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Digital Twins in Critical Care: What, When, How, Where, Why?

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Abstract: Healthcare and intensive care unit (ICU) medicine in particular, are facing a devastating tsunami of rising demand multiplied by increasing chronic disease and aging demographics, which is unmatched by society's ability to pay. Digital technologies and automation have brought significant productivity gains to many industries, and manufacturing in particular, but not yet to medicine. In manufacturing, digital twins, model-based optimisation of manufacturing systems and equipment, are a rapidly growing means of further enhancing productivity and quality. This concept intersects well with the model-based decision support and control just beginning to emerge into clinical use, offering the opportunity to personalise care, and improve its quality and productivity. This article presents digital twins in a manufacturing concept and translates it into clinical practice, and then reviews the state of the art in key areas of ICU medicine.

Keywords: Digital Twins, ICU, Critical Care, Physiological Modeling, Virtual Patient, Virtual Cohort.

1. INTRODUCTION

Intensive care unit (ICU) patients are very complex and highly variable, making management difficult. Aging demographics, chronic disease, and increasing life spans are driving increasing cost and reducing equity of access to care (Baumol et al., 2012, Dombovy, 2002, Halpern, 2009, Halpern, 2011, Orsini et al., 2014, Shorr, 2002, Truog et al., 2006, van Exel et al., 2015). There is thus a significant need to improve productivity and quality of care.

Personalised care using patient-specific models identified from clinical data offers the means to directly manage intra- and inter- patient (Chase et al., 2018b) variability. It adds automation to care, using digital technologies to improve quality and cost, as in many other sectors, but much less in medicine (Baumol et al., 2012, Economist, 2011, Micklethwait, 2011). Thus, some level of automation will be necessary given society's increasing inability to meet rising costs and provide equal equity of access to care (OECD, 2015).

Hyper-automation and digital twins (DT) capture the essence of this model-based approach and are a major growth area in manufacturing (Cimino et al., 2019, Panetta, 2019). Reduced cost and optimisation arise from using sensor data to monitor, model, and manage real-world systems. In medicine, the difference is the humans in the loop, patient and clinicians.

This review translates digital twin definitions into the medical application space. It focuses on the models and methods required for hyper-automation, especially the impact of the humans in the loop in cyber-physical-human systems who are not as integral in the manufacturing case. Finally, this state of the art review explores the key technical and innovation uptake issues required to successfully bring DTs into medical care.

2. DIGITAL TWINS AND VIRTUAL PATIENTS

2.1 Digital Twin Definition

Digital twins have risen at the intersection of Industry 4.0 and the internet of things (IoT) relying on converging technologies in big data, sensors, and cloud computing. A DT is "*a virtual copy of a system able to interact with the physical system in a bi-directional way*" (Cimino et al., 2019, Kritzinger et al., 2018). They are cyber-physical-systems. The bi-directional exchange of information synchronizes virtual system response to match the physical system to "*forecast and optimise the behavior of the physical system in real time*".

In manufacturing digital twins sit on top of a "*control layer*" of supporting technologies, under a top layer of "*enterprise resource planning*" which integrates organizational functions and goals into the use of the DT. This DT organisation is simplified and shown schematically in Fig. 1. In Fig. 1 both upper and lower layers inform the DT and its design / use. The DT itself is connected through the control layer to its physical counterpart in real-time and uses modeling and computation to continually update the virtual twin (Negri et al., 2017).

DTs are defined by their integration (Kritzinger et al., 2018). A digital model (DM) has no interaction with the physical system. A digital shadow (DS) is updated with data from the

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physical system, but does not inform its control. A DT arises when physical system data is used to update the DM, and the resulting simulation is used to control the physical system. To date, there are few true DTs in use (Cimino et al., 2019).

