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Determining the appropriate model complexity for patient-specific advice on mechanical ventilation

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Abstract: Mathematical physiological models can be applied in medical decision support systems. To do so requires consideration of the necessary model complexity. Models that simulate changes in the individual patient are required, meaning that models should have a complexity where parameters can be uniquely identified at the bedside from clinical data and where the models adequately represent the individual patient's (patho)physiology. This paper describes the models included in a system for providing decision support for mechanical ventilation. Models of pulmonary gas exchange, respiratory mechanics, acid-base, and respiratory control are described. The parameters of these models are presented along with the necessary clinical data required for their estimation and the parameter estimation process. In doing so, the paper highlights the need for simple, minimal models for application at the bedside, directed toward well-defined clinical problems.

Keywords: mathematical modeling; mechanical ventilation; parameter estimation.

Introduction

Mathematical physiological models have been applied in medicine to address problems in quite different domains. These include, but are not limited to, education, clinical, and experimental research, and bedside clinical decision support. These different application domains can be seen in the fields of anesthesia and intensive care medicine. Mathematical models are the core of many anesthesia education systems [11, 29], where models are used with a graphical user interface and/or manikins to simulate patient response to critical events. The use of these models

typically requires that parameter values be set to describe a scenario and changes made in parameter values and inputs to simulate clinical events. There is no need for these parameters to be estimated from clinical data and, as such, the models are not constrained by the need for unique identifiability of model parameters. The appropriateness of the models lies in their potential to simulate many complex scenarios rather than in understanding the (patho)physiology of an individual patient.

For clinical and experimental research, physiological models are often used to describe a physiological response to an intervention. The models are usually required to be of a level of complexity such that parameter values can be uniquely estimated from measured data, providing insight into the underlying physiology. Often, experiments will include measurements in addition to those available in routine clinical care, allowing for unique identification of a greater number of parameters and providing a deeper physiological understanding. Such studies have been the basis for the core of physiological knowledge that exists to describe systems relevant in anesthesia and intensive care, including gas-exchange [17] and pulmonary mechanics [3].

The use of physiological modeling in clinical decision support presents different problems. Models that simulate changes in the individual patient in the clinical setting are required. The complexity of the models is, therefore, constrained by the need for unique identifiability of parameter values estimated for the individual patient, which is further dictated by the data available in the clinical setting. Selected models, therefore, need to be either “minimal” in the sense that they have uniquely identifiable parameters, adequately describe clinical data, and still reflect patient (patho)physiology. Alternatively, more complex models need to be constrained by fixing some of the parameter values to constant values reflecting a population of patients. In this way, a subset of parameters are uniquely identifiable, effectively making these models “minimal” in terms of the parameters. The development and appropriate use of minimal models is constrained not only by the availability of measurements, but often also by the frequency of measurements. In the application of glucose models in the ICU, the willingness to measure glucose concentration frequently determines how often parameters can be re-estimated and affects the predictive capability of the models [33]. The addition of extra

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measurements or procedures may be attractive to provide a deeper understanding of the patient, but this should be done with caution if the decision support system is to be applied in departments low on expertise and resources, exactly those where the use of clinical decision support might have the most benefit.

The complexity of the models is further constrained by the time frame of the decision to be supported. Systems applying closed-loop algorithms in rapid response to patient changes may require modeling of system dynamics. Decision support systems used as open-loop systems, i.e. those interacting with the clinician such that decisions are only required periodically may only require modeling of steady-state conditions.

In designing physiological model-based decision support systems, it is, therefore, important that the clinical problem and constraints are fully understood. What are the decisions to be supported and when? What is the timing of the decision-making process? What data are routinely available? When answering these questions, the problem becomes one of finding the appropriate minimal model complexity, a task where it is often more difficult to decide what to leave out of the model than what to include.

This paper describes the mathematical models included in the decision support system for mechanical ventilation, known in its research version as the INVENT system [36, 43] and in its commercial version as Beacon Caresystem [38] (Mermaid Care, Nørresundby, Denmark). In describing these models, the paper focuses on parameter identification rather than a description of the system as a whole. To do so, the clinical problem of mechanical ventilation is first summarized and conclusions are drawn as to the necessary physiological systems requiring models to address this problem and the nature of those models. These models are then addressed in turn, including discussion of the necessary measurements required to identify parameters and the clinical availability of these measurements. For each model, a description of the parameter estimation process is presented along with typical values of model parameters. The integration of the models into the whole system is then described, again with focus on the parameterization of the system, with a final section describing how the models are used as part of the system.

The clinical problem – selecting the appropriate ventilator settings

Selecting the appropriate settings for mechanical ventilation can be seen as a process of optimizing competing

goals for the individual patient. Selecting the correct level of inspired oxygen can be seen as a balance between the risks of over-oxygenation, including absorption atelectasis and oxygen toxicity, and under-oxygenation, including hypoxemia. Selecting appropriate volumes, pressures, and frequencies can be seen as a balance between the risks of over-ventilation by applying excessive pressure(s), volume, and/or frequency, resulting in ventilator-induced lung injury (VILI), and acidosis due to under-ventilation. For patients with spontaneous breathing activity in support modes of ventilation, selecting the appropriate support can be seen as a balance between the risk of respiratory muscle atrophy due to over-support and the risk of respiratory muscle fatigue or respiratory stress due to under-support.

The correct balance points for these competing goals depend upon the individual patient's physiology, and consideration of the balances, therefore, determines which models of physiological systems are required by a system for suggesting ventilator settings. The correct balance between over- and under-oxygenation depends upon oxygen delivery and utilization, with oxygen delivery depending upon pulmonary gas exchange, circulation, and blood hemoglobin and acid-base status. The correct balance between the risks of VILI and acidosis depends on the mechanical properties and gas exchange of the patient's lungs, the patient's circulation and acid-base status, as well as the carbon dioxide production. The correct balance between over- and under-support of the patient depends upon the patient's respiratory drive and the consequent changes in respiratory pattern that occur with changes in ventilator support or with changes in metabolism. To provide an adequate description of the patient so as to provide advice on appropriate mechanical ventilator settings, therefore, requires mathematical models describing, or the direct measurement of pulmonary gas exchange, lung mechanics, circulation, acid-base status, respiratory drive, and metabolism.

In addition to understanding the necessary systems to be considered, it is also important to understand the timeframe of decisions and, therefore, the time for which a model should be able to predict. Current clinical practice typically involves modification of ventilator settings followed by a period of time to evaluate the patient's response. This time is typically in the order of 30 min to an hour, or even longer, a time period where it is typical for the above-mentioned physiological systems to have reached steady state. The models considered here reflect this, and include representation of steady-state conditions.

The following section considers each physiological system in turn and the mathematical models used

to describe these in the literature and those included in the Beacon system. For two of these systems, circulation and metabolism, it is assumed that direct measurement or reasonable approximation of measurements exists. In the case of circulation, cardiac output (CO) is input into the system either from direct measurement or through an ideal body-weight-adjusted cardiac index. Metabolism is directly measured using indirect calorimetry and capnography measurement of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production/elimination ($\dot{V}CO_2$).

For each model, the data required for unique parameter identification is described and placed in the context of both the typical data available in the clinical setting and other less commonly used measurements. In the case of an estimated CO, the results of sensitivity analysis are used to comment on this approximation. In considering these systems and measurements, a set of minimal models, their associated measurements, and parameter estimation is proposed, one for each physiological system. For each of these models, typical values of model parameters are provided.

