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Estimating the Impact of Peritoneal Perfluorocarbon Perfusion on Carbon Dioxide Transport Dynamics in a Laboratory Animal

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***Abstract*— This paper identifies a state-space model of the impact of the peritoneal perfusion of an oxygenated perfluorocarbon (PFC) on the dynamics of carbon dioxide (CO_2) transport in a large laboratory animal. Previous research shows that such perfusion has the potential to enable the peritoneal cavity to serve as a "third lung" that supplements oxygenation during hypoxia. However, the effect of this potential treatment modality on CO_2 transport dynamics remains relatively unexplored. The paper addresses this gap by: *(i)* proposing a three-compartment model of CO_2 transport dynamics; *(ii)* utilizing time scale separation to simplify it into a residualized single-compartment model; and *(iii)* parameterizing the model using experimental data. Two experimental datasets are used for parameterization, involving the use of reduced minute ventilation to induce hypercarbia both *(i)* with and *(ii)* without PFC perfusion. Fisher analysis is used for quantifying the resulting model parameter uncertainties. The outcomes of this analysis strongly suggest a positive impact of perfusion on CO_2 clearance, with further validation experiments planned as future work.**

I. Introduction

This paper examines the impact of the perfusion (or circulation) of an oxygenated perfluorocarbon (PFC) through the peritoneal cavity of a hypercarbic large animal on the dynamics of carbon dioxide (CO_2) transport. The paper is motivated by the need to provide life-saving support to patients with respiratory failure. Even before the COVID-19 pandemic, more than 100,000 patients suffering from respiratory failure due to acute respiratory distress syndrome (ARDS) required hospitalization annually in the U.S. alone [1]. Respiratory failure occurs when a patient is unable to adequately take up enough oxygen and/or clear enough CO_2. If delivering supplemental oxygen to a spontaneously breathing patient does not provide adequate support, then the next step is typically to intubate the patient, such that a mechanical ventilator can supplement their respiration by assisting them with positive pressure breaths. Intubation allows for both higher levels of inspired oxygen, to treat hypoxia, and increased minute ventilation, to treat hypercarbia. Unfortunately, positive pressure ventilation can trigger a cascade of further lung damage, leading to ventilator induced lung injury (VILI) [2], [3]. If a patient exceeds the support that can be provided by a mechanical ventilator, then the only current modality for additional support is extra-corporeal membrane oxygenation (ECMO). In this technique, blood is withdrawn from the body, externally oxygenated, and pumped back into the patient. Unfortunately, ECMO is a scarce, costly resource that requires high degrees of expertise, both for initiation and the subsequent continuous monitoring. Also, ECMO is accompanied by a host of complications and exclusion criteria that render it a nonviable option for many patients, even if they are in a facility where it is available [4].

This paper is motivated by a third potential treatment modality for patients with respiratory failure, namely, the circulation of an oxygenated PFC through the patient's abdominal cavity. PFCs are dense, inert liquids offering extraordinary O_2 and CO_2 solubility levels [5], [6]. The literature already examines the use of PFCs as blood substitutes and/or oxygen carriers in medical applications [7], [8]. The literature also examines *liquid ventilation*, where the lungs are flooded with an oxygenated PFC in an attempt to facilitate gas transport [9]. In contrast to liquid ventilation, perfusing an oxygenated PFC through the abdominal cavity allows this cavity to potentially be used as a "third lung" that transports oxygen to the patient through mechanisms such as diffusion. This helps rest the lungs: an important goal given risks such as VILI.

Previous research in the literature shows that the "third lung" approach can be effective in supplementing O_2 transport in both laboratory rabbits [10] and pigs [11]. More recent research explores the enteral perfusion of oxygenated PFCs as an alternative to peritoneal perfusion [12], as well as alternative O_2 carriers for peritoneal oxygenation in laboratory rats [13]. Finally, the literature examines gas and solute transport dynamics in both the cardiopulmonary and peritoneal tissue systems [14], [15], [16], [17], [18], [19], [20]. This includes the development of experimentally-validated, physics-based state-space models of cardiopulmonary CO_2 transport dynamics, as well as the use of these models for model-based mechanical ventilator control [21], [22], [23].

