Digital Twins and Automation of Care in the Intensive Care Unit

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Abstract: Healthcare is under increasing demand pressure as societies age and expectations rise, multiplied by increasing incidence of chronic diseases and decreasing available funding. The fundamental issue is the signal lack of productivity gains in medical care over the last four decades with the advent of digital technologies compared to many other fields of human endeavour. There is thus a need to bring digital technologies and automation to improve productivity and personalise care, improving costs and outcomes for patients and providers. Cyber-physical human systems (CPHS), mixing digital technologies, computation, clinical staff, and patient physiology, offer a route forward.

Critical care is one of the most technology laden areas of healthcare, one of the biggest areas of patient growth with demographic change, and one of the costliest areas of care. Consuming 8-10% of healthcare expenditure (0.8-1.5% GDP) for less than 1% of patients, the intensive care unit (ICU) presents a major opportunity for CPHS systems to have an impact in creating the productive, next-generation care required to meet the demand for improved productivity and care.

Personalised care, moving from today's "*one size fits all*" protocolised care to adaptive, model-based "*one method fits all*" care through model-based automation or clinician in the loop semi-automation is the means by which CPHS can enter this realm to positive impact. More specifically, digital twins or virtual patient models, personalised at the bedside in real-time, provide the means to optimise care by linking sensor measurements to outcome focused care actions, enabling personalised control.

Digital twins and so-called hyper-automation solutions have been leading technology trends for the last few years, but have yet to come to medicine. This review covers the increasing development of digital twins for medicine, and intensive care in particular, as the foundation for CPHS medical automation to improve care and productivity to meet rising demand. It covers the integrated role played by social sciences in the development, translation, and adoption of innovation, where medicine is historically conservative in adopting innovative solutions and technologies. It ends with a vision of the future from technical, social-behavioural, and combined overall perspectives for digital twins in this domain.

CPHS solutions founded on digital twins offer the potential for a step change in ICU care, simultaneously increasing productivity, personalisation, and quality of outcomes, while reducing the cost of care. Where the ICU is technology laden and thus most susceptible to this form of automation and disruption, the approach is general and will eventually spread to further areas of healthcare.

Keywords: Digital Twins; Personalised Care; Critical Care; ICU; CPHS; Model-based Control; Decision Support; Innovation; Technology Adoption; Cyber-Physical-Human-Systems; Automation.

1.0 Introduction:

Healthcare and intensive care unit (ICU) medicine, in particular, are facing a devastating tsunami of rising demand due to aging demand multiplied by increasing chronic disease and increasing inequity of access to care. The difficulty arises where increases in demand are not matched by society's ability to pay. In contrast, digital technologies, particularly software, increased data, and automation, have brought significant productivity gains to many industries, and manufacturing in particular. However, such productivity gains have not yet come to the field of medicine.

At the cutting edge of modern manufacturing, digital twins, model-based optimisation of manufacturing systems and equipment, are a rapidly growing means of further enhancing productivity and quality [65,155,197], and are a major growth technology trend overall [210,211]. They represent the next step towards increased automation, and improved productivity and quality, as well as the foundation for an emerging range of digital services.

This concept intersects well with the model-based decision support and control just beginning to emerge into clinical use in medicine and diabetes in particular [166,169,268] It is especially relevant to the technology laden ICU [55,56,81,192]. In medicine, digital twins offer the opportunity to personalise care, as well as providing the foundation digital models and methods upon which automation can be introduced to care.

More specifically, ICU medicine involves a wide range of sensors and devices to measure patient state and further devices to deliver care. These existing technologies, such as infusions pumps and mechanical ventilators, are relatively simple devices mechanically and electronically. They thus provide an excellent foundation upon which to develop digital twins as all sensor and actuation technologies exist. In particular, increasing automation will bring these systems into use as cyber-physical-human systems (CPHS), with a human in the control loop, such as the nurse or clinician, as well as the human physiological system being controlled or managed.

This chapter presents digital twins in a manufacturing concept and translates it into clinical practice. It then reviews the state of the art in key areas of ICU medicine to show how these CPHS represent a future of personalised, productive, and, outside of the ICU, patient-led care. Next it covers the role of social-behavioural sciences in innovation and technology uptake, where innovation can be stifled during implementation, and where the term "*disruptive innovation*" does not always carry the same context in healthcare settings as in technology fields, and may exclude a range of high impact frugal or process innovations [250]. The final section covers future research challenges and visions, delineating the key hurdles to seeing digital twins move "*from research bench to clinical bedside*".

1.1 Economic context:

Healthcare in developed countries is growing at an annualised rate of 5-9% annually [97,188] and consumes 10-18% of GDP [208], all of which is far faster than GDP growth in these countries. Thus, the ability to provide care is outpaced by the demand for care, creating significant stress on the ability to deliver equity of access to care [109,168,198], and increased rationing of care in response [14,144,292]. Intensive care medicine is one of the most technology-laden areas of healthcare. It consumes ~1-2% of GDP (or ~10% of health budgets) in modern countries, while treating 0.1% of patients or less [44,118,145].

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 [15,89,119,120,209,246,270,279]. This issue has been particularly highlighted during the Covid-19 pandemic, where the ICU bed numbers became a household topic as ICU services were "overrun" with patient demand [4,17,69,236], which in turn required innovative strategies to manage patient load and care [8,16,30,57,58,79,124,158,284,298], not all of which were proven safe or effective (e.g. [242]).

Thus, there is a significant need to improve both the productivity and quality of care. In fact, the need for improved productivity of care can be traced to poor and very low uptake of productivity enhancing innovations in healthcare delivery [15,95,188,190]. As a result, there has been increasing discussion of digital forms of healthcare delivery in economics focused discussions [95,96,188], as well as clinical studies and editorials [28,41,109,119,168,287], with some studies noting the increasing burden on patients themselves.

Personalised care using patient-specific models identified from clinical data offers the means to directly manage the significant intra- and inter- patient variability characterising the ICU patient [55]. It adds automation to care, using digital technologies to improve quality and cost, as in many other sectors, but much less in medicine [15,94,188]. Thus, some level of automation will be necessary to improve the productivity, personalisation, and quality of care given society's increasing inability to meet rising costs and provide equal equity of access to care [15,28,207].

1.2 Healthcare context:
Intensive care unit (ICU) patients are complex and highly variable, making management difficult. Aging demographics, chronic disease, and increasing life spans drive increasing patient complexity and cost, which in turn increases length of stay and reduces equity of access to care [15,89,119,120,209,246,270,279]. Reduced equity of access to care increases poor outcomes [20,115,198], such as increased mortality due to reduced opportunity for timely care [72,120,209,270], creating further inequity. This positive feedback loop has negative consequences, but highlights the significant need to improve productivity and quality of care to address this issue, and applies to both ICU care, as well as healthcare in general.

