoT enabled CPS. Cyber-Physical Systems (CPS) are key components of embedded systems and play a critical role in DT, for example, IoT enabled mCPS are transformational to precision healthcare and the data generated from mCPS sensors can be used to learn about patients. But associated risks and vulnerabilities are not well understood, therefore more work is needed to drive SbD which can only be achieved if all aspects, including security, are considered from the outset [86] across all framework tiers. Furthermore, the increase in the interconnectivity and heterogeneity of medical devices and an extensive adoption of disruptive technologies across different sectors in smart cities have inherent cybersecurity threats with a large threat surface and a potential serious impact in the event of a security breach. Therefore, a citizen-centric approach in precision healthcare with a layered security mechanism is needed as part of SbD.

6.2 *To Secure Against Inherent and Emerging Threats Through Defence-in-Depth Mechanisms Across All DT Domains*

One of the great concerns with IT infrastructure, smart devices and IoT as fundamental supporting elements for DT in precision healthcare is cybersecurity. While collecting, moving and managing colossal amounts of data is underpinned by robust infrastructures, the proliferation of smart technologies and their implementation across smart city sectors are moving too fast for development of standards [87]. If the proposed DT and relevant frameworks for delivery of precision healthcare lack suitable security techniques and methods applied consistently across physical, cyber and data domains the DT concept remains vulnerable by design. A robust DT implementation requires threat modelling of the inherent security challenges of components and enabling technologies that makeup DT, as shown in Fig. 4, many of which are reported in recent studies [88, 89]. Most devices that makeup healthcare applications and DT in delivery of precision healthcare are wireless by nature and involve humans, therefore data privacy and security are major concerns. Whether the application of the sensor devices is wearable or implantable in humans [24] or it is part of intelligent control, emergency planning [7, 56] or used for remote surgery [23], the security threats in smart devices are significant. These threats can be summarised as Boot Process Vulnerabilities, Hardware Exploitation, Chip-Level Exploitation, Encryption and Hash Function Implementations, Backdoors in Remote Access Channels, and Software Exploitation [88]. For example, CPS, key components of DT, attract compromised-key attacks due to many sensors using

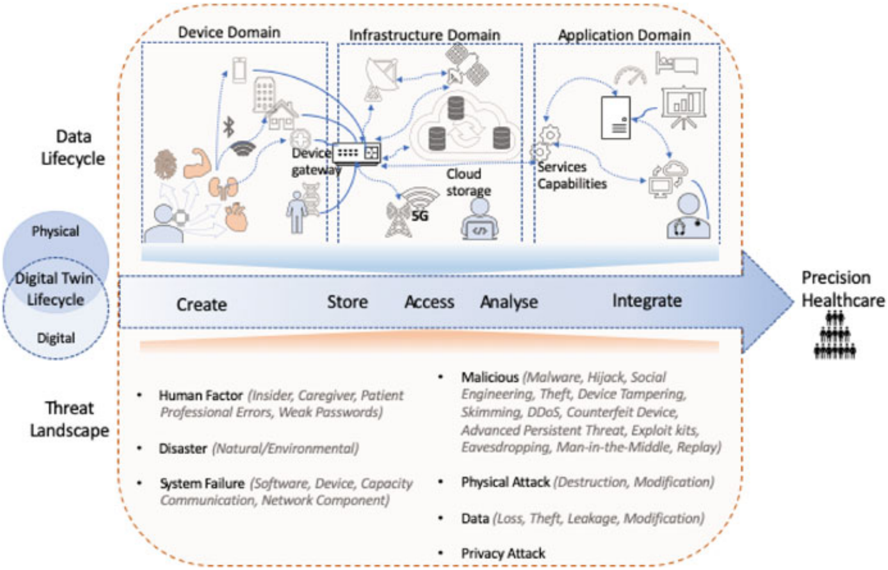

Fig. 4 Inherent and emerging threat landscape across digital twins concept in precision healthcare