The above literature, while encouraging, does not provide an experimentally-parameterized, control-oriented model of

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the system-level impact of the "third lung" intervention on CO_2 transport in large laboratory animals. Building blocks for such a model already exist in the literature, including models of cardiopulmonary CO_2 transport and detailed models of gas transport within the tissue lining of the peritoneal cavity. However, to the best of the authors' knowledge, the literature lacks an experimentally-parameterized model capturing the interplay and coupling between the dynamics of these separate compartments. Such a model can potentially enable future research on the model-based control of the "third lung" intervention in both large animals and (eventually) human patients.

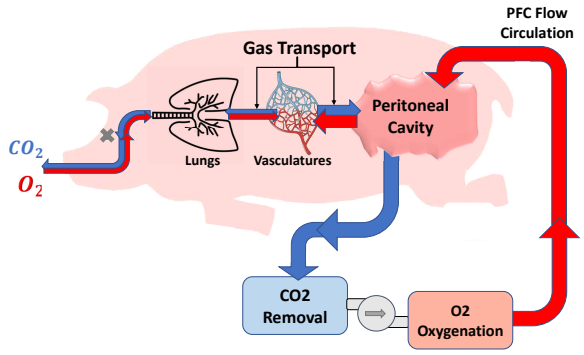

Fig. 1: Third lung schematic

Fig. (1) provides a high-level schematic of a setup built by the authors to perform experimental studies on the "third lung" concept, described in more depth in a separate article [24]. The setup is designed for perfusing a mix of cis- and trans- perfluorodecalin, a well-studied PFC, through the abdomens of laboratory swine. Neat (i.e., pure) perfluorodecalin is used, since the intent of perfusion is the facilitation of gas transport, in contrast to experiments where perfluorodecalin is used as a blood substitute and emulsification is therefore needed. The setup first draws PFC from the animal using active suction, then removes CO_2 from the PFC, oxygenates it, and finally returns it to the animal's abdomen using a peristaltic pump. The success of the third lung intervention depends on the degree to which O_2 and CO_2 diffuse between the body's vasculature and the PFC inside the peritoneal cavity.

Four IACUC-approved animal experiments have been performed to date using the above setup. The experiments focused on different aspects of the third lung intervention, including O_2/CO_2 transport, peritoneal cavity pressure dynamics, and setup/technology troubleshooting. This paper presents preliminary results from a "deep dive" into the dynamics of CO_2 transport during the second of these four experiments. This is the only experiment that *(i)* examined hypercarbia and *(ii)* did not suffer from a documented/proven leakage in the mechanical ventilator used for inducing hypercabia. Minute ventilation was deliberately manipulated to induce hypercarbia twice during this experiment: once with and once without PFC perfusion. The remainder of this paper focuses on developing and fitting a state-space model to these two hypercarbia episodes/datasets. Future work will pursue additional animal experiments, one goal being the continued validation and refinement of the state-space model presented here for multiple perfusion episodes and/or animals.

The remainder of this paper is organized as follows. Section II presents a simple model of CO_2 transport dynamics in the laboratory animal. Section III parameterizes this model from experimental data. Section IV performs uncertainty quantification on the resulting parameter estimates. Finally, section V summarizes the paper's conclusions.

II. Proposed CO_2 Transport Model

This section models the dynamics of CO_2 transport using a three-compartment representation of: *(i)* the lungs, *(ii)* the vasculature, and *(iii)* the PFC stored in the peritoneal cavity. Fig. (2) shows these compartments and their connections. The symbols V_l, V_v, and V_p denote the effective volumes of the lungs, vasculature, and peritoneal compartments, respectively (in liters). Moreover, the symbols P_l, P_v, and P_p denote the partial pressures of CO_2 in these three compartments, respectively (in $mmHg$). The model has four input variables, namely, the instantaneous volumetric flowrates of inspired air, $u_1(t)$, exhaled air, $u_1'(t)$, PFC inflow into the animal, $u_2(t)$, and PFC drainage out of the animal, $u_2'(t)$, in liters per minute. Moreover, the model has five state variables, namely: the partial pressures of CO_2 in all three compartments plus the time-varying volumes of the lungs and PFC storage compartment. Given these definitions, we propose the following fifth-order, three-compartment state-space model:

$$\begin{aligned}
\frac{dV_l}{dt} &= u_1 - u_1', \frac{dV_p}{dt} = u_2 - u_2' \\
\frac{d}{dt}\left(\frac{P_l}{R'T}V_l\right) &= -u_1'\frac{P_l}{R'T} + k_{lv}(P_v - P_l) \\
\frac{d}{dt}(P_v H_v V_v) &= k_{lv}(P_l - P_v) + k_{vp}(P_p - P_v) + w \\
\frac{d}{dt}(P_p H_p V_p) &= k_{vp}(P_v - P_p) - u_2' P_p H_p
\end{aligned} \tag{1}$$