Personalised care using patient-specific mathematical models, which are personalised to the patient using system identification methods and clinical data, offer the means to directly manage intra- and inter- patient variability [55]. In particular, ICU patient state is highly variable in key areas such as glycemic control [92,98,163,273] and mechanical ventilation [60,146,167], and can include differences due to sex [84,147,275], which can further contribute to inequity of access to both care and outcomes, which disproportionately affect the poorer segments of society [5,20,99,237]. Thus, such model-based care represents a potential means to improve outcomes by personalising care, and to also improve equity by enabling automation, improved productivity, and (thus) greater access to (better) care.

There is a further advantage to using deterministic models based on directly modeled physics and mechanics to guide care. Specifically, the reduction or elimination of personal and systemic bias. Bias in care, particularly racial bias, is increasingly being discovered via analyses of care and outcomes [117,180,238,259]. Racial biases often also mask or duplicate socioeconomic biases. However, a deterministic model-based care approach is strictly numerical and model driven, a "*one method fits all*" form of care [51,55].

In particular, racial or sex differences play zero role because the computational model used contains only direct physical mechanics terms identified and personalised using objective measured clinical data. Clinical data such as blood glucose level or airway pressure and flow are not biased or able to be biased as they are objective measures. Thus, physics models, objective measured data, and system identification methods offer a potentially powerful means to remove race, sex, socioeconomic status and other biases from care decisions.

As noted, the key difference is deterministic models. In particular and in contrast, machine learning and artificial intelligence approaches are data driven and increasingly touted as a healthcare solution. However, the data and resulting data driven algorithms can have unintentional bias, carrying over into care recommendations [199,206,289]. Thus, a deterministic, fully objective, model-based approach can significantly reduce, or eliminate, bias in the care delivery, which is a significant gain from implementing a model-based DT approach in its own right, even if no other gain was obtained from their use.

Thus, enabling automation, using digital technologies can improve quality and cost, an outcome which has occurred in many industries, but much less so in medicine [15,94,188]. Hence, from a healthcare context, automation and personalisation enable healthcare futures with improved equity of access to care and outcomes. In particular, improved equity of access not possible today nor with incremental changes in healthcare productivity.

1.3 Technology context:

ICU medicine is one of the most technology-laden areas of medicine, where the doctor or nurse almost always touches some form of technology, such as a ventilator or infusion pump, in treating the patient [271]. In turn, high levels of technology require understanding of the associated human factors and ergonomics for effective use [35,36,47]. Automation can streamline this process and current ICU technologies could be readily automated with existing wireless and wired technologies [108,141]. However, there is a significant lack of interoperability between devices, which hinders this process, despite calls for greater interoperability and human-centred automation in ICU care [90,116,140,226].

Thus, there is no automation technology barrier to automating critical and core areas of ICU care, such as drug and fluid delivery for glycemic control and cardiovascular management, or mechanical ventilation. These areas cover 90-100% of ICU patients, and are leading causes of ICU admission, length of stay, mortality, and, thus, cost. Equally, the hardware technology itself is often relatively simple [123,169,212,226]. The missing elements are in the area of digital twin modeling for clinical application, or virtual patients, and the difficulty in using them to find the appropriate model-based metrics upon which to titrate care [52,55].

In particular, computational physiological models can combine medical data and model identification methods to generate a “virtual patient” representing a given patient in a particular state and point of time for a given organ or physiological system (eg metabolic, cardiovascular, pulmonary). What is missing is a collection of accurate, validated virtual patient or digital twin models for use at the bedside to automate care. In particular, there are no accepted standards for modeling approach, model identifiability, or accepted levels of model validation, although some have been proposed [53,55]. Thus, the technological issue is one of linking existing bedside care delivery technologies and known communication and control technologies to their clinical medicine application.

Specifically, the lack of accurate, implementable virtual patient or digital twin models is the primary technical and scientific hurdle to linking measurements and care delivery devices to automate care in an accurate, personalised fashion.

1.4 Overall problem and need:

Hyper-automation and digital twins (DT) capture the essence of this potential model-based approach. They are also a major growth area in manufacturing technology [65,210]. 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, both the patients and the clinicians, where the former is the system controlled and the latter is part of the control or patient management. Both introduce cyber-physical-human aspects into DT implementation.

This chapter addresses the key modeling and social science links missing in bringing DTs to use in ICU medicine, including translating these concepts into a medical space. Specifically, how models can be created and effectively integrated into clinically applied DTs in the ICU, and how to address barriers to uptake of innovation in medicine [295]. Both issues hinder the creation of cyber-physical human systems (CPHS) in medical care, where one is a technical question and the other a social science question.

Given the deep interaction of physiology, medicine, and clinical practice with both modeling and identification methods in creating healthcare delivery digital twins, as well as the significant literature in each area alone, this review provides several added references to ensure suitable supporting citations for any interested reader to follow-up any specific area. The chapter should thus serve as a relatively complete reference to the current state of the art for a reader from any relevant background.

2.0 Digital Twins and CPHS:

2.1 Digital Twin / Virtual Patient Definition:
Digital twins arise at the intersection of Industry 4.0 and the internet of things (IoT). A DT is "*a virtual copy of a system able to interact with the physical system in a bi-directional way*" [65,155]. Bi-directional information exchange synchronizes virtual system response to match the physical system to "*forecast and optimise the behavior of the physical system in real time*".

In the manufacturing context, digital twins sit in the middle, on top of a "*control layer*" of supporting technologies, and under an "*enterprise resource planning*" layer integrating organizational functions and goals into how the DT is applied (**Figure 1**). The upper and lower layers both inform the DT and its design and use. The middle layer 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 digital twin (model) [197].

More specifically, DTs are defined by their integration [155]. A ***digital model*** (DM) does not interact with the physical system. A ***digital shadow*** (DS) has one-direction flow, updated with data from the physical system without returning a control input. A ***digital twin*** or DT arises when the DM is updated from physical system data, and the resulting simulation is used to control the physical system, or specifically, two-directional data flow integrating both the enterprise and control levels to create a full system.

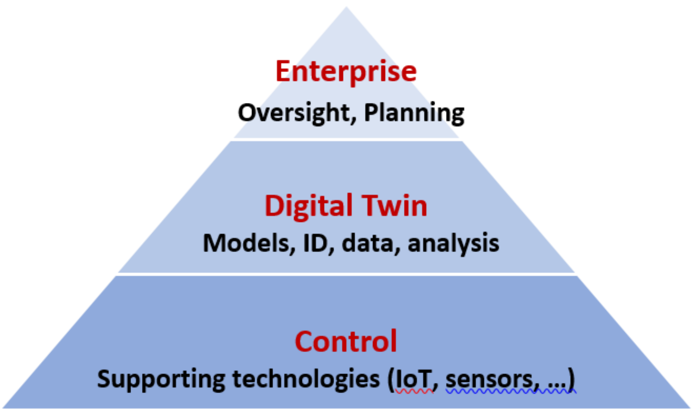

Figure 1: The DT lies between supporting technologies and a guiding organisation level or protocol, where this figure is based on [59].

In medicine, the physical system is the patient and their particular organ or physiological system to be managed. The control layer is created by communication and command/control technologies, sometimes referred to as the medical internet of things [108,141], and connect the sensor measurements and care delivery technologies to the DT model. The enterprise layer defines how a DT model is applied clinically, typically via an agreed protocol for care using the DT [49,55]. The result is the control loop in **Figure 2**, showing also the main elements of **Figure 1**, where bi-directional information to and from the DT is clear.

Specific to the DT model, **Figure 3** shows the specific steps for model updating and subsequent use to predict patient-specific response in a real-time loop. **Figure 3** thus defines a "virtual patient" in the context of its application. Virtual patient or DT models are thus the core of a DT application in medicine, where, as noted, control layer technologies connecting the DT model to sensors and delivery devices are within current technology capabilities.

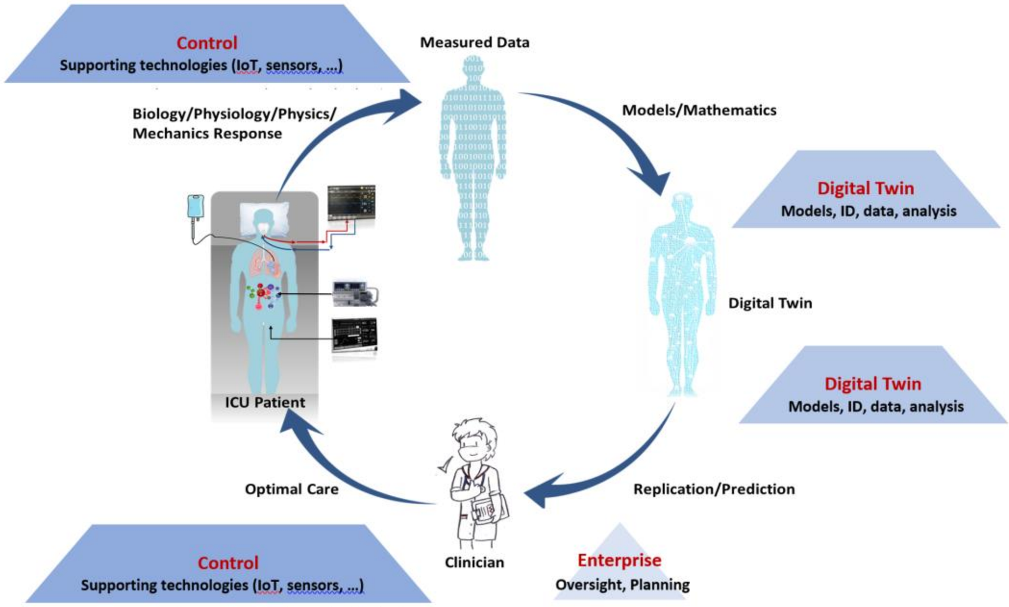

Figure 2: DT control loop in medicine with clinical staff in the control loop and main elements or blocks of **Figure 1** schematically showing where they are applied in this application loop.

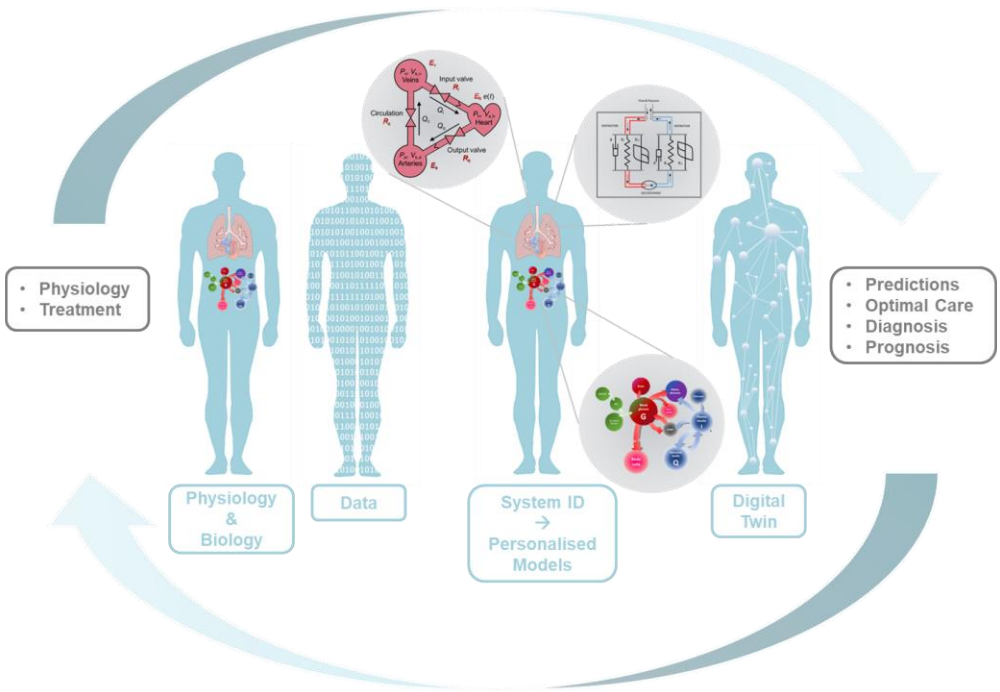

Figure 3: DT model creation and updating from clinical data, leading to prediction of response, and subsequent new data.

From **Figures 2-3** interventions are optimised via prediction and a clinically agreed protocol for using the DT within the clinical workflow [47,257,286]. In this framework, the protocol is derived from clinical standards and local approaches to care, and thus comes from the Enterprise level of **Figure 1**. Finally, the clinician in the loop in **Figure 2** is there primarily for safety, but could be removed given full automation. Full automation creates a "*human-in-the-plant*" system when fully automated, and is also a "*human-in-the-controller*" element if clinical input is required to confirm choices or for safety [240].

2.2 Requirements in an ICU context:

Given either interoperable devices and communications (e.g. [108,200,258]) or clinical personnel in the loop, the requirements for a DT model in an ICU context thus include:

- *Physiological relevance*
- *Clinical relevance*
- *Treatment sensitivity, practically identifiable from clinically available data (non-additionally invasively via no new sensors added is preferred).*

Physiological relevance requires a model structure capturing relevant dynamics. To be useful, these models must be able to reproduce the measurable physiological dynamics to the resolution of available sensors [37,174,296]. *Clinical relevance* emphasises models simulated in 'clinical real-time' used to make predictions about changes in care to guide decisions, where the model inputs and outputs match the clinical situation. These two requirements thus define the feasible range of model structure and complexity.

A *treatment sensitivity identifiable from clinically available data* is the crucial element in titrating care, assessing rate of change of output variable per unit of input administered. For example, insulin sensitivity [26,50,52,67,75,76,88,121,126,128,159,162,170,171,173,183,215,218,290] in metabolism and recruitment elastance in pulmonary mechanics [13,40,60,230-234,251,255,256,277,278], where they capture patient state and are often clinically used in simpler forms to guide care [21,34,38-40,105,114,157,219,253]. In cardiovascular management these sensitivities do not yet exist as the desired outcome metrics of stroke volume or stressed blood volume cannot yet be directly measured, requiring a model-based sensor from which to derive a sensitivity [139,142,178,179,204,222,297], where these measures increasingly called for clinically to guide care [42,43]. The final element is the requirement to be *practically identifiable* using available clinical measurements so further invasive measures are not required [6,7,66,87,174,217,243]. Overall, these requirements limit both minimum and maximum model complexity and structure, within which a DT model and DT system solution can exist for a given problem.

Implicitly, these requirements also include specific cyber-physical-human-system aspects from two perspectives. From the patient perspective, the modeling captures their human physical state from the available measurements. Equally, from the clinical staff perspective, model inputs and outputs representing only key available metrics places the models and resulting digital twins directly into the same care space clinical staff occupy. Thus, these model requirements implicitly include human-centred aspects of care, and with an enterprise level protocol they also include the human input to, and control of, care.

2.3 Digital twin models in key areas of ICU care and relative to requirements:

Physiological models are very common in the scientific, particularly engineering science, literature. These models cover a range of ICU and other areas of care, physiological systems, and potential clinical applications. All these models can be assessed by their potential use as one of three specific types of system models. In particular: **1**) digital models (**DM**); **2**) digital shadows (**DS**); or **3**) digital twin (**DT**) models. Thus, the clinical requirements in Section 2.2.

link these models to their potential clinical uses, and DT models sit within the middle control layer of **Figures 1-3**.

In particular, by use, most models are, in fact, DMs, used to analyse information, validated offline, but with no ability to be personalised or updated. Models capable of being personalised from data in a clinically relevant timeframe, or “clinical real-time”, are DS. Very few offer the clinical real-time identification and prediction accuracy to optimise patient-specific care as a DT model. More simply, there is a hierarchy comprising many models (DM), relatively very few can be identified and personalised using available clinical data (DS), and only a few of those remaining offer prediction accuracy able to guide care [54].

There is also the ability to call upon a growing range of models, methods, and databases, ranging from simple to detailed and at multiple scales of physiology, space, and time (e.g. [11,19,22,29,33,37,46,48,51,70,71,75,77,107,127,133,136,143,182,202,215,218,221,247,261,264-266,269,283,290,291,299]). However, for deterministic, physiologically relevant digital twin models, the overall approach relies on identifying patient-specific and time-varying parameters capturing all relevant intra- and inter- patient variability for use in titrating care to clinically recognised endpoints. These parameters typically relate clinical inputs or care to clinical outputs or metrics defining (successful) response to care.

These “sensitivities” are the key, as they provide an input-output relationship reflecting patient status and response to care, and can thus be used to titrate delivery. However, this approach thus defines the feasible model structure and complexity. Specifically, it segregates more complex anatomically and biophysically based models (referred to as ‘physiome models’) to an informative role, by requiring simpler models for immediate use at the bedside (referred to as ‘bedside models’).

In more detail, physiome models can provide significant insight into dysfunction at levels bedside models, with their simpler single organ and/or single system dynamics, cannot [74,131,132,134,135,227,239,247,261-264,266,282,294]. Physiome models can be patient-specific, but require significant amounts of data, which are often not typically available at the ICU bedside, thus precluding use in real-time care. In contrast, the last 10-15 years has seen growing numbers of model-based sensors and decision support systems in critical care (e.g. [24,25,68,80,91,100,102,160,165,172,189,214,216,222,225,231,233-235,257,280,281]), including in some very rare cases their implementation as a standard of care. There is thus growing interest in using computational models to guide care of ICU patients.

Thus, in a DT context, medicine and physiology offer many DMs, models informed by data, but not receiving real-time patient data [132,201,239,282]. However, most are too complex to be personalized in real-time with available data [7,18,45,55,87,223,224,243]. The vast majority of physiome models fit this category. There are several examples in the metabolic [1,56,78], pulmonary [31,32,192,260,264], and cardiovascular areas [81,134,239,247].

DS models are increasingly common, differentiated by their identifiability from the relatively limited clinical data typically available at the ICU bedside [51,56,82,192], which effectively limits these models complexity. They have been used to assess new medical technology applications [301,302] and protocols [102,274]. However, very few to none are used in regular care, and thus are not DT models, where it is important to note < 1% of model-based decision support systems are implemented beyond testing, let alone as a standard care [106,288].

A DT model is further differentiated from a DS by its (critical) ability to accurately predict the outcome to changes in care or dosing, and to do so in clinical real-time for decision support. DT models innately include application and are very rare. In short, while many models exist, few are identifiable, and even fewer can accurately predict patient-specific response to clinically reasonable changes in care well enough to guide care.

In cardiovascular systems modeling DT models and model-based sensors are just emerging for tracking key clinical and physiological variables like stroke volume and stressed blood volume over major changes in patient state or care [81,195,196]. For pulmonary mechanics, the first accurate predictive models have emerged since 2018 [191,193,194], culminating in very accurate nonlinear models of mechanics capturing all key metrics in ventilation care [150,254,300]. Finally, the metabolic area is furthest along with several DS models [26,101,102,149,164,177,187,214,281,290]. There are also full DT models in standard of care use in ICU and NICU (neonatal ICU) care [85,86,100,128,149,252], as well as in outpatient diabetes [27,154,267].

Prediction accuracy requires validation to ensure trust in the methods and approach, based on accuracy relative to clinical metrics and goals, as defined in [55]. The gold standard is the ability to capture a cohort of patients with accurate prediction so entire cohorts of predictions match, or a cohort-based cross validation. To date, only one model has achieved this outcome (twice) across multiple cohorts, which was in the metabolic modeling domain [50,86]. Patient-level prediction accuracy has been demonstrated for any model in standard of care use, as noted above, but has also been recently demonstrated for pulmonary models [254,300]. Cardiovascular models are not beyond the DS level at this time, and thus not yet validated for DT use in care.

Validation of prediction accuracy defines the level of confidence in a given DT model meeting all other requirements. It is the key element verifying whether a potential DT model can make the last step for use in care, where a model alone is not enough. In short, prediction is the key to turning a model that meets the requirements of a DT, into a DT suitable for guiding care.

2.4 Review of digital twins in automation of ICU care:
As stated, there are extremely few DT models in use in care at this time. They are all part of metabolic control systems [27,85,86,100,128,149,154,252,267]. In particular, the STAR and eMPC glycemic control systems in ICU care, and similar artificial pancreas solution for type 1 diabetes, are the exemplars. There are thus three examples of such models with largely automated control, despite a human control element in the loop (per **Figure 2**). An equally limited selection of truly well-validated models is the limiting factor in greater examples.

Relevant to core ICU care areas, pulmonary models have very achieved the level of prediction accuracy necessary for use in care as a DT in all common mechanical ventilation modes [150,254,300]. However, they are not yet in use as a DT, although clinical trials are planned [148]. These DS models do show a pathway to DT automation using accurate prediction of key outcomes to guide care. For example to safely set positive end expiratory pressure to minimise lung elastance [2,110], maximise recruited lung volume [272,285], and simultaneously minimise the risk of over distension and ventilator induced lung injury [12]. Such multi-dimensional optimisation problems are typical in mechanical ventilation [181,192] and can be best managed via an objective, automated DT instead of relying on clinical experience and intuition, which can over simplify such problems due to their higher dimensionality.

Equally, cardiovascular management is only nearing the digital shadow, DS, phase. In particular, recent models enable personalised model-based sensors to assess key metrics to guide care, which are unmeasurable without extensive invasive measures otherwise. These measures, such as stroke volume and stressed blood volume (perfusion) [195,196,248,249], will enable similar predictive accuracy and the ability to personalise and optimise a very difficult, multi-dimensional clinical optimisation problem [81].

The question thus arises as to what are the major aspects hindering adoption and uptake?

The only bi-directional DTs in clinical ICU use are also not fully automated, with a human in the loop (e.g. [149,252]). Thus, where a proven, validated DT model exists, the main element missing reverts to being technological, and is 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.

This issue has been a great source of difficulty for proprietary and other reasons [129,138,140,184,226,241,293]. It will grow importance and be a greater hurdle as more DT models able to be automated emerge. Whether this is addressed by change within the medical and healthcare industries and infrastructure, or via open source approaches remains to be seen and is outside the scope of this review.

2.5 Summary:
The key element to implementing digital twins in ICU, or any area of healthcare, is the need for an accurate DT model, able to be readily personalised and accurate in prediction to guide care. While there are many models in many core areas of care, few are able to be digital shadows (DS), and far fewer have been validated in their prediction accuracy or use as digital twins (DT). There are further issues of technology interoperability hindering full automation, which can be resolved through either added, external sensors, or via greater access. Beyond the technological, there are social factors affecting uptake, which are addressed in the next section [295].

3.0 Role of Social-Behavioral Sciences:

3.1 Introduction:
Having 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. Worryingly, patients benefit from only 30-50% of validated healthcare technologies [113,245]. If the issues surrounding technology implementation are not remediated, at least half of the DTs that pass rigorous clinical validation will fail to be successfully adopted into ICU healthcare practices.

Considerations of factors other than technical aspects of DTs is the key to enabling successful adoption. From a social-behavioural perspective, technology adoption is more than the acceptance of new technology in an environment. Sustainable adoption requires new technology to be integrated into the everyday processes of the healthcare delivery unit [3], and for the use of technology to be 'normalised' as part of protocolised healthcare. This requires consideration of social factors at the individual, the team/unit, and the organisational system levels, and the dynamic inter-relationships across these levels.

Socialisation of new technology to clinical staff can begin prior to its implementation into workplaces. That is, staff should be engaged at the technology development stage, when aspects of need, ergonomics, and ease-of-use are deliberated. Co-design principles not only ensure compatibility of DTs with existing practices, but generate a sense of ownership over its final design with staff [23,161,175,186], increasing the likelihood of successful adoption.

3.2 Barriers to Innovation Adoption:
Majority of barriers to technology adoption relate to individual employee perceptions, including their past experience with technology [104,152,185,244], perceptions of the new technology's usability, the expected benefits of the innovation (system usefulness; Kruse et al., 2016), and ease of use [104]. Other factors driving technology adoption decisions relate to individuals' motivation to use the technology [238], their ability to learn to use the technology [237] and

their level of trust towards the technology [240].

Emotion-based elements can similarly hinder the adoption process, with the fear of technology being the most commonly cited negative emotion surrounding technology adoption. Clinical staff can be fearful of procedural changes at work and of the implications of technology on their professional identity [152,156], including the possibility of aspects of their role being replaced by technology and their professional credibility undermined [152]. The capacity to provide high-standard quality of care is a core value in healthcare professionals [151]. Therefore, the introduction of new technology can give rise to fears of depersonalisation of healthcare, and thereby fears of reduced quality of care [104,152,176,185].

In addition to individual cognitive and emotional factors related to adoption, consideration should be placed on the hierarchical nature of healthcare and the group-level social dynamics. Healthcare delivery teams rely heavily on conformity through hierarchical decision-making processes to maintain performance and minimise risk [130]. Power dynamics across specialists–nurses, clinical–non-clinical staff, and unit-level managers–medical decision-makers likely influence the process of technology adoption. Rigid hierarchical structures within units and teams are known barriers to communication and collaboration [9] and likely hinder opportunities for peer support, which could otherwise assist the adoption process. Peer attitudes can also be a barrier to adoption, specifically in the case where an influential peer is resistant to adoption [104,111,112,276].

At the organizational system-level, communications from healthcare management about and support for technology use is crucial for sustainable uptake [104,137,156,244]. Clear communications about the need for new technology and appropriate change management processes [153], in addition to workload management to enable appropriate levels of engagement with technology and training prior to implementation [93], clearly increase the likelihood of adoption.

In addition to these organization-level factors, barriers to technology adoption can be reduced if healthcare practitioners are involved, or in some cases, even drive, the technology development. In particular, practitioners in supervisory roles can play the part of change leaders: offering both instrumental (e.g., consistent and clear communication about the change [137]) and relational support (e.g., instilling a positive learning culture supportive of the new technology [295]) to staff.

3.3 Ergonomics and Co-Design:

The development stage of new medical innovation is an opportunity to engage clinical staff, the intended end-users, to commit to and accept the new technology. This participatory, co-design process involves 1) developers gaining insight into the working lives of the end-users through accessing contextual knowledge, and 2) a feedback loop between developers and end-users, creating opportunities for mutual learning and understanding of the usability of the innovation under development [122].

The co-design process relies on multiple information gathering methods, where insights are gained through observations and interactions with end-users (e.g., via ethnography, interviews). Mutual learning can occur through these informal interactions and more deliberately as part of the design process, such as hosting in-person informational workshops for end-users [103], and prototyping iterations of the innovation with end-users. Formal and informal interaction and information gathering can be triangulated with data on usage of various technologies and processes, creating a richer and more nuanced perspective of activities relating to technology implementation. Basing the development of technology on a more comprehensive understanding of how it can work in the healthcare context will increase the likelihood that it is deemed relevant by the end-user.

Through participatory co-design, siloed thinking between technology developers and end-users is reduced [10]. At its best, co-design involves boundary-less interaction between developer and users, resulting in the final technology being fit for purpose and able to meet the unique needs of the end-users and their healthcare context [205]. When successful, cognitive and emotional barriers preventing successful adoption can be addressed and alleviated at the stage of development. Staff are empowered by their involvement [83], which will allow for quicker buy-in during the implementation period.

Co-design is not without its challenges, however. In any participatory project, barriers can occur at the collaboration (e.g., power hierarchies; lack of psychological safety to raise concerns), organisation (e.g., lack of staff training in using the new technology), process (e.g., lacking connection to other developments), dissemination (e.g., reliance on a few insiders for spreading co-created knowledge), and information collection stages (e.g., poor choice of methods [220]). Further, developers and end-users are typically from different fields and have different expertise, and this diverse understanding of knowledge and values can hinder collaborative co-design [229].

Within the context of healthcare, tensions of co-design involve balancing the need for change versus resistance to change, focusing on patient-centred outcomes versus staff-centred needs, and balancing the value of innovation versus financial constraints [73]. A clear obstacle to successful co-design is resource constraints. Collaborating on technology development is often an extended, time-consuming process, potentially taking staff away from their core tasks, resulting in frustration and work overload. Investing in a sustainable participatory approach that allows for end-user engagement in design is likely to reduce multiple barriers to successful implementation, ultimately leading to the anticipated benefits of technology such as more accurate, objective, and equitable treatment approaches.

3.4 Summary (key takeaways):

Digital twins offer a unique opportunity to transform ICU care. However, this opportunity carries significant potential change in process and how care is given, along with change in the range and complexity of digital tools employed in care. They are also cyber-physical-human-systems. Both aspects require careful consideration of the social science aspects in both usability and ergonomics, as well as design and implementation directly addressing innovation adoption.

To successfully implement novel technology and achieve end-user uptake, a number of social-behavioural factors need to be considered at the individual, team and enterprise levels of healthcare system. The existing research on barriers to technology adoption mainly focus on the individual employee perspective, and has so far not managed to solve the problem. We propose that the solution lies in understanding and addressing the socio-relational aspects of the system, particularly those centered on the decision-makers at the enterprise level who enable technology adoption and uptake.

Similarly, success in technology adoption requires early engagement of end-users—the medical staff. Co-design principles can enable this and result in the innovation filling a gap in healthcare delivery needs. Yet, the success of co-design is also burdened with challenges, including resource constraints such as end-users' time to engage in the development process.

4.0 Future Research Challenges and Visions:

4.1 Technology vision of the future of CPHS in ICU care:

The science and technology for all necessary elements of DTs in ICU care already exist. There are modeling hurdles to overcome, but those elements are already under development with some models and other elements already in standard of care use. Thus, the primary technological hurdle to a future with significant use of digital twins in care is one of incumbent barriers to entry in making medical devices interoperable, a nascent area in its own right [129,138,184,293], where some have taken to creating their own interoperability [166,169].

An interoperable future, enabling digital twins in care would create low cost, commoditised devices, most of which are relatively simple and which is a relatively new field itself [123,203,212,213,228]. These emerging devices would not only reduce costs, but separate hardware and the data in the device, including command and control. In essence, such a change would create the opportunity for digital twins and full automation where incumbent barriers make this very difficult currently. **Figure 4** shows how unlocking these elements could create new opportunities for digital twins and cyber-physical-human systems in healthcare, including new products and services to further optimise care and outcomes.

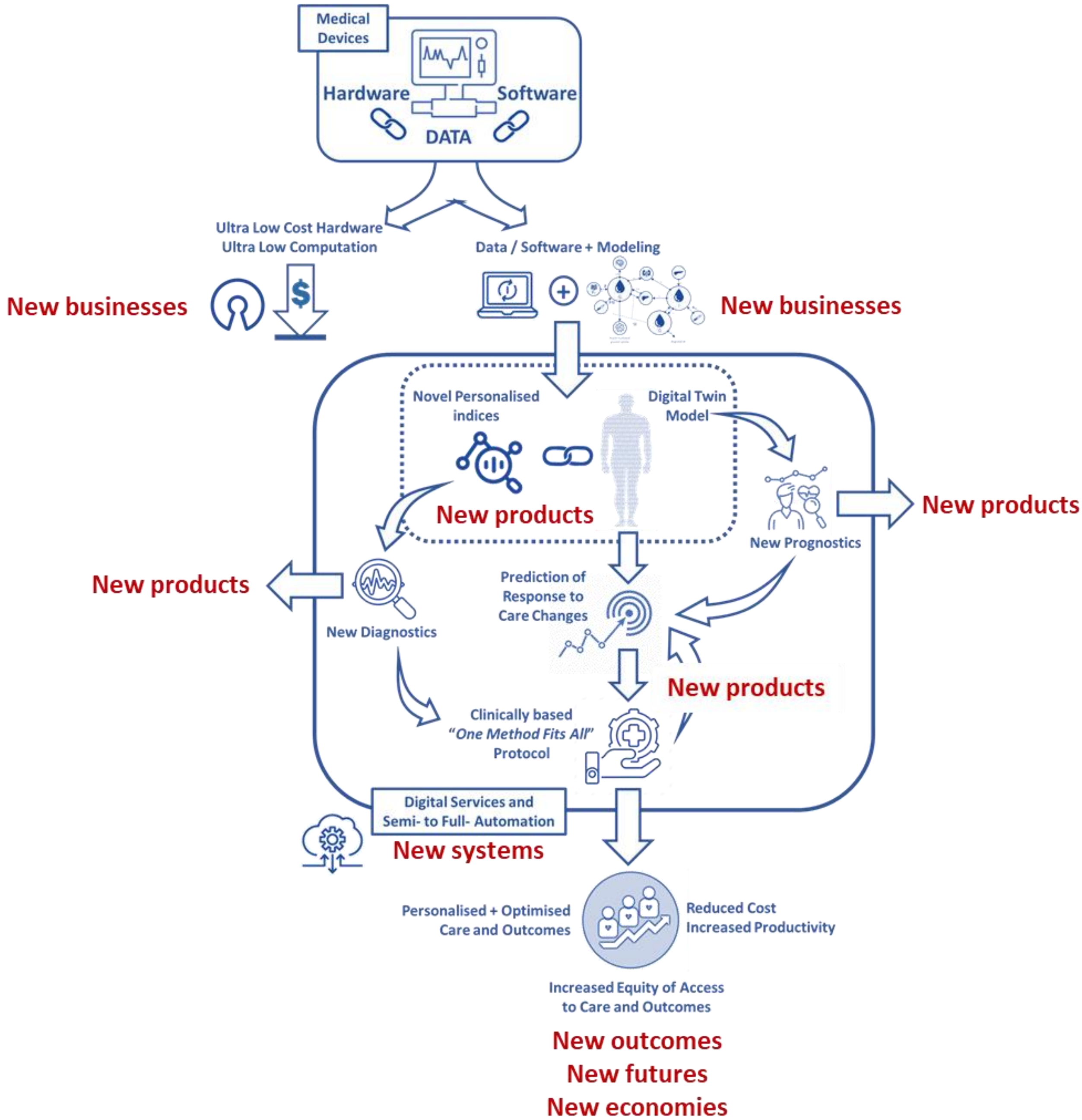

Figure 4: Technology vision of a possible future of CPHS in ICU care by separating the hardware of medical devices from the software, control, and data these devices also contain

and link together within the device.

Importantly, this path leads to interoperability. Equally, separating the hardware and computational aspects of a device is not new or novel in general, although it is a significant disruption to medical devices today. In particular, the well-accepted "Christenson model" of innovative disruption [63] envisaged innovations emerging as novel, or even higher cost, solutions for specific areas, which grow to provide dominant solutions in many fields holding to a given status quo solution.

In this case, digital twins emerging elsewhere may more significantly alter the status quo of ICU care delivery than other areas, which have already made significant productivity gains. The aspect of being wedded to a status quo solution to the detriment of productivity and innovation is thus particularly relevant to healthcare and its need to embrace novel solutions from other fields to enhance productivity and create social, as well as economic, change [64], where personalised care is a core element of this disruption [61,62].

A clear analogy arises in portable memory storage, where larger portable disk drives have given way memory sticks and portable solid state drives, which in turn are yielding to cloud data storage. A similar virtualisation of computational elements, moving hardware to the cloud, has further delinked computation, data, and the hardware or location upon which it occurs. Digital twins in manufacturing already make use of these virtualised solutions, and their arrival into healthcare should not be surprising.

Finally, writing on healthcare and innovation in social change, Christensen et al wrote: "*What's required is expanded support for organizations that are approaching social-sector problems in a fundamentally new way and creating scalable, sustainable, systems-changing solutions*." [64]. This vision matches ours, where enhanced DT models and interoperable/open devices can create this sustainable change to fundamentally alter ICU care, and health care in general. In particular, where much of this computation and data are decentralised or cloud based (even if locally cloud based for security), there will be increasing separation of hardware from software, data, and computation. Thus, these types of digital twin solutions will, in turn, fundamentally impact society and its equity of access to care and outcomes.

4.2 Social-Behavioral Sciences vision of the future of CPHS in ICU care:
Across development and implementation of healthcare innovation the common underlying theme is that fostering relationships is required to ensure innovation uptake. Within the implementation stage, this can involve decision-makers engaging with managers, early adopters, and staff of influence. At the development stage, this can involve engaging clinical staff in the development of technology from the outset; i.e., decision-makers prioritising developers' access to staff who will be the eventual users of the technology. Thereby, the future of CPHS in ICU care from a social-behavioural science perspective includes a commitment from the enterprise-level in the socialisation of novel technology, such as DTs, into healthcare workplaces. Ultimately, the buy-in for CPHS needs to occur at the highest enterprise level among the decision makers themselves.

We present a framework for supporting medical decision-makers in understanding and managing the social dynamics around technology adoption attitudes, which are the cognitive and emotional inclinations to *"accept, embrace, and adopt a particular plan to purposefully alter the status quo*" ([125]; pp. 235). Considering workplace social dynamics as a social feedback loop between the individual and other groups of people in the work system, there are three key relationships within a healthcare context containing social feedback loops: clinical staff and **1**) their team members; **2**) their supervisors; and **3**) their patients (**Figure 5**). Taken together, while an individual staff member may have a predisposed inclination towards technology (e.g., history with similar technology), attitudes are further constructed when they engage with or hear of team members, supervisors, and/or patient opinions of new technology.

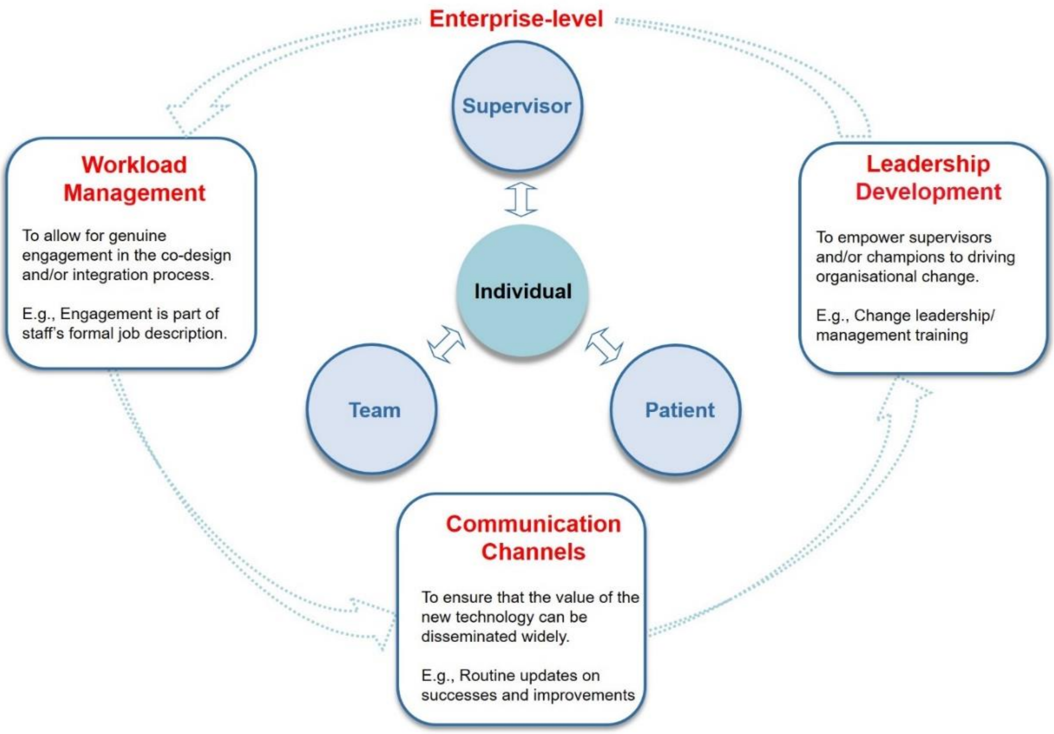

Figure 5: A framework around social feedback loops for medical decision-makers to drive innovation adoption in healthcare [295].

Equally, without adoption, innovation cannot thrive. Within this framework it is now possible to consider technology adoption as a dynamic temporal process which requires medical decision-makers' commitment over time. Further, introducing a new technology seldom is a concise event, the acceptance and adoption take place over time, and thus could be considered a manageable process, which can be optimised to maximise impact for patients, caregivers, and healthcare systems.

Therefore, we recommend three specific management areas for medical decision-makers to invest in to socialise technology adoption:

1. We suggest clinical staff workload should be managed at all times to enable genuine engagement in developing and integrating new technology in healthcare workplaces. We further recommend staff's availability to designers (to aid co-design of technology) and for training (to learn how to integrate new technology in the workplace) be part of their official job description that is prioritised.
2. We suggest formal and informal communications are set up across healthcare organisation so information about the use and value of the new technology can be disseminated widely. We further recommend medical decision-makers encourage and reinforce feedback from clinical staff regarding the technology (e.g., follow through with suggestions for improvement, celebrate small adoption successes of individual or team champions).
3. We suggest clinical staff in positions of power and influence (e.g., supervisory role, champions) be trained and supported in managing organisational change, as technology adoption is a change in the workplace. We further recommend development opportunities focus on both the instrumental (e.g., routine communications about the new technology) and emotional aspects of change leadership (e.g., managing diverse attitudes regarding the new technology).

4.3 Joint vision of the future and challenges to overcome:

Given this segregated discussion, there is significant overlap between technical and social sciences in the creation and implementation, including adoption, of DTs in ICU and in healthcare in general. **Figure 6** shows how these roles overlap in this timeline, including the impact of social dynamics over all stages of this process. In particular, the technical and scientific development of DTs for healthcare, though nascent, has overlooked the key role social sciences can play in making these innovations a clinical reality, including the role of social dynamics in all these interactions.

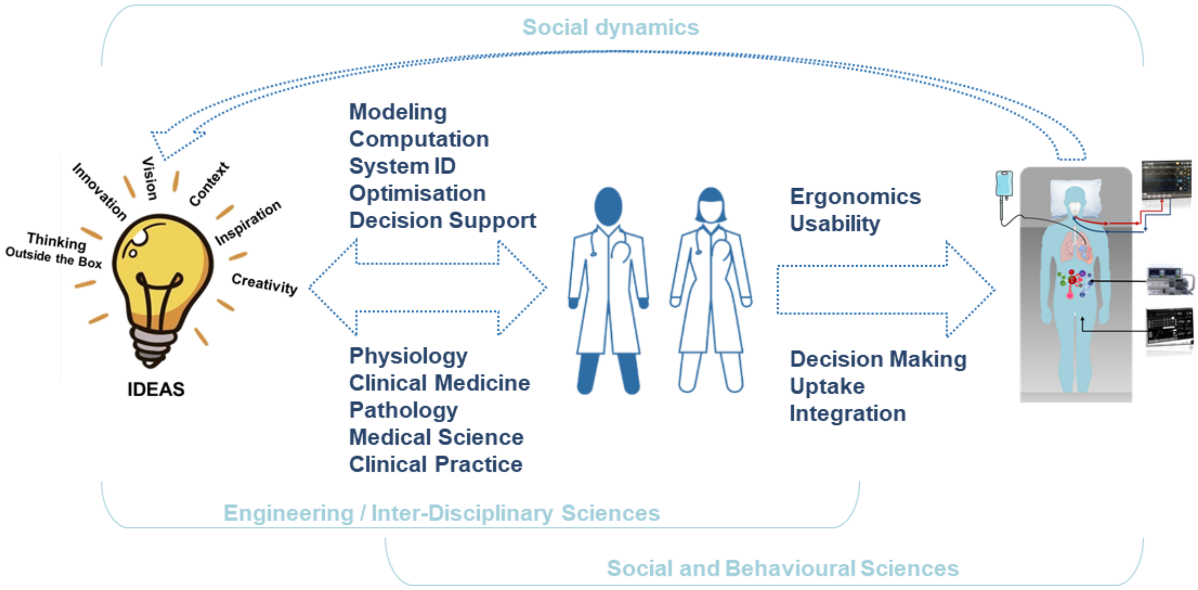

Figure 6: The overlapping roles of technical sciences and social and behavioural sciences in taking DT innovation from "science bench to clinical bedside".

As noted, issues of clinical and patient uptake are addressed via social sciences engagement in the technology development. However, ethics have not been explicitly addressed in this framework. However, ethics is implicit in every step of the development and uptake process. In particular, the clinical trials to develop and prove these CPHS and digital twin systems require ethics approval from each centre, each of which will reflect their local or national perspectives. Thus, these issues are directly addressed within the process.

Overall, **Figure 6** summarises the joint vision for DT innovation and its use to improve care and outcomes. This view envisions co-design, development, and implementation will be able to optimise innovation outcomes at all stages of development. As a result, it envisions a tighter connection along the engineering-clinical-social science axis, which needs to work in as highly integrated a manner as possible to maximise the potential outcomes and benefits for patients, clinical staff, healthcare systems, and society.

5.0 Conclusions:

Digital twins are emerging in manufacturing and for optimising the use of advanced, complex systems, such as aircraft engines. These overtly technology focused digital twins can be readily automated, and with the right digital twin model, controlled and optimised with little to no human intervention outside of setting goals for utilisation. However, the first key outcome from this state-of-the-art analysis is translating digital twins to healthcare, and the ICU in particular, requires consideration of the human(s) in the loop.

In particular, digital twins in the ICU are cyber-physical-human-systems. There is human input not only at the enterprise level to protocolised care, but also in terms of the patient, where modeling is more nonlinear and less certain than with purely physical, technological systems. Further, there is the clinical staff in the loop, doctors and nurses particularly, who use the digital twin in care, and have to work with it within a highly dynamic, highly variable work environment. These aspects force translation of the digital twin concept and approach to ICU care to significant consider these human constraints and inputs.

Technologically, the key missing element to fully automate care is the digital twin model, where automating command and control signals from devices presents no specific technical hurdle. Thus, while device interoperability is significantly limited, open devices are emerging to enable digital twins in this space, and new business models can emerge where the data is separated from the hardware used to deliver care, creating new opportunities to improve care and healthcare economics.

Digital twin models are extremely limited. There are significant constraints on their complexity created by the need for real-time identification from limited data, and their need to mesh well within variable clinical workflows so they are able to be effectively integrated into the wider care of the patient. As a result, there is a significant lack of digital twin models in use, but, in contrast, significant opportunity to create and validate them to meet these constraints and emerging validation requirements.

Finally, this analysis recommends far greater co-design and overlap between the engineering sciences leading digital twin research and modeling, and the clinical end-users. This co-design includes not just frameworks to enhance adoption of what is a significant innovation in the delivery of healthcare, but also creating the means to enable clinical staff to see this significant change in a positive manner and to further champion these changes in the clinical space. This co-design would significantly enable faster adoption and uptake of new ideas into ICU care to benefit patients and healthcare systems alike, and clearly highlight the ongoing cyber-physical-human-system aspects of digital twins in healthcare.

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