Mathematical models of pulmonary gas exchange

Mathematical models of pulmonary gas exchange are required to simulate the effects of ventilator changes on arterial oxygen and acid-base status. It is well recognized that the major abnormality associated with gas exchange is the mismatch between ventilation and perfusion in the lungs [17]. For patients with pulmonary abnormalities, different regions of the lung can present with different ventilation/perfusion (\dot{V}/\dot{Q}) ratios. These range from a \dot{V}/\dot{Q} of zero, i.e. pulmonary shunt, where blood passes through non-ventilated regions of the lung without being involved in gas exchange, to a \dot{V}/\dot{Q} of infinity, i.e. alveolar dead space, where regions of the lung without blood flow are ventilated. The reference technique for assessing pulmonary gas exchange is the Multiple Inert Gas Elimination Technique (MIGET) [52]. This technique uses a mix of six inert gases and measurement at steady-state conditions of their retention and excretion, along with parameter estimation and smoothing techniques, to identify parameters describing the ventilation and perfusion of a 50-compartment model of the lung [52, 53]. In clinical practice, description of gas exchange is limited to single lumped parameters describing the effects of abnormalities of O_2 and CO_2 exchange. For O_2 , the most common index is PaO_2/FIO_2 , which primarily lumps oxygenation abnormalities

due to regions of the lung with pulmonary shunt and low \dot{V}/\dot{Q} [21]. This index requires measurement of blood gas, although some studies have proposed use of a SpO_2/FIO_2 index, which allows for continuous measurement [5, 9]. For CO_2 , the arterial-to-end-expired partial pressure gradient has been used to approximate the lumped effects of high \dot{V}/\dot{Q} and alveolar dead space on CO_2 elimination, with this requiring use of arterial blood gas (ABG) and capnography [2]. These clinical indices have a number of limitations. The PaO_2/FIO_2 index has shown to be very sensitive to changes in FIO_2 , such that changes in FIO_2 can result in changes in patient classification [21]. In addition, lack of mathematical integration of these indices can have consequences for their interpretation. For example, a large pulmonary shunt will cause mixed venous blood to mix with arterial blood, generating a greater gradient of end-tidal-to-arterial $PaCO_2$ not due to alveolar dead space or high \dot{V}/\dot{Q} [14].

Figure 1A illustrates the complexity of the model of pulmonary gas exchange included in the Beacon system. A subset of the whole model is illustrated so as to highlight the parameterization of the model. The model includes two ventilated and perfused lung compartments and pulmonary shunt, and three parameters. These are pulmonary shunt, the fraction of alveolar ventilation (\dot{V}_A) to one of the ventilated compartments (fA_2), and the fraction of non-shunted blood flow to the same ventilated compartment (f_2). As illustrated, two sets of equations are included in this model to describe the transport of O_2 and CO_2 . These include the relationship between $\dot{V}O_2$, $\dot{V}CO_2$, and gas transport in each of the two ventilated compartments (Figure 1, Equations 1–3); expired fraction of gases calculated as the mixing of the two ventilated compartments (Figure 1, Equation 4); the partial pressure of gas in the blood of each ventilated compartment (Figure 1, Equations 5 and 6); the mixing of blood from the three lung compartments (Figure 1, Equation 7); and mass balance and Fick equations describing O_2 and CO_2 exchange at the lungs and tissues (Figure 1, Equations 8 and 9) [23]. In addition, the model includes representation of the acid-base and oxygenation status in each of the blood compartments, with the equations of this model described in the next section. Values of shunt, fA_2 , and f_2 can be uniquely estimated from the measurement of a single ABG; a measured or estimated cardiac output; indirect calorimetric measurements of inspiratory and end expiratory O_2 and CO_2 , $\dot{V}O_2$, and $\dot{V}CO_2$; measurement of respiratory flow and, hence, volume; and measurements of SpO_2 taken at 3–5 different FIO_2 levels [18, 42].

Figure 1B illustrates measured data and model simulations describing the relationship between end-tidal

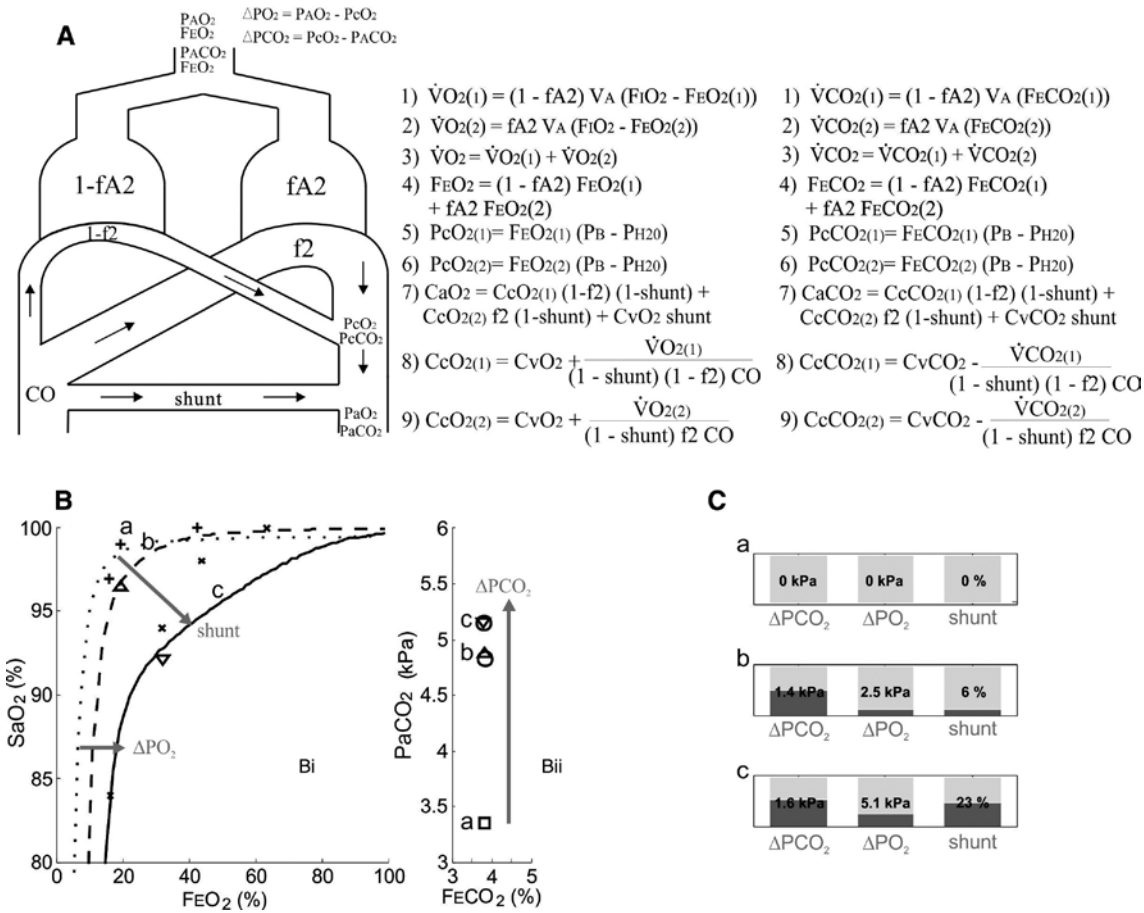


Figure 1: (A) The pulmonary component of a model of gas exchange and all equations excluding those describing acid-base status and oxygenation of blood; (B) model simulations and fit to data illustrating: no gas exchange abnormality (dotted line Bia, square Biia); severe gas exchange abnormality and PEEP=5 cm H₂O [$F_{E}O_2/SpO_2$ (crosses “x”, Bic), $F_{E}O_2/SaO_2$ (inverted triangle, Bic), $F_{E}CO_2/PaCO_2$ (inverted triangle, Biic), model simulation of best fit (solid line, Bic; circle Biic)]; severe gas exchange abnormality and PEEP=15 cm H₂O [$F_{E}O_2/SpO_2$ (crosses “+”, Bib), $F_{E}O_2/SaO_2$ (triangle, Bib), $F_{E}CO_2/PaCO_2$ (triangle, Biic) model simulation of best fit (dashed line, Bib; circle Biib)]. (C) Illustration of shunt, ΔPO_2 and ΔPCO_2 for: no gas exchange abnormality (a), severe gas exchange abnormality and PEEP=5 cm H₂O (c); severe gas exchange abnormality and PEEP=15 cm H₂O (b).