cryptographic keys for the handshake protocols which include authenticity checks [90]. But despite the overall system hardening, the supporting infrastructure can be tampered with to embed malicious software or monitoring feature thus creating a backdoor [23, 91, 92] for easier access and possible data or Intellectual Property (IP) theft at a later time. Therefore, security measures to counter the threats must be considered and resolved during the design phases and innovative countermeasures are required to support modern defence-in-depth approach. Sensor designs have few external security features and therefore are prone to physical tampering. In addition to secure storage of data, existing protection methods can be used in securing DT hardware, for example through use of the Trusted Platform Module (TPM) chip, binding the software to the DT hardware. Physical access to the facilities should be restricted and supported by strong multi-factor or biometric authentication. A taxonomy of aspects that should be included in countering security threats include systems, administrative, physical, technical, information and finally healthcare data [24, 93]. Developing a concept of DT for remote surgery using mobile networks includes many different engineering fields including robotics, computer sciences and IT infrastructure development. Other applications of DT in the delivery of precision healthcare interact with different smart sectors like smart building, smart homes or smart transport. Smart cities include automated systems that can introduce and support the intelligent management of precision health components including data, medical equipment and management and supervision of public health [52]. Therefore, delivery of precision healthcare is truly cross-disciplinary and requires significant research with security embedded in its design from the outset.

6.3 To Mitigate the Human Factor

Security issues arising from the DT-based concept are numerous and due to the direct human involvement security is one of the most important aspects to consider. Precision Health aims to make healthcare more accessible and integrates monitoring and diagnosis into patients' everyday lives through use of smartwatches to measure pulse and heart-rate, electrocardiography patches to detect arrhythmias, clothes integrated sensors for early disease detection, epidermal electronics that measure vital signs to environmental exposure or vital implantable devices like pacemakers to name a few [21]. Although human factor is an important dimension in CPN ecosystems, it is acknowledged as an inherent weakness that is often overlooked and significantly underestimated [55, 94]. Intruders can exploit this vulnerability and phishing attacks continue to increase constituting a serious threat in the cyberspace with evidence of seeking out the emerging IoT and smart devices as a target [95]. Furthermore, there is an existent threat from human insiders in the workplace [67, 96] including human error, non-compliance, unauthorised access, fraud or industrial espionage. As a proprietary digital content, DT requires protection in terms of IP [23], therefore security mechanism is required to distinguish normal and malicious behaviours [97].

6.4 To Comply with and Influence the Development the Regulatory Landscape

The regulatory landscape is very diverse and lacks standards and criteria. Local, national and international laws and legal frameworks are a key element of effective public health policy and practice. For instance, precision health will produce more data, but the information gained could identify the patient's disease risk with far-reaching consequences. In the US the Genetic Information Non-discrimination Act 2014 (GINA) prohibits genetic discrimination by employers under the federal law since 2008 but this does not extend to other sectors such as insurers. With the increased value of genomic information in precision healthcare more comprehensive legislation is needed. The Health Insurance Portability and Accountability Act (HIPPA), an organisation-centric regulation, protect health information within the healthcare providers remit but does not extend to cover medical device companies who are not obliged to implement secure communication channels [21]. In the European Union, the General Data Protection Regulation (GDPR), a consumer-centric regulation, enforces data protection by design. Although there are attempts to publish baseline recommendations, due to the complexity and diversity of the IoT-based applications defining baseline security is a major challenge and there is no common approach to IoT security [98]. Beyond IoT security, regulatory concerns in other smart sectors that directly impact the delivery of precision healthcare are yet to be addressed. In the US, the National Institute of Standards and Technology

(NIST) developed guidelines for the Network of 'Things' [99], the Department for Homeland Security published strategic principles for security of IoT [100], the U.S. Department of Health and Human Services Food and Drug Administration (FDA) Center for Devices and Radiological Health covers recommendations on managing post-market cybersecurity vulnerabilities of marketed and distribute medical devices [101] but they are non-binding. The "Internet of Things Cybersecurity Improvement Act of 2017" was introduced to set the minimum set of requirements for IoT implementations [102]. Additionally, the IT security catalogue from ISO contains multi-part standards focusing on Internet of Things (IoT) Reference Architecture namely the ISO/IEC 30141:2018, Security Techniques ISO/IEC 27001:2013, and ISO/IEC 27002:2013, which are concerned with information security management practices. This fragile ecosystem is governed by the fragmentation of standards [98] due to the speed of the technology evolution.