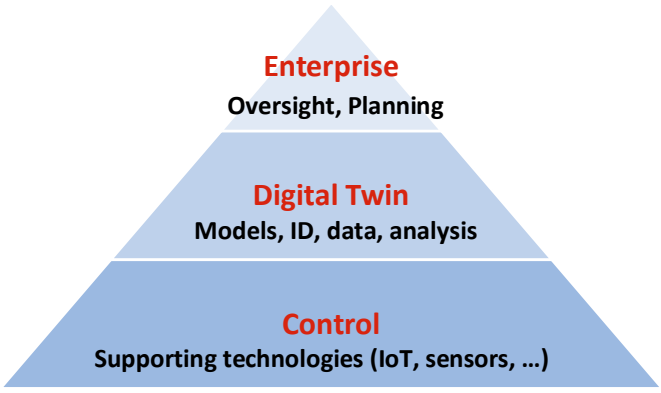

Figure 1: DT structure between supporting technologies (IoT, sensors, communications) and an enterprise layer integrating DT use into meeting organizational goals (overall protocols, oversight, and planning), based on (Chen, 2005).

2.2 Digital Twins in Medicine

In medicine, the physical system is the patient, or a particular organ or physiological system to be managed. A human is also in the loop clinically, particularly in the enterprise layer (Fig. 1) where protocolised use of a DT is designed, integrated, and managed in care (Chase et al., 2016, Chase et al., 2018b). Within the framework of Fig. 1 a DT in medicine would fit in a control loop in Fig. 2, where bi-directional information to and from the DT is clear in the loop. The modeling and DT update process is illustrated in Fig. 3, where the incoming data in Fig. 2 can be used to update the model at any time to provide accurate prediction in response to proposed interventions.

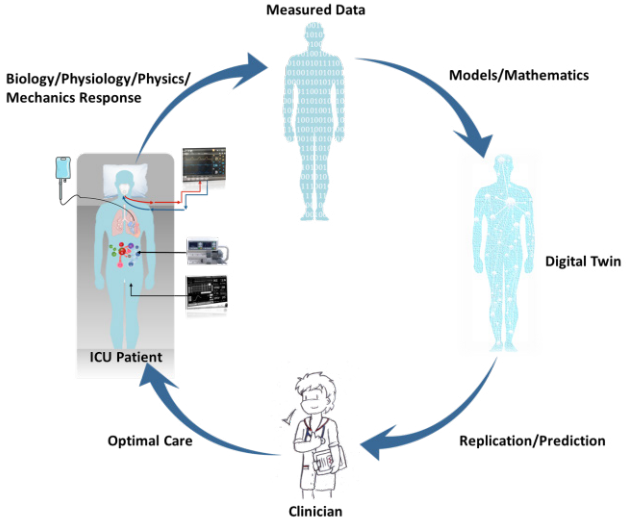

Figure 2: DT control loop in medicine with clinical staff in the control loop.

How interventions are optimised in a medical DT is based on a protocol to optimise patient care, by clinical staff at the "enterprise" level in Fig. 1. Finally, it is important to note the clinician in the loop in Fig. 2 is there for safety, but can be fully removed in full automation.

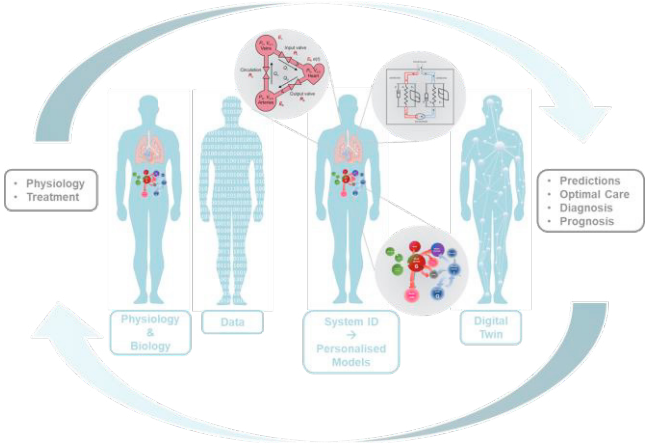

Figure 3: DT model creation and updating from clinical data.

2.3 Virtual Patients (Digital Twin Models and Methods)

Medicine and physiology offer many DMs, models informed by data, but not receiving real-time patient data (Hunter et al., 2010, Nickerson et al., 2016, Safaei et al., 2016, Viceconti et al., 2016). However, most are too complex to be personalized in real-time with available data (Chase et al., 2018b).