oxygen ($F_{E}O_2$) and arterial oxygen saturation (SaO_2) (Figure 1-Bi), and end-tidal carbon dioxide ($F_{E}CO_2$) and arterial partial pressure of carbon dioxide ($PaCO_2$) (Figure 1-Bii), in three situations. Dotted lines (Bia) and the square (Biia) describe simulated values in the absence of gas exchange abnormality, i.e. the situation of zero pulmonary shunt and $fA2$ and $f2$ values such that both compartments are ventilated with a \dot{V}/\dot{Q} ratio=1. In the case of constant $\dot{V}O_2$, Figure 1-Bi could instead be plotted with $F_{i}O_2$ on the x-axis, and a similar interpretation performed. The solid line (c) and dashed line (b) in Figure 1-Bi illustrate simulations following model fit to data (crosses and triangles) from a single patient with acute respiratory distress syndrome (ARDS), ventilated with a positive end-expiratory pressure of 5 cm H₂O (c: solid line, “x” and inverted triangle) and PEEP set to 15 cm H₂O following a recruitment maneuver (b: dashed

line, “+” and triangle). The relationship between $F_{E}CO_2$ and $PaCO_2$ for this patient at these PEEP levels is shown in Figure 1-Bii, with points (a), (b), and (c) describing data (triangles) and model simulations (square and circles), in the absence of gas exchanges abnormality, at PEEP=5 cm H₂O and at PEEP=15 cm H₂O, respectively.

Fitting is performed as follows. $\dot{V}A$ is calculated from measured minute ventilation through estimation of serial dead space (V_{ds}). CO , $\dot{V}O_2$, $\dot{V}CO_2$, $F_{E}O_2$, and $F_{E}CO_2$ are fixed at measured values. Model fitting then occurs by searching for the combination of shunt, $fA2$, and $f2$, which provides the minimum solution of the error function describing the weighted residual sum of square (WRSS) fit. This error function applies the difference between simulated arterial saturation (SsO_2) and arterial partial pressure ($P_{s}CO_2$) and measured values of SpO_2 , arterial SaO_2 , and $PaCO_2$, as described previously [18]:

$$\text{WRSS} = \frac{4}{n} \sum_{i=1}^n \left(\frac{(\text{SsO}_2 - \text{SpO}_2)^2}{0.02^2} \right) + \frac{(\text{SsO}_2 - \text{SaO}_2)^2}{0.005^2} + \frac{(\text{PsCO}_2 - \text{PaCO}_2)^2}{0.09^2}$$

where the weights 0.02, 0.005, and 0.09 represent the standard deviation (SD) for measurement error of SpO_2 , SaO_2 , and PaCO_2 , respectively [18].

On estimation of shunt, fA_2 , and f_2 , \dot{V}/\dot{Q} distributions can be calculated for each of the two ventilated compartments. As f_2 , fA_2 , and \dot{V}/\dot{Q} ratios are difficult to interpret at the bedside, these values are converted into a) a drop in the partial pressure from end-tidal to end-capillary PO_2 prior to mixing with shunted venous blood, i.e. ΔPO_2 , and b) a drop in the partial pressure from end-capillary to end-tidal PCO_2 , i.e. ΔPCO_2 . ΔPO_2 describes the drop in partial pressure of oxygen from alveolar gas to capillary blood due to low \dot{V}/\dot{Q} regions in the lung, and when reported in kPa, this is almost identical to the necessary increase in inspired oxygen fraction above room air to counter the effect of low \dot{V}/\dot{Q} on O_2 exchange. As the oxygen level of a pulmonary shunt is, by definition, unresponsive to changes in inspired oxygen, ΔPO_2 represents the increase in FIO_2 or FEO_2 which saturates all hemoglobin passing through ventilated regions. Any further increase in FIO_2 will result only in increased transport of dissolved oxygen. As the solubility of oxygen in blood is poor, increase in FIO_2 in this range results in little change in SaO_2 . ΔPCO_2 represents the drop in CO_2 partial pressure due to high \dot{V}/\dot{Q} regions in the lung, which can be counteracted by an increase in $\dot{V}A$ not reaching high \dot{V}/\dot{Q} regions of the lungs.

The measurements described above allow for the unique identification of shunt, ΔPO_2 , and ΔPCO_2 . While no formal analysis of the identifiability has been performed, Figure 1-Bi illustrates why this is the case. Low \dot{V}/\dot{Q} regions of the lung result in poor arterial blood oxygenation, which is responsive to changes in FIO_2 or FEO_2 . The vertical drop in SaO_2 in relation to FEO_2 illustrates the portion of the curve which provides information on ΔPO_2 , with increased values of ΔPO_2 shifting this curve to the right as illustrated by the arrow labeled ΔPO_2 in Figure 1-Bi. As pulmonary shunt is not responsive to changes in FIO_2 or FEO_2 , the portion of the curve where arterial SO_2 changes little with FEO_2 provides information on pulmonary shunt, resulting in a depression in the shoulder of the curve as illustrated by the arrow labeled shunt on Figure Bi. The relationship between end-tidal CO_2 and arterial, illustrated in Figure 1-Bii, provides information on ΔPCO_2 , as indicated by the arrow ΔPCO_2 on Figure 1-Bii. Values for shunt, ΔPO_2 , and ΔPCO_2 are illustrated for the three situations in

Figure 1C. Performing recruitment and increasing PEEP to 15 cm H_2O reduced shunt, with a negligible increase in ΔPCO_2 and a marginal increase in ΔPO_2 , perhaps due to shunted regions of the lung having low \dot{V}/\dot{Q} on recruitment.

This model has been validated in a number of clinical and experimental studies. In the experimental setting, the model has been shown to describe MIGET retention and excretion data collected from an animal model of lung damage, with the resulting model parameters capable of describing arterial oxygenation levels [39, 40]. In clinical studies, the model has been shown to be a great improvement in describing oxygen data when compared to the $\text{PaO}_2/\text{FIO}_2$ ratio [21] to describe changes in gas exchange peri-operatively [22, 24, 34, 35] and to describe data from ICU patients [20, 23]. Typical values of shunt, ΔPO_2 , and ΔPCO_2 have been reported for 16 mechanically ventilated patients [20] with values of shunt = $25.0 \pm 10.6\%$ (mean and SD), $\Delta\text{PO}_2 = 6.1$ (5.0–9.7) kPa (median and IQR), and $\Delta\text{PCO}_2 = 1.8 \pm 1.0$ (mean and SD).

The use of this model at the bedside, to predict arterial oxygen and CO_2 levels, requires a number of measurements be available routinely. CO , $\dot{V}\text{O}_2$, and $\dot{V}\text{CO}_2$, continuous SpO_2 , ventilation volume, and an ABG are required as input. $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ are available through indirect calorimetry and capnography. The use of capnography is relatively widespread, but this is not the case for indirect calorimetry. Adoption of this model, therefore, requires new instrumentation at the bedside. The Beacon Caresystem is equipped with capnography and indirect calorimetry, as are GE ventilators through the E-COVX model. CO is seldom measured; however, it has been shown that parameter estimates are reasonably insensitive to error, and an ideal weight-adjusted approximation is reasonable for robust parameter estimation [20]. A single ABG, at strategic time points, and continuous SpO_2 measurement are routine in clinical practice. Measurement of ventilation volume is also routinely performed by the ventilator, or can be obtained through flow measurements included in indirect calorimetry. Simulated changes in respiratory volume are dependent upon lung mechanics and respiratory drive, so effective simulation of arterial blood gas levels on modifying ventilator pressures or volumes requires integration of the pulmonary gas exchange models with other systems described in this paper.