7 Ethical Implications of the Emerging Paradigm

Precision healthcare is an evolving field and many technologies that will support the delivery of its objectives are in early stages of development or are yet to be developed. While technological innovations are potentially transformational, they bring about numerous challenges. The solutions to a novel approach to healthcare are complex, influenced by technological developments, socio-political aspects and different healthcare models. The multifaceted nature of the ethical issues apart from privacy, confidentiality and regulatory aspect should consider social justice, informed consent and marginalised groups. Difficulties in defining a universal meaning for ethics is largely due to the varied interpretations and multi-layered environments. This section will focus on the ethical implications of the emerging paradigm of the novel technological applications of digital twinning in precision healthcare at an individual, healthcare, research and technology levels.

At an individual level, there is an increased enthusiasm to use technologies, wearable sensors or implants to promote and manage health through individual participation. However, this may give rise to issues of equality and social justice, therefore inadvertently counterbalance the desired effect of improving the populations' healthcare [38]. Therefore, a commitment to consistent approach to access precision healthcare is required. Additionally, the use of wearable or implantable health monitoring devices is supported by real-time data collection capabilities and combined with the application of digital twinning technologies produce large datasets about patients including Electronic Health Records, genome sequences and behavioural data. There are significant risks in collecting, transmitting and storing data containing personal information and in practice can be ethically challenging to gather and manage. Lack of transparency and possible malicious use could be detrimental; therefore, it is important to be clear and consistent in the commitment of informed consent and privacy to maintain the patients' trust in the delivery of precision health.

At healthcare level, the data collection process can be very costly and even harmful to the patients, which highlights the question of how to achieve the balance to maximise the benefit but limit the burden. For example, should treatment be repeated, even if it causes risk to patient to gather the data or should it be based on reported patient outcomes? Next, aspects of precision healthcare need to be defined that will be supported using the acquired datasets, for instance, preventative, early diagnosis, therapeutic or chronic conditions. Questions could arise if markets and data monetisation are the ultimate drivers of implementing DT in precision healthcare thus mechanisms would be required for the delivery of precision healthcare for the disadvantaged groups.

At research level, the promise of precision healthcare goes far beyond treating those who are already symptomatic with illness or enabling the individual to take a more active role in management of their health. The capability to proactively prevent disease generates valuable raw data that drives health research and blurs the boundary between care and research. A growing number of organisations including health research, technology, life sciences work collaboratively to develop a common harmonised framework of approaches to enable secure and responsible sharing of genomics and clinical data to enable scientific progress and advancement in medicine in a highly ethical, secure and responsible manner [33]. Researchers who seek to leverage digital technologies research programs in the delivery of precision health should consistently maintain informed consent, autonomy of choice and should handle the data with integrity and transparency.

Finally, at the technology level, digitisation is borderless, and the data flows are global. Whilst the large-scale collection of data brings societal and individual benefits, the large-scale collection, transformation, convergence and aggregation is a substantial regulatory challenge [103]. The ability to collect large amounts of information, have consequences for the patient's safety, freedom and privacy. Therefore, strong regulatory and governance structure is required to ensure that appropriate security-by-design, regulation and audit frameworks are adopted, and transparency of the DT and its storage structure are maintained to safeguard the patient's rights to safety, informed consent and privacy.

8 Conclusion

The aim of this proactive patient care is to pre-empt the disease through preventative medicine and early detection, which could change the societal culture by empowering the individual to prevent their own disease. Traditionally, individual's age, family tree and more recently genetic screening were some of the key aspects of establishing a person's disease risk [21]. However, other factors affecting the person's wellbeing and disease including environmental, demographic, socio-economic or biological in a constantly changing landscape are not detected during routine health screening. Precision healthcare develops the concept of the precision approach and converges the individual to the population capitalising on smart use of big data by understanding and linking the individual-level data with the wider societal context [32]. Thus, the emerging concept of precision healthcare encourages preventative medicine, early detection and monitoring based on the patient's individual risk.

The advent of precision healthcare will see technology-driven digital transformation of the health service that will enable customised patient outcomes through novel and targeted medical approaches. To improve patients' health and wellbeing, the demand for intelligent, data-centric smart healthcare models using technological innovation and artificial intelligence (AI) is increasing. Few studies explored the potential of DT for precision healthcare and proposed frameworks usually linking the physical, cyber and data domains to the current and future needs of healthcare. DT pairs individual physical artefacts with digital models reflecting their status in real-time. Creating a live model for healthcare services introduces better risk assessment and evaluation without disturbing daily activities. The frameworks ranged from modelling and simulation of emergency units' performance in hospitals in the event of major incidents to the optimisation of healthcare delivery systems for the elderly or those with chronic diseases.

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