The above model neglects the concentrations of CO_2 in both inhaled air and PFC inflow. The symbol R' denotes the specific gas constant for CO_2, and T denotes CO_2 gas temperature (approximated as constant in time). Therefore, by the ideal gas law, $P_l/R'T$ is the mass of exhaled CO_2 per unit volume of exhaled breath (i.e., a "density" term). The product of this density with the lung volume quantifies the mass of CO_2 in the lung compartment. The rate of change of this mass is governed by two phenomena, namely: advection to exhaled breaths and transport between the lungs and vasculature. This transport is assumed to be a linear function of the difference in partial pressure between these two compartments, with some proportionality constant k_{lv}. Similarly, a proportionality constant k_{vp} governs the rate of diffusive mass transport between the vasculature and the peritoneal cavity. The coefficients H_v and H_p are effective Henry's law constants for the vasculature and peritoneal cavity compartments (i.e., blood and PFC), respectively, and

$w(t)$ is a metabolic CO_2 mass generation rate, assumed constant.

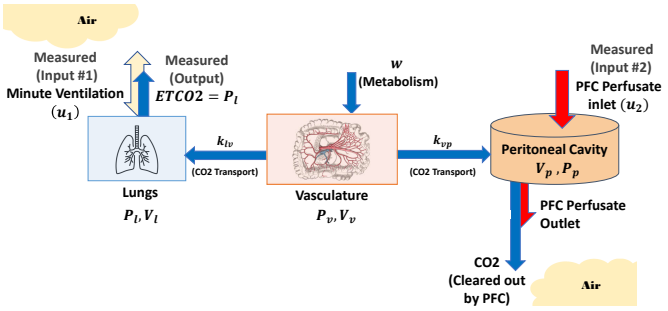

Fig. 2: A three-compartment model for representing the CO_2 removal dynamics.

To fit the above model to animal test data, one must estimate its unknown constant parameters plus 5 initial states. Model order reduction can help simplify this exercise. Towards this goal, we note that the focus of this work is on the slow evolution of CO_2 gas concentrations in the above three compartments, over the course of minutes (i.e., hundreds of seconds), as a result of perfusion. Considering a typical breathing frequency of 15-20 breaths per minute, we conjecture that the frequency with which real-time lung volume, $V_l(t)$, changes is much faster than the time scale of interest. Therefore, we approximate $V_l(t)$ as being constant, thereby eliminating the state equation for $V_l(t)$ and concluding that $u_1(t) \approx u_1'(t)$. A similar argument can be made regarding the perfused volume of PFC in the peritoneal compartment, which can be as small as 2-3 liters and is often replenished as fast as 4-5 liters per minute or more. Therefore, we approximate $V_p(t)$ as constant, implying that $u_2(t) \approx u_2'(t)$ and simplify the state-space model to:

$$\begin{aligned}
\frac{d}{dt}\left(\frac{P_l}{R'T}V_l\right) &= -u_1\frac{P_l}{R'T} + k_{lv}(P_v - P_l) \\
\frac{d}{dt}\left(P_v H_v V_v\right) &= k_{lv}(P_l - P_v) + k_{vp}(P_p - P_v) + w \\
\frac{d}{dt}\left(P_p H_p V_p\right) &= k_{vp}(P_v - P_p) - u_2 P_p H_p
\end{aligned} \tag{2}$$

Further model simplification is possible through the following time scale separation argument. Consider the dynamics of the partial pressure of CO_2 in the lung compartment:

$$\frac{dP_l}{dt} = \left[-\left(\frac{V_1}{u_1}\right)^{-1} - \frac{k_{lv}R'T}{V_l}\right]P_l + \frac{k_{lv}R'T}{V_l}P_v \tag{3}$$