Probably the most demanding change in clinical practice for introduction of this model is the need for 3–5 different FIO_2 levels introducing a 10-min procedure at the bedside. Closed-loop control of this procedure would eliminate this problem; however, the Beacon system currently runs in an open-loop mode providing advice on several

different ventilators. To overcome this, the Beacon system initially reduces the complexity of model fit, fitting only to a single $\text{FIO}_2/\text{SaO}_2$ level. This assumption effectively lumps shunt and low \dot{V}/\dot{Q} on system startup. Following advice on FIO_2 level, the system monitors patient SpO_2 response. If this response deviates from that predicted, then a request for an FIO_2 variation is presented. The model is, therefore, only completely identified if required to provide patient advice.

Mathematical models of respiratory system mechanics

Mathematical models of respiratory system mechanics are required to simulate the effects of ventilator changes on patient ventilation, to ensure that volumes, flows, and pressures delivered to the patient limit ventilator-induced lung injury, while ensuring adequate ventilation to prevent or limit the accumulation of CO_2 .

The major problems associated with respiratory system mechanics are the increase in resistance to flow and reduction in respiratory compliance, associated with mechanical ventilation and disease [3]. As in the case of gas exchange, the presentation of these abnormalities can be highly heterogeneous across the respiratory system, and the modeling problem is that of identifying a model that can capture the necessary degree of heterogeneity from routinely available clinical measurements. Experimental techniques include procedures to obtain extra information such as interruption of inspiratory or expiratory flow [4] or low flow inflation [31] to separate resistance and elastance components. Extra measurement technology includes the use of esophageal catheters to separate the elastance properties of the lungs and chest wall [32]. Mathematical model approaches range from one compartmental representation of a single airway and single lung unit to multi-compartmental models including gas re-distribution or viscoelastic properties [48], and complex simulation models of airway structure [16]. At the bedside, measurements of flow and pressure taken at the airway limit model identification to a single compartment lung model, regardless of the use of interruption procedures or esophageal catheters [3]. For patients without spontaneous breathing and in volume control modes of mechanical ventilation, ventilator pauses are part of the inspiratory pattern and provide some separation of resistance and compliance components. Current clinical practice is, however, such that where possible, patients are encouraged to breath spontaneously to preserve

respiratory muscle function. For these patients, measurement of pulmonary mechanics is complicated further by the combination of both ventilator and respiratory muscle pressures during inspiration [15]. Without measurement of esophageal pressure, separation of these pressures is difficult, although specialized modes with small periods of changes in inspiratory pressure or delayed valve opening may provide extra information [58, 59].

These constraints mean that the mathematical complexity describing respiratory system mechanics included in Beacon is very limited. A simple one-compartment model is applied along with pressure and flow measurements taken at the mouth, without extra measurements or maneuvers. In volume control ventilator modes, respiratory system compliance and resistance are identified. For all other modes, a lumped dynamic respiratory system compliance (C_{dyn}), described here as the volume delivered per $\text{cm H}_2\text{O}$ pressure provided by the ventilator, is identified, with values of this re-estimated at differing ventilator settings. As respiratory system compliance is well understood to be non-linear, the system re-estimates parameter values in response to changes in ventilation, only providing advice on small step changes in volume or pressure, where the linearity of the model may be appropriate.

For patients in supported modes of mechanical ventilation, values of C_{dyn} can be much higher than those reflecting only the mechanical properties of the respiratory system. These values no longer reflect respiratory system mechanics alone but also the driving pressure (ΔP) of the respiratory muscles (P_{mus}) [27]. Larraza et al. [27] reported calculated values of C_{dyn} as high as $200 \text{ ml/cm H}_2\text{O}$ on reducing pressure support (PS) to $3\text{--}4 \text{ cm H}_2\text{O}$. Values of C_{dyn} in excess of $70 \text{ ml/cm H}_2\text{O}$ are unlikely to be due to the mechanical properties of the respiratory system. These values may, therefore, provide valuable information on the patient's ability to increase P_{mus} on reduction of ventilator support. This simple model of respiratory system mechanics can be uniquely identified from measurements of pressure and flow taken at the mouth or by the ventilator.

Mathematical models of acid-base

Mathematical models of the acid-base chemistry and oxygenation status of blood are required to simulate the effects of ventilator changes on pH, PCO_2 , PO_2 , and SO_2 , to ensure that volumes, flows, and pressures delivered to the patient prevent acidosis and that inspired oxygen levels ensure adequate oxygen delivery.

The acid-base chemistry of blood included in Beacon includes a large number of chemical reactions as illustrated in Figure 2 [37, 41]. This model is used to represent steady-state conditions in arterial, venous, and lung capillary blood. The model includes lumped bicarbonate and non-bicarbonate buffer reactions (R1r, R2r) describing buffering in plasma. In the erythrocyte fraction of blood, hemoglobin is written as $Hb(RH)_bNH_3^+$ to reflect the side chain $(RH)_b$ and amino end (NH_3^+) buffering sites. Hemoglobin binding to H^+ , O_2 , and CO_2 is drawn as three blocks of reaction equations A–C. Blocks A and B represent the binding of H^+ to the amino end of the hemoglobin molecule protein chains and the oxygenated and deoxygenated forms of these. Block C represents the binding of H^+ to the side chains of the amino acids.

The formulation of the model is then as eight mass balance equations (1r–5r), one to describe each of the components of blood with some redundancy, and nine mass action equations (6r–14r), one for each reaction equation, with the remaining three reaction equations (R15r–R17r) representing the oxygen binding to hemoglobin, including a published model of the oxygen dissociation curve (ODC) [46, 47] (Equation 15r). The remaining equations account for the physico-chemical properties of blood, including the solubility of O_2 and CO_2 in plasma and red

blood cells (18r–21r), the fractions of plasma and erythrocyte (22r, 23r), and a modified form [45] of the empirical relationship relating pH in the plasma and red blood cells, derived by Funder and Weith [13], to describe the link between plasma and red blood cell acid-base status without the need to represent electrolyte transport across cell membranes. This simplification means that the model cannot calculate values of electrolytes in the plasma and red blood cells, as can newer models by Wolf [54, 55].

pK values have been estimated for each of the equations described in detail in Rees and Andreassen [37]. These are not patient-specific and were part of model formulation. By fixing pKa values, all variables included in the model can then be uniquely identified from one measurement of each of the six components. The six measures are 1) one representing CO_2 ($PaCO_2$, HCO_3^- , tCO_2 , etc.), 2) one representing acid or buffer base (pH, BE, etc.), 3, 4) two representing oxygen (SaO_2 , PaO_2); note: two are required so as to calibrate the ODC through the estimation of 2,3-diphosphoglycerate (2,3-DPG), 5) one representing hemoglobin (Hb), and 6) one representing plasma protein concentration (albumin, total protein, etc). Aside from measurements of plasma protein, $PaCO_2$, pH, SaO_2 , PaO_2 , and Hb are all measured in an ABG. The model can, therefore, be solved uniquely from a single blood gas and

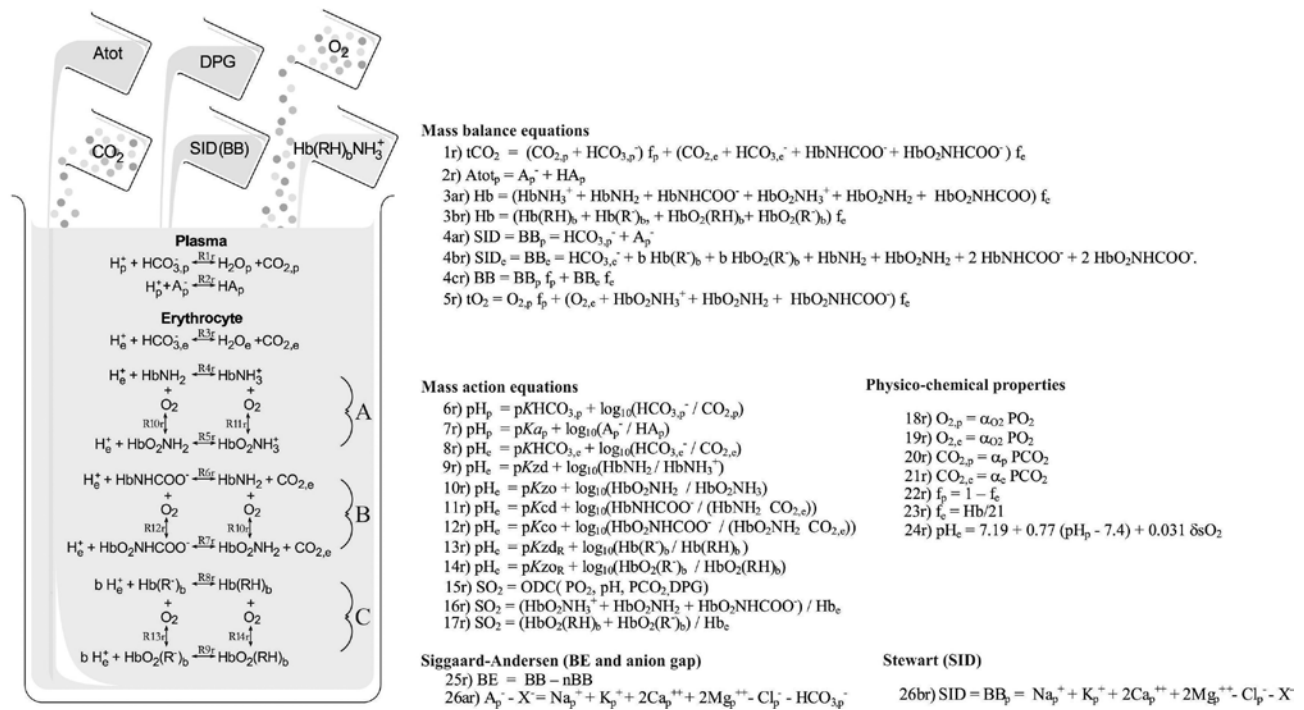


Figure 2: A mathematical model of the acid-base chemistry in blood [41].

(With kind permission from Springer Science + Business Media: Rees SE, Klæstrup E, Handy J, Andreassen S, Kristensen SR. Mathematical modeling of the acid-base chemistry and oxygenation of blood – a mass balance, mass action approach including plasma and red blood cells. Eur J Appl Physiol 2010; 108: 485, Figure 1B).

a population value of non-bicarbonate buffering in the plasma. As the plasma protein buffer is relatively small compared to others, approximating this value has little impact on calculations.

This model of the acid-base chemistry of blood has been validated and shown to describe the addition or removal of CO₂ or strong acid to plasma and blood and the effects of deoxygenating erythrocyte or blood at a wide range of values of pH and PCO₂ [37]. In addition, the models have been shown to accurately simulate the mixing of blood with different PCO₂ and PO₂ levels, as occurs when blood drains from different \dot{V}/\dot{Q} regions in the lungs, or from different organs [41].

In addition to the model of acid-base in blood, the system includes a model of acid-base of interstitial fluid and tissue [1]. This model is necessary as bicarbonate distributes between blood and interstitial fluid, meaning that simulations of changes in arterial acid-base on varying ventilation will be dependent upon this distribution of bicarbonate. This model includes reaction equations similar to blood, as illustrated in Figure 4, and values of the pKs of these reactions and other chemical properties are estimated and fixed as described previously [1]. The volume of interstitial fluid is assumed to be 9.5 l [1]. When combined with the model of blood, this model has been shown to describe the well-known distribution of bicarbonate between blood and interstitial fluid [1, 6].

The mathematical model of acid-base is applied in the system to represent blood under numerous different conditions (Figure 4). On measurement and input of the arterial acid-base status, values of Hb and 2,3-DPG are fixed to arterial values for all applications of this model in the system. Other variables (PaCO₂, pH, SaO₂, PaO₂) are calculated according to the conditions of the blood at that location. Values in pulmonary blood are calculated using the gas exchange model via equilibration of blood and gas values of PCO₂ and PO₂. Mixed venous values are calculated from measured arterial values and values of $\dot{V}O_2$, $\dot{V}CO_2$, and CO. Interstitial values of PCO₂ and HCO₃ are assumed to be equal to those in the mixed venous blood, as can be assumed for steady-state conditions. In doing so, excess concentration of buffer base is calculated for the combination of blood, interstitial fluid, and tissues, taking into account the buffer mass in each compartment. This system's base excess (BEs) is the patient-specific parameter, such that for changes in ventilation, BEs can exchange between the three compartments, but in the absence of anaerobic metabolism, total BEs is constant [54]. BEs is calculated as

$$BEs = \frac{BE_{it}(V_i + V_t) + BE_a V_a + BE_{mv} V_{mv}}{V_i + V_t + V_a + V_{mv}}$$

where BE_{it} is BE in the combined interstitial and fluid pool, and V_i, V_t, V_a, and V_{mv} are the volumes of the interstitial fluid, tissue, arterial, and mixed venous compartments, respectively, which are assumed constant [1].

Respiratory drive

To prevent respiratory muscle atrophy and expedite weaning from mechanical ventilation, it is typical that, where possible, sedation is reduced to a level where the patient's respiratory control system initiates the timing and, to some degree, the depth of breathing [7]. Mechanical ventilation is normally used in this situation to support the patient's breathing, typically providing a fixed ventilator pressure (PS) when the ventilator identifies an attempt to breathe.

When ventilating patients with PS, the clinical challenge is to determine the level of PS which reduces the risk of respiratory muscle atrophy and promotes weaning, without stressing or exhausting the patient and causing diaphragm fatigue [8], or introducing asynchrony between the patient and the ventilator [7]. This patient stress can be seen in an increased ratio of the breathing frequency to tidal volume (VT), known as the rapid shallow breathing index [56], and as an increased metabolism due to elevated work by the respiratory muscles [8]. To support this process, mathematical models are, therefore, required, which simulate the individual patient's response to changes in PS, i.e. models of the chemoreceptor regulation of breathing. Models that can simulate changes in respiratory frequency (fR), VT, and $\dot{V}A$ are required, where simulations using these models are responsive to changes in ventilator settings or changes in physiological response, such as increase in metabolism.

Chemoreceptor control of breathing occurs via central and peripheral chemoreceptors. Peripheral chemoreceptors are located in the carotid bodies and are responsive to rapid changes in arterial acid-base or PaO₂ [44]. Central chemoreceptors are located in the medulla oblongata, are surrounded by cerebral spinal fluid (CSF), and are, therefore, responsive to changes in pH in the CSF. These account for the majority of ventilator responses [30]. As CO₂ passes freely through the blood-brain barrier, PCO₂ values in the CSF follow plasma values closely. pH_{CSF} can, however, differ from plasma, with values depending on the buffering properties of the CSF. These can be modified

in disease states such as chronic obstructive pulmonary disease (COPD), where increased plasma bicarbonate will result in elevated values in the CSF [30]. An increased CSF bicarbonate concentration increases the buffering of CSF, meaning that pH_{CSF} changes are less responsive to changes in PCO_2 , and in this situation, central drive is reduced. Respiratory drive can also be reduced due to the effects of anesthesia and analgesia. In this case, pH_{CSF} may respond well to changes in arterial PCO_2 , but the brain signal response to respiratory muscles can be reduced and, as such, \dot{V}_A may not be sufficient so as to normalize either pH_{CSF} or pHa [44].

Figure 3 illustrates the mathematical models of CSF (3A) and respiratory drive (3B) included in the Beacon system, as described previously [26–28]. The CSF model is a modified version of that of Duffin [12]. This model includes mass-action equations describing water, phosphate, and albumin dissociation (1–3), formation of bicarbonate and carbonate (4–5), electrical neutrality (6), and equations describing the relationship between arterial and CSF PCO_2 (7) and HCO_3^- (8).

Patient-specific tuning of the model of CSF occurs on measurement of a blood gas. In this situation, Equation 8 is solved to calculate the steady-state bicarbonate concentration in the CSF $[\text{HCO}_3^-]$ from arterial values [26].

The solution of Equations 1–7 then allows calculation of the CSF strong ion difference (SID_{CSF}), with this fixed as a patient-specific parameter until a new blood gas is input. Simulations are then performed using this model through the unique solution of Equations 1–7 on changes in arterial PaCO_2 , with the model simulating values of the hydrogen ion concentration ($[\text{H}^+]_{\text{CSF}}$) or pH (pH_{CSF}) in the CSF, according to the patient-specific SID_{CSF}.

Figure 3B illustrates the model of respiratory control of Duffin with modifications as described previously [26]. This model includes equations describing peripheral drive (D_p) as a linear function of the arterial hydrogen ion concentration ($[\text{H}^+]_a$) above a threshold (T_p) (9), with the slope of this function (S_p) dependent on the value of PaO_2 along with a scaling (A) and a threshold (P_0) parameter. Mechanically ventilated patients are typically ventilated with an inspired oxygen fraction so as to prevent hypoxemia, so values of peripheral drive parameters (A , P_0 , T_p) are set to constants as described previously [26]. Central drive (D_c) is a linear function of the difference between the $[\text{H}^+]_{\text{CSF}}$ and the central threshold (T_c) (10), with the slope of this function being the sensitivity of central chemoreceptors (S_c). \dot{V}_A is then calculated as the sum of D_p and D_c and a constant value of wakefulness drive (D_w), as described previously [26]. The patient-specific parameters

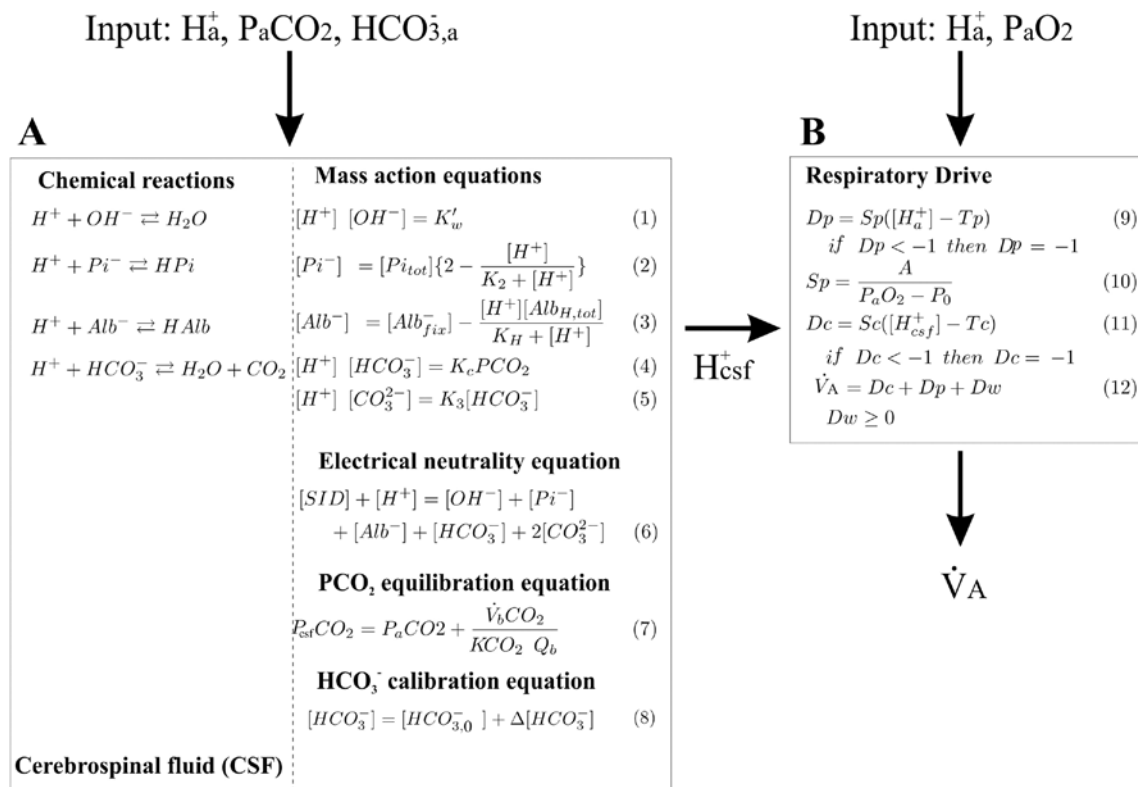


Figure 3: Mathematical model of the buffering properties of cerebrospinal fluid (3A) and respiratory drive (3B).

of this model are T_c and Sc . As shown previously [26], it is not possible to estimate both T_c and Sc uniquely from measurements of blood gas and ventilation. Sc is, therefore, fixed at a population value and T_c uniquely estimated so as to characterize D_c .

Patient-specific tuning of the model of respiratory drive (Figure 3B) occurs on measurement of a blood gas. In this situation, the value of $[H^+csf]$ simulated by the CSF model is used as input to the model of respiratory drive along with measured PaO_2 and $[H^+]$. The model can then be used to simulate values of $\dot{V}A$ depending upon patient-specific values of T_c . The values of T_c are estimated so that the simulated $\dot{V}A$ is equivalent to that calculated from measured minute ventilation and V_{ds} . In this way, T_c describes the link between the patient's $\dot{V}A$ and the current $[H^+csf]$. Simulations of changes in $\dot{V}A$ on variation of $[H^+csf]$ are then performed using this model through the solution of Equations 9–12 according to the patient-specific T_c .

This model has been validated in two clinical studies [27, 28]. When the values of SID_{csf} and T_c were estimated from measurements of ventilation and a single ABG at a baseline ventilator setting, the model was shown to accurately simulate values of fR , arterial pH, and end-tidal CO_2 at five different levels of ventilator support. This was shown in 12 patients ventilated using volume support ventilation [28] and a further 12 patients in PS ventilation [27]. The range of values of parameters seen in these patients was for SID_{csf} from 26.1 mmol/l to 43.9 mmol/l, and for T_c from 34.9 nmol/l to 53.8 nmol/l.

The use of these models requires periodic measurement of ABGs to re-estimate both SID_{csf} and T_c , which represent the two parameters describing regulation of D_c . This is likely following changes in patient treatment such as reduction in anesthesia or analgesia where drive can be modified [44]. In these situations, simulations of $\dot{V}A$ performed using the models are likely to be incorrect, resulting in poor simulation of fR and end-tidal CO_2 . This information is valuable as it identifies a possible change in respiratory drive following a change in therapy. The Beacon system uses this information to direct the clinician to the need for performing a new blood gas, with the system using these results to re-estimate parameter values describing CSF and respiratory drive.

Combining these models into a single predictive model

Figure 4 illustrates the model components and their interaction in terms of inputs and outputs. Each model

component is illustrated within a dashed line block, with the exception of the model of blood acid-base. Several versions of this model are applied to characterize blood in different conditions, and a symbol illustrating the blood gas model is depicted to show where this model is used. In addition, measurement inputs are illustrated within solid line blocks. Measurements of VT , ΔP , fR , FIO_2 , FEO_2 , $FECO_2$, $\dot{V}O_2$, and $\dot{V}CO_2$ are obtained from indirect calorimetry; SpO_2 from pulse oximetry; and SaO_2 , PaO_2 , $PaCO_2$, pHa , Hb , and abnormal forms of Hb ($COHb$, $MetHb$) from an ABG. CO is either measured or estimated by the clinician, and manually entered. Measurements are used both in parameter estimation and to evaluate model simulations.

Parameter estimation only proceeds when the patient's respiration is considered stable, as indicated by stable values of $FECO_2$ and FEO_2 . Clinical maneuvers such as suctioning, physiotherapy, etc. generate great variability in these values and, therefore, result in postponement of both parameter estimation and calculation of advice. Parameter estimation proceeds as follows. A value of V_{ds} is obtained from analysis of the CO_2 signal and respiratory flow. This value, along with fR and VT , is used to calculate the effective $\dot{V}A$. Values of shunt, ΔPO_2 , and ΔPCO_2 are estimated from the relationship between arterial and end-tidal O_2 and CO_2 levels, as described in the pulmonary gas exchange model section. C_{dyn} is estimated from VT and ΔP . Blood model parameters, i.e. Hb and 2,3-DPG are estimated for all the various uses of the model, with Hb set to that measured in arterial blood and 2,3-DPG, estimated by fitting the ODC of blood to SaO_2 and PaO_2 . Mixed venous, interstitial, and tissue values are then calculated as described in the section on modeling of acid-base chemistry, and BEs is calculated.

SID_{csf} is calculated from the arterial blood measurement as described in the respiratory drive model section, and measured $PaCO_2$ is then used with the SID_{csf} to calculate pH_{csf}/H^+csf . The relationship between pH_{csf}/H^+csf and $\dot{V}A$ is then used to estimate T_c , which characterizes changes in the patient's respiratory drive not due to changes in CSF buffering.

The complete set of model parameter values (V_{ds} , shunt, ΔPO_2 , ΔPCO_2 , C_{dyn} , Hb , 2,3-DPG, BEs , CO , SID_{csf} , and T_c) are then fixed, and patient-specific simulations can be performed. Simulations are performed for two purposes. The first is to evaluate whether the models are a good description of the patient's current state. In this case, simulations are performed frequently by the system (30 s–2 min) and model-simulated values are compared with measured values, with these comparisons performed for variables that are measured non-invasively and on a

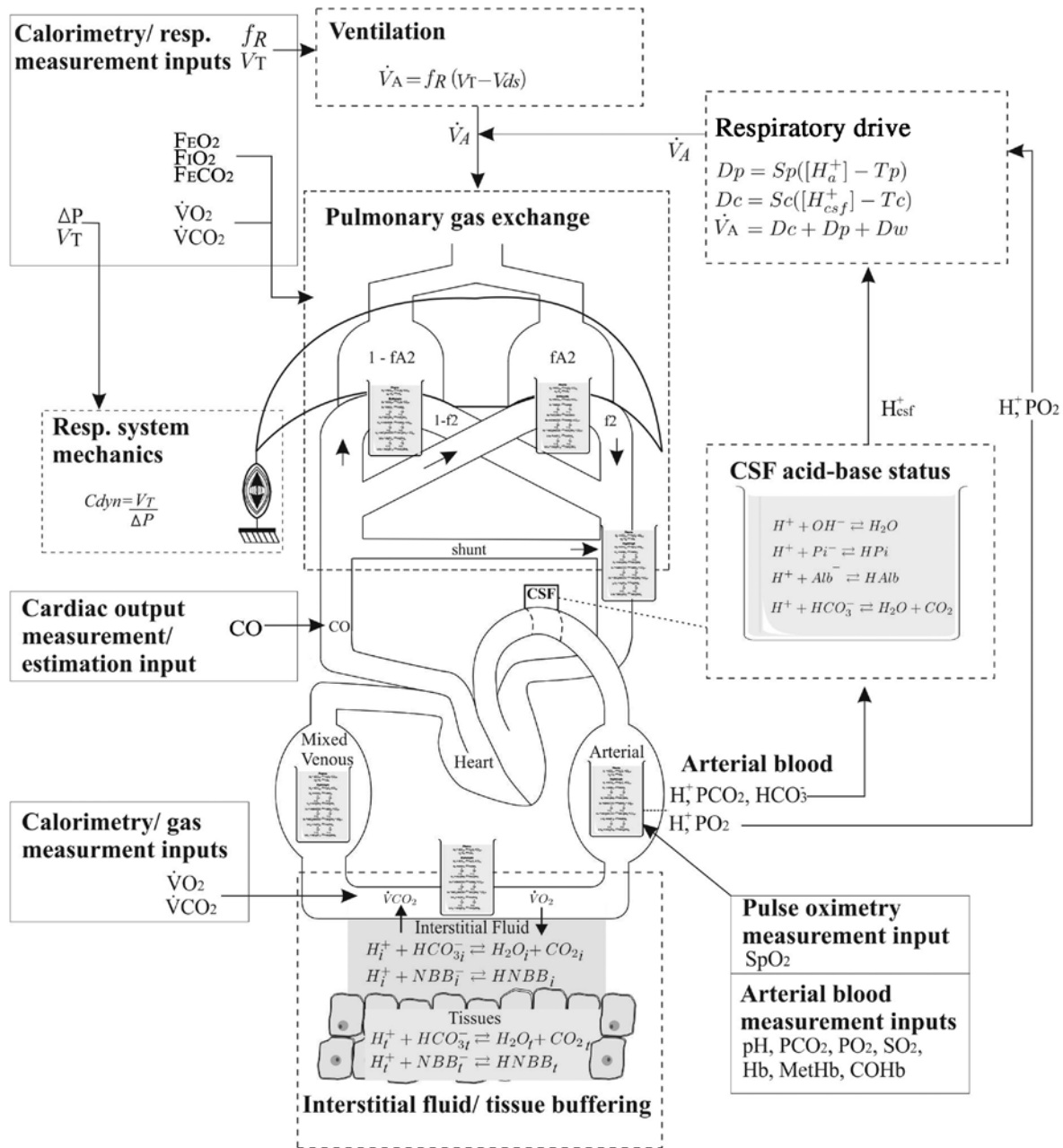


Figure 4: Mathematical models (dashed boxes) of and data input (solid boxes) to the integrated model. Arrows and associated variables illustrate data flow as input to or between models.

breath-by-breath basis, i.e. f_R , $F_{E_{O_2}}$, $F_{E_{CO_2}}$, SpO_2 . If the models are a poor fit, advice is not generated, and the models are re-tuned. Parameters not requiring a blood gas (V_{ds} , C_{dyn}) are re-estimated first and the simulation is repeated. If model simulations remain poor, then the system requests a new blood gas from the user and parameter estimation is repeated. In this way, the user is directed to performing blood gases when the patient state is poorly described. This occurs when the patient state changes, such as an increase in respiratory drive on reduction of

sedation, as described in the section describing the respiratory drive model.

From model predictions to system advice

The second purpose of model simulation is to generate patient-specific advice. As described previously,

mechanical ventilation can be seen as a process optimizing competing goals, finding the correct balance between: over- and under-oxygenation and the consequent risks of oxygen toxicity or hypoxemia; over- and under-ventilation and the consequent risks of lung injury or acidosis; and, in support modes of ventilation, the balance between over- and under-support and the consequent risks of respiratory muscle atrophy or fatigue and patient stress. To optimize these balances, measurements and model-simulated variables are considered surrogates for the risks associated with each of these balances, and penalty functions are associated with each of these surrogate variables [19, 43]. Figure 5A illustrates the screen of the Beacon system with advice for a patient ventilated in pressure support mode. The hexagon on the right hand side of the screen presents visualization of the patient state in terms of these balances, with the three vertical axes on the hexagon presenting the three balances. The position of the symbols on the hexagon are determined by the penalty value for the risk associated for each balance. The blue symbol represents the current state and the gray the simulated state according to the advice. Figure 5B illustrates the same

screen, but with the corners of the hexagon activated to show the current, simulated, and advised values of surrogate variables, i.e. values of variables from the models. Oxygen toxicity is represented as FIO_2 , hypoxemia as SaO_2 and mixed venous oxygen saturation (SvO_2), lung trauma as plateau pressure and PEEP allowing calculation of ΔP , and respiratory frequency, acidosis as arterial pH, respiratory muscle atrophy as respiratory frequency weighted according to the degree of spontaneous breathing, and patient stress as the ratio between respiratory frequency and tidal volume, i.e. the rapid shallow breathing index. The left hand side of the screen shows the current, simulated, and advised settings. The simulated settings are scroll wheels which allow the user to simulate changes to the ventilator strategy. Simulated changes interactively modify the position of the gray symbol on the hexagon and the values of the surrogate variables illustrated at the corners of the hexagon.

Advice is only generated when the patient is considered stable and when model simulations are a reasonable fit to continuous data, as described above. It is potentially a great advantage of model-based systems that consistency



Figure 5: Simulation user interface of Beacon following a piece of advice for a single patient, without (5A) and with (5B) surrogate variables displayed.

between simulations and measurements is required before advice is generated. Incorrectly entered or noisy measurements are likely to lead to poor model simulations and, therefore, prevent generation of advice in these situations. For the system presented here, poor model fit results in requests for further information, requiring the user to reconsider potentially incorrect data. In addition to these requirements, a minimum waiting time of 10 min is taken to calculate a new advice following changes in ventilator settings, to allow for the full effect of changes to be seen. In calculating advice, the system first calculates a target, defined as the ventilator settings resulting in the minimum combination of penalties. Advice is generated as a step toward this target, so as to avoid overly aggressive advice. Changes to the ventilator settings are manual and controlled by the user. Any change in ventilator settings, advised or otherwise, will result in the system checking for stable respiration, as indicated by stable values of FECO_2 and FEO_2 , followed by evaluation of the model fit and re-tuning if necessary, and re-calculation of both the target and advice. In addition, the system includes a set of learning algorithms, published previously [19], which allow the system to adapt to the patient's response to ventilator settings such as an increased metabolism on lowering pressure support, or changes in dynamic compliance.

Discussion

This paper has presented an example of the selection of models for inclusion in a physiological model-based decision support system for mechanical ventilation, originally known in its research version as INVENT, and now in its commercial version as the Beacon Caresystem. In doing so, the clinical problem has been presented and models justified, considering the timing of the decision and, hence, the modeling complexity required; the ability of the models to represent physiology; the measurements routinely available or to be introduced; and the ability to uniquely identify model parameters from these measurements. These issues have been highlighted through description of the models in the Beacon system, but need for their consideration is, we believe, general in the design of systems to provide advice generated from the solution of mathematical models at the bedside, in a clinical environment with limited data.

To provide advice on the correct values of FIO_2 , VT or inspiratory pressure, and fR, we would argue that models are required that describe pulmonary gas exchange, lung mechanics, acid-base status, CSF, and respiratory drive.

As clinical decisions selecting ventilator settings typically occur at a minimum of every 30–60 min, and these physiological systems typically reach steady state between therapeutic interventions, it has been chosen to implement these models representing only steady-state conditions. This eliminates the need for representation and numerical solution of differential equations. This has computational benefits, and it has been shown that where system dynamics are included, care should be taken in system design to combine models effectively and minimize computational time [25]. It also introduces limitations. These models are not intended for analyzing breath-by-breath data and providing ventilator assistance proportional to patient need depending upon the individual breath, such as the case for specialized ventilator modes such as proportional assist ventilation (PAV) [57] or neurally adjusted ventilator assist (NAVA) [49]. Indeed, the approach and models presented here might be used in synergy with such approaches to optimize both overall strategy and the individual breath. In addition, the lack of a dynamic circulatory model prevents analysis of respiratory-circulatory interaction, which can provide valuable information on blood volume status [10]. This paper has also focused on the version of Beacon (Beacon 3) which does not provide advice on PEEP. Models of the effects of PEEP on gas exchange, respiratory systems mechanics, or diaphragm position have not, therefore, been discussed in this paper.

It is necessary when applying these simple “minimal” models that their ability to describe physiology is well understood and proper experimental evaluation has been performed. The majority of models presented here have been shown to provide a reasonable description of patient physiology. The model of gas exchange has been compared with the reference MIGET technique [39, 40], and shown superior to the $\text{PaO}_2/\text{FIO}_2$ ratio [21]. The model of acid-base status of blood has been shown to simulate the mixing of blood [41], and when combined with the interstitial tissue model, can simulate bicarbonate distribution between these compartments [1]. The model of respiratory drive has been shown to simulate the patient's response to changes in volume and pressure support [27, 28]. The model of respiratory mechanics is probably that which is least descriptive of patient state. However, as described, only few respiratory mechanics parameters can be identified at the bedside without either introduction of respiratory maneuvers, which can only be applied in the absence of respiratory muscle activity, or with the introduction of esophageal catheters. Both of these introduce complexity into clinical practice, and the approach adopted here is to use a simple linear model, re-estimating parameter values in response to changes in ventilation and providing advice

on small step changes in ventilation, where the assumption of model linearity may be appropriate.

To uniquely identify the models presented here requires measurement of respiratory flow, pressure, O_2 , and CO_2 , consistent with indirect calorimetry; pulse oximetry; estimated or measured values of CO; periodic measurement of ABG; and, for estimation of all gas exchange parameters, a 10-min procedure varying FIO_2 . Use of the modeling complexity presented here, therefore, requires introduction of indirect calorimetry. This sensor technology is part of the Beacon system but requires placement of a sensor in the respiratory circuit between the patient and the ventilator. All other measurements are part of routine clinical practice and the system advises on periodic measurement of ABG when model simulations of SpO_2 and respiratory measurements differ from measured values. The 10-min procedure for varying FIO_2 is required for the gas exchange model to be fully identified. This is only requested by the system when arterial SpO_2 cannot be simulated accurately. In addition, recent attempts have been made to speed this process. Rule-based suggestions of FIO_2 control included in Beacon have shown that the process can be completed in 7.2 ± 2.4 min [51], and further reduction in time has been shown possible by fitting gas exchange parameters to data describing the dynamic response to FIO_2 change [50].

This paper has highlighted the need for simple, minimal models for application at the bedside, directed toward well-defined clinical problems. The need for minimal models having few parameters requiring identification can be seen as an advantage. Much of the physiology presented here has been well understood for many decades and is no longer challenged in the physiological literature. While research proceeds into newer, often deeper physiological understanding, engineers are faced with a wealth of well-founded physiological knowledge from which decision support systems can be built. Such systems, based on physiological models tuned to the individual patient, may be important tools in providing individualized patient treatment. In an age of increasing complexity of physiological models and the harvesting of large amounts of “big” data, it is perhaps worth reminding ourselves of the power of simple physiological understanding combined with routinely available measurements systematically applied at the bedside.

Conflict of interest statement: S.E. Rees and D.S. Karbing are minor shareholders and have performed consultancy work for Mermaid Care A/S who manufacture the Beacon Care system. S.E. Rees is a member of the board at Mermaid Care A/S.

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