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A computational cardiopulmonary physiology simulator accurately predicts individual patient responses to changes in mechanical ventilator settings*

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Abstract— **We present new results validating the capability of a high-fidelity computational simulator to accurately predict the responses of individual patients with acute respiratory distress syndrome to changes in mechanical ventilator settings. 26 pairs of data-points comprising arterial blood gasses collected before and after changes in inspiratory pressure, PEEP, FiO_2, and I:E ratio from six mechanically ventilated patients were used for this study. Parallelized global optimization algorithms running on a high-performance computing cluster were used to match the simulator to each initial data point. Mean absolute percentage errors between the simulator predicted values of PaO_2 and $PaCO_2$ and the patient data after changing ventilator parameters were 10.3% and 12.6%, respectively. Decreasing the complexity of the simulator by reducing the number of independent alveolar compartments reduced the accuracy of its predictions.**

Clinical Relevance— **These results provide further evidence that our computational simulator can accurately reproduce patient responses to mechanical ventilation, highlighting its usefulness as a clinical research tool.**

I. Introduction

Computer simulation offers a new approach to traditional medical research that is particularly well suited to investigating treatment of critical respiratory illness using mechanical ventilation. Critically ill patients are monitored in great detail, providing extensive high-quality data for model design, configuration and patient-matching. Models based on this data can incorporate very complex system dynamics that can be validated against responses of individual patients, for use as investigational surrogates. Simulation offers the potential to "look inside" the patient, opening up the possibility of rationally "designing" new mechanical ventilation strategies *in silico* by exploiting the speed, reproducibility, and cost-effectiveness of "virtual" patient trials. In contrast to trials on both animal models and human patients, *in silico* models of individualised patient and disease pathology are completely configurable and reproducible – different ventilation strategies can be applied to the same spectrum or subset of virtual patients, in order to quantitatively compare their effectiveness in multiple different scenarios, and to optimise settings for different clinical objectives and particular patient groups or individuals. Such "virtual" trials could allow future clinical trials to be honed and directed, accelerating the achievement of impactful changes in clinical practice.

The process of validating the predictive capability of cardiopulmonary simulators in the context of mechanical ventilation is complicated by the scarcity of appropriate patient data in the literature. Most clinical studies publish only statistical data reporting mean and standard deviations across a patient cohort, rather than individual patient data. In addition, vanishingly few studies report measurements of individual patient arterial blood gasses before, and soon after, changes in mechanical ventilator settings.

The computational simulator used here has been under continuous development for over 25 years and has been applied in numerous clinical studies [1-9]. Previous studies evaluating its predictive validity have considered changes in fraction of inspired oxygen (FiO_2), ventilatory frequency or tidal volume under volume control mode ventilation [2]. Here, we evaluate the simulator's ability to predict patient responses to changes in FiO_2, positive end expiratory pressure (PEEP), inspiratory pressure (P_{insp}), and ratio of the duration of inspiratory and expiratory phases (I:E ratio), using data from patients under pressure control mode ventilation [10].

A second objective of the study is to examine the effect of changing the complexity of the simulator on its predictive capability. The simulator incorporates a user-defined number of alveolar compartments for gas exchange, as well as viscoelastic compliance behaviour, interdependent blood-gas solubilities, and heterogeneous distributions of pulmonary ventilation and perfusion. The computational complexity of the optimisation-based model matching process is strongly dependent on the number of alveolar compartments, and so we sought to determine the trade-off between model complexity and predictive performance.

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II. METHODS

A. Patient Data

Data previously collected from six mechanically ventilated patients (Draeger Evita, BiPAP) from the ICU at the Royal Hallamshire Hospital in the UK were used for this study [10]. All the patients had a primary diagnosis of acute respiratory distress syndrome, characterised by reduced functional residual capacity, reduced arterial oxygen, and reduced lung compliance, and had no history of asthma or other chronic lung disorders. 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}), positive end expiratory pressure (PEEP), the ratio of inspiratory to expiratory time (I:E) and the fraction of inspired oxygen (FiO_2). After a measurement period of 15 minutes at pre-study ventilator settings, one of the ventilator parameters was altered and another 15 minutes measurement period commenced before returning the ventilator parameter to its pre-study value.

During each measurement period, cardiovascular parameters were continuously recorded. Measurements requiring manual intervention, including cardiac output, were taken at the bedside. Arterial and venous blood gas measurements were analyzed from blood samples withdrawn from the patient during the measurement period. From this database of readings and their corresponding ventilator settings, 26 pairs of data points were used in this investigation (initial ventilator settings and patient measurements at time T0 and subsequent ventilator settings and patient measurements at time T1).

B. The Computational Simulator

The computational simulator used in this investigation represents multiple interacting organ systems and incorporates a high level of physiological detail, including multiple alveolar compartments, multi-compartmental gas exchange, viscoelastic compliance behavior, interdependent blood-gas solubility and hemoglobin behavior and heterogeneous distributions of pulmonary ventilation and perfusion.

Each model component is described as several mass conserving functions and solved as algebraic equations, obtained, or approximated from the published literature, experimental data, and clinical observations. These equations are solved in series in an iterative manner so that solving one equation at the current time instant determines the values of the independent variables in the next equation. At the end of each iteration, the results of the solution of the final equations determine the independent variables of the first equation for the next iteration. The iterative process continues for a predetermined time, with each iteration representing a 'time slice' *t* of real physiological time (set to 30 ms). At the first iteration, an initial set of independent variables are chosen based on values selected by the user. The user can alter these initial variables to investigate the response of the model or to simulate different pathophysiological conditions. Subsequent iterations update the model parameters.

The pulmonary model consists of the mechanical ventilation equipment, anatomical and alveolar deadspace, anatomical and alveolar shunts, ventilated alveolar compartments and corresponding perfused capillary compartments. The pressure differential created by the mechanical ventilator drives the flow of gas through the system. The series deadspace (SD) is located between the mouth and the alveolar compartments and consists of the trachea, bronchi and bronchioles, where no gas exchange occurs. Inhaled gases pass through the SD during inspiration and alveolar gases pass through the SD during expiration. No mixing between the compartments of the SD is assumed. Each alveolar compartment has a unique and configurable alveolar compliance, alveolar inlet resistance, vascular resistance, extrinsic (interstitial) pressure and threshold opening pressure. The alveolar compartments are arranged in parallel and interact with the series deadspace with respect to the movement of gases. The flow of air into the alveolar compartments is achieved by a positive pressure provided by the ventilator and the air moves along the pressure gradient. Figure 1 shows a diagrammatic representation of the model. For a complete description of the model and its underlying mathematical principles, the reader is referred to the Additional File 1 in [9].

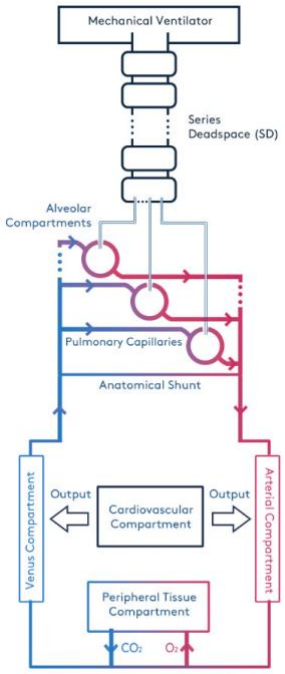

Figure 1. Diagrammatic representation of the simulator

C. Optimization-based matching to patient data

The model parameters were matched to each of the chosen data points using genetic algorithms (GAs). In recent years genetic algorithms have become an increasingly popular technique used in scenarios of small and large search parameters making it ideal for use in physiological modelling scenarios. This method allows for the parameters of each individual alveolar compartment to be independently adjusted

in order to create a level of heterogeneity that reflects the effects of acute respiratory disease.

The model matching optimization problem is set up to minimize the difference between the model outputs for a given set of ventilator parameters and the corresponding physiological measurements from the patient. The model parameters determined during the optimization include Extrinsic Pressure (P_{ext}), Alveolar Stiffness (k_{stiff}), Threshold Opening Pressures (TOP), Pulmonary Vascular Resistance (V_{comp}) and Bronchial Resistance (R_{comp}) for each alveolar compartments, as well as values for Respiratory Quotient (RQ), Oxygen Consumption (VO_2), Hemoglobin Concentration (Hb), Volume of Anatomical Dead Space (V_D), Upper Airway Resistance (UB_{resist}), anatomical shunt ($Shunt_{anat}$) and Base Excess (BE). The optimization problem is formulated to find the configuration of model parameters (x) that minimizes the difference between the model outputs $\hat{Y}$ (for a given set of ventilator parameters) and the patient data Y. This error is captured by a cost function J given by:

$$\min_x J = \sqrt{\sum_{i=1}^{9} w_i \left(\frac{\hat{Y}_i - Y_i}{Y_i}\right)^2} \quad (1)$$

where

$$Y = [PaO_2, PaCO_2, V_T, pHa, HCO_3] \quad (2)$$

The model outputs $\hat{Y}$, optimized using the cost function are partial pressures of oxygen (PaO_2), partial pressures of carbon dioxide ($PaCO_2$), tidal volume (V_T), arterial blood pH (pHa) and bicarbonate level (HCO_3). Weighting factors, w_i, were implemented in the cost function to prioritize matching of PaO_2 and $PaCO_2$.

The optimization algorithm returns a set of model parameters that optimally match the model outputs to the patient data for each initial set of ventilator settings (time T_0). Using this parameterization of the model, the relevant ventilator setting in the simulator was changed as specified in the data, the simulator was run for the same amount of time as in the clinical setting, and the model outputs were compared with the new patient data (time T_1).

To investigate the effects of the complexity of the model on the accuracy of the model's predictions, the global optimization problem was solved for each initial ventilator setting from the selected dataset for the model configured to have 100, 50, 25 and 10 alveolar compartments. The number of parameters to be optimized using the GA is given by

$$N_p = P_{alv} \times N_{comp} + P_{phys} \quad (3)$$

where

$$P_{alv} = 5 \;\; P_{phys} = 7 \quad (4)$$

P_{alv} is the number of alveolar parameters to be set in each alveolar compartment, N_{comp} is the number of alveolar compartments and P_{phys} is the number of other physiological parameters to be set in the genetic algorithm. Thus, the computational complexity of the optimization problem reduces significantly as the number of alveolar compartments reduces.

The optimizations required for the model matching were performed using the global optimization toolbox and parallel computing toolbox in MATLAB 2020a. The code was implemented in the 'Orac' high performance computing cluster provided by the University of Warwick (2352 x Intel Xeon E5-2680 v4 2.4 GHz Broadwell cores; 28 cores per node; 84 nodes; 128 GB DDR4 memory per node). A summary of the average computation time taken for the GA to match the data for each number of compartments is shown in Table 1. Significant reductions in computation time were seen with the reduction in the number of alveolar compartments.

Table 1. Summary of computation time to match model parameters to one Patient

Number of Compartments	Average Computation Time (hours)
100	40
50	30
25	15
10	9

III. Results

A comparison of the simulator outputs for each of the 26 pairs of patient data when using 100 alveolar compartments in the model is shown in Table 2. Mean absolute percentage errors between model outputs and patient data for PaO_2 and $PaCO_2$ at the initial (matched) time point T_0 were 2.1% and 3.9%, respectively. After changes to ventilator settings, mean absolute percentage errors between the simulator predicted values of PaO_2 and $PaCO_2$ and the patient data were 10.3% and 12.6%, respectively. As shown in Figure 2, reducing the number of alveolar compartments in the model from 100 to 50, 25 and 10 resulted in progressively larger mean absolute prediction errors.

IV. Discussion & Conclusions

A key requirement for computational simulators, if they are to be used for research into current and novel ventilation strategies, is that they accurately predict the responses of individual patients to changes in ventilator settings. Our results demonstrate that the cardiopulmonary simulator considered here responds correctly to changes in multiple different ventilator settings, with low errors between predicted values of PaO_2 and $PaCO_2$ and the values measured in individual patients.

A necessary condition for achieving high predictive accuracy is that the simulator includes a sufficiently complex representation of the respiratory system, and the pathophysiology associated with the underlying disease state. This is clearly demonstrated by the results in Figure 2, which show a significant drop in the predictive capability of the simulator as the number of independent alveoli included in the model is reduced. Given that the adult lung contains an average of 480 million alveoli, whose physical characteristics are made highly heterogeneous by ARDS, it is unsurprising

Table 2. Model computed arterial blood gas values versus individual patient data, before and after changes in ventilator settings

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

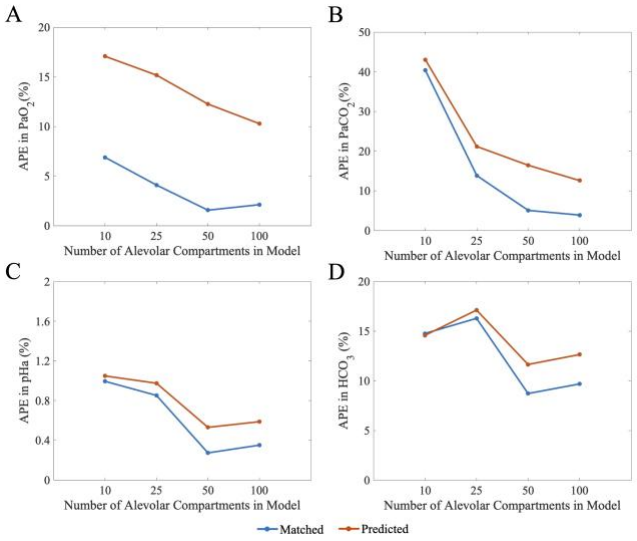

Figure 2. Mean average percentage error for (A) PaO_2 (%) (B) $PaCO_2$ (%) (C) pHa (%) and (D) HCO_3 (%) at time T_0 (matched, in blue) and T_1,(predicted, in orange) versus the number of alveolar compartments.

that a minimum level of complexity in its mathematical representation is required. Research is ongoing by the authors to further reduce the computational burden associated with this high-fidelity simulator so that it can be used for real-time applications.

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