

Goal-Directed Therapy for General ICU Patients Using Aggregated Multi-Objective Optimisation

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Abstract: SOPAVent (Simulation of Patients under Artificial Ventilation) is a blood gas model able to simulate patient ventilatory parameters subject to mechanical ventilation in the intensive care unit (ICU). In this paper, the SOPAVent model is further developed into a continuously updated model of patient ventilatory condition. The extended version of the model is used as the core component for a goal-directed optimisation strategy which aims to provide adaptive decision support for ventilatory therapy. Two objective functions are aggregated in an effort to interpret medical goals into an optimisation problem. The settings of the optimisation strategy are fine-tuned based on medical-goals and medical prioritization rather than mathematical optimality of solutions. The final decision support system is tested via a series of closed-loop simulations by assuming different clinical scenarios. Results show that the decision support system provides the correct advice for ventilator settings following adequate prioritization of competing medical goals.

1. INTRODUCTION

Mechanical ventilation is an important part of intensive care therapy as it aims to ensure sufficient patient oxygenation and also prevent the build-up of excessive carbon dioxide, which can lead to acidosis. However, meeting these goals simultaneously often leads to excessive airway pressure and tidal volume, which can cause lung injury. Therefore, the management of mechanical ventilation often requires the optimisation of ventilator settings to achieve the best compromise among such competing goals.

The need for a mechanical ventilation management decision support system (DSS) has long been recognized and many systems were designed (Rutledge *et al.*, 1993; Laubscher *et al.*, 1994; Dojat *et al.*, 1997; McKinley *et al.*, 2001). However, only a few of these designs employed model-based techniques. Compared with knowledge-based systems, model-based systems can provide more objective decisions and also support clinicians to understand better the patient's physiological state.

A totally non-invasive ventilated patient hybrid model was previously developed by our group (Wang *et al.*, 2007) based on an earlier mathematical model called SOPAVent (Goode, 2001). By having such a patient model, patient states responding to different ventilator settings can be predicted. If clinical goals for mechanical ventilation can be described by objective functions, then optimal ventilator settings can be found via optimisation.

In this paper, the design and validation of such a model-based goal-directed mechanical ventilation management decision support system are presented. The paper is organised as follows: first, the SOPAVent model is described, including the extension of the model to simulate patients with evolving

clinical conditions; second, the design of the model-based DSS using aggregated multi-objective optimisation is described; third, the closed-loop validation of the DSS is presented and finally, conclusions are drawn in relation to the overall study.

2. SOPAVent MODEL

SOPAVent (Simulation of Patients under Artificial Ventilation) describes the blood gas exchange and transport together with lung mechanics based on respiratory physiology and mass balance equations. The model uses a compartmental structure (see Fig. 1), where the circulatory system is represented by lumped arterial, tissue, venous and pulmonary compartments. The lung is sub-divided into three compartments; (1) an ideal alveolus, where all gas exchange takes place with a perfusion-diffusion ratio of unity; (2) a dead space representing lung areas that are ventilated but not perfused, and (3) a shunt that is a fraction of cardiac output, representing both anatomical shunts and lung areas that are perfused but not ventilated. The descriptions of the model equations can be seen in the Appendix of this paper.

The inputs to the model are the ventilator settings (FiO₂, PEEP, P_{insp}, V_{rate}, T_{insp}) and the outputs from the model are the arterial blood gases (PaO₂, PaCO₂ and pHa) and tidal volume (VT). A group of model parameters are required from the patient to enable the model to be patient-specific. In order to use SOPAVent to design an adaptive decision support system for mechanical ventilation management, significant improvements have been included in the original SOPAVent. These are as follows:

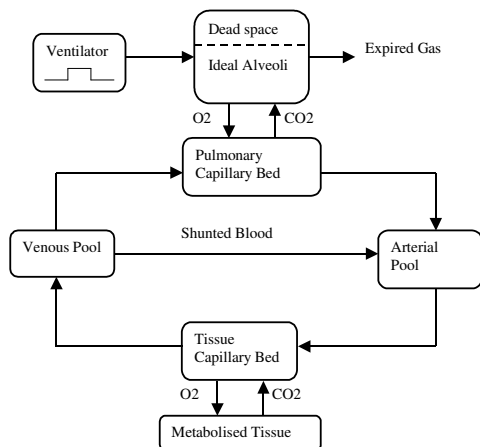


Fig. 1. Schematic diagram of the SOPAVent model.