DS models are increasingly common, able to be personalised, and are differentiated by their identifiability from relatively limited clinical data in many cases (Chase et al., 2011b, Chase et al., 2019, Desaive et al., 2019, Morton et al., 2019b). They have been used to assess new medical technology applications (Zhou et al., 2018, Zhou et al., 2019) and protocols (Fisk et al., 2012, Uyttendaele et al., 2018). However, very few are used in regular care, and thus are not DTs, where < 1% of model-based decision support systems are implemented beyond testing, let alone standard care (Garg et al., 2005, Wears et al., 2005).

Finally, a virtual patient (VP) is a DS, DM, or DT model able to be identified from relevant bedside data, and providing accurate prediction validation in response to modeled inputs (Fig. 4). A collection of VPs creates a virtual cohort (VC) where VPs created from retrospective data can be grouped into a VC for developing and optimizing new protocols. A VP model suitable for being a digital twin should be validated in the ability to accurately predict patient-specific outcomes to specific interventions, as well as accurately capturing cohort response in simulating a new protocol over a unit, where the first enables the DT and the second allows the protocol to be optimised for the "*enterprise layer*" in Fig. 1 and is based on clinical goals (Chase et al., 2018a, Chase et al., 2018b).

2.4 Application of DTs in ICU Medicine

There are 3-4 core areas of ICU medicine: glycemic control (GC); cardiovascular (CVS) care; sedation delivery (SD); and mechanical ventilation (MV). They affect 30-80% of all ICU patient and suffer variability in care and outcomes due to lack of physiological insight from the data available leading to difficulty in managing inter- and intra- patient variability. Moreover, they have significant negative impact from both over or under delivering of care, and are a leading cause of ICU admission, length of stay, cost, and/or mortality. Thus, each core area could gain significant advantage from a DT providing a far clearer physiological picture of patient state

from the data available (Chase et al., 2018b). In each area, virtual patient models exist at levels ranging from DM to DT in their integration with the patient (Figs. 1-2) and into care.

GC is the most advanced area. There are multiple metabolic system models based on decades of research (Chase et al., 2011a, Chase et al., 2018b). However, relatively few have achieved patient level validation (Hovorka et al., 2008, Le Compte et al., 2009, Lin et al., 2011, Van Herpe et al., 2006, Wilinska et al., 2008). GC protocols have been optimised using these models (Blaha et al., 2016, Evans et al., 2012, Fisk et al., 2012, Knopp et al., 2019, Le Compte et al., 2011, Lonergan et al., 2006, Mesotten et al., 2017, Pielmeier et al., 2010, Van Herpe et al., 2013, Wilinska et al., 2008). However, very few have delivered clinical results very close to those simulated before implementation (Chase et al., 2007, Fisk et al., 2012, Knopp et al., 2019, Wilinska et al., 2011). Similarly, at the cohort level, validation has only been presented for one model in multiple ICU capacities, including cross validation from randomised trial data (Chase et al., 2007, Chase et al., 2010, Dickson et al., 2018, Fisk et al., 2012).

MV virtual patient models are much less advanced, as only two models accurately capture predict lung mechanics evolution with changing ventilator settings (Morton et al., 2019a, Morton et al., 2020, Zhou et al., 2021). In particular, critical metrics, such as recruitment volume retained as pressures change, peak volume and pressures, lung elastances, and work of breathing. These metrics offer more accurate insight not previously available to optimise MV, where MV doubles the cost per day (Dasta et al., 2005). They are currently entering first clinical trials (Kim et al., 2020b), and have been tested in neonatal cohorts (Kim et al., 2019, Kim et al., 2020a).

Finally, for SD only fundamental models have been developed with no virtual patient or cohort validation (Rudge et al., 2006). Similarly, CVS has developed models to estimate key parameters for clinically managing circulation and cardiac stroke volume (Murphy et al., 2020a, Murphy et al., 2020b, Pironet et al., 2015, Smith et al., 2020a, Smith et al., 2020b, Smith et al., 2021). Both areas have foundation elements for a DM, but have not progressed to DT solutions at this time.

2.5 What is Missing?

The only bi-directional DTs in clinical ICU use are in GC, and they are not fully automated with a human in the loop (Knopp et al., 2019, Stewart et al., 2016). Thus, the main element missing is technological and not model or control based. Specifically, there is a need to create greater interoperability and access to data from the range of ventilators and infusion pumps in the ICU, which has been a great source of difficulty due to proprietary and other reasons.(Hudson et al., 2018, Jaleel et al., 2020, Mavrogiorgou et al., 2019).

3. INNOVATION UPTAKE

Having all the technologies, models, and protocols to create DTs for use as standard of care is not enough. The "*enterprise layer*" of Fig. 1 also includes decision making on adoption of new standards of care. Adoption is a decision made at both the ICU and clinician level, as well as higher management and/or a health system level.

Alarmingly, patients are reported to benefit from only 30-50% of the validated healthcare technologies (Grol, 2001, Schuster et al., 2005), indicating at least half of healthcare innovations fail to be successfully adopted, even after being clinically validated in earlier development stages.

We consider *technology adoption* to be the acceptance, integration, and use of new technology in an environment. This requires consideration of factors at the individual, the team/unit, and the organisational system levels.

3.1 Factors Impacting Technology Adoption

Majority of research on technology adoption focuses on factors relating to individual employees, including employees' past experience with technology (Gagnon et al., 2012, Koivunen et al., 2018, McGinn et al., 2011, Schreiweis et al., 2019), perceptions of the new technology's usability, the expected benefits of the innovation (system usefulness; Kruse et al., 2016), and ease of use (Gagnon et al., 2012). The cognitive processes from learning how to use the technology (Koivunen et al., 2018), motivation to use the technology (McGinn et al., 2011), and trusting the technology (Lluch, 2011) also drive technology adoption decisions.

Furthermore, emotion-based factors can similarly hinder the adoption process, such as fear of technology (e.g., changes at work, Koivunen and Saranto, 2018; Kruse et al., 2016; fear of depersonalization of healthcare, Lluch, 2011; fear of being replaced by technology, undermined credibility, impact on professional identity, Koivunen and Saranto, 2018; fear of reduced quality of care, Gagnon et al., 2012; Koivunen and Saranto, 2018; McGinn et al., 2011) and disinterest towards the technology (Koivunen et al., 2018). Importantly, the capacity to provide high-standard quality of care is a core value in healthcare professionals (Ko et al., 2018) and thereby the introduction of new technology may give rise to fear of reduced quality of care.

While individual factors are crucial to consider in advancing adoption, the hierarchical nature of healthcare must also be considered. Healthcare delivery teams rely on conformity through hierarchical decision-making processes to maintain performance and minimise risk (Hughes et al., 2016). The power dynamics likely influence the process of technology adoption, as hierarchy within teams can hinder communication and collaboration (Baker et al., 2011) and reduce opportunities for peer support in the adoption process. Furthermore, colleagues' negative attitudes resisting technology is a known barrier, particularly so when the resistance comes from an influential peer (Gagnon et al., 2012, Greenhalgh et al., 2010, Greenhalgh et al., 2017, van Deen et al., 2019).

3.2 A Way Forward

Successful technology adoption requires an approach that considers the individual, team, and system factors that can influence uptake. This includes previous history with technology, perceptions and emotions towards technology, how technology impacts the delivery of quality of care, and the hierarchical structure and power dynamics of the healthcare delivery sector. At the organizational system-level, communications about and support for technology use from

healthcare management is crucial for sustainable uptake (Gagnon et al., 2012, Ingebrigtsen et al., 2014, Kruse et al., 2016, Schreiweis et al., 2019).

The extensive research greatly contributes to the knowledge and understanding of the technology adoption problem, although mainly from an individual employee's perspective. Indeed, *the problem still exists.* There is a further need to address the socio-relational aspects of the system, particularly those centered on the decision-makers who enable technology adoption and uptake.

5. CONCLUSION

ICU medical care needs dramatic productivity improvements to ensure better care, meet dramatically growing demand, and provide continuing equity of access. This review shows there are a few DTs already in use, and the foundation elements for significant growth in the nearer future. However, there is a strong need to address both the technology of interoperability and the social science of innovation uptake to ensure these solutions reach their potential impact in transforming care.

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