Mathematical Modelling of Carbon Dioxide Exchange in Hollow Fiber Membrane Oxygenator

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Abstract. The main objective of this study is to simulate the carbon dioxide (CO$_2$) blood-gas exchange in membrane oxygenator, evaluate the effect of sweep gas flow rate on CO$_2$ partial pressure ($pCO_2$) and to determine the response of $pCO_2$ to the step change of sweep gas flow rate. In extension to the simulation of gas transfer in membrane oxygenator, open-loop response on sweep gas flow rate was applied to the developed mathematical model to prove its effect on CO$_2$ removal rate. Three sweep gas flow rates were set, i.e. 1 L/min ($Qg/Qb=0.5$), 2 L/min ($Qg/Qb=1$) and 4 L/min ($Qg/Qb=2$) and the simulated $pCO_2$ in artery was observed. Next, one-way ANOVA test was performed to determine the significant difference in CO$_2$ removal rate between these gas flow rates. For the next test, sweep gas flow rate was changed at $t=60$ second and $t=120$ second of simulation, to evaluate how $pCO_2$ will response to the step change of gas flow rate. As the result, the highest CO$_2$ removal observed when $Qg/Qb=2$, as compared to gas-blood ratio of 1 and 0.5. The ANOVA test also proved the significant difference in simulated $pCO_2$ for each flow rate. For the last test, a proportional response of $pCO_2$ towards the change of sweep gas flow rate was highlighted. In conclusion, the rate of CO$_2$ removal from blood can be manipulated by sweep gas flow rate and this rate can be adjusted to achieve the optimum performance of membrane oxygenator for CO$_2$ sequestration.

Keywords: Membrane oxygenator, carbon dioxide removal, mathematical modelling, open-loop control, one-way ANOVA.

1. Introduction

Blood oxygenators are commonly used as artificial lung in extracorporeal circulation circuit. This artificial lungs are used to maintain physiologic oxygen (O$_2$) and carbon dioxide (CO$_2$) level in blood [1-3] and also used as respiratory assist device to allow time for the native lung to heal by reducing mechanical ventilation setting [4, 5]. There are two types of blood oxygenators that have been invented, which are bubble oxygenators and membrane oxygenators. Unfortunately, there are various adverse effects reported for bubble oxygenators, such as significant damage of blood constituent due to direct contact between blood and air surfaces, platelet and alveolar sequestration, contribute to higher risk of air embolism (micro- and macro-) and much more [6-9]. For these reasons, more reliable membrane oxygenators dominate the current market. Hence, the focus of present study is solely on the
membrane oxygenators, in terms of mathematical modelling and variables that can be manipulated to optimize its function.

Since membrane oxygenators dominate the current market, its latest and most reliable design are always in demand. Numerous investigations are conducted to improve their design and offer the best performance. In early years, building and testing membrane oxygenator prototypes was conducted by trial and error process. This process can be time consuming and expensive. With the development of computer-assisted model, cost for trial and error in manufacturing and testing for multiple produced prototype design can be minimized [10]. Using this method, mathematical modelling and simulation of gas exchange (O2 and CO2) in membrane oxygenator can be conducted, which enable the prediction of gas transfer in membrane oxygenator. Then, the experimental measurement is conducted for the same model to identify mass transfer coefficient and validate the model [2]. Once the model is validated, the prototype is developed based on it for the next production stage.

The theoretical idea of O2 and CO2 diffusion in membrane oxygenator was previously analyzed and experimentally determined by Weissman and Mockros [11, 12] by considering the reaction between oxygen and hemoglobin. Analysis of O2 transfer rate was calculated and also the improvement in O2 transfer rate for different configuration of oxygenator. Based on the analysis, it was concluded that tubular oxygenator is practical for this purpose. This works had been extended by Mockros and Leonard [13] for a compact cross-flow tubular oxygenators to determine partial pressure of O2 by incorporating oxygen-haemoglobin reaction which exists in the blood.

Inspired by the hallmark work by Mockros and Leonard [13], Vaslef et. al [14] developed their own mathematical model to predict O2 transfer, but they were using semi-empirical theoretical. The observation proved that the predicted O2 transfer rate was closed to experiment measurement.

Apart of O2 modelling, Svitek and Federspiel [2] developed a mathematical model that able to predict CO2 removal exchange rate in hollow fiber membrane oxygenator using semi-empirical approach. Based on the results reported by these authors [2], it was clearly shown that the difference between predicted CO2 exchange rates (using mathematical model) and measured experimental data did not differs much, which varies in the range of 6% to 9% accordingly to the blood flow rate. This observation thus validates the mathematical model that was developed in the reported study.

Mathematical modelling also could be used to determine the best design for membrane oxygenator. For example, Matsuda and Sakai [15] investigated the effect of number of tied hollow fiber on blood flow in terms of friction factor and mass transfer coefficient. They found an inverse proportional relationship between numbers of tied hollow fiber on O2 transfer rate, and proved that single hollow fiber is the most effective design for optimum O2 transfer rate. Tabesh et al. [16] then use a theoretical model to evaluate the design of hollow fiber membrane oxygenator in terms of geometric data, configuration properties and design specification for 6 commercial oxygenators. Vaslef et al. [10] also used the computer method to validate their prototype device of implantable artificial lung in order to reduce the cost for trial-and-error manufacturing using the same method employed by Hormes et al. [17].

As an advanced works in numeric analysis and designing of membrane oxygenator, Turri and Yanagihara [18] developed a two-dimensional computer-assisted numeric simulator which takes account for blood buffering capacity. In addition to their successful in predicting O2 and CO2 mass exchange as compared with the experimental value, the researchers also concluded there was no effect of blood base excess on CO2 mass exchange rate. For the effect of sweep gas flow rate, it were reported that only CO2 exchange rate was affected by the sweep gas flow rate, whilst O2 exchange rate shows no significant increasing as the sweep gas flow rate increased. All these findings showed the
great contribution of mathematical modelling and process simulation in the development of membrane oxygenators.

2. Methodology
Basically, the simulation is adopted from the mathematical model that been developed by Hexamer and Werner [19], which is the reformulated model by Hill et al. [20, 21]. This model is a mathematical description of gas diffusion process (O_2 and CO_2) in membrane oxygenator and comprised of three main compartments: gas (g), plasma (pl) and red blood cell (rbc). In each compartment, volume balances are calculated for five state variables, namely O_2 partial pressure (pO_2), CO_2 partial pressure (pCO_2), bicarbonate, carbamate and hydrogenium [22, 23]. Due to the chemical binding of O_2 and CO_2 within the blood, gas transfer in this model is considered as highly non-linear. The generic model used is displayed in Figure 1.

![Figure 1. The generic model](image)

From figure 1, there are few assumptions can be made:
- i. Compartment’s volume and its flow rate is assumed to be constant (\( Q_{in} = Q_{out} \)).
- ii. There is optimal mixing inside the compartment ([\( C \)]_{in} = [\( C \)]_{out}).

From these assumptions, volume change rate for both gas (CO_2 and O_2) stored in a compartment can be written as:

\[ V_b \frac{d[C]}{dt} = Q_{b, in}[C]_{in} - Q_{b, out}[C]_{out} + D_i(p_{ext} - p_i) + R_i \]  

(1)

Where [\( C \)] denotes the concentration of component ‘i’, \( V_b \) denotes the volume of the compartment, \( Q_{b, in} \) and \( Q_{b, out} \) represent flow rates of blood (in and out) and [\( C \)]_{in}, [\( C \)]_{out} are the concentration at inflow and outflow of the compartment. On the other hand, \( D_i \) is the bulk diffusion capacity, which its mass transfer is driven by gradient of partial pressure, \( p_{ext} - p_i \). Finally, \( R_i \) then stands for gain/loss of the substrate due to chemical reactions. For the equations below, gas, whole blood, plasma and red blood cell are represents by subscript of g, b, pl and rbc, respectively. For simplicity, the charge of hydrogen ion (H^+) and bicarbonate ion (HCO_3^-) are neglected in the symbol [19].

2.1. Gas Compartment
Gas compartment is also modelled based on the equation (1), with assumption that no volume loses occur across the membrane (\( Q_g = constant \)).

\[ V_g \frac{dF_{O_2}}{dt} = Q_g(F_{O_2, in} - F_{O_2}) - D_{O_2}(pO_2 - pO_2) \]  

(2)

\[ V_g \frac{dF_{CO_2}}{dt} = Q_g(F_{CO_2, in} - F_{CO_2}) - D_{CO_2}(pCO_2 - pCO_2) \]  

(3)
The dependency of gas fraction-partial pressure was derived from Henry’s law as [24-29]:

\[ p_{O_2,g} = p_{bar} \cdot F_{iO_2} \]  
(4)

\[ p_{CO_2,g} = p_{bar} \cdot F_{iCO_2} \]  
(5)

Where \( p_{O_2,g} \) and \( p_{CO_2,g} \) is partial pressure of O\(_2\) and CO\(_2\), respectively, \( p_{bar} \) is the atmospheric pressure (mmHg), \( F_{iO_2} \) is O\(_2\) fraction in mixing gases and \( F_{iCO_2} \) is CO\(_2\) fraction in mixing gases.

There are three assumptions are made in this case [29]:
1. \( F_{iCO_2} \) in equation [5] is zero (since there is no CO\(_2\) is used in sweep gas)
2. There are perfect mixing condition in gas compartment (\( F_{iO_2, in} = F_{iO_2} \) and \( F_{iCO_2, in} = F_{iCO_2} \))
3. No flow difference occur (\( \dot{Q}_{g, in} = \dot{Q}_{g, out} = \dot{Q}_{g} \))

By substituting (4) and (5) into (2) and (3), the equations can be rearranged as:

\[ V_g \frac{dp_{O_2}}{dt} = \dot{Q}_{g}(pO_2_{g, in} - pO_2_g) - p_{bar} \cdot D_{O_2}(pO_2_g - pO_2_b) \]  
(6)

\[ V_g \frac{dp_{CO_2}}{dt} = \dot{Q}_{g}(pCO_2_{g, in} - pCO_2_g) - p_{bar} \cdot D_{CO_2}(pCO_2_g - pCO_2_b) \]  
(7)

2.2. Carbon dioxide transfer in blood compartment

Prior to the equation of blood-gas transfer, the volumes and flow for plasma and red blood cell are defined as:

\[ V_{rbc} = V_p \cdot hct \]  
(8)

\[ V_{pt} = V_p \cdot (1 - hct) \]  
(9)

\[ \dot{Q}_{rbc} = \dot{Q}_p \cdot hct \]  
(10)

\[ \dot{Q}_{pt} = \dot{Q}_p \cdot (1 - hct) \]  
(11)

Then, the equations for CO\(_2\) transfer are:

\[ V_{pt} \alpha_{CO_2} \frac{dP_{CO_2, pt}}{dt} = \dot{Q}_{pt}([CO_2]_{pt, in} - [CO_2]_{pt}) + D_{CO_2,m}(P_{CO_2, pt} - P_{CO_2, pt}) + D_{CO_2,rbc}(P_{CO_2, rbc} - P_{CO_2, pt}) + V_{pt} \cdot R_{HC03, pt} \]  
(12)

For plasma part, and

\[ V_{rbc} \alpha_{CO_2} \frac{dP_{CO_2, rbc}}{dt} = \dot{Q}_{rbc}([CO_2]_{rbc, in} - [CO_2]_{rbc}) + D_{CO_2,rbc}(P_{CO_2, rbc} - P_{CO_2, rbc}) + V_{pt} \cdot R_{HC03, rbc} - \dot{V}_{rbc} \frac{d[carb]}{dt} \]  
(13)

For the red blood cell part;

Where:

\[ [CO_2]_{pt} = \alpha_{CO_2} P_{CO_2, pt} \]  
(14)

\[ [CO_2]_{rbc} = \alpha_{CO_2} P_{CO_2, rbc} \]  
(15)

\[ R_{HC03, pt} = -k_u \alpha_{CO_2} P_{CO_2, pt} + \frac{k_e}{k} [H]_{pt} [HC03]_{pt} \]  
(16)

\[ R_{HC03, rbc} = cat \cdot (-k_u \alpha_{CO_2} P_{CO_2, rbc} + \frac{k_e}{k} [H]_{rbc} [HC03]_{rbc} \]  
(17)
Equations (12) and (13) are obtained from assumption that the concentration of CO₂ in both plasma and red blood cell are linked to the partial pressure via the solubility coefficient.

Next, the equations for bicarbonate transfer for plasma ([HCO₃]ₚ) and red blood cell ([HCO₃]ᵣbc) are:

\[
V_{pt} \frac{d[HCO₃]_{pt}}{dt} = \dot{Q}_{pt} ([HCO₃]_{pt,in} - [HCO₃]_{pt}) - D_{HCO₃, rbc} ([HCO₃]_{pt} - \frac{[HCO₃]_{rbc}}{r}) - V_{pt} R_{HCO₃, pt}  
\] (18)

\[
V_{rbc} \frac{d[HCO₃]_{rbc}}{dt} = \dot{Q}_{rbc} ([HCO₃]_{rbc,in} - [HCO₃]_{rbc}) + D_{HCO₃, rbc} ([HCO₃]_{pt} - \frac{[HCO₃]_{rbc}}{r}) - V_{pt} R_{HCO₃, rbc} 
\] (19)

Alphabet ‘r’ in equation (16) and (17), is the result of [HCO₃] diffusion across red blood cell membrane and some complex biochemical effects [29]. It is defined as:

\[r = (0.058 p_{H_{virt}} - 0.437)S - 0.529 p_{H_{virt}} + 4.6 \] (20)

Equation (18) then influences virtual pH-value, which is the important determinant in pO₂ measurement:

\[p_{H_{virt}} = -\log(r[H]_{rbc}) \] (21)

The diffusion capacity \(D_{CO₂, rbc}\) and \(D_{HCO₃, rbc}\) used in equations (10), (11), (16) and (17) are estimated from in-vitro measurements [20]:

\[D_{CO₂, rbc} = \frac{0.693 \cdot a_{CO₂}}{r_{rbc}} \cdot \frac{V_{rbc} \cdot V_{pt}}{V_{rbc} + V_{pt}} \] (22)

\[D_{HCO₃, rbc} = \frac{0.693 \cdot V_{rbc} \cdot V_{pt}}{r_{HCO₃}} \cdot \frac{V_{rbc} V_{pt}}{V_{rbc} + V_{pt}} \] (23)

Carbamino reaction in equation (11) and (24) is due to direct bound between part of CO₂ within red blood cell and haemoglobin. The substance that produced from this reaction is called carbamate (carb):

\[
V_{rbc} \frac{d[carb]}{dt} = \dot{Q}_{rbc} ([carb]_{in} - [carb]) + k_a [CO₂]_{rbc} \cdot V_{rbc} ([Hb] - [carb]) \cdot \frac{k_{a5}}{k_{a2} + [H]_{rbc}} \frac{k_{a5}}{k_{a2} + [H]_{rbc}} - V_{rbc} \frac{k_{a3}(1-S)}{k_{a2} + [H]_{rbc}} \frac{k_{a3}(1-S)}{k_{a2} + [H]_{rbc}} \] (24)

Lastly, exchange of hydrogen ion in plasma ([H]ₚ) and red blood cell ([H]ᵣbc) are described by its hydrogen ion concentration:

\[
V_{pt} \frac{d[H]_{pt}}{dt} = \dot{Q}_{pt} ([H]_{pt,in} - [H]_{pt}) - V_{pt} \frac{2.303}{\rho_{pt}} [H]_{pt} \cdot R_{HCO₃, pt} \] (25)

\[
V_{rbc} \frac{d[H]_{rbc}}{dt} = \dot{Q}_{rbc} ([H]_{rbc,in} - [H]_{rbc}) + V_{rbc} \frac{2.303}{\rho_{rbc}} [H]_{rbc} \cdot (R_{HCO₃, rbc} + 1.5 \frac{d[carb]}{dt} - 0.6 \cdot CAP \frac{dS}{dt} ) \] (26)
Note that all the initial values, oxygenator parameters, biophysical and chemical parameters mentioned in the equations above are defined in Appendix 1. Due to the objectives and scope of this study, only CO\textsubscript{2} transfer will be considered, while the simulation of O\textsubscript{2} diffusion across hollow fiber membrane can be reviewed elsewhere [24-26, 30-32].

The simulation of gas diffusion in membrane oxygenator (equations (2) –(26)) was implemented in MATLAB/SIMULINK environment to calculate volume balance for state variables in blood-gas diffusion with respect to time.

In addition to the process simulation, open loop control study was conducted to determine the controllable factor that influence gas transfer rate in membrane oxygenator. There are many references which stated that pCO\textsubscript{2} is controlled by sweep gas flow rate, while pO\textsubscript{2} is controlled by blood flow rate and oxygen fraction in gas compartment [33-35]. In fact, this determinant factor were also had successfully proven using in both in vitro [36, 37] and in vivo study [38-40] or even through simulation via computer-assisted approach [18]. Thus, the mathematical model used for this present study was simulated using three flow rates of sweep gas, which are 1 L/min, 2 L/min and 4 L/min, while the blood flow rate was kept constant as 2 L/min (Table 1). These flow rates are chosen based on the ratio suggested by The Food and Drug Administration (FDA) in their guidance for cardiopulmonary bypass oxygenator [41].

| Sweep gas flow rate (L/min) | Blood flow rate (L/min) | Qg/Qb ratio |
|----------------------------|-------------------------|-------------|
| 1                          | 2                       | 0.5         |
| 2                          | 2                       | 1.0         |
| 4                          | 2                       | 2.0         |

Next, a statistical test (one-way ANOVA) was performed using two approaches, which were statistical software (Statistical Package for the Social Sciences or SPSS) and MATLAB. This is to ensure the accuracy and validity of our statistical analysis. ANOVA (analysis of variance) is an extension of t-test, which determine equality between several means by comparing their variance among groups relative to variance within groups [42, 43]. Using ANOVA, the mean between two or more samples distribution can be determined if it differ significantly from one another with significant level set as \(\alpha = 0.05\) (95% confidential interval) [44].

Lastly, upon the proof of strong relationship between the gas flow rate and rate of CO\textsubscript{2} clearance, another test was conducted. In this test, two time periods of \(t=60\) second and \(t= 120\) second were isolated, where the gas flow was changed markedly. This is to see how the simulated pCO\textsubscript{2} respond accordingly to the change of sweep gas flow rate.

### 3. Results and discussions

Simulation result of CO\textsubscript{2} transfer across membrane oxygenator is depicted in Figure 2. From the figure, it can be seen that Qg/Qb= 2 has the highest CO\textsubscript{2} removal rate as compared to the other two. The increasing in pCO\textsubscript{2} clearance rate is proportional to the elevation of sweep gas flow rate. This finding agrees with the result reported by [18, 36-38] which advocated that the sweep gas flow rate has effect on measured pCO\textsubscript{2} under constant rate of blood flow.
Figure 2: Simulated pCO₂ for three total sweep gas flow rate

A membrane oxygenator comprised of thousands microporous hollow fiber membranes that allows gas exchange between gas and blood compartment. In most design, sweep gas (commonly O₂) will flows through the inside lumen of the hollow fiber, while blood flows outside the hollow fiber. During extracorporeal circulation, O₂ in sweep gas area will diffuses down its concentration gradient across membrane wall into the blood, while CO₂ will diffuse down its concentration gradient from blood into the sweep gas area, which is then removed when the sweep gas exit the oxygenator [45]. According to Cove et al. [46], there are three major factors that influence the amount of gas transfer in membrane oxygenator, which are concentration gradient, contact time between membrane-blood and membrane diffusion characteristics. Adjusting the sweep gas flow rate will affect the concentration gradient of CO₂ in membrane oxygenator. The increment of sweep gas flow rate depreciates CO₂ accumulation along sweep gas pathway [36]. Consequently, the fractional concentration of CO₂ in sweep gas is reduced, while O₂ fractional concentration is elevated. Increasing in pCO₂ concentration gradient between blood and gas phase then augments CO₂ removal [47]. This explains why the simulated pCO₂ in artery reduced as the sweep gas flow rate increased.

Due to the proven relationship between pCO₂ and sweep gas flow rate, statistical analysis was performed in order to provide statistical evidence between these three flow rates. As tabulated in Table 2, mean for simulated pCO₂ of three flow rates showed great deviation between each other with 36.153 mmHg, 20.070 and 12.052 for rate ratio (Qg/Qb) of 0.5, 1.0 and 2.0, respectively. Results obtained from ANOVA test then proved the significant difference, where p-value= 0.000.

| Qg/Qb | Mean ± standard deviation (pCO₂) | P-Value |
|-------|----------------------------------|---------|
| 0.5   | 35.153 ± 1.831                   |         |
| 1.0   | 20.070 ± 3.699                   | 0.000a  |
| 2.0   | 12.052 ± 5.329                   |         |

*a Significant difference (ANOVA, p<0.05)
The present work was then extended to investigate how the simulated pCO₂ in artery respond to the change of sweep gas flow rate at each step change of flow rate. The behaviour of this model is illustrated in Figure 3. During the initial sweep gas flow rate (1 L/min), initialization process occurred for simulated pCO₂ until it reaches constant at 35.27 mmHg. Then, the sweep gas flow rate was adjusted to 2 L/min for another 60 seconds. In conjunction with this change, the pCO₂ took approximately 15 seconds to become stable at 18.96 mmHg. Finally, the pCO₂ reached back to 35.27 mmHg when the flow rate was set back to 1 L/min. The simulation results agree with the pattern of pCO₂ response reported by Hexamer et al. [19], which the simulated pCO₂ change with respect to the changing of gas flow rate. It also takes some time to achieve steady state.

![Figure 3: Simulated pCO₂ response to step change of total sweep gas flow rate](image)

These findings are great indicators for the application of closed-loop control strategy to membrane oxygenator in controlling pCO₂ in blood. According to Chung et al. [48], CO₂ is more soluble than O₂, hence it diffuses faster than O₂. Due to this advantage, CO₂ is transfers approximately 10 times more efficiently than O₂ [48]. Rapid diffusion of CO₂ that leaves blood will cause hypocapnia (state of reduced CO₂ in blood, where pCO₂ < 35 mmHg at sea level [49]). To prevent this problem, a good automated controller is needed to ensure pCO₂ do not fall below 35 mmHg. This will be investigated in our future work as an extension for this present study.

4. Conclusion
There is significant difference in pCO₂ reading for three sweep gas flow rates (1 L/min, 2 L/min and 4 L/min), and simulation results clearly show that the pCO₂ removal rate has proportional relationship with sweep gas flow rate. Future works shall include various control and advanced strategies of this model for closed loop system in order to obtain the optimal CO₂ partial pressure for blood purification process.

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References

[1] Manap H H and Abdul Wahab A K 2016 Extracorporeal carbon dioxide removal (ECCO2R) in respiratory deficiency and current investigations on its improvement: a review Journal of Artificial Organs 1-10.

[2] Svitek R G and Federspiel W J 2008 A mathematical model to predict CO2 removal in hollow fiber membrane oxygenators Ann Biomed Eng. 36:6 992-1003.

[3] Finney S J 2014 Extracorporeal support for patients with acute respiratory distress syndrome Eur Respir Rev. 23:133 379-89.

[4] Zwischenberger J B et al. 1999 Percutaneous extracorporeal arteriovenous CO2 removal for severe respiratory failure Ann Thorac Surg. 68:1 181-7.

[5] Zwischenberger J B et al. 2001 Percutaneous extracorporeal arteriovenous carbon dioxide removal improves survival in respiratory distress syndrome: A prospective randomized outcomes study in adult sheep The Journal of Thoracic and Cardiovascular Surgery 121:3 542-551.

[6] Lim M W 2006 The history of extracorporeal oxygenators. Anaesthesia 61:10 984-95.

[7] Akhter M 1996 Pulmonary reperfusion injury : A comparison of bubble and membrane oxygenators Indian Journal of Thoracic and Cardiovascular Surgery 12:1 11-14.

[8] Pearson D T and McArdle B 1989 Haemocompatibility of membrane and bubble oxygenators. Perfusion 4:1 9-24.

[9] Medtronic Incorporation 2004 Design and principle of the extracorporeal circuit Techniques in extracorporeal circulation, 4th Edn. Ed Kay P H and Munsch C M (USA: CRC Press).

[10] Vaslef S N et al 1994 Computer-assisted design of an implantable, intrathoracic artificial lung Artif Organs 18:11 813-7.

[11] Weissman M H and Mockros L F 1967 Oxygen transfer to blood flowing in round tubes Journal of the Engineering Mechanics Division 93:6 225-244.

[12] Weissman M H and Mockros L F 1969 Oxygen and carbon dioxide transfer in membrane oxygenators Medical and Biological Engineering 7:2 169-184.

[13] Mockros L F and Leonard R 1985 Compact cross-flow tubular oxygenators Trans Am Soc Artif Intern Organs 31 628-33.

[14] Vaslef S N et al.1994 Use of a mathematical model to predict oxygen transfer rates in hollow fiber membrane oxygenators ASAIO J. 40:4 990-6.

[15] Matsuda N. and Sakai K 2000 Blood flow and oxygen transfer rate of an outside blood flow membrane oxygenator Journal of Membrane Science 170:2 153-158.

[16] Tabesh H et al. 2012 A theoretical model for evaluation of the design of a hollow-fiber membrane oxygenator J Artif Organs 15:4 347-56.

[17] Hormes M et al. 2011 A validated CFD model to predict O(2) and CO(2) transfer within hollow fiber membrane oxygenators Int J Artif Organs 34:3 317-25.

[18] Turri F and Yanagihara J I Computer-Assisted Numerical Analysis for Oxygen and Carbon Dioxide Mass Transfer in Blood Oxygenators Artificial Organs 35:6 579-592.

[19] Hexamer M and Werner J 2003 A mathematical model for the gas transfer in an oxygenator, in IFAC Conference on Modelling and Control in Biomedical System, D. Feng and E. Carson, Editors. 2003: Melbourne, Australia. p. 409-414.

[20] Hill E P, Power G G and Longo L D 1973 Mathematical simulation of pulmonary O2 and CO2 exchange American Journal of Physiology -- Legacy Content 224:4 904-917.

[21] Hill E P, Power G G and Longo L D 1973 A mathematical model of carbon dioxide transfer in the placenta and its interaction with oxygen. American Journal of Physiology -- Legacy Content 224:2 283-299.

[22] Hexamer M, Werner J and Misgeld B J E 2009 Concepts for Simplifying Automatic Blood-Gas Control during Extracorporeal Circulation, in World Congress on Medical Physics and Biomedical Engineering, September 7 - 12, 2009, Munich, Germany:
[23] Hexamer M et al. 2004 Automatic control of the extra-corporal bypass: system analysis, modelling and evaluation of different control modes Biomed Tech (Berl) 49:11 316-21.

[24] Walter M et al. 2012 Closed Loop Physiological ECMO Control, in 5th European Conference of the International Federation for Medical and Biological Engineering: 14–18 September 2011, Budapest, Hungary Ed Jobbágy A (Springer Berlin Heidelberg: Berlin, Heidelberg) p. 319-322.

[25] Walter M et al. 2016 Assistive Control of Extracorporeal Oxygenation Systems, in 12th German Russian Conference on Biomedical Engineering: Suzdal, Russia.

[26] Walter M et al. 2010 Automatisierung und Fehlerdiagnose bei der extrakorporalen Membranoxygenierung (Automation and Fault Supervision for Extracorporeal Membrane Oxygenation Systems) Automatisierungstechnik 58 277-285.

[27] Walter M et al. 2009 Automation of long term extracorporeal oxygenation systems in Control Conference (ECC) European.

[28] Walter M et al. 2010 A physiological model for extracorporeal oxygenation controller design Conf Proc IEEE Eng Med Biol Soc p. 434-7.

[29] Misgeld B J E 2007 Automatic control of the heart-lung machine. Ruhr-University Bochum: Germany.

[30] Kopp R et al. 2016 Automatic Control of Veno-Venous Extracorporeal Lung Assist Artificial Organs 40:10 992-998.

[31] Walter M et al. 2009 Automation of long term extracorporeal oxygenation systems in European Control Conference (ECC).

[32] Walter M et al. 2010 A physiological model for extracorporeal oxygenation controller design 2010 Annual International Conference of the IEEE Engineering in Medicine and Biology.

[33] Gravlee G P 2008 Cardiopulmonary Bypass: Principles and Practice (USA: Lippincott Williams & Wilkins)

[34] Estafanous F G, Barash P G and Reves J G 2001 Cardiac anesthesia: Principles and clinical practice (USA: Lippincott Williams & Wilkins)

[35] Richard C. et al. 2014 Extracorporeal life support for patients with acute respiratory distress syndrome: report of a Consensus Conference Ann Intensive Care 4 15.

[36] Federspiel W J and Haulert B G 1996 Sweep gas flowrate and CO2 exchange in artificial lungs Artificial Organs 20:9 1050-1052.

[37] Hout M S, Hattler B G and Federspiel W J 2000 Validation of a model for flow-dependent carbon dioxide exchange in artificial lungs Artif Organs 24:2 114-8.

[38] Karabulut H et al. 2002 Adjustment of sweep gas flow during cardiopulmonary bypass Perfusion 17:5 353-6.

[39] Park M et al. 2016 Factors associated with blood oxygen partial pressure and carbon dioxide partial pressure regulation during respiratory extracorporeal membrane oxygenation support: data from a swine model Revista Brasileira de Terapia Intensiva 28 11-18.

[40] Schmidt M et al. 2013 Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults Intensive Care Medicine 39:5 838-846.

[41] U.S. Food and Drug Administration 2000 Guidance for Cardiopulmonary Bypass Oxygenators 510(k) Submissions; Final Guidance for Industry and FDA Staff [Retrieved on 5 January 2017]; Available from: http://www.fda.gov/RegulatoryInformation/Guidances/ucm073668.htm.

[42] Ostertagov E and Ostertag O 2013 Methodology and Application of One-way ANOVA. American Journal of Mechanical Engineering 1:7 256-261.

[43] Larson M G 2008 Analysis of Variance Circulation 117:1 115-121.

[44] Manap H H, Tahir N M and Yassin A I M 2011 Statistical analysis of Parkinson disease gait classification using Artificial Neural Network. 2011 IEEE International Symposium on Signal Processing and Information Technology (ISSPIT).
Appendix 1

Table 3: Oxygenator venous input conditions.

| Symbol   | Variable                          | Value       | Unit   |
|----------|-----------------------------------|-------------|--------|
| $[CO_2]_{pl}$ | CO$_2$ concentration (plasma) | 0.00138     | M      |
| $P_{CO_2,pl}$ | CO$_2$ partial pressure (plasma) | 46          | mmHg   |
| $[CO_2]_{rbc}$ | CO$_2$ concentration (red blood cell) | 0.00138     | M      |
| $P_{CO_2,rbc}$ | CO$_2$ partial pressure (red blood cell) | 46          | mmHg   |
| $[HCO_3]_{pl}$ | Bicarbonate concentration (plasma) | 0.0263      | M      |
| $P_{CO_3,pl}$ | Bicarbonate concentration (red blood cell) | 0.0182      | M      |
| $r$ | Ratio (from equation [20]) | 0.69        | -      |
| $[H]_{pl}$ | Hydrogen concentration (plasma) | 42.3 X 10$^{-9}$ | M     |
| $[H]_{rbc}$ | Hydrogen concentration (red blood cell) | 61 X 10$^{-9}$ | M     |
| $[carb]$ | Carbamino concentration | 0.00235 | M      |
| $P_{O_2,g}$ | O$_2$ partial pressure in gas compartment | - | mmHg |
| $P_{CO_2,g}$ | CO$_2$ partial pressure in gas compartment | - | mmHg |
| $Q_b$ | Blood flow rate | 2 | L/min |
| $Q_g$ | Total gas flow rate | Refer table 1 | L/min |
| hct | hematocrit | 0.3 | - |
| $F_{O_2}$ | O$_2$ fraction in mixing gas (sweep gas) | 66% | - |
| $F_{CO_2}$ | CO$_2$ fraction in mixing gas (sweep gas) | 0% | - |

Table 4: Oxygenator parameters.

| Symbol   | Parameter            | Value      | Unit          |
|----------|----------------------|------------|---------------|
| $V_b$    |                      | 0.25       | Liter         |
| $V_g$    |                      | 0.10       | Liter         |
| $P_{bar}$ |                      | 760        | mmHg          |
| $D_{O_2,m}$ |                  | 11.291     | µL/(mmHg sec) |
| $D_{CO_2,m}$ |                | 414.64     | µL/(mmHg sec) |

[45] Federspiel W J and Henchir K 2008 Lung, Artificial: Basic Principles and Current Applications *Encyclopedia of Biomaterials and Biomedical Engineering, Second Edition (Online Version)* (USA: CRC Press) p1661-1672.

[46] Cove M E, MacLaren G, Federspiel W J and Kellum J A 2012 Crit Care 16 232.

[47] Scaravilli V, Zanella A, Sangalli F and Patroniti N 2014 Basic aspect of physiology during ECMO support, eds. F. Sangalli, A. Pesenti, N. Patroniti *ECMO-Extracorporeal Life Support in Adults* (Italy: Springer-Verlag)

[48] Chung M, Shiloh A L and Carlese A 2014 Monitoring of the Adult Patient on Venoarterial Extracorporeal Membrane Oxygenation *The Scientific World Journal* 2014 10.

[49] Solano C. M E., Ichel Castillo B., Maria C. Niño de Mejia 2012 Hypocapnia in Neuroanesthesia: Current Situation. *Colombian Journal of Anesthesiology* 40:2, 137-144.
Table 5: Biophysical and biochemical parameters.

| Symbol | Parameter                                      | Value       | Unit          |
|--------|-----------------------------------------------|-------------|---------------|
| $\alpha_{O2}$ | O$_2$ solubility                             | 1.35 X 10$^{-6}$ | M/mmHg       |
| $\alpha_{CO2}$ | CO$_2$ solubility                           | 3 X 10$^{-5}$ | M/mmHg       |
| $\beta_{pl}$ | Plasma buffer capacity                      | 6 X 10$^{-3}$ | mol/pH       |
| $\beta_{rbc}$ | Red blood cell buffer capacity              | 57.7 X 10$^{-3}$ | mol/pH     |
| $cat$ | Carbonic anhydrase catalysis factor        | 13000       | -             |
| $[Hb]_{rbc}$ | Red blood cell haemoglobin concentration    | 20.7 X 10$^{-1}$ | M             |
| $k$ | Carbonic acid dissociation equilibrium constant | 5.5 X 10$^{-4}$ | M             |
| $k_u$ | CO$_2$ hydration reaction forward rate constant | 0.12 | sec$^{-1}$    |
| $k_v$ | CO$_2$ hydration reaction reverse rate constant | 89 | sec$^{-1}$   |
| $k_a$ | CO$_2$-hemoglobin reaction forward constant  | 5000 | M/sec$^{-1}$ |
| $k_c$ | Carbamate ionisation constant               | 2.4 X 10$^{-3}$ | -             |
| $k_{so}$ | Oxygenated haemoglobin amino group ionisation constant | 8.4 X 10$^{-9}$ | M             |
| $k_{sr}$ | Reduced haemoglobin amino group ionisation constant | 7.2 X 10$^{-8}$ | M             |
| $\tau_{rbc}$ | Half-time of red cell membrane diffusion    | 0.001 | sec       |
| $\tau_{HCO3}$ | Half-time of red blood cell membrane chloride shift | 0.2 | sec       |