First, SOPAVent was improved to become a totally non-invasive model after developing new estimation methods for the following model parameters: shunt, relative dead space (K_d), CO_2 production (VCO_2), oxygen consumption (VO_2) and cardiac output (CO). CO is estimated by using a population median method (Kwok *et al.*, 2004a). VCO_2 and K_d are estimated using two data driven models. VO_2 is then derived based on VCO_2 and a fixed respiratory quotient (RQ). Shunt is estimated via the secant method based on model tuning (Wang *et al.*, 2007).

Second, SOPAVent was extended to simulate patients from a stable clinical state to an evolving clinical condition. Following consultation with expert ICU clinicians, the model parameters relating to shunt, K_d , VCO_2 , VO_2 and airway resistance (Raw) were all deemed to be important indicators of the patient clinical states. From the SOPAVent model sensitivity analysis (Goode, 2001), these parameters are also the most sensitive ones to the model predictions. Therefore, a continuously updated SOPAVent model was designed by continuously updating these five key model parameters.

From the K_d , VCO_2 , VO_2 , shunt and Raw estimation methods, it can be seen that, in order to update these parameters continuously, the PaO_2 , PaCO_2 , ventilator settings, EtCO_2 and VT measurements from the patients are required. These parameters are all routinely measured continuously in ICU except PaO_2 and PaCO_2 . Therefore, the model predicted PaO_2 and PaCO_2 are used for parameter estimation so that the five key model parameters can be updated at the same frequency. It is worth noting that the PaO_2 and PaCO_2 data are replaced by real measurements once they are measured. The model updating frequency was taken to be 30 minutes. The updated model structure is shown in Fig. 2.

The continuously updated SOPAVent model was validated using five patients data collected from the patient data management system (PDMS) located in the Sheffield Royal Hallamshire Hospital general ICU (UK). The model predictions were compared with the measured blood gas and tidal volume. The estimated model parameters, i.e. K_d and VCO_2 , were also compared with the measured ones. One typical patient validation result is shown in Fig. 3. Because the blood gases are neither measured frequently nor regularly,

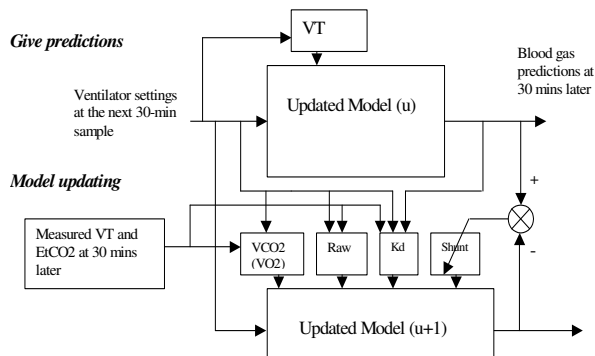


Fig. 2. The structure of the continuously updated SOPAVent model.

the sub-figures in the second row represent the specific model predictions, whose time were closest to the measured blood gas and yet were prior to it, with the measured data. The summary of the five patients validation results are presented in Table 1.

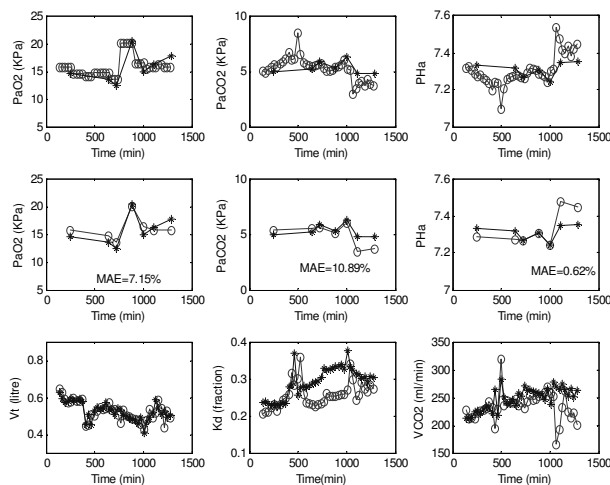


Fig. 3. The continuously updated model validation results. ‘o’ indicates the predicted results while ‘*’ stands for the real measurements.

As can be seen from the validation results, the continuously updated model can simulate the patient condition continuously and provide good patient state (blood gas and tidal volume) predictions subject to the patient clinical state changes and different ventilator settings. The model parameter estimations seem to agree with the measurements generally. The relatively large K_d estimation error reflects the current limitations of the K_d model which are due to the model inputs unavailability and its complex physiological interactions.