The term V_l/u_1 is the ratio of lung volume to inhalation rate (or, equivalently, minute ventilation). This term represents a "replenishment time" for the lungs. In the limit as this term approaches zero, it dominates the dynamics of P_l. Moreover, the time constant associated with those dynamics decreases to the point where one can *residualize* the dynamics of P_l by examining them at equilibrium:

$$0 \approx -u_1\frac{P_l}{R'T} + k_{lv}(P_v - P_l) \tag{4}$$

Solving the above for P_l gives:

$$P_l = \frac{k_{lv}}{k_{lv} + u_1/R'T}P_v \tag{5}$$

Finally, plugging the above expression into the state equation for P_v gives:

$$\dot{P}_v H_v V_v = -k_{lv}\frac{u_1/R'T}{k_{lv} + u_1/R'T}P_v + k_{vp}(P_p - P_v) + w \tag{6}$$

The term $k_{lv}\frac{u_1/R'T}{k_{lv}+u_1/R'T}P_v$ represents diffusion-based CO_2 mass transport from the vasculature to the lungs, assuming that the latter compartment's dynamics are infinitely fast. The structure of this term reveals a diminishing gas transport benefit associated with higher breathing rates. For small values of u_1, CO_2 mass transport increases approximately linearly with u_1. However, for values of u_1 much larger than $k_{lv}R'T$, mass transport is governed predominantly by the constant k_{lv}. This observation makes intuitive sense: it suggests that faster breathing benefits CO_2 transport only up to the point where diffusion-based transport between the vasculature and the lungs becomes the rate-limiting transport phenomenon. Applying a similar residualization to the peritoneal cavity's CO_2 dynamics simplifies the above state-space model further, to a first-order model:

$$\dot{P}_v H_v V_v = -k_{lv}\frac{u_1/R'T}{k_{lv} + u_1/R'T}P_v - k_{vp}\frac{u_2 H_p}{k_{vp} + u_2 H_p}P_v + w \tag{7}$$

The above state equation predicts that higher PFC perfusion flowrates will improve mass transport, at least up to a point of diminishing returns where u_2 is much larger than $k_{pv}R'T$. This creates motivation for pushing PFC perfusion flowrates to high values. Unfortunately, doing so comes with the risk of elevated peritoneal cavity pressures, and possibly abdominal compartment syndrome. Taking this into account, this paper makes the conservative assumption that the PFC perfusion flowrate, u_2, is sufficiently small to the point where $u_2 H_p$ may potentially be much smaller than k_{vp}. This makes it possible to simplify the above state equation as follows:

$$\dot{P}_v H_v V_v = -k_{lv}\frac{u_1/R'T}{k_{lv} + u_1/R'T}P_v - u_2 H_p P_v + w \tag{8}$$

This concludes the paper's effort to model "third lung" CO_2 gas transport dynamics. Lumping this model's parameters allows it to be rewritten in terms of the following state and output equations:

$$\dot{P}_v = -a_1\frac{u_1}{a_2 + u_1}P_v - a_3 u_2 P_v + a_4, P_l = \frac{1}{1 + u_1/a_2}P_v \tag{9}$$

where the output equation provides a quasi-steady expression for the P_l in terms of P_v, and the model's lumped-parameter constants are given by: $a_1 = \frac{k_{lv}}{H_v V_v}$, $a_2 = k_{lv}R'T$, $a_3 = \frac{H_p}{H_v V_v}$, and $a_4 = \frac{w}{H_v V_v}$.

III. Parameterizing CO_2 Transport Dynamics

Four "third lung" animal experiments have been performed to date. A companion paper describes the setup used in these experiments, emphasizing its data acquisition and control capabilities [24]. Two of the animal experiments involved reducing the respiration rate provided by a mechanical ventilator to adult pigs, rendering them hypercarbic. Tests performed on the mechanical ventilator, following one of these hypercarbia experiments, uncovered significant leakage in the ventilator. The main goal of this section is to fit the proposed state-space model to the remaining hypercabia experiment, the second animal experiment of four to date. Future research will involve efforts to validate this modeling work further, using additional animal experiments.

Figs. (3) and (4) show the results of the above parameterization exercise. The top plot in each figure is the animal's real-time minute ventilation (i.e., inhalation/exhalation). The middle plot in each figure is the volumetric flowrate at which PFC is supplied to the animal. Fig. (3) corresponds to a hypercarbia attempt with no perfusion, whereas Fig. (4) corresponds to a perfusion attempt. The bottom plot in each figure compares the measured animal end-tidal CO_2, or ETCO2 (reflecting the amount of carbon dioxide in exhaled air) to the predictions of the proposed model. The model's parameters are obtained by solving a single optimization problem covering both hypercarbia episodes simultaneously. This problem can be written as follows:

$$\begin{aligned} \min_{a_{1,..,4},\hat{P}_v(T_1),\hat{P}_v(T_2)} & \sum_k [y_m(t_k) - \hat{y}(t_k)]^2 \\ s.t.: \dot{\hat{P}}_v &= -a_1 \frac{u_1}{a_2 + u_1} \hat{P}_v - a_3 u_2 \hat{P}_v + a_4 \\ \hat{y}(t) &= \frac{1}{1 + u_1(t)/a_2} \hat{P}_v(t) \end{aligned} \tag{10}$$

The optimization objective in the above problem statement is to minimize the sum of the squared ETCO2 prediction errors over all moments in time, for both of the above hypercarbia episodes. The index k refers to different moments in time when ETCO2 is sampled experimentally, and the ranges of values of k are selected to correspond to the two hypercarbia episodes. Optimization proceeds with respect to the initial conditions for the partial pressure of CO_2 in the vasculature compartment for both hypercarbia episodes, as well as the parameters a_1, a_2, a_3, a_4. The proposed gas exchange model is applied as a dynamic constraint on the optimization problem. Because of the diminishing impact of minute ventilation on gas exchange, as well as the bilinearity of the PFC flowrate-driven CO_2 clearance dynamics, this is a nonlinear, nonconvex optimal estimation problem. A particle swarm algorithm is used for solving this problem, leading to the curve fits in Figs. (3,4).

The curve fits in Figs. (3,4) correspond to the following parameter values: $a_1 = 5.6 \times 10^{-3} [\frac{Kg.mmHg}{mol.min}]$, $a_2 = 7.89 [\frac{J.L}{mol.min}]$, $a_3 = 1.55 \times 10^{-4} [\frac{Kg.mmHg}{J.L}]$, and $a_4 = 3.1 \times 10^{-2} [mmHg/min]$. Moreover, the optimal initial partial pressures of CO_2 in the vasculature compartment, corresponding

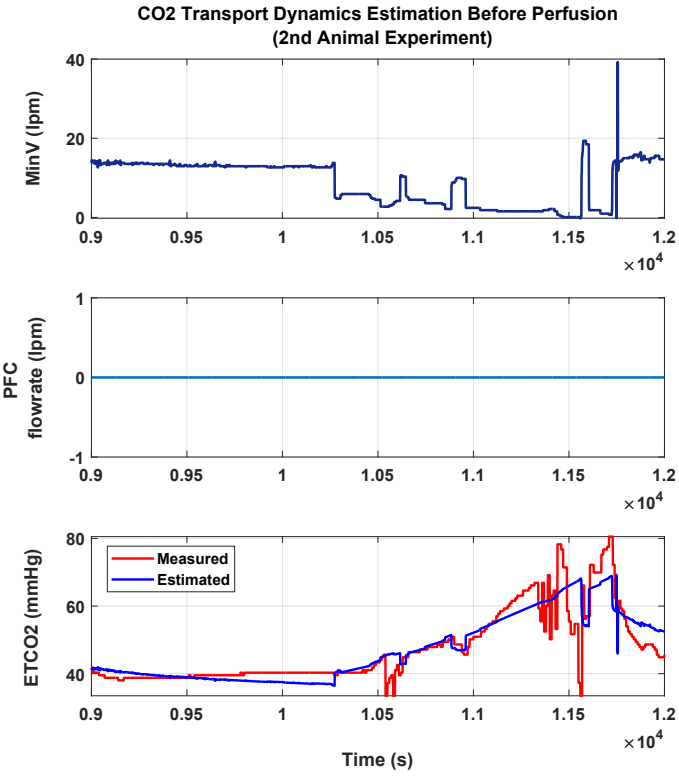

Fig. 3: Estimated vs. measured $ETCO_2$ without perfusion.

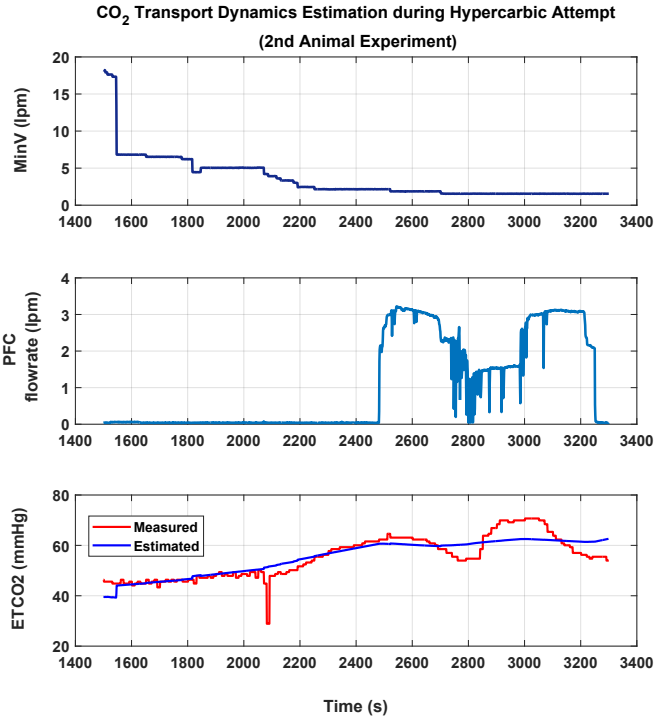

Fig. 4: Estimated vs. measured $ETCO_2$ with perfusion

to these curve fits, are 48.9 and 48.7 mmHg for the episodes without and with perfusion, respectively. All of these parameter values are interior-optimal, in the sense that they are not governed by *a priori* parameter estimation bounds.

Perhaps the most important of the above parameter/state estimates, for the purposes of this paper, is the estimate of a_3. This estimate suggests that for each additional liter per minute of PFC perfusate flow, the test animal is able to reduce its vasculature compartment's partial pressure of CO_2 by 1.55×10^{-4} mmHg per second per mmHg of this partial pressure. For example, if the partial pressure of CO_2 in the vasculature compartment is 45 mmHg, and if PFC is perfused through the animal at 3 liters per minute, then perfusion will reduce this partial pressure by $3 \times 45 \times 1.55 \times 10^{-4} \times 60 \approx 1.26$ mmHg per minute. Comparing this number to $60 \times a_4 = 60 \times 3.1 \times 10^{-2} \approx 1.86$ mmHg per minute suggests that PFC perfusion, alone, at a volumetric flow rate of 3 liters per minute, is potentially capable of removing approximately 68% of all the CO_2 generated by the test animal's metabolism during perfusion, assuming a CO_2 partial pressure of 45mmHg in the vasculature compartment.

The above result, while encouraging, must be taken with a grain of salt. Uncertainty quantification tools such as Fisher information analysis can help provide confidence bounds on this result, as discussed below.

IV. Identifiability analysis for CO_2 transport dynamics

This section uses Fisher information analysis to obtain approximate estimates of the estimation errors associated with the previous section. Fig. (5) shows a histogram of the ETCO2 prediction errors - or residuals - for the two hypercarbia episodes examined in this paper. Moreover, Fig. (6) shows the autocorrelations of these residuals. Both figures are generated for a sampling time step of 10 seconds, corresponding to the communication time step of the capnograph used in the animal experiments. Together, these two figures suggest that the ETCO2 prediction residuals may not be independent, identically distributed (iid). One possible explanation for this observation may be that the ETCO2 measurement noise itself is not iid. Another possible explanation may be that the simple model used in this article for predicting ETCO2 does not necessarily capture the full dynamics of test animal gas transport. Examples of potentially important unmodeled dynamics include advection-driven transport time delays between the lungs, vasculature, and peritoneal compartments. In addition to these observations, it is important to note that the nonlinearity of the assumed ETCO2 gas transport dynamics in terms of the underlying estimation parameters implies that Fisher information analysis will furnish a local - as opposed to global - quantification of parameter identifiability.

With the above important caveats in mind, the proposed gas transport dynamics model was simulated for perturbed values of all six unknown model parameters and initial conditions. The magnitude of the perturbation was set to 0.1% of the nominal value of each parameter, leading to

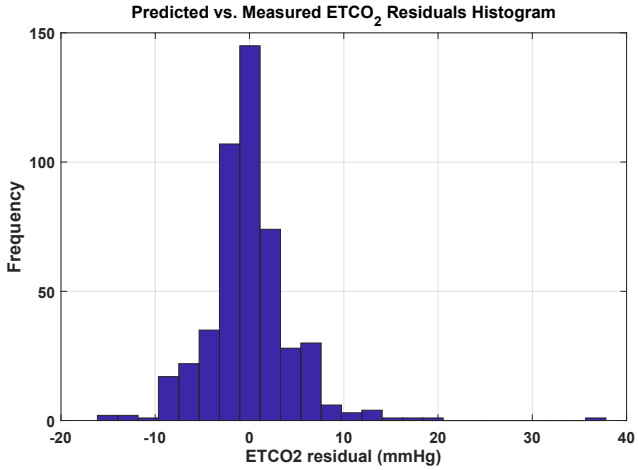

Fig. 5: Histogram of ETCO2 residuals

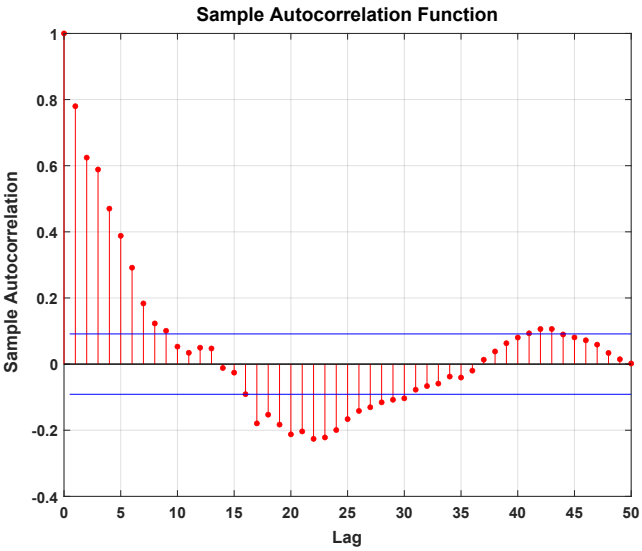

Fig. 6: Auto-correlation of ETCO2

a numerical computation of Fisher information. Based on this numerical computation, the $\pm 3\sigma$ Cramér-Rao estimation bounds on the model's parameters were found to be as shown in Table (I).

TABLE I: CO_2 dynamics lumped parameters estimation

Parameters	Values [Unit]
a_1	$5.6\times10^{-3} \pm 6.15 \times 10^{-4}$ $[\frac{Kg.mmHg}{mol.min}]$
a_2	7.89 ± 0.78 $[\frac{J.L}{mol.min}]$
a_3	$1.55\times10^{-4} \pm 1.28 \times 10^{-5}$ $[\frac{Kg.mmHg}{J.L}]$
a_4	$3.1\times10^{-2} \pm 1.3 \times 10^{-3}$ $[mmHg/min]$

The above estimation error bounds are encouraging, in

the sense that they suggest that the peritoneal perfusion of oxygenated PFC is indeed potentially effective as a mechanism for CO_2 clearance. In particular, the fact that the $\pm 3\sigma$ bounds on the parameter a_3 are both positive suggests that such perfusion is successful in CO_2 clearance, even when parameter estimation errors are accounted for through Fisher uncertainty quantification. Further validation of this conclusion, through additional animal experiments, is both important and warranted, given the outcomes of this paper.

V. Conclusions

This paper examines the modeling, parameterization, and identifiability analysis for the underlying CO_2 gas transport in a novel extra-pulmonary ventilation experiment. The paper provides experimental insights into a primary function of this ventilator, namely, CO_2 removal. Based on the results of this study, CO_2 concentration is indeed diminishing as a result of peritoneal PFC perfusion in a hypercarbic test animal. Moreover, the uncertainty quantification of the estimated parameters in this paper illustrates the accuracy with which the parameters are identified. Future work will focus on further validation of these outcomes, recognizing the importance of such validation using datasets not used for modeling fitting, both for multiple animals and multiple perfusion events per animal. One potentially valuable future focus area is the development of novel sensors capable of directly measuring dissolved CO_2 concentration in PFC.

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References

[1] E. Eworuke, J. M. Major, and L. I. G. McClain, "National incidence rates for acute respiratory distress syndrome (ards) and ards cause-specific factors in the united states (2006–2014)," *Journal of critical care*, vol. 47, pp. 192–197, 2018.

[2] A. Anzueto, F. Frutos-Vivar, A. Esteban, I. Alía, L. Brochard, T. Stewart, S. Benito, M. J. Tobin, J. Elizalde, F. Palizas, *et al.*, "Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients," *Intensive care medicine*, vol. 30, no. 4, pp. 612–619, 2004.

[3] S. F. Marasco, G. Lukas, M. McDonald, J. McMillan, and B. Ihle, