Model-based Management of Cardiovascular Failure: Where Medicine and Control Systems Converge

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Abstract:

Cardiovascular disease is growing epidemically worldwide, multiplying the impact of increasingly aging populations on intensive care unit (ICU) demand. It is the leading cause of ICU admission, length of stay, mortality and, as a result, cost. Hence, there is a significant need to bring the gains in productivity enabled by automation and control systems technologies, which have arisen in so many sectors, to medicine and this field in particular. This review presents the background to the problem and the main issues arising in care from a control systems technology perspective. It then presents a vision of a more automated future with specific goals in the areas of dynamic systems modeling, system identification and control. These areas are reviewed, followed by specific recommendations for the field, where control systems expertise can be leveraged to best advantage.

Keywords: Cardiovascular, Control Systems, System Identification, Identifiability, Intensive Care, ICU, Critical Care.

1.0 Introduction:

Acute cardiac/circulatory failure (ACF) and shock are defined by the inability of the heart and circulation to provide oxygen delivery to meet tissue demands [1]. It affects ~30% of intensive care unit (ICU) patients [2], and is a leading cause of ICU admission, length of stay, mortality, and cost [3]. Mechanical ventilation, fluid resuscitation and administration of inotropes are key elements of shock early management, where the latter two directly impact heart function and circulatory performance in providing perfusion to organs and peripheral tissues. For patients with chronic cardiac failure or acute cardiac failure who cannot be stabilized with fluids and inotropes, circulatory support devices could be used to support the failing ventricle and maintain adequate perfusion. Short-term assistance such as extracorporeal life support and extracorporeal membrane oxygenation are used first before a more permanent solution is planned with, for example, implantable ventricular assist devices (VAD) [4].

In the acute phase, fluid resuscitation is typically the main effort [1, 2] and inotropes are used to support cardiac ejection [5]. Fluid resuscitation primarily supports the circulation in adding fluid to the circulation to provide greater perfusion pressure, as ACF and sepsis patients suffer from reduced systemic pressures [6]. It has the secondary effect of increasing blood ejected by the heart due to increasing the preload to the heart. In contrast, inotrope drugs induce greater heart muscle contraction to increase the volume of blood ejected and increase perfusion pressures [7]. The goal in both cases is increased cardiac output (CO) via larger stroke volume (SV) of blood ejected per beat [1] to increase stressed blood volume (SBV) and tissue perfusion to exchange oxygen and wastes, and mitigate organ failure [8]. Hence, they are both concerned with managing cardiac and circulatory control.

Currently, measurements of CO, arterial pressures (AP), and central venous pressure (CVP) are the key metrics used to guide care and determine response to fluid and inotrope therapy [1, 2, 9]. However, CO is only intermittently monitored, has major limitations in its measurement, and requires frequent recalibration when conditions change, which is when it is most needed to be accurate [10]. As a result, "*no CO monitoring device has fulfilled an independent ideal validation*" [11], and no other continuous, calibration free measure of SV exists according to recent European consensus statements on care in ACF and shock [1]. Equally, CVP and AP data is often under-utilized despite the wealth of data they

contain [2, 12], as pressures are only moderately correlated with the SV and SBV volumes desired. Finally, there is no non-invasive, continuous means to directly measure SV, SBV or perfusion [13], making the overall control problem difficult as only moderate surrogate measures are available and models linking them to the desired metrics do not exist and/or are not yet proven [14].

Equally, inotrope therapy and cardiac function would appear easy to titrate using systemic pressures from a standard catheter. However, recent studies have shown titrating inotrope drugs to a target mean arterial pressure is not necessarily effective, may result in far greater doses than necessary with associated negative effects, and lower pressure targets may offer better outcomes for some patients [15]. Again, this result arises because the clinically available measurements are imperfect surrogates of the desire quantities for managing and controlling this medical problem.

Hence, there are few reliable measures available to guide fluid therapy and inotrope delivery. As a result, prediction of fluid responsiveness is "*still difficult*" [2, 16, 17], and "*pragmatic endpoints are difficult to define*" [2]. Hence, only ~50% of interventions are effective, with the rest having a deleterious or no effect [2, 18]. Unsurprisingly, a recent survey [19] on fluid resuscitation showed 43% of fluid challenges are performed without using hemodynamic metrics, essentially dead reckoning control of a difficult, highly nonlinear system. Static indices, such as CVP, are used 36% of the time, despite repeatedly proving ineffective [19, 20]. Therefore, only 21% of fluid challenges use dynamic indices as recommended by European ESICM consensus guidelines [1], and many of these, as noted, still fail. The result is patients receive too much volume that is ineffective and effectively "drowns the patient" creating increased reliance on mechanical ventilation and further care issues [21]. As noted, the same holds true for inotrope drug delivery.

Why?

First, dynamic indices can only be applied to between 2% [22] and 42% [23] of ICU patients.

Second, they are influenced by many external variables, and often ineffective, where several studies found a "*grey zone*" covering 24% [24] to 62% [25] of patients where dynamic indices were inconclusive.

Third, reports of several technical issues indicate dynamic indices are difficult to implement clinically, further reducing impact and effectiveness [22, 25, 26].

Both cases suffer from the use of poor surrogate measures, variable patient-specific responses, and poor insight in actual patient condition. These issues lead to poor, highly variable, and ineffective care. As a result, there has been little to no improvement in patient outcomes despite a wealth of technology

Hence, there is a major unmet clinical need for next-generation solutions linking technology and modeling to create better answers, and specifically asking us, as a field, to:

1. *Use Advanced Modeling to Create* non-additionally-invasive ICU measurements for real-time measurement of SV and perfusion or stressed blood volume (SBV), creating better measurements of the direct variables we wish to control.

2. *Optimally use* these 2 new, not previously available measures to clarify the physiological picture and create next-generation, model-based protocols to personalize and optimize fluid therapy – a "*one method fits all*" approach personalizing care, versus today's ineffective "*one size fits all*" protocolised care, where these 2 new measures were not previously available.

Achieving these goals will significantly advance the state of the art and state of care in ACF and shock patients. They move well beyond current, ineffective indices that are unable to directly measure the real desired endpoints of managing ACF, SV and SBV perfusion. Finally, they offer the opportunity to link continuous use of standard measurements to computation, to provide the measurements necessary to close the loop and apply model-based control systems to create the personalized and automated care defining the future of medicine.

Control systems in all its areas can be seen to play a major role. From dynamic systems modeling and validation to system identification and signal processing, there is a technology need in medicine. This

review examines cardiovascular systems and future medicine in this light based on the clinical needs defined in this section.

2.0 Vision of the Future:

The problem can be summarised as the inability to separate the need for one of the 2 main therapeutic approaches, fluid resuscitation or inotrope drug therapy, where with current measurements doctors cannot determine whether inotrope or fluid resuscitation is either necessary or will be successful. More precisely, the problem is defined by the gap between the measurements that can be made, and those that are desired. This gap creates an opening wherein dynamic systems modelling and system identification using clinical data to create patient-specific and real-time measures clearly separating the patient need for these therapies.

In particular, real-time measures of beat-to-beat stroke volume (SV) and stressed blood volume (SBV) as a surrogate of perfusion would offer the ability to monitor critical cardiovascular function in terms of managing both direct cardiac failure and circulatory control failure – two main components of ACF in the critically ill. Model-based measures calculated from real-time data, thus offer the ability to monitor patient-specific condition and response to core treatments in real-time. This capability naturally leads to the potential to partially or entirely automate this aspect of care using fundamental control systems concepts and approaches.

More specifically, models can serve multiple uses in creating the necessarily functions for automation. First, in tandem with system identification methods they can transform, in this environment, noisy pressure measurements from typically used arterial and venous catheters, into “crisp” flows and volumes necessary to assess cardiac function (SV) and perfusion (SBV). For SV, it is a direct conversion from measurement(s) to metric. For SBV, it is the aggregation of several independent measurements into a whole, a further aspect or area in which automation systems excel. In all cases, fundamental automation tools mixing dynamic systems modelling with system identification enables personalising the models to the patient for use in treatment decisions.

Treatment decisions are the last area for automation. This aspect requires further models, whether statistical models or dynamic deterministic models, to turn measurements and patient-specific models into treatment decisions. In particular, such measures could be linked to responses to therapy using

either pharmacodynamics (PD) style models [27-29], as done in areas such as glycemic control [14, 30-34], sedation management [35-37], and anaesthesia [38-40], or to statistical models or receiver operating characteristic curves, as frequently used in medicine [41-43]. Computational fluid dynamics (CFD) models can also facilitate complex surgical treatment like valve replacement [44, 45]. In either case, there is the complete link from measurements to effective metrics for making personalised, patient-specific decisions, all of which defines an automated, feedback controlled control system. This vision is shown schematically in **Figure 1**.

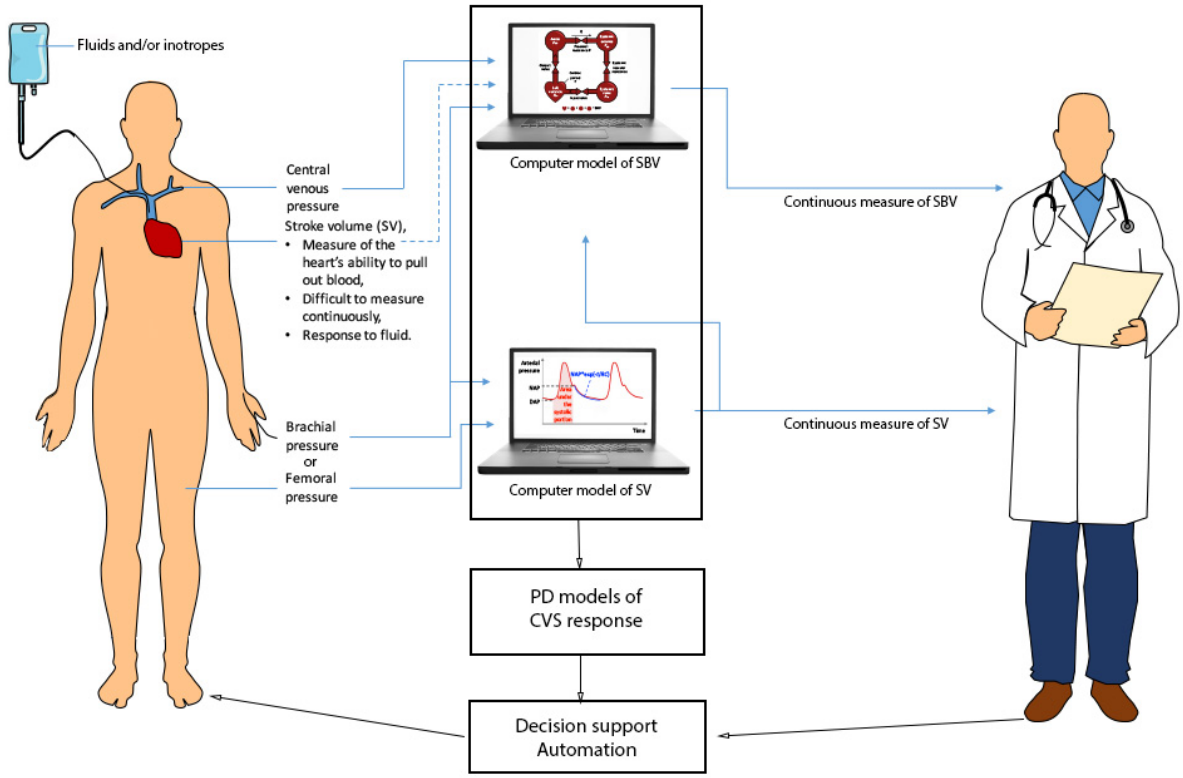

Figure 1: Partial automation with doctor in the loop or full automation without.

Hence, this vision of the future envisions fully or partially automated management of complex cardiovascular and circulatory failure using fundamental dynamic systems modelling, system identification, and control technologies. This approach would also radically transform health care from changing from current "*one size fits all*" protocolised care, which can be problematic in the ICU [46-48], to a "*one method fits all*" personalised care, based on physiological models.

The goal of this review is to characterise the state of the art in respect to these areas and provide recommendations on future directions to achieve the promise.

3.0 State of the Art:

Computational methods have revolutionised the quality and productivity of output in a wide range of industries over the last two decades, but not nearly so much in medicine [49-51]. Concomitantly, medicine and health care systems are increasingly unable to pay the increasing costs in the face of demographics and growing chronic disease [52]. In ICU medicine, and cardiovascular care in particular, computational physiological models offer a major opportunity to personalise care, by combining the increasing level of real-time clinical data with system identification methods to generate "virtual patient" [14, 31, 53, 54] models to represent patients directly, the first step towards automating care.

In particular, there is, in general, an increasing range of physiological models, methods and databases, from simple to high complexity multi-scale models (e.g. [30-32, 34, 53-81]). Other reviews have delineated how each type of model might be used to guide care [14]. Validated models paired with appropriate identification methods thus offer the foundation for translating computation to care. The following sections outline the state of this art in relation to cardiovascular systems and ACF in particular.

3.1 Dynamic System Models of the Cardiovascular System:

There are a wealth of cardiovascular models. CFD modelling allows the characterization of complex physiological flows fields in the cardiovascular system or in prosthetic heart valves [82, 83]. Combined with imaging techniques, CFD allows to assess metrics that cannot be measured directly such as wall shear stress [84]. Complex physiome models capture the heart alone, but have also been created for the entire heart and circulation [60, 69]. Increasingly, there are simplified systems and bond graph approaches to make these models computationally tractable and lower intensity [85-87]. However, these models still suffer from a level of complexity that does not permit ready identification [14], limiting their use in the context reviewed here.

In contrast, simplified "*bedside models*" offer identifiability, but at different scales of resolution [14]. Cardiovascular models of this type include the well-known Windkessel model [88-96], and a wide range of offshoots developed for a range of purposes [97, 98]. While the Windkessel model is linear and serves as a foundation for many models, there are nonlinear versions applied to a range of applications.

In particular, multiple chamber models have been used for a range of purposes, such as diagnosing pulmonary embolism [99-101], sepsis [102, 103], and testing the impact of fluid therapy [13]. However, even limited models with 6-8 chambers, a bare representation of the cardiovascular system, can suffer difficulties with identification [103-105]. Hence, a greater level of simplification is required, which may further limit the potential applicability due to lost resolution.

As defined in the Introduction, output measures that reflect clinical goals in cardiovascular management, include as beat to beat stroke volume and stressed blood volume [13, 106-111]. Both measures have been called for clinically to guide care [1, 112]. However, there are no direct measurements of these values and they are typically estimated intermittently, and not in real-time, by surrogate measures. In addition, they can require frequent recalibration during cardiovascular instability [112-117], which is when they are most desired and useful. Hence, existing measures and surrogates are not viable for automation and control.

Model-based measures of these values do exist [13, 106] and could be used to develop the sensitivities for inotrope and/or fluid resuscitation in a pharmacodynamics framework to better guide care as suggested in this review. The conversion of similar metrics to this type of framework has been done in glycemic control [14, 30-34], anaesthesia [38-40], and agitation-sedation care [35, 37, 118] in the ICU. However, this translation has not yet been performed in the cardiovascular arena for these aspects of care in ACF, or in any other therapy, as yet.

More specifically, real-time model-based estimation of SV has been developed using a Windkessel based model and the concept of reservoir pressure [119]. This metric has delivered the beat-to-beat estimate of SV to well-within the 30% error [106] found in competitive cardiac output devices [120, 121]. It is important to note here that SV is not cardiac output. The former is the output of the heart and a measure of heart muscle capacity, while the latter is a measure of the return of blood to the heart and captures only an average value SV whose beat-to-beat variability can be important [122-124].

The model requires a dual pressure measurement of arterial pressure at one of the aortic, sub-aortic, or femoral arteries to assess pressure and pulse wave velocity to enable identification [125], and

requires only a single, initial calibration via echocardiography or similar imaging. More specifically, it is a model-based measurement or sensor, and can provide real-time values with limited computation well-within current computing and signal processing capability.

Hence, an effective single compartment model has been used with clinical data to provide a real-time SV measure [125]. The model is identifiable and recent improvements [126] have begun to optimise its implementation to ensure identification is robust. It has been validated in animal studies of sepsis, inotrope therapy and fluid resuscitation, both alone and in sepsis induced by endotoxin infusion [125].

SBV is a measure of perfusion, or specifically the body's ability to perfuse tissues, and therefore a surrogate measure of circulatory control and tone. Low SBV would indicate a fluid responsive patient [13, 110], where assessing fluid responsiveness is a "holy grail" of ICU care given the frequency of its use and its potential downsides when excessive fluid is given [127, 128], and the fact, as noted previously, that fluid responsiveness is difficult to predict and to assess [25, 128, 129].

The only current model able to assess SBV is a 3 compartment model of the left heart or systemic circulation [13]. Previously, such a low order and limited model would not have been considered viable for guiding care as it skips the entire pulmonary circulation. However, given measures of arterial and central venous pressures, overlapping those required to determine SV, it can identify an estimate of the stressed blood volume in the entire circulation, and is identifiable [130, 131].

Importantly, stressed blood volume cannot be directly measured practically or ethically in a clinical situation [108]. As a result, calibration is not possible, although the value should be within known total blood volume limits. However, equally, it is also not necessary, as trends in the value assessed per kg of body mass should be all that is necessary to guide care. Hence, it is a real-time estimate of a real, but not directly measurable, physiological variable with potentially significant use in guiding care in ACF.

To date, model-based SBV has been validated in animal trials of inotrope and fluid resuscitation [13]. Initial results showed an area over 80% or 0.80 under the receiver operating characteristic (ROC) curve in predicting fluid responsiveness [132]. Few clinical metrics reach this value and none have been

repeatable [13] in use. However, this model-based estimate offers the potential to do better since it is entirely objective and calculated, and does not rely on implementing, sometimes complex, clinical procedures to assess potential fluid responsiveness.

Overall, a wide range of cardiovascular dynamic systems models exist in the literature. Most are not identifiable and/or too complex for use in real-time measures or estimates of cardiovascular state. Fewer still have addressed SV or SBV directly, and have focused instead on physiological understanding versus application to care, which is the differentiator in the development of the models presented. Those few remaining models are relatively very simple and limited to specific endpoints, which helps ensure the identifiability and robustness necessary for medical applications and any form of automation and closed-loop control.

3.2 Model Validation:

Model validation is a difficult topic. Many models in physiology focus on the ability to fit the data, meeting the simplest standard of containing the requisite dynamics, or more than the minimum dynamics necessary. However, such limited validation does not ensure the dynamics modelled are those produced by the actual system. As a result, forward prediction has emerged as the necessary minimum in physiological modelling for decision support [14], where the identified model needs to be able to accurately predict, in advance, the outcome of a clinical intervention or change in care. This approach, and prediction in specific, requires a patient-specific model, which in turn requires the model to be identifiable, as well.

A recent review [14] developed a framework for validation, beginning at prediction. It also proposed validation in predicting the outcome of groups of experiments or clinical interventions over cohorts, expanding from single virtual patient predictions using an identified model, to prediction accuracy across groups of patients, an added level of robustness. Finally, it proposed cohort level cross-validation using independent clinical data to identify similar cohorts and test their prediction on the protocols or interventions applied to the other cohort, the highest level of validation. To date, none of the models for SV or SBV, or any identifiable cardiovascular model to the author's knowledge, has passed the first

level of prediction. Hence, there is significant room for developing these and similar models and their validation in this framework as the field advances.

3.3 Data, System Identification, and Identifiability:

These and any similar models require real-time data to deliver real-time measures. In this aspect, cardiovascular monitoring offers a wealth of potential with a range of real-time, relatively high resolution pressure catheters typically used in cardiovascular monitoring. As noted previously, these catheters offer pressure waveform data suitable for these models. However, their use has begun to decline as the wealth of data has not delivered better outcomes for patients (e.g. [133-137]). This review posits this difficulty is due to the inability to process real-time data with the human mind in the way a computational model can. More specifically, data availability is high, so the feedback control and automation concepts presented in this review offer the opportunity to find value for patients although their use has remained minimal to date.

A wide range of identification methods exists for physiological and other forms of dynamic system models (e.g. [33, 58, 138-149]), which are well reviewed elsewhere [140, 141]. In physiological modelling convex methods, such as least squares and integral-based methods have been preferred [130]. However, nonlinear optimisation has also been used in cardiovascular and other physiological models [100-103]. Hence, there is no lack of methods, and the typical issue remains around whether the model with available measures is identifiable [150, 151], and in particular, practically identifiable [150]. In the specific cases noted for SV and SBV formal identifiability analyses and practical identifiability have been demonstrated [131], and are a necessary step in model development.

3.4 Dynamic Models and Methods for Decision Support to Guide Care:

The last step, transforming model-based, patient specific measures into treatment decisions requires decision support, which comes in many forms, including model-based, black-box or machine learning based, rules-based and others [152, 153]. This review focuses on the use of deterministic models and methods to predict the outcomes of treatment, and use these predictions to optimise care relative to measurable clinical goals. This outcome has already been achieved in the area of glycemic control in

the ICU [154, 155] and in type 1 diabetes [156, 157], including both direct and unique, stochastic risk-based dosing control [155].

The overall approach relies on the ability to identify patient-specific, time-varying parameters from data. A patient specific model enables management of the significant intra- and inter- patient variability found in the typical ICU patient and in ACF in particular. Such “sensitivities” can be the key to model-based and personalised care, providing the relationship reflecting patient status and response to the treatment, as a metric useful in titrating care. This approach employs deterministic, identifiable physiological models to achieve this end.

In the specific case of ACF and cardiovascular management reviewed here, measures of SV and SBV represent the desired and direct physiological outcomes of clinical interventions with inotropes and fluid resuscitation. In the simplest sense, there is a measurement and a response, and modelling such dose response dynamics is a well-known field [58], including the use of a dose-response sensitivity to capture inter- and intra- patient variability [14]. Hence, the mathematical and engineering mechanics of creating these models is not necessarily difficult given the measures.

The final link in automated or partially automated control is linking these measures and models with a goal of optimising the measure (SV or SBV) to a clinical target using the desired intervention (inotropes and fluid resuscitation). Given eventual engineering and clinical validation of these metrics, this further step is eminently possible with methods known today, and already proven in other medical and ICU applications [118, 155]. Overall, automation would offer potential new avenues to address key clinical questions on inotrope and fluid resuscitation therapies in circulatory management, which are major issues in the field limiting patient outcomes and increasing costs [1, 158-164].

4.0 Recommendations:

From this analysis and review there are significant areas where future cardiovascular management and its clinical needs can, and very likely will, cross over into the realms typically covered by control systems engineers. In cardiovascular management existing devices already provide real-time measurement and the potential for control of cardiovascular condition and clinical care. However, the means to make best use of these measurements is lacking. The following recommendations might therefore be made from a control systems perspective, defining questions or needs the field can contribute to answering:

- **Better Models**: To date, models are limited in number and level of validation, creating an open field for new developments, including in the inclusion or clinical use of devices, such as ventricular assist devices [88, 165-168] or prosthetic heart valves [169, 170] in an automated care framework.

Model-based beat to beat stroke volume and stressed blood volume [13, 106], and other more detailed lumped parameter physiological models used for real-time diagnosis (e.g. [102, 103, 171, 172]), have been created with the goal of creating the right measures to monitor and eventually guide inotrope dosing and fluid management in real-time. However, all these models and methods are relatively complex, making identification difficult with limited pressure data.

Thus, the first recommendation could be seen in a standard system identification and control systems framework to be in direct conflict with the following recommendation:

- **Improved Identifiability and Identification**: Complex models are difficult to identify with limited pressure measurements typically available. Further, their identifiability is difficult to prove. There is thus a major need for improved identification methods, as well as identifiability analyses to show the theoretical and practical identifiability of current and new models. In particular, as models increase physiological relevance and resolution, identifiability becomes much harder or impossible without either new measurements or new data or assumptions to reduce the variables and render these models more identifiable.

This second recommendation leads to a third recommendation to directly address this conflict:

- **New Sensors**: The prior conflict in recommendations can also be ameliorated by the development of new sensor hardware, as well as model-based sensors. New sensors would allow more parameters to be identified, leading to more patient-specific models and more personalised care. External devices such as VAD have also a great potential to be used as model-based sensors, enabling for example, the measurement of the blood flow rate, based on electric current in the magnetic bearing that supports the rotor of the VAD [173].

All three recommendations clearly show the crossover of this bio-engineering area with traditional control systems theory and methods. They also drive home the key areas where current methods are lacking, and new approaches and technologies could have significant impact on the field, as well as on patients.

It must finally be noted that new technology alone cannot guarantee better outcomes or improved costs. Clinical uptake and acceptance of novel sensors, methods and automation is necessary to see successful research results translated to clinical practice. While the economic arguments in favour of improved care via automation are very strong, translation will require clinical champions and successful clinical trials showing both improved outcomes and reduced costs, without which uptake will be blocked by either clinical failure or economic failure to improve care without increasing costs.

5.0 Conclusions:

This review presented an overview of the range of current cardiovascular models available for use in model-based care to personalise and optimise care and patient outcomes in a high cost, high mortality area. It also demonstrated how these models are limited by complexity and identifiability, and how models of critical metrics to guide care are simpler and potentially more suitable for real-time care and control. More generally, the area of model-based and automated cardiovascular and circulatory management is highly complex and only just emerging, where other physiological systems and areas of care are more developed.

Longer term, the development of pharmacodynamics models to guide care leads to the emergence of virtual patient models to develop new optimised, and automated, clinical methods of care and spur the development of new devices and systems to improve care based on the insight gained. As a result, the review also shows that while the field itself is emerging, the results to date are narrow. Hence, there is significant room for innovation and new approaches, particularly as more engineers become engaged and clinicians become increasingly willing to take on more novel approaches driven by rapid changes in technology.

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