Modeling Mechanical Ventilation *In Silico*—Potential and Pitfalls

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Abstract

Computer simulation offers a fresh approach to traditional medical research that is particularly well suited to investigating issues related to mechanical ventilation. Patients receiving mechanical ventilation are routinely monitored in great detail, providing extensive high-quality data-streams for model design and configuration. Models based on such data can incorporate very complex system dynamics that can be validated against patient responses for use as investigational surrogates. Crucially, simulation offers the potential to "look inside" the patient, allowing unimpeded access to all variables of interest. In contrast to trials on both animal models and human patients, *in silico* models are completely configurable and reproducible; for example, different ventilator settings can be applied to an identical virtual patient, or the same settings applied to different patients, to understand their mode of action and quantitatively compare their effectiveness. Here, we review progress on the mathematical modeling and computer simulation of human anatomy, physiology, and pathophysiology in the context of mechanical ventilation, with an emphasis on the clinical applications of this approach in various disease states. We present new results highlighting the link between model complexity and predictive capability, using data on the responses of individual patients with acute respiratory distress syndrome to changes in multiple ventilator settings. The current limitations and potential of *in silico* modeling are discussed from a clinical perspective, and future challenges and research directions highlighted.

Keywords
- mechanical ventilation
- mathematical modeling
- computer simulation

#Equal contributions.

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"All models are wrong, some are useful"—George Box[1]

A model can be most generally defined as any simplified version of reality[2] resulting in a representation of real-life form and function.[3] Models can take many forms—physical, conceptual, verbal, mathematical, etc.—and they are often implicitly used in standard medical research; for example, studies that examine a relationship between surrogate and clinical outcomes rely on an underlying model that relates the two. For the purpose of this article, a "model" will refer to a mathematical or geometric description of physiological processes and anatomical organization.[4]

A detailed discussion of the possible approaches to the development and implementation of mathematical models is beyond the scope of this article, but in the most general sense, two different approaches can be taken.[2] The first, often described as a "black box" approach, derives a quantitative description of a physiological system based solely on data (typically inputs applied to the system and outputs collected from measurements). These data-driven models are generally most appropriate where there is a lack of knowledge concerning the underlying physiology. The second approach, which we focus on here, involves mechanistically modeling the system by explicitly describing the underlying physiology using mathematical equations.[5] A major advantage of this approach is that the resulting model can provide mechanistic insights[6] into why, and how, a particular intervention or treatment can provide benefit.[7]

Seeking to gain new understanding of a system as complex as the respiratory system using traditional experimental approaches is extremely challenging.[8] An ideal approach would allow for the simplification of some confounding heterogeneity, while retaining an ability to monitor clinically meaningful outcomes, or their surrogate markers. Mathematical models that can be implemented on computers to produce virtual replicas of individual patients[9] could provide an important new tool for clinical research, allowing the possibility of rapid hypothesis testing,[10] without any ethical or patient-safety concerns.

However, the respiratory system represents a substantial challenge for physiological modeling, due to its inherent complexity, and to the continuing difficulty in "looking inside" the lung. During the process of breathing, there are numerous mechanical and physical forces acting on the organ system at several levels of complexity and resolution.[11] The earliest attempts at a simple mathematical description of the respiratory system are over 70 years old.[12,13] The earliest *in silico* implementations of respiratory system models on digital computers date to over 50 years ago[14,15] and work in this area has continued to expand in scope and complexity,[16,17] with recent efforts focusing on developing highly integrated representations of the respiratory and cardiovascular systems.[18–20] Although the term *in silico* is not rigorously defined, it can be placed within the context in which experimentation and research into the human body take place within a triad of *in vivo* (within or utilizing the living organism), *in vitro* (outside the organism), or *in silico* (using computer simulations).[21] Thus, *in silico* refers to the use of computer software to simulate, monitor, and experiment with physiological processes for the purposes of medical research.

In Silico Modeling in the Context of Mechanical Ventilation

Mechanical ventilation (MV) is used extensively in critical illness, and recent epidemiological work has indicated that the incidence of MV for non-surgical reasons in the United States was over 300 persons per million of the adult population.[22] The need for MV increased dramatically beyond this level during the COVID-19 pandemic.[23] One challenge in conducting research among critically ill patients receiving MV is the heterogeneous nature and severity of their pathologies. Whether due to the syndromic nature of critical illness,[24] or the interaction between therapy and context within an individual patient,[25] the results and meaning of randomized controlled trials (RCTs) are often unclear.[26] Relatively few RCTs into novel MV strategies have shown beneficial impact of the intervention on the survival of patients.[27] Many methodological problems compound research in this setting, and the majority of important achievements that have improved mortality are the results of improvements in recognizing deteriorations in patients and avoiding iatrogenic harm.[28]

A significant body of research exists in which various approaches have been applied to modeling the geometry and physiological behavior of the respiratory system under MV, especially within the engineering literature.[13,29] The precise details of these approaches vary widely in terms of approach and complexity, and results exhibit varying degrees of clinical relevance. In the following, we focus on work which has demonstrated direct clinical applicability and insight, identifying key themes and areas of relevance.

Acute Respiratory Distress Syndrome

One of the most important areas for the clinical application of MV is for respiratory support in patients with acute respiratory distress syndrome (ARDS), which affects around 10% of patients admitted to intensive care units (ICUs), and 25% of patients who require MV.[30] *In silico* modeling has yielded important insights into several areas relating to the pathophysiology and ventilatory management of this condition.

Modeling ARDS Pathophysiology

There have been several attempts to accurately model key pathophysiology involved in ARDS. One successful approach has resulted in the ability to recreate not just the behavior of the respiratory system under MV but also interactions with the cardiovascular system, to successfully replicate individual patients with ARDS.[31] A contrasting, more simplified, approach is the development and validation of a physiologically relevant respiratory model that captures compliance and resistance within a single compartment lung model.[32] Another study utilized a hybrid approach combining

computational modeling with real-time electrical impedance tomography to predict global and local ventilatory quantities for a given patient with ARDS.[33] Another model investigated the effect of severe injury on how compliance changes with more severe injury, giving mechanistic insight into how the "volume history" of the injured lung affects the tendency for de-recruitment in ARDS.[34] Other integrated models of cardiopulmonary physiology have been developed, but focus was on their ability to replicate and respond to hypoxia and hypercapnia data in healthy patients, rather than the ability to simulate individual ARDS patients.[19] Computational fluid dynamics has also been a promising approach to simulate pulmonary pathophysiology.[35,36]

Diagnosing ARDS

The utility of modeling to assist with the diagnosis of ARDS has also been examined. It is known that ARDS is underrecognized based on standard diagnostic criteria,[30] and recent expert opinion has added to the debate around whether the current diagnostic criteria for ARDS is indeed sufficient to encompass such a heterogeneous range of pathophysiology.[37] One study found that using a simple ARDS model led to reclassification of disease in approximately 30% of cases.[38] There is clearly a large potential for *in silico* modeling to contribute to deeper phenotypic and mechanistic insight in this complex and heterogeneous condition.

Optimizing Mechanical Ventilation

Research into optimization of MV in ARDS has been a particularly fruitful area for *in silico* modeling. This includes insight into the titration of positive end-expiratory pressure (PEEP), the avoidance of ventilator-induced lung injury (VILI), evaluation of recruitment maneuvers, and the calculation and integration of patient factors (such as spontaneous breathing effort and age) when considering MV settings.

The titration of PEEP is traditionally performed using standardized protocols based on previous RCTs,[39] often incorporating a mix of clinician experience. Mathematical modeling has yielded important insights regarding the optimization of PEEP. For example, modeling work in which optimal PEEP was determined using a detailed interrogation of elastance suggested that PEEP was often set at a level below the optimum for patients.[40] In contrast with this, the potential for an inappropriately high PEEP to paradoxically lead to decreased oxygen delivery to tissues has also been elucidated using modeling.[41] Detailed models have also been developed that can predict mechanical responses to altered PEEP,[42] and a desktop application named CURE Soft has been developed which can be used for real-time optimization of MV (in particular PEEP).[43] A single center RCT comparing the use of this system with the standard therapy is currently underway.[44]

VILI refers to the phenomenon whereby lung tissue can be injured when the ventilator delivers breaths that are too large (volutrauma), pressures that are too great (barotrauma), or repeated cycles of alveolar collapse and reopening (atelectasis). The primary goal of MV is now recognized as managing the balance between achieving effective oxygenation of the patient while avoiding VILI in heterogeneous, injured lung tissue.[45] It is not possible to measure the occurrence of VILI directly, but surrogate markers such as the driving pressure and mechanical power delivered to the lung, and thresholds of elastance have been proposed. Modeling has provided insights into the mechanistic basis of RCT-derived associations between VILI indicators such as driving pressure and mortality,[46] and allowed different VILI indicators to be compared in terms of their suitability as "targets" for maximally protective ventilation.[47] Stochastic modeling has been used to create patient-specific models to predict future elastance ranges for a patient, yielding a range for minute volume that will minimize VILI,[48] though further clinical testing is needed to verify this approach. The problem of minimizing VILI while adequately oxygenating a patient can be framed as an "optimization problem," in which values known to represent harm are given to the computational model as clear boundaries within which a solution representing safe ventilation is found. Using this approach, it is indeed possible to simulate individual patient physiology and determine safe limits.[29,49] *In silico* modeling has also been used to examine the molecular level changes that take place during the poorly understood mechanisms that underlie VILI,[50] opening up the possibility for new avenues to treatment and prevention.

Recruitment maneuvers (RMs), in which various ventilation protocols are used to re-inflate lung tissue that has collapsed (or has become "derecruited") constitute another important area for the application of modeling in ARDS research, with much debate still surrounding best clinical practice in this area.[51] *In silico* work has allowed direct quantitative comparisons of RMs on the virtual patients with differing severities of ARDS, suggesting that patients with severe ARDS are likely to gain greater benefit from RMs than patients with mild or moderate disease,[52] indicating that short-term protective changes in cardiac output may be warranted pre-emptively, and identifying thresholds of PEEP to achieve and sustain recruitment.[53] Other studies have predicted lung mechanics during RMs in volume and pressure control modes,[54,55] suggesting that RMs can behave unpredictably due to multiple stability states within the injured lung,[56] and showing how titration of airway pressures based on variations in intra-tidal mechanics may mitigate processes associated with injury due to derecruitment.[57] Airway network models has allowed the examination of stresses within different portions of lung tissue, identifying areas most at risk of injury during RMs.[58]

Another important aspect of optimizing MV in ARDS involves taking account of patient specific factors and how they can alter what constitutes ideal therapy. For example, a detailed model of the geometry of the respiratory system has been designed to reflect known changes consistent with aging.[59] Simulation of respiratory mechanics and lung function under different aging conditions outlined the dynamic deterioration of lung function due to aging, illustrating the importance of taking account of the effects of aging when subjecting older patients to MV. Considering the

spontaneous effort of breathing that can be executed by the ventilated patient is another critical issue in ensuring protective ventilation. Simulations using a "Gaussian Effort Model" have been used successfully to illuminate the interactions between a ventilator and the breathing patient.[60] Taking into account patient resistance and elastance with each breath has also been shown to be possible, improving the estimation of respiratory mechanics, providing clinicians with measurements that can assist therapeutic optimisation.[61] Other work in this area has shown clear potential to improve fully and partially assisted modes of MV.[62,63]

In silico modeling offers a safe environment in which to compare the effects and potential of novel and different modes of ventilation. For example, work has shown that moderately high-frequency ventilation could allow safe reduction of tidal volumes and airway pressures in ARDS patients,[64] but also illustrates mechanisms by which injury can be induced when these frequencies become too high and interact with innate physical properties of lung tissue.[65]

Pediatric and Neonatal Mechanical Ventilation

Research into the use of modeling to investigate MV strategies in pediatric and neonatal ARDS patients is significantly less well advanced than in adults. A simple simulator that can represent pediatric patients was presented in Flechelles et al,[66] but this model has not yet been validated against patient data and is restricted to patients greater than 7 years old. A detailed simulator of cardiopulmonary ARDS pathophysiology has been adapted to match data from a large cohort of pediatric ARDS patients aged between 1 month and 18 years of age,[67] and was used to analyze potential strategies for achieving more protective ventilation.[47]

The extremely small volumes of neonates' lungs, as well as their large respiratory and vascular resistances make simulating the neonatal respiratory system challenging. Physiological features such as lung volume, cardiac output, oxygen consumption, and airway resistance are weight dependent in neonates, and some parameters such as pulmonary vascular resistance are highly variable during the first hours of life. Initial work on the development of the first simulator for mechanically ventilated neonates was presented in.[68]

Weaning from Mechanical Ventilation

The way in which ARDS patients are weaned from MV is increasingly being recognized as a crucial part of their treatment. Research seems to support the use of standardized protocols, but the heterogeneity of patients within some studies highlights the need for caution when considering any particular example,[69] and multiple metanalyses of the conduct of spontaneous breathing trials show that neither the use of a method involving a T-piece nor pressure support demonstrates a clear benefit.[70,71]

This marks an important area where *in silico* simulation may be able to offer insight. A single-center RCT is currently underway in which a model-based decision support tool will be used to guide weaning compared with standard care (the iCareWean trial). The system used is based on a set of physiological models including models of pulmonary gas exchange, acid–base chemistry, lung mechanics, and respiratory drive.[72]

COVID-19 ARDS

The debate about apparent phenotypes of COVID-19 patients during the global pandemic offered an opportunity for *in silico* testing to investigate the pathophysiology of this disease. This work involved adapting a previously validated computational simulator of standard ARDS to develop quantitative insights into the key pathophysiologic differences between the COVID-19 ARDS against conventional ARDS, and to assess the impact of different PEEP, fraction of inhaled oxygen (FiO_2), and tidal volume settings.[73] This work found that introducing disruption of alveolar gas-exchange due to the effects of pneumonitis and increased microthrombi-related vascular resistance, produced levels of ventilation perfusion mismatch and hypoxemia consistent with data from COVID-19 ARDS patients. In addition, the model suggested that the use of standard PEEP/FiO_2 tables[39] and high PEEP strategies could be harmful in some early-stage COVID-19 ARDS patients.

In response to equipment shortages, many institutions explored the development of a shared ventilation strategy in which a single ventilator could be used to ventilate multiple patients simultaneously.[74] Given the enormous ethical complexity involved in testing or implementing such an approach, *in silico* testing offered an ideal environment in which to explore the approach. A group was able to use simulation to provide proof-of-concept for an algorithm to better match patients in different hypothetical scenarios of a single shared ventilator using ARDSNet protocols and analysis of lung mechanics.[75]

Other Mechanical Ventilation Contexts

MV is employed in a variety of other contexts, many of which are amenable to research using mathematical modeling. Research has shown that the pathophysiology of mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) can be simulated with accuracy and indeed replicas of individual patients can be created using optimization algorithms and high-performance computation.[76] Using this approach, MV settings that successfully managed the trade-off between ensuring adequate gas exchange and minimizing the risk of VILI for COPD patients were investigated. A different large-scale collaborative project is also seeking to address the complexity involved in accurately modeling the multiscale challenges associated with obstructive pathologies such as asthma and COPD.[8]

An innovative use for mathematical modeling has been in the realm of simulating MV strategies for patients with injury to the lung secondary to explosive blast forces. Primary blast lung injury (PBLI) caused by exposure to high-intensity pressure waves is associated with injury to parenchymal tissue and marked ventilation-perfusion mismatch. A mathematical model of PBLI was used to examine how the heterogeneity of resultant damaged tissue affects gas flow and forces within the parenchyma.[77] Another

study has been able to accurately simulate the pathophysiology involved in PBLI,[78] and used this approach to test different MV strategies, concluding that airway pressure release ventilation represented a potentially useful approach in this patient group.[79]

Other work has used integrated cardiopulmonary modeling to assess how therapies that mechanically support the cardiovascular system interact with MV, and the implications of these interactions. One study analyzed the effect of the interaction between MV and cardiac output when a biventricular pacemaker is used, and gives insight into the clinical implications of this interaction.[80] Other work has explored the effects of similar interactions when an intra-aortic balloon pump is used.[81]

Finally, models that incorporate virtual geometries derived from computed tomography (CT) images of patients have been used to investigate "noisy ventilation," in which the patient receives variable tidal volumes, opening up the possibility of optimizing ventilation for patients who are not critically ill, but are being ventilated as an adjunct to other therapies such as surgical intervention.[82]

Education and Training

Education to enable understanding of the principles and practice of safe MV is an important area for providers and professionals in training. Unfortunately, best principles and evidence-based practice are often not provided,[30] for a variety of reasons.[83] The potential for computational models to illustrate physiological principles and act as educational tools has been apparent for at least 50 years.[84] *In silico* simulation offers an effective alternative to didactic and passive teaching strategies, as complex physiological simulations offer the chance to demonstrate the physiological response of a virtual patient, or an isolated portion of their physiology, to a variety of interventions.[85] This can be done rapidly, repeatedly, remotely, and at no risk to real patients. As such, it is unsurprising to see the increasing deployment of *in silico* models in this area.[86] For example, a recent study proposed the use of a lumped parameter model, CARDIOSIM, for educational purposes[87] in which the system can demonstrate the physiology involved in MV[88] and simulate the interaction between MV and devices that support the functioning of the cardiovascular system.[89] Systems that can illustrate the safe principles of MV have been proposed to help enable understanding of the effects of pre-existing disease on therapeutic management.[90] Attempts have been made to create open online resources,[91] though not all these are functional.[92] One system that is functional and is in use in various contexts is the Pulse Physiology Engine, an open-source software application designed to enable accurate and consistent real-time simulations for improved medical training and clinical decision-making.[93] Its open-source nature allows for ease of expansion[94] into many areas. This mathematical model can also be deployed in high fidelity manikins, and small trials comparing the use of manikins versus screen-based simulation have suggested the former approach produces superior outcomes.[95]

Challenges for *In Silico* Modeling of Mechanical Ventilation

Despite the many innovations and potential applications of this approach, the integration of mathematical modeling, in all its various forms, into clinical practice still presents some serious challenges. Clearly, one of the main challenges moving forward is moving *in silico* modeling from a place where it can describe events to where it can inform interventions that shape events. At an institutional level, there exists a disconnect or unfamiliarity between engineering-focused modelers and patient-facing clinicians, which can hinder the integration of complex models into clinical practice.[10]

The search for clinically meaningful outcomes is not straightforward, especially within the realm of critically ill patients, and traditional clinical research in the ICU environment is fraught with challenges. *In silico* modeling offers a potential way to sidestep some of these challenges and provide an alternative pathway to clinical innovation. However, the cornerstone and gold standard of evidence-based medicine remains the randomized control trial. This presents an apparent "Catch-22" situation, in which *in silico* modeling is used to work around inevitable challenges to performing RCTs, yet confirmation of the predictions of the *in silico* model in a RCT is ultimately necessary to convince clinicians of the benefit of the approach.[69,96] One way to resolve this paradox is to conceptualize modeling as a tool for designing "better" (i.e., more likely to be successful) RCTs, via for example patient stratification in highly heterogeneous cohorts, rapid initial comparison of different potential interventions on *in silico* patient cohorts, "screening," and removal of interventions that are unlikely to be successful, etc.

An inescapable reality of any modeling approach is that some amount of simplification is involved in the representation of the underlying reality. This emphasizes the importance of asking models the right question in the right context, but also highlights a limitation; studies performed using mathematical and computational modeling cannot be configured to match real human subjects exactly.[97–99] The challenge is therefore to find models which are *complex enough* to adequately describe and predict the pathophysiological aspects of the patient's condition in which the clinician is interested. In the context of MV, a key requirement for clinically applicable models is obviously that they can accurately predict the effects of changing ventilator settings on the patient.

To illustrate the link between model complexity and predictive capability, we present here some new results validating the capability of the cardiopulmonary simulator described in previous publications[18,31,41,46,47,52,53,64,100] to match and predict the responses of individual ARDS patients to changes in MV settings (►**Fig. 1**) for a schematic of this model. Data previously collected from six mechanically ventilated patients (Draeger Evita, BiPAP) from the ICU at the Royal Hallamshire Hospital in the United Kingdom were used for this study.[35] All the patients had a primary diagnosis of ARDS, characterized by reduced functional residual capacity, reduced arterial oxygen, and reduced lung compliance, and had no history of asthma or other chronic lung disorders.

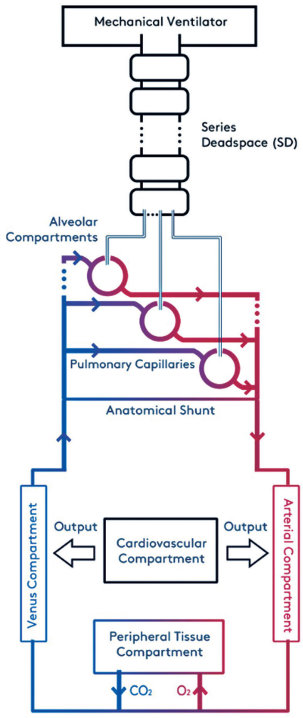

Fig. 1 Diagrammatic representation of the ICSM cardiopulmonary simulator.

All patients were fully sedated, were stable on the ventilator, and were undergoing the standard invasive monitoring procedures for that ICU. Four ventilator parameters were available for changes: inspiratory pressure (P_{insp}), end expiratory pressure (PEEP), the ratio of inspiratory to expiratory time (T_i:T_e), and the fraction of inspired oxygen (FiO_2). Ventilator settings were changed one at a time, and measurements of the patient's hemodynamic, respiratory, and blood gas variables were taken before and after each change. This yielded a database of 26 pairs of data points (initial ventilator settings and patient measurements at time T_0 and subsequent ventilator settings and patient measurements at time T_1), collated from six patients (►**Table 1**).

To test the capability of the simulator to predict the patients' responses to changes in ventilator settings, for each pair of data points the simulator was first matched to the data at time T_0, using advanced global optimization algorithms. In this process, ventilator settings in the simulator were fixed to match those recorded at T_0. The optimization algorithm then tries to minimize the difference between the patient measurements made at T_0 and the corresponding outputs of the simulator. This is achieved by iteratively adjusting, within physiologically reasonable ranges, the following model parameters: extrinsic pressure, alveolar stiffness, threshold opening pressures, pulmonary vascular resistance, and bronchial resistance, for each of the 100 independent alveolar compartments in the model, as well as values for respiratory quotient, oxygen consumption, hemoglobin concentration, volume of anatomical dead space, upper airway resistance, and anatomical shunt. Once the simulator parameters that give the closest match to the patient data at time T_0 are found, all model parameters are fixed, and the relevant ventilator setting in the simulator is changed to that recorded in the data at time T_1. Predicted values of PaO_2 and $PaCO_2$ produced by the simulator are then compared with those from the patient measurements made at time T_1.

As shown in ►**Table 1**, for the vast majority of the 26 pairs of data points the simulator can both accurately match the patient data at time T_0 and predict the patient's responses to the change in ventilator setting recorded at time T_1, with low mean absolute percentage errors between simulator outputs and patient data being recorded for both PaO_2 and $PaCO_2$. To investigate the link between model complexity and predictive capability, we repeated the matching process whilst reducing the number of independent alveolar compartments in the model from 100 to 50, 25 and 10. The impact on the accuracy of the model's predictions is shown in ►**Fig. 2**—reducing the complexity of the model produces a steep decline in its predictive capability. To quote a famous scientist, "It can scarcely be denied that the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience.[101]"

Future Research Directions

Sir Cyril Chantler stated that "Medicine used to be simple, ineffective, and relatively safe. Now it is complex, effective, and potentially dangerous."[102] The intensive care environment is an especially notable example of a highly complex environment, wherein many systems (from the cellular to the institutional) react and interact across multiple hierarchies. This complexity makes *in silico* approaches particularly useful to evaluate new treatment strategies, inform decision making, monitor responses, and aid training. In the context of MV, two distinct directions for future clinical applications can be identified—models to guide real-time decision support (or to assist in the development of fully automated) systems, and models for use as research tools.

In Silico Models for Patient Management

Currently, management of patients on MVs is largely based on protocols derived from large-scale clinical trials, with ventilator settings periodically adjusted by clinicians whose workloads are increasingly unsustainable. Truly personalized treatment requires rapid and frequent interventions based on changes in the patient's state that are often not achievable within current ICU constraints—a recent study found that important targets for oxygen saturation in mechanically ventilated neonates were being achieved only 40% of the time.[103] Computerized decision support systems, or fully automated "closed-loop" ventilation systems, could potentially reduce clinician workload while providing patients with more rapid personalized interventions—*in silico* models will form the core of both.

Table 1 Simulated values of PaO_2 and $PaCO_2$ versus patient data for 26 pairs of ventilator settings and arterial blood gasses taken from six ARDS patients. Ventilator settings that were changed between times T_0 and T_1 are reported. The simulator was configured with the same ventilator settings as reported in the data at time T_0, and model parameters were matched to the corresponding patient measurements using global optimization algorithms. Ventilator settings were then changed in the simulator according to each set of patient data, and simulated values of PaO_2 and $PaCO_2$ are compared with new patient arterial blood gasses taken at time T_1. The absolute % error is the magnitude of the difference between the measured value and the simulated value, divided by the measured value, and then multiplied by 100

Ventilator setting at T_0	Data PaO_2 (kPa)	Matched PaO_2 (kPa)	Absolute % error	Data $PaCO_2$ (kPa)	Matched $PaCO_2$ (kPa)	Absolute % error	Ventilator setting at T_1	Data PaO_2 (kPa)	Predicted PaO_2 (kPa)	Absolute % error	Data $PaCO_2$ (kPa)	Predicted $PaCO_2$ (kPa)	Absolute % error
PEEP = 7	14.6	14.6	0.0	6.7	7.4	10.4	PEEP = 2.5	13.1	13.6	3.8	6.2	6.0	3.2
PEEP = 2.5	13.1	12.6	3.8	6.2	6.9	11.3	PEEP = 7.5	13.5	13.3	1.5	6.4	8.8	37.5
PEEP = 7.5	15.6	15.9	1.9	6.5	6.7	3.1	PEEP = 2.5	13.5	13.7	1.5	5.7	5.4	5.3
PEEP = 2.5	13.5	13.5	0.1	5.7	5.6	1.2	PEEP = 7.5	13.9	14.5	4.3	6.1	7.4	21.3
FiO_2 = 0.57	13.9	14.0	0.5	6.1	6.2	1.6	FiO_2 = 0.67	18.4	16.4	10.9	6.0	6.2	3.3
FiO_2 = 0.67	18.4	18.1	1.6	6.0	6.2	3.3	FiO_2 = 0.47	11.3	13.1	15.9	7.1	6.2	12.7
FiO_2 = 0.47	11.3	11.4	0.9	7.1	7.1	0.0	FiO_2 = 0.57	13.8	12.4	10.1	6.7	7.1	6.0
P_{insp} = 28	13.8	13.9	0.7	6.7	6.8	1.5	P_{insp} = 23	12.1	13.2	9.1	7.9	9.4	19.0
P_{insp} = 23	12.1	12.1	0.0	7.9	8.8	11.4	P_{insp} = 28	14.1	11.9	15.6	6.6	6.1	7.6
P_{insp} = 25	20.0	20	0.0	4.9	4.7	4.1	P_{insp} = 20	11.0	18.3	66.4	6.2	7.1	14.5
P_{insp} = 20	11.0	11.7	6.4	6.2	6.1	1.6	P_{insp} = 25	14.2	11.4	19.7	5.8	4.2	27.6
P_{insp} = 25	14.2	14.7	3.5	5.8	5.6	3.4	P_{insp} = 30	15.2	14.5	4.6	5.5	4.3	21.8
P_{insp} = 30	15.2	14.9	2.0	5.5	5.5	0.0	P_{insp} = 25	15.1	14.9	1.3	5.5	7.5	36.4
PEEP = 7	15.4	14.8	3.9	5.9	5.5	6.8	PEEP = 2	14.6	11.6	20.5	5.7	4.1	28.1
FiO_2 = 0.4	14.3	14.4	0.7	5.6	5.6	0.0	FiO_2 = 0.45	16.7	15.8	5.4	5.7	5.6	1.8
FiO_2 = 0.60	15.7	15.7	0.0	5.4	5.6	3.7	FiO_2 = 0.50	13.7	13.2	3.6	5.4	5.7	5.6
FiO_2 = 0.50	13.7	13.8	0.7	5.4	5.9	9.3	FiO_2 = 0.40	12.0	12	0.0	5.5	5.9	7.3
FiO_2 = 0.4	12.0	12.1	0.8	5.5	5.7	3.6	FiO_2 = 0.50	19.0	14	26.3	5.3	5.7	7.5
P_{insp} = 35	19.0	18.3	3.7	5.3	5.3	0.0	P_{insp} = 40	24.2	19.3	20.2	5.0	4.1	18.0
P_{insp} = 40	24.2	23	5.0	5.0	4.8	4.0	P_{insp} = 35	23.1	21.1	8.7	5.4	6.1	13.0
P_{insp} = 35	23.1	22.5	2.6	5.4	5.4	0.0	P_{insp} = 30	22.7	22.5	0.9	5.7	5.4	5.3
P_{insp} = 25	19.8	19.7	0.5	7.3	7.4	1.4	P_{insp} = 31	22.5	20.4	9.3	4.9	4.8	2.0
I:E = 0.66	14.4	14.6	1.4	5.1	5.2	2.0	I:E = 0.5	14.5	14.4	0.7	4.7	5.1	8.5
I:E = 0.5	14.5	15.3	5.5	4.7	4.2	10.6	I:E = 0.33	14.2	14.5	2.1	4.8	4.7	2.1
I:E = 0.33	14.2	14.9	4.9	4.8	4.8	0.0	I:E = 0.5	14.6	14.2	2.7	4.9	4.8	2.0
PEEP = 10	15.5	14.9	3.9	4.6	4.3	6.5	PEEP = 15	15.8	15.5	1.9	5.1	4.6	9.8
Mean absolute percentage error (%)			2.1			3.9				10.3			12.6

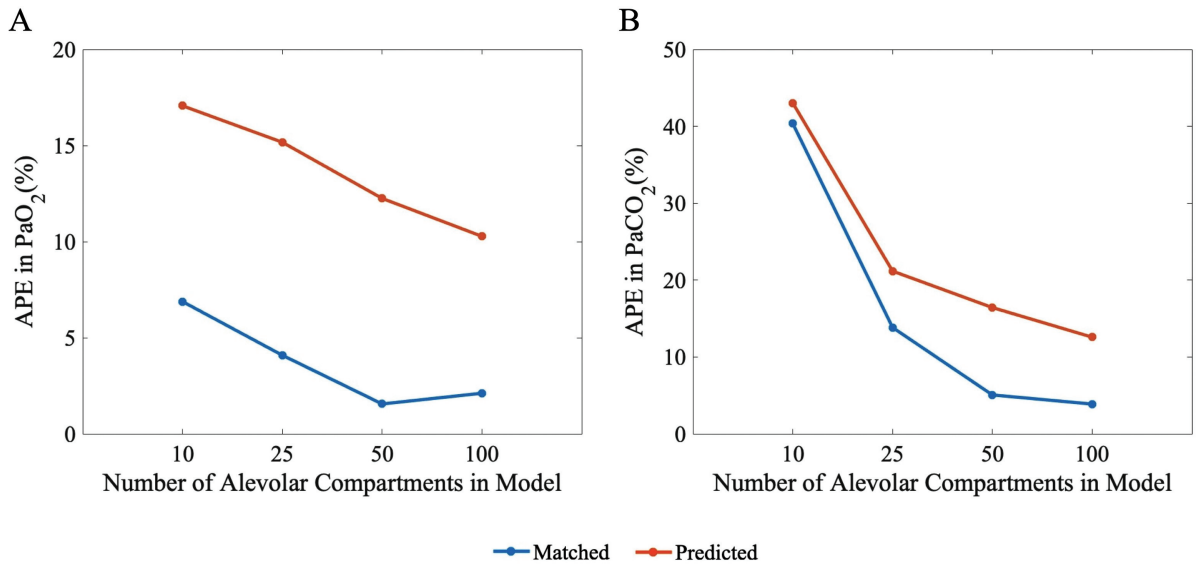

Fig. 2 Average percentage error between 26 sets of patient data and corresponding simulator outputs for **(A)** PaO_2 and **(B)** $PaCO_2$ at time T_0 (matched) and T_1 (predicted) as the number of independent alveolar compartments in the model is varied.

Early proposals for decision support systems (DSS) relied heavily on rule-based clinical heuristics,[104,105] but more modern systems have begun to integrate *in silico* models to drive decisions.[72,98,106] In a recent study, a DSS retrospectively evaluated treatment in 16 intensive care patient cases, with physiological models fitted to the retrospective data and then used to simulate patient response to changes in therapy.[107] Compared with the baseline ventilator settings set as part of routine clinical care, the system suggested lower tidal volumes and inspired oxygen fraction, but higher frequency. Another study retrospectively examined the ability of a model driven DSS to advise on pressure support (PS) levels in a critically ill patient. The system advised on low values of PS while acting to preserve respiratory muscle function and preventing passive lung inflation. It also minimized FIO_2 maintaining SpO_2 at safe and beneficial values.[108] A protocol has recently been published for a multicenter RCT to compare MV in ARDS patients following use of this DSS to that of standard routine care, with the primary outcome defined as a reduction in driving pressure across all severities and phases of ARDS.[109] A key requirement for the models employed in all such systems is the ability to run in real-time on standard low-cost computing platforms. Managing the trade-off between the resulting limitations on model complexity and its predictive capability will be a key challenge for future development of such systems. It also seems likely that such systems will increasingly be challenged by artificial intelligence-based algorithms leveraging large-scale data analytics rather than mechanistic models.[110]

Although both DSS and fully automated ventilator control systems have clear potential for improving the care of critically ill patients, an under-researched question concerns how they should be best deployed in the ICU environment. For example, should they be deployed using standalone "apps" that can even run on a standard tablet, or remotely access high-performance computing platforms via a bedside laptop, or be integrated into next-generation ventilators? A related question concerns how their outputs can be most effectively communicated to clinicians, to avoid generating yet more numbers in an already crowded sea of information, or more alarms or guidance notifications that risk being ignored in favor of familiarity.

In Silico Models as Research Tools

Within the realm of medical research, *in silico* models are now increasingly recognized as having huge potential to facilitate the difficult, time-consuming and costly work of designing large real-world RCTs in critical care.[21] The models available now enable us to create replicas of real patients that have been proven to behave as expected, raising the interesting possibility of generating a "biobank" of virtual patients who can be utilized for virtual trials. Data-only systems like this exist,[111] although they are not tied to any specific model. Biobanks of *in silico* patients based on validated models[100] could radically improve the design of RCTs by allowing for more exact patient stratification, and providing initial results on the likely effects of novel treatments that could be used to optimize trial protocols and reduce the likelihood of negative outcomes. The potential for studies based on *in silico* models to inform treatment is also being increasingly recognized in areas of medicine where it is essentially impossible to carry out RCTs, such as emergency medicine and responses to mass casualty events.[112]

Beyond the realm of RCTs, the use of *in silico* models in preclinical research into MV will continue to expand, as such models begin to match or surpass the clinical relevance of animal or *in vitro* models. An important factor to consider here is the inevitable continuous improvement in the fidelity and predictive capability of *in silico* models, as more and better data become available for model construction and validation, and as the availability of low-cost computing power continues to increase.

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Conflict of Interest
None declared.

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