The successful development of this non-invasive continuously updated ventilated patient model has formed the basis for developing an adaptive model-based decision support system for mechanical ventilation management in general ICU.

Table 1. The continuously updated model validation results (Mean Absolute Error (%))

Patient	PaO2	PaCO2	pH	VT	Kd	VCO2
One	15.76	14.35	0.98	10.35	16.25	10.09
Two	7.15	10.89	0.62	4.93	14.62	7.95
Three	11.54	17.05	1.13	12.18	17.57	21.22
Four	12.28	3.66	0.61	3.83	21.77	10.21
Five	11.94	11.18	0.80	4.44	15.93	10.78
Mean	11.73	11.43	0.83	7.15	17.23	12.05

3. A DECISION SUPPORT SYSTEM

3.1 Background

As already stated, mechanical ventilation must optimise oxygenation levels and carbon dioxide build up. Oxygenation is usually indicated by PaO2 and carbon dioxide level is usually reflected through PaCO2. However, the ventilation strategies that only meet PaO2 and PaCO2 targets are not always the optimal ones. Meeting the targets PaO2 and PaCO2 often requires an excessive airway pressure, tidal volume and FiO2, which could in turn be harmful to the patient (ARDSnetwork, 2000). Therefore, any optimal ventilation strategy should represent a compromise between maintaining the PaO2 and PaCO2 within their acceptable ranges and minimizing the side effects of mechanical ventilation.

3.2 Method

Based on the medical goals relating to mechanical ventilation management, finding an optimal ventilation therapy is truly a multi-objective optimisation problem. Using the SOPAVent model, the patient outcomes for different ventilator settings can be predicted. Therefore, the desired ventilator settings are those that lead to the smallest error with the ventilation management targets. However, because the targets are competing, a compromise must be achieved. In this study, the aggregated multi-objective optimisation method is used. It uses the weight parameters to define the relative importance/prioritisation of each objective and sums the competing objectives into one objective function. Therefore, the solution can be found using a single objective optimisation method. After allocating the suitable weight parameters, the optimal ventilator settings are then derived by searching within the ventilator settings input range and the settings that generate the minimal objective function value will be provided as the decision support system outputs. In the following, the details of the designing of the objective function based on the medical goals and medical prioritisation are described.

The current DSS is designed to only provide FiO2, P_{insp} and V_{rate} setting advice because of the unproven SOPAVent model prediction performance on PEEP and T_{insp}. Because FiO2 mainly affects the oxygenation of the patient while P_{insp} and V_{rate} mainly influence the minute volume ventilation, it was decided to divide the DSS into the FiO2 and P_{insp}/V_{rate} subsystems. In order to generate a clinically meaningful ventilator setting advice, the FiO2, P_{insp} and V_{rate} search ranges are as defined in Table 2.

Table 2. The ventilator setting input range

	FiO2 (%)	P _{insp} (cmH2O)	V _{rate}
Input range	[30 100]	[5 40]	[4 20]

Following consultation with expert ICU clinicians, the PaO2, PaCO2, PIP and VT control targets were chosen as those shown in Table 3 where it can be seen that in clinical practice, a compromise among the many competing goals must be achieved.

Table 3. The targets of ventilator management for general ICU patients during the acute phase

	PaO2 (kPa)	PaCO2 (kPa)	PIP (cmH2O)	VT(ml/body weight (kg))
Normal range	11-13	5 - 6	≤ 30	≤ 7
Acceptable range	10-14	4 - 7	≤ 35	≤ 8

P_{insp} / V_{rate} subsystem

In the P_{insp} / V_{rate} subsystem, the main goals are to maintain the patient PaCO2 within the normal range while avoid excessive airway pressure (PIP) and tidal volume (VT). Using the aggregated multi-objective optimisation method, the objective function for P_{insp} / V_{rate} subsystem is designed as follows:

$$J = \lambda_1 \cdot \left(\frac{PaCO2_t - PaCO2}{PaCO2_max} \right)^2 + \lambda_2 \cdot \left(\frac{VT_t - VT}{VT_max} \right)^2 \quad (1)$$

Subject to:

$$5 \leq P_{insp} \leq 40, 4 \leq V_{rate} \leq 20;$$

Where,

$$PaCO2_t = 5 \text{ kPa (PaCO2 target);}$$

$$PaCO2_max = 20 \text{ kPa;}$$

$$VT_t = 7 \text{ ml / kg (VT target);}$$

$$VT_max = 1500 \text{ ml;}$$

$$\lambda_1 \geq 0; \lambda_2 \geq 0;$$

PaCO2, VT are the SOPAVent predictions.

Objective function (1) consists of the weighted square sums of the normalized PaCO₂ control and the VT control errors. It should be noted that the search for P_{insp} may introduce a large PIP as well. Initially, a PIP penalty function was designed in the objective function. However, after investigations, it was found that the PIP constraints can automatically be met by the VT control goals (both limit the high P_{insp}). Therefore, the PIP constraint is omitted in the objective function.

For the aggregated multi-objective optimisation, the choice of the weighting parameters is very crucial. It decides on the relative importance of the individual goals and whether the optimal compromise among the competing goals can be achieved or not. In this paper, the weight parameters λ_1 and λ_2 were chosen after assessing the PaCO₂ and VT control errors based on different weight values. Five ICU patient data were used to construct the simulated patient. After combining different weight values and consulting the control results with clinicians, it was decided that 0.4 and 0.6 were the best settings for the λ_1 and λ_2 to achieve the desired compromise among the medical goals.

The optimisation is conducted using the Genetic Algorithm (GA) based technique (Goldberg, 1989) because of its capability of searching relatively large solution spaces. The random combination of P_{insp} and V_{rate} are searched and the values that generate the minimal objective function value are found.

FiO₂ subsystem

The main goal for FiO₂ subsystem is to maintain PaO₂ within the normal range. The same method developed by our group (Kwok *et al.*, 2004b) is applied. It is briefly summarized as follows. By evaluating the SOPAVent oxygen transport equations at steady-state, the first derivative of PaO₂ to FiO₂ can be derived. The Newton method is then used to search for the FiO₂ in order to achieve the PaO₂ target.

The search for FiO₂ to meet the PaO₂ target can be described by the following equation:

$$f(FiO_2) = SOPAVent(FiO_2, \delta) - PaO_{2_t} = 0 \quad (2)$$

Where δ stands for the model parameters and PaO_{2_t} is the target PaO₂ which is defined as 12 kPa. The iterative formula is:

$$FiO_{2(n+1)} = FiO_{2(n)} - \frac{SOPAVent(FiO_{2(n)}, \delta) - PaO_{2_t}}{\left. \frac{\partial PaO_2}{\partial FiO_2} \right|_{FiO_{2(n)}}} \quad (3)$$

Where FiO₂(n) denotes the nth approximation of FiO₂.

4. CLOSED-LOOP VALIDATION OF THE DECISION SUPPORT SYSTEM

In Section 3, a mechanical ventilation management decision support system (DSS) is developed based on SOPAVent patient model and a model-based optimisation method. By transferring the medical goals of the mechanical ventilation

into an aggregated objective function, suitable ventilator settings can be derived using optimisation of such objective function. Based on the continuously updated SOPAVent model, the DSS should be able to adapt to the patient state changes and provide adaptive decision support for ventilation management. In this Section, the performance of the adaptive DSS is evaluated using closed-loop simulations.

The structure of the closed-loop simulation is shown in Fig. 4. The aim of the closed-loop validation is to assess the system's ability to deal with different scenarios that may occur in the actual clinical environment and to evaluate whether the DSS can produce consistent performances on achieving the optimal compromise between the competing goals.

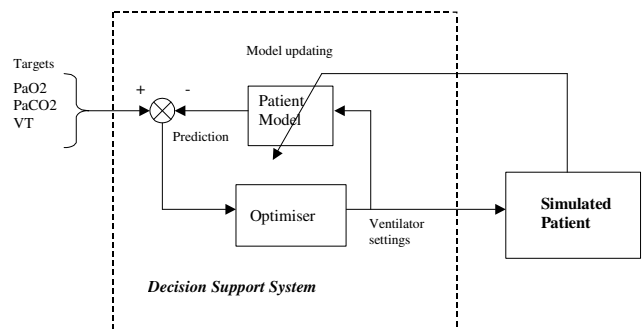


Fig. 4. The adaptive ventilator management decision support system.

In the actual clinical environment, the patient's condition may deteriorate or improve over time. Therefore, four scenarios can be defined as follows:

- 1) A slow increase in shunt;
- 2) A slow increase in K_d;
- 3) An acute increase in shunt which then returns to the baseline level after 1 hour;
- 4) An acute increase in K_d which then returns to the baseline level after 1 hour.

The DSS was designed to generate the ventilator setting advice every 30 min. In the simulation, the patient was represented by the SOPAVent model. The simulated patient parameters were changed according to the designed scenarios listed above. At every 30 min, the simulated patient data (PaO₂, PaCO₂, VT, Ventilator settings, EtCO₂) were input to the DSS to update the patient model. Thereafter, the 'optimal' ventilator settings were derived using an optimisation based on the patient model prediction and the defined objective functions. The derived ventilator settings were then input to the simulated patient to simulate the next 30 min patient states. Each simulation lasted 4 hours and started with a 30-minute period of stabilization where the simulated patient's ventilator settings were maintained at the initial values.

Five ICU patient data were used to validate the DSS by constructing the simulated patient initial scenarios. The

results show that the DSS can generate a satisfactory and a consistent performance for each scenario and for all patients. Due to space limitations, only two typical results are presented (as shown in Figs. 5 and 6). The simulated patient was constructed for a patient whose weight, height, age and gender were 57kg, 173cm, 68 years and male respectively.

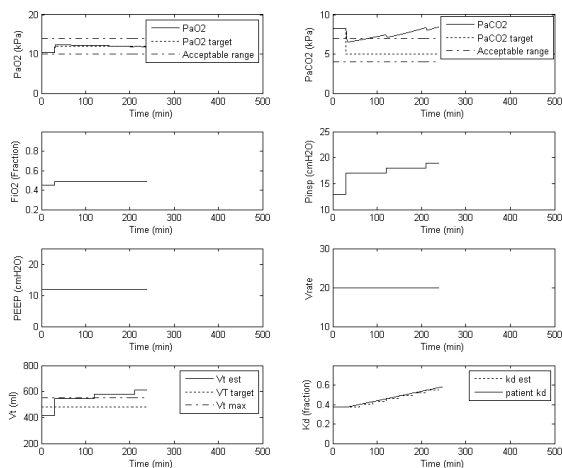


Fig. 5. The closed-loop simulation results for the patient with a slow increase in Kd.

Fig. 5 shows how the patient clinical state and ventilator settings change when the Kd was increased from 0.37 to 0.58 over the 210 minutes. It can be seen that initially the patient had a high PaCO₂ at 8.26 kPa but a low VT at almost 6ml/kg. The Vrate setting was 20, which was already the maximal setting. After the initial 30-min stabilization, the DSS responded correctly by increasing the P_{insp} from 13 to 17 cmH₂O. The advice on the P_{insp} setting seems to have met the medical goals as it led to a reduction in the PaCO₂ into the acceptable range while not generating an excessive tidal volume and airway pressure. With the Kd increasing, the PaCO₂ will increase if the ventilator settings were to remain unchanged. In the current simulation, the DSS generated the best compromise among the competing goals by slightly increasing the P_{insp} with Kd increasing. At the end of the simulation, both VT and PaCO₂ were beyond their acceptable ranges with the continuous increase in Kd. However, this just indicated the limitation of mechanical ventilation. If the patient continued deteriorating, then a sub-optimal solution must be accepted.

Fig. 6 shows the changes in the patient clinical state and ventilator settings when the patient shunt was increased slightly from 11% to 22% over the 210 minutes. Normally, the increase in shunt should reduce the PaO₂ if the ventilator settings were kept the same. This was reflected by the slow decline in PaO₂ between two sampling points in the figure. Every 30 minutes, the patient measurements were input to the DSS. The system responded correctly by increasing FiO₂. This improved the PaO₂ and kept it close to the target level. For the other mechanical ventilation management goals, it can be seen that P_{insp} was changed appropriately to maintain

the conflicting targets, PaCO₂ and VT, within their acceptable ranges.

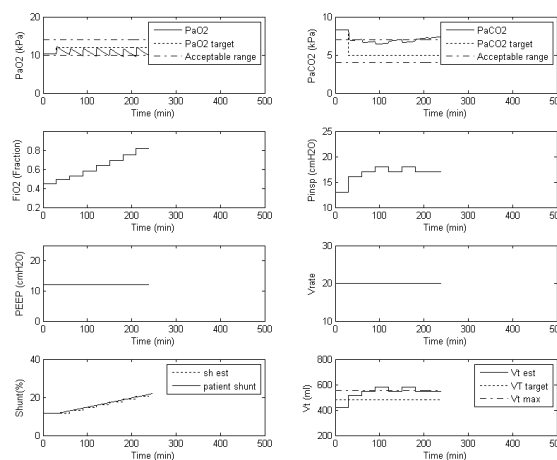


Fig. 6. The closed-loop simulation results for the patient with a slow increase in shunt.

From the closed-loop simulation results, it can be concluded that the DSS can respond correctly subject to the patient state changes and competing ventilation management targets. However, it should be noted that the simulated patient with designed scenarios may introduce some problems. For example, the Kd updating in patient model cannot use the Kd data-driven model because the simulated patient data are far different from the real patient data which are used for Kd model training. Therefore, in the simulation study, the estimated Kd is directly set as the same value as the simulated patient.

5. CONCLUSIONS

The management of mechanical ventilation in general ICU is complex and includes more often than not competing goals. In this paper, a goal-directed model-based adaptive decision support system for mechanically ventilated patient management is presented. Based on a ventilated patient hybrid model called SOPAVent, the optimal ventilator settings are derived using an aggregated multi-objective optimisation. The DSS is validated via a series of closed-loop simulations and the results show that the system can adapt to the patient clinical state changes and respond correctly in order to achieve an overall optimal patient therapy. Future work will include the management of the side effects of FiO₂ (i.e. oxygen toxicity) into the FiO₂ subsystem and also the clinical validation of the decision support system.

ACKNOWLEDGEMENT

All authors wish to acknowledge the help/support from Drs Hoi Fei Kwok and Kevin M Goode during the course of this project.

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$$\frac{\partial CaO_2}{\partial t} \cdot Va = \dot{Q}_t \cdot [X \cdot CvO_2 + (1-X) \cdot CpO_2 - CaO_2] \quad (A1)$$

$$\frac{\partial CtO_2}{\partial t} \cdot Vt = \dot{Q}_t \cdot [CaO_2 - CtO_2] - \dot{V}o_2 \quad (A2)$$

$$\frac{\partial CvO_2}{\partial t} \cdot Vv = \dot{Q}_t \cdot [CtO_2 - CvO_2] \quad (A3)$$

$$\frac{\partial CpO_2}{\partial t} \cdot Vp = \dot{Q}_t \cdot (1-X) \cdot [(CvO_2 - CpO_2) + O_2Diff] \quad (A4)$$

$$\frac{\partial CAO_2}{\partial t} \cdot VA = RR \cdot (Vt - Vd) \cdot (FiO_2 - CAO_2 / 1000) - \dot{Q}_t \cdot (1-X) \cdot O_2Diff \quad (A5)$$

Where VA, Va, Vt, Vv, Vp indicate the volumes of alveolar, arterial, tissue, venous, and pulmonary compartments respectively (litres); \dot{Q}_t , cardiac output (ml blood/min); X, Fraction of blood shunted past lungs; VO₂, O₂ consumption by tissues (ml O₂/min); VD, Alveolar dead space volume (ml); VT, Tidal volume (ml); RR, Respiratory rate (breath/min); CAO₂, Alveolar O₂ content (ml O₂/l gas); CxO₂, where x=a, t, v, p – arterial, tissue, venous and pulmonary O₂ content respectively (ml O₂/l blood); t, Time (min); FiO₂, Inspired O₂ gas fraction.

The gas exchange between the ideal alveolus and the pulmonary compartment is driven by the pressure gradient across the different boundary for each gas (A6). Embedded in the model is an inverse gas dissociation functions that convert O₂ contents to partial pressure (A7).

$$O_2Diff = Bo_2 \cdot (Pmean \cdot (CAO_2 / 1000) - PpO_2) \quad (A6)$$

[ml O₂/l blood]

$$P_pO_2 = f_{inv}(C_pO_2) \quad (A7)$$

where, PpO₂, Pulmonary partial pressure of O₂ (kPa); Pmean, mean airway pressure (kPa); and BO₂ is the diffusion coefficient expressed in terms of ml O₂/kPa/l blood.

Whilst only equations pertaining to the diffusion and circulation of O₂ are presented here, there exists a set of similar equations for CO₂ within the model.

A lung mechanics model is included into SOPAVent to predict tidal volume (VT) as shown in (A8).

$$V_T = P_{insp} \cdot C \cdot (1 - \exp(-\frac{60t_i}{V_{rate} \cdot Raw \cdot C})) \quad (A8)$$

Where C is the lung compliance, Raw is the airway resistance and t_i is the fraction of inspiratory time in one ventilatory cycle.

Appendix. SOPAVent EQUATIONS

The transport of O₂ is described by the following 5 linked differential equations (Goode, 2001);