Chapter 5
Patient-Specific Modeling for Critical Care

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5.1 Introduction

Decision-making in critical care occurs on a time scale of hours, minutes, or even seconds and requires synthesizing large amounts of patient-specific (PS) data. It is therefore sensible to make use of PS modeling applications in critical care since they offer tools for integrating disparate data into a single system view and leverage computing power to provide decision support information in a timely manner. PS modeling can be used to aid diagnosis, to estimate occult physiological variables, and to test potential therapies in silico before administering them to a patient. They can therefore help clinicians determine what happened to the patient in the past, what is happening in the present, and what will happen in the future.

PS models are computational representations of human anatomy, physiology, or pathology that are tuned to match data from one individual as opposed to data from a population. These models supply clinicians with decision support information that is applicable to a single patient rather than a patient group. Generally, PS modeling systems developed for critical care scenarios must be computationally tractable enough to provide this decision support information in real or near-real time. This is an important distinction between critical care PS models and those developed for less time-sensitive scenarios (such as predicting a patient's response to cardiac resynchronization therapy, for example (Chap. 10, [18, 19])). Because computational timeliness is an issue, critical care PS models are usually limited to algebraic or ordinary differential equations (ODEs) and are optimized to simulate only those PS features that are essential for providing accurate decision support information. Hence, researchers in critical care PS modeling often adopt a "simple first" approach to model development. The goal of this approach is to identify effective, "minimal models" that keep computational burdens small but still provide accurate decision support information. Minimal models also have the advantage of being easier to

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understand and use once deployed. This advantage is crucial because in time-sensitive scenarios, it is essential to optimize not only the computational overhead of the modeling system being used but also the user's interaction with the system.

Critical care environments are often data-rich, since clinicians must monitor unstable patients thoroughly and continuously. Therefore, critical care PS modelers have the advantage of access to large amounts of detailed physiological data. Modelers can leverage this abundance to create PS simulations that are accurate on a high-resolution time scale, a luxury often unavailable outside the critical care setting. By representing a patient systemically, rather than in a reductionist manner, PS models can coalesce these large critical care datasets into a single, coherent picture of a patient's status. For example, given a PS hemodynamic model, ECG signals can be used to drive the simulated heart, from which the blood flow can be obtained. The latter can be constrained by afterload data derived from the patient's arterial catheter.

Despite over a century of quantitative biological modeling, only recently has the store of biological knowledge and computational power become sufficient to achieve the long-sought goal of applying PS quantitative modeling to real-time clinical decision-making. The first section of this chapter describes several examples of recent PS modeling applications in critical care, some of which are based on models created decades earlier. Working from these examples, the second section describes the major challenges currently faced by researchers in critical care PS modeling.

5.2 Examples of Patient-Specific Modeling in Critical Care

Although the field of applied PS modeling is relatively young, some important examples of applications in critical care exist. Many involve simulating cardiovascular or blood glucose dynamics, as these systems must be managed closely in the critical care environment.

5.2.1 Hemodynamic Models

Maintaining a patient's hemodynamic homeostasis is a primary task in critical care, and it is not surprising that many critical care PS models simulate cardiovascular dynamics. Figure 5.1a shows a basic example of a hemodynamic model used for estimating a patient's systemic vascular resistance (SVR). Given its simplicity, one may not think of this as a PS model in the modern sense, but it is nonetheless a computational representation of a patient's physiology, which is parameterized to match PS pressure and flow data. This particular model is based on the fluid analog of Ohm's Law. As Ohm's Law relates voltage and current to electrical resistance, the fluid analog relates a pressure difference and fluid flow to fluid resistance. This model,

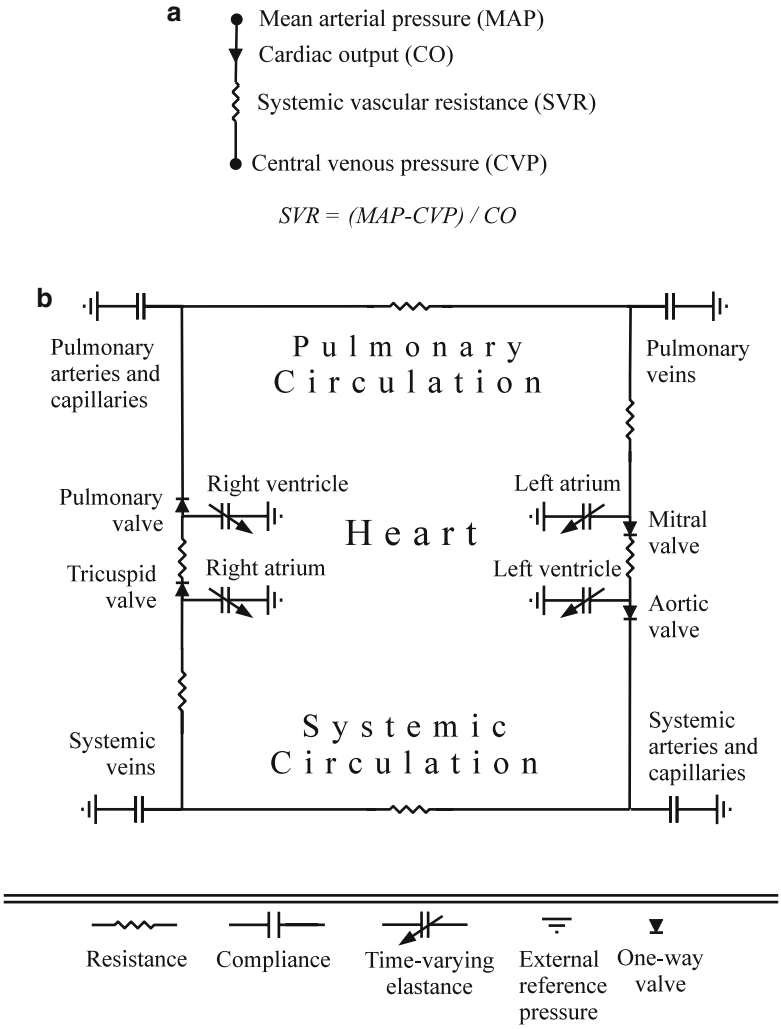

Fig. 5.1 Lumped-parameter, hemodynamic models. (**a**) A simple electrical analog model of blood flow through the systemic vasculature for estimating systemic vascular resistance. (**b**) A more complex electrical analog model that simulates blood pressures, flows, and volumes throughout the cardiovascular system

which has been in use for decades, treats the systemic vasculature as a single resistive element. It is computationally simple and provides an estimate of an important physiological variable that helps medical decision-making.

Figure 5.1b illustrates a more complicated hemodynamic model based on fluid analogs of electrical transmission laws. The model uses a collection of Windkessel ("wind-chamber," see below) compartments [10, 32] to simulate segments in the circulation that not only provide energy loss via resistive pathways but also energy

storage via vessel compliance. This kind of formulation allows the modeler to account for blood volumes (analogous to electrical charge) throughout circulatory compartments along with blood pressures and flows. Although this model does not directly correspond to any published PS modeling application, it is used here to illustrate a common modeling technique used in hemodynamic simulations. The code for the model in Fig. 5.1b includes a set of algebraic equations and ODEs that are solved using numerical, as opposed to analytical, methods. In the interest of model sharing and reproducibility, this code is presented in the appendix. It is written in the Mathematical Modeling Language (MML) used for simulations within the free JSim environment [17]. A digital copy of the original model file is also available from the author upon request.

The hemodynamic modeling techniques used to create the models in Fig. 5.1 are by no means new (see, for example, [30]). These so-called "lumped parameter" models (they lump groups of resistive and/or capacitive elements together) have been used in the past to estimate cardiac output (CO) [8, 25, 38], to study the effects of orthostatic stress on the cardiovascular system [15], to analyze the Valsalva and Forced Vital Capacity maneuvers [23], to predict hemodynamics in traumatic brain injury patients [37] (see below), and to create educational tools in physiology [7, 34]. However, it is only within the last 10–20 years that computing power has increased to the point where models of this complexity can be solved within a time frame that is realistic for critical care decision-making.

5.2.1.1 Cardiac Output Estimation

The gold-standard measurement of CO is thermodilution, a procedure that requires an indwelling catheter. Therefore, less-invasive means of obtaining accurate CO would substantially reduce patient health risks. Emphasizing this fact, Kouchoukos et al. [20] referred to the creation of a reliable, noninvasive continuous CO measurement technique as an "El Dorado." Several researchers have explored the use of models like those in Fig. 5.1 for estimating cardiac output (CO) from more readily available, less risky continuous measurements like arterial blood pressure (ABP) and heart rate (HR).

The origins of the hemodynamic models applied to the problem of CO estimation can be traced to work done by Otto Frank over 100 years ago [10, 32]. In 1899, Frank published the first major quantitative study that related systemic arterial system properties to arterial pressures and flows. His widely used Windkessel model, which simulates a compliant, fluid-filled chamber, laid the foundation for much of the hemodynamic modeling work that has followed, including model-based CO estimation studies.

One of the first PS model-based CO estimation methods to emerge was that of Wesseling et al. [38]. Their "Model Flow" method relies on a simple three-element Windkessel model of blood flow out of the left ventricle and into the systemic circulation. In order to compute a continuous CO estimate, this method relies on PS age, ABP, and HR data along with an initial CO measurement used to calibrate the model.

A recent study by De Wilde et al. [8] also describes the development of a model-based CO estimation technique called Hemac that is similar to the Wesseling

Model Flow method. Whereas the Model Flow method uses an aortic pressure–volume relationship (compliance) based on population-averaged in vitro data, the Hemac method bases the relationship on PS data obtained from in vivo measurements on the aorta. In a recent clinical study, authors showed that the Model Flow and Hemac CO estimation methods were more accurate than three other methods not based on models, including the commercially available LiDCO CO estimation system [22]. However, this particular study was limited to 24 surgical patients without congestive heart failure, with normal heart rhythm and reasonable peripheral circulation. Indeed, one of the current challenges in the field of CO estimation is to demonstrate a method's utility across a broad spectrum of patient conditions.

Neal and Bassingthwaighte [25] have also recently published a model-based CO and total blood volume estimation method using a hemodynamic model similar to the one in Fig. 5.1b. Based on the work of Lu et al. [23], their model was constructed using a network of Windkessel compartments that simulate blood pressures, flows, and volumes in a 21-segment representation of the cardiovascular system. The authors created an algorithm that tuned this hemodynamic model to match a baseline set of hemodynamics from a given subject. The tuned parameters were then used in an open-loop version of the model to estimate CO from mean ABP and HR data obtained from single subjects. Unlike other CO estimation techniques, this method does not require an invasively obtained ABP curve, but uses mean ABP instead, which can be estimated noninvasively. Although the Neal and Bassingthwaighte CO estimation method provided good estimates of CO in preclinical studies, the tuning procedure used to match baseline PS data took hours to compute using commercially available desktop processing power. This bottleneck must be removed either through an increase in computational power or a simplification of the tuning process and/or model design before such a method becomes viable in a critical care setting.

Exemplified by the Neal and Bassingthwaighte model, one of the major challenges in PS modeling lies in creating computationally efficient tuning methods for matching model output to PS data. These methods can be time-intensive, since multiple model runs are often required to complete the tuning process. Researchers have addressed this issue recently and created methods for reducing the burden of parameter tuning in detailed hemodynamic models [14, 29]. These methods are discussed below in Sect. 5.3, "Current challenges."

5.2.1.2 Simulating Response to Traumatic Brain Injury

Hemodynamic PS modeling has also been applied to the treatment of traumatic brain injury in pediatric patients. Wakeland et al. [37] developed a six-compartment ODE-based model that simulates blood pressures, volumes, and flows in intracranial arteries, capillaries, and volumes. The model also simulates the aggregated CSF volume, brain tissue volume, and (if applicable) intra- and extracranial hematoma volumes. In a clinical study, researchers used this model to anticipate individual patients' responses to head of bed tilt and respiratory rate change therapies. They first tuned the model to PS hemodynamic data obtained from an initial instance of

one of these physiological challenges. Then, using the newly parameterized model, they simulated the effects of future challenges, and compared the model's predictions of intracranial pressure with data from actual challenges performed during the same therapy session (within 2–3 h) and in subsequent sessions performed on other days. The researchers demonstrated that their PS modeling system could be implemented in a critical care environment and used to make predictions about individual patient's responses to traumatic brain injury therapy. However, they obtained only modest success when they validated model predictions against data from nine pediatric ICU patients. Model predictions made within a single therapy session were favorable in 27% of these cases, and those made between sessions were favorable in 10% of cases. Wakeland et al. propose that their system may be improved by adding more physiological detail to their model and by incorporating higher resolution clinical data. Additionally, as in the Neal and Bassingthwaighte model, the Wakeland et al. PS modeling application requires a significant amount of time for model tuning (in excess of 20 min) and stands to benefit from more efficient tuning methods and increases in computing power.

5.2.2 Models of Glucose and Insulin Dynamics

The management of blood glucose levels in ICU patients is also a major challenge in critical care. Even nondiabetic patients can suffer from hyperglycemia in the ICU, a condition that worsens hospital outcomes due to increased susceptibility to infection, myocardial infarction, and other illnesses. At the same time, improper treatment of hyperglycemia can result in hypoglycemia, which is also associated with impaired outcomes.

5.2.2.1 Controlling Blood Glucose Levels

PS models have recently been applied to predict and control blood glucose levels in ICU patients at risk for hyper- and hypoglycemia. Van Herpe et al. [36] developed a system for predicting blood glucose levels in ICU patients based on system identification techniques. In this method, the underlying physiological system responsible for glucose dynamics is treated as a black box, and optimization methods are used to find an empirically-based, single-equation model that accurately relates a set of input data (initial blood glucose levels, body temperature, flow of carbohydrate calories, etc.) to output data (predicted blood glucose levels). They demonstrated that an adaptive modeling system that alters their model to account for PS features was more accurate in predicting future blood glucose values in the ICU.

In 2008, Chase and colleagues [5] published a clinical validation study assessing the impact on patient mortality of a PS model-based glucose control system implemented in an ICU. They showed that their "Specialised Relative Insulin Nutrition Tables" (SPRINT) system reduced the hospital mortality of ICU patients by 26%

for those staying 3 days or more. Mortality was reduced by 32% for patients staying 4 days or more and 35% for patients staying 5 days or more. This study provides an important example of a PS modeling application that has passed through the processes of design, development, preclinical testing and clinical testing and emerged as a valuable tool for the ICU. Time will tell whether SPRINT is widely adopted as a standard of care.

There are several important features of the SPRINT system that contribute to its success. First, the system is based on a time-tested model of insulin and glucose dynamics called the Bergman minimal model [2, 3]. This ODE-based model simulates time courses of insulin and glucose following injection of insulin into a patient's bloodstream. By tuning the model parameters to match PS data obtained from intravenous glucose tolerance tests, the model provides indexes of a patient's insulin sensitivity, glucose effectiveness, and first-phase insulin response. These three model parameters provide the ICU clinician with a thorough view of a patient's glucose homeostasis, and can help guide the administration of insulin for controlling blood glucose levels.

The Bergman model's simplicity has likely contributed to its viability and adoption as a clinical and educational tool. SPRINT is based on an extended Bergman model but is still simple enough to be translated into a paper-based protocol in an ICU. Thus, no interaction with a computer is required to employ the SPRINT system and model results can be retrieved immediately. As shown by the reductions in mortality of the large patient population studied by Chase et al., this minimal approach to PS modeling can prove effective despite its simplicity.

To further illustrate the value of blood glucose modeling, researchers have recently found that the insulin sensitivity variable computed by the SPRINT model can be used as a negative predictor of sepsis in ICU patients [28]. This provides an example of how PS modeling can help clinicians with challenging diagnostic tasks and also demonstrates an important, perhaps overlooked value in model-based estimation of physiological variables. As surrogates for unavailable or overly risky in vivo measurements, these variables can be used as additional biomarkers to aid clinical diagnoses and prognoses. To provide a second example, Neal and Bassingthwaighte found that their model-derived total blood volume loss estimates predicted survival/nonsurvival following severe hemorrhage in pigs [25]. Obtaining an actual total blood volume measurement on a person (or a pig) in a critical care scenario is not feasible; therefore, clinicians have no way of knowing the predictive value of this variable for survival, time to death, etc. However, a model-based estimate of total blood volume can be used as a surrogate measurement and can be tested for its predictive value, as can any other physiological variable computed by a PS model.

5.3 Current Challenges

Although much progress has been made in applying computational PS modeling systems to challenges in critical care, these applications have yet to become widely adopted standards. Considering the computational power presently available to

clinicians and the fact that PS models used in critical care must often rely on time-tested, minimal models, it is somewhat surprising that more success stories of applied PS modeling in critical care do not exist. The field of PS modeling as a whole is young, and researchers face many challenges in translating modeling work performed in the biomedical research realm into useful, clinically validated tools.

5.3.1 Clinical Validation

Many current efforts in PS modeling for critical care are at the stage where computationally timely models have been built and can be parameterized to match individual patient data, but have yet to be validated against large-n clinical data sets [27]. These kinds of validation studies can be financially and temporally expensive since they require IRB approval, patient recruitment, and data collection. It is only after data have been collected from human subjects that the iterative cycle of refining the PS modeling application under development begins.

During the validation process researchers often find that their models need to be revised to generate accurate simulations. This process can involve increasing the model's detail, replacing/editing components of the model, or testing out an entirely new model design. Such revisions can be cumbersome and difficult, especially with models of higher complexity. Currently, researchers have access to few tools that would make the revision of more complex models less cumbersome and error-prone. The potential utility of a modular modeling approach that addresses these issues is discussed below in the "Model interoperability" section.

As discussed by Neal and Kerckhoffs [27], even when researchers are able to successfully test and validate their PS models against a significant number of patients, the question remains whether their system, once deployed, will actually effect clinical decision-making and improve patient outcomes. Whereas large-n validation studies have been the traditional endpoint of biosimulation modeling research, PS modelers will be faced with the additional task of deploying PS modeling systems into a clinical setting and demonstrating their effectiveness as decision support tools. The process does not end there, however. In order for a PS modeling system to become a standard of care it will require approval by the FDA, or similar regulatory agencies in other countries as a medical device.

5.3.2 Timely Tuning Methods

One of the challenges in using more modern, detailed physiological models to simulate PS phenomena lies in tuning the models to match PS data. Whereas a simple fluid dynamics model like that of Wesseling et al. [38] has a minimum number of free parameters to adjust, a more sophisticated, multicompartment model like that of Neal and Bassingthwaighte requires tuning scores of parameter values. In lieu of this computational hurdle, researchers have created more streamlined tuning

procedures for multicompartment hemodynamic models. For example, Pope et al. [29] employed parameter sensitivity and subset selection methods to reduce the complexity of a multicompartment cardiovascular model used to identify biomarkers that distinguish between healthy young and elderly populations. Additionally, Hann et al. [14] developed an "integral-based parameter identification method" that can be used to quickly and accurately tune a minimal cardiovascular model to match PS data. This integral-based approach was also applied in creating the successful SPRINT system discussed above. Models that employ adaptation rules also seem promising in reducing the number of parameters (Chap. 2).

5.3.3 Variability in Patient Anatomy, Physiology and Clinical Scenario

Each patient in a critical care scenario is unique, and the importance of developing accurate, automated tuning algorithms that account for differences between patients cannot be overstated. However, if a patient presents with a feature that violates the underlying assumptions of a model, often the only way to account for this abnormality is to change the equations of the model itself. For example, suppose a clinician would like to use a cardiovascular model such as that in Fig. 5.1b to simulate the hemodynamics of an infant undergoing surgery to repair Tetralogy of Fallot. In this case, the patient's anatomy is different from the anatomy assumed in the computational model, due to a ventricular septal defect and overriding aorta. The clinician will require a new model that includes an abnormal arrangement of blood flow before and possibly after the surgical procedure (because the end goal of some heart defect surgeries is a noncanonical arrangement of blood flow). Furthermore, if a cardiopulmonary bypass (CPB) machine is employed during the surgical procedure, the simulation must account for its use as well. None of these conditions would be present in a model that assumes canonical cardiovascular anatomy. Therefore, given the anatomical and physiological variation present in humans and the variation in clinical scenarios between patients, there is a general challenge to devise a modeling approach that can readily account for this diversity. This challenge must be addressed if PS modeling is to realize its full potential in critical care.

There are two solutions to this challenge: precoordination and postcoordination of models. Pre-coordinating models to account for the variations in blood flow described above would require modeling each possible noncanonical blood flow arrangement ahead of time, either using separate models for each arrangement, or model "switches" that toggle between flow arrangements in a single model. This solution requires model developers to anticipate every possible noncanonical arrangement of blood flow whether due to patient anatomy or the application of artificial shunting mechanisms (such as a CPB machine). The approach presents a potentially intractable combinatorial problem, given the number of separate models or switchable model subcomponents that must be created to account for all blood flow arrangements.

A more scalable, manageable, and flexible approach to this complex problem is to postcoordinate the models. In this approach, users have access to a repository of

smaller, interoperable, modular models that can be recombined "on the fly" to simulate a wide variety of PS conditions. For example, if a patient goes on CPB, a CPB module can be retrieved from the repository, and then merged with a PS systemic circulation model (perhaps extracted from the system in Fig. 5.1b) to simulate the rerouting of the patient's blood flow through the bypass machine. As a design principle, modularity is a time-tested method of dealing with complexity [1], and it has been leveraged in a myriad of industrial fields to organize and optimize the creation of complex products [33]. A modular approach to PS modeling would theoretically provide a means for clinicians to create PS models across a wide spectrum of clinical cases. In the next section, I provide more details on biosimulation model interoperability and its applicability in creating PS models for critical care.

5.3.4 Model Interoperability

Because modelers usually choose to code in whatever simulation language is most comfortable for them, published physiological models that may have applicability in critical care are coded in a variety of languages for a variety of simulation platforms. Consequently, these models are not readily shareable or reproducible between research groups. Model code often languishes on laboratory hard drives when it could be built upon and/or repurposed to address clinically relevant problems. Some researchers have tackled this issue and developed methods that facilitate the reuse of published biosimulation models. For example, systems biologists, who focus on modeling chemical networks, have created a number of standards for model reproduction among their research community. The Systems Biology Markup Language (SBML [16]), an XML-based model description format, is one such standard that acts as a *lingua franca* for encoding chemical network models. Using a common set of SBML parsing and simulation tools, systems biologists can readily reuse models coded by independent research groups. The systems biology community has also created other standards for curating published models in a centralized database [21] and for describing the tasks required for the reproduction of published model results [24].

This work within the systems biology community is an example of a success story in addressing the larger issue of biosimulation model interoperability. However, a standard like SBML does not scale beyond the chemical network domain. Furthermore, most of the modeling applications described above simulate phenomena at the tissue or organ level. Therefore, as discussed by Neal and Kerckhoffs [27], to encourage model interoperability, the PS modeling community needs standards for describing, curating, and reproducing models that scale beyond chemical networks to include higher levels of biological organization. These standards can be applied not only as part of the modular, postcoordination PS modeling approach described above but also to encourage model reuse and development among the greater modeling community.

Currently, the most ambitious attempt to create a model description standard that applies across physical modeling scales and modeling languages is the Semantic Simulation (SemSim) approach [26]. In this approach, the codewords and mathematical

dependencies of existing biosimulation models are annotated against concepts in standardized reference sources like the Foundational Model of Anatomy (FMA, [31]), the Gene Ontology (GO, [13]), the Chemical Entities of Biological Interest (ChEBI) ontology [9], and the Ontology of Physics for Biology (OPB, [6]). Once annotated within the SemSim format, physiological models become semantically interoperable, allowing for more automation of common modeling tasks. When a user combines multiple SemSim models, the merged model not only compiles, but also is biologically meaningful. For example, a user may want to combine a heart model with a systemic circulatory model. Suppose both models include a codeword that gives values for left ventricular (LV) outflow but in the heart model this codeword is a variable output, whereas LV outflow is a static parameter in the systemic circulatory model. Semantic interoperability helps automate the merging of these models into a biologically meaningful result. Cast in the SemSim format, a computer can recognize that both models simulate LV outflow, and thus, the user may want to couple the models at that point so that LV outflow from the heart model replaces the static LV outflow codeword in the systemic circulatory model. Without semantic composability, there is no way to automate this merging process beyond simply copying blocks of code from one model into another, and in doing so, there is no guarantee that the result will be biologically consistent. With semantic interoperability, a computer can recognize that having two different codewords that simulate the same physical property is contradictory, and can prompt the user to resolve the contradiction, thus retaining biological meaning in the merged model.

Semantic interoperability is just one level of model interoperability and is an important step in reaching even higher, more powerful levels of interoperability. The US military, specifically the Simulation Interoperability Standards Organization (SISO), has been researching this issue to optimize the creation of defense-related simulations. Tolk et al. [35] define six levels of interoperability for simulation systems: technical, syntactic, semantic, pragmatic, dynamic, and conceptual.

- *Technical interoperability*. A protocol exists for exchanging data (bits) between participating model components.
- *Syntactic interoperability*. A common data format is applied to share information between model components.
- *Semantic interoperability*. The meaning of the data is shared between model components.
- *Pragmatic interoperability*. The use of the data (i.e., the context of its application) is shared between model components.
- *Dynamic interoperability*. Components react to time-dependent changes in their internal assumptions and constraints. The effect of the system's operation is shared between model components.
- *Conceptual interoperability*. Model components share a common understanding of the assumptions and constraints of a simulation's abstraction of reality.

Presently, most interoperability solutions in software engineering and simulation only provide the technical and syntactic levels. However, researchers are now exploring how Semantic Web technologies can help realize semantic and pragmatic interoperability for simulations [4, 11, 12, 26].

The issue of model interoperability has been stressed here because to fully tap the potential of PS modeling in critical care, modeling applications must be able to account for unforeseen patient conditions, must be designed for use by nonengineers, and must be optimized for efficiency. A modular approach using minimal, optimized, interoperable models is the most logical design paradigm that addresses all of these issues. Although a challenging area of research, model interoperability is a potentially powerful catalyst for the development of PS modeling in critical care. A modular modeling approach will also help streamline the cumbersome, iterative model design cycle discussed above by eliminating common hand-coding tasks and coding-related errors.

This being said, modular PS modeling has its own limitations to consider as well. While researchers can validate single standalone models against empirical data, there is no way to do this for all the possible recombinations of model components from a repository of modular models. Therefore, while the individual component models that comprise a composite PS model may be validated individually, the composite model may not. Validating all the possible model recombinations from a repository of model components is not tractable. Therefore, clinicians composing novel PS models "on the fly" must realize that such models may not have been tested against empirical data prior to use. Instead of attempting to validate all possible recombinations of the model repository components, a modular modeling system will have to be validated by analyzing whether the composite models *as a group* successfully matched empirical data, improved patient outcomes, etc. Furthermore, because modular modeling allows the user to create novel models, flexible, adaptable parameter tuning programs will also be required to match model output to patient data.

5.4 Vision for the Future

Much work remains before more PS modeling systems become standards of care in critical care environments. With access to sophisticated modeling tools and scores of published models, many modelers have begun testing their work in preclinical and/or clinical settings. Thus, many PS modeling efforts are at the validation stage, one of the main challenges that researchers currently face in PS modeling in general. However, PS modeling researchers must ultimately go beyond the traditional endpoints of modeling research so they not only demonstrate that their models are valid but also that their modeling systems actually improve medical decisions and patient outcomes when implemented in a critical care environment.

Another research area that must be explored before PS modeling becomes a standard of care involves identifying the optimal means of deploying and using a PS modeling system in the clinical environment. If a modeling system requires in-depth quantitative knowledge of the model(s) involved in simulating patient dynamics, specialized technicians will be required to manipulate the system. In this case it may be most logical for clinical centers to develop modeling cores with members specializing in PS modeling applications. Alternatively, if a modeling system does not

require in-depth, technical knowledge to tune and execute, specialization may not be required. In this case, critical care physicians and nurses will be able to use the modeling systems themselves (as is the case with the SPRINT protocol). Initially, PS modeling systems will focus on delivering accurate PS information to the clinician, and usability improvements will occur later, as the utility of such systems is demonstrated. Once demonstrated, we will likely see interface improvements that make PS modeling accessible to a broad spectrum of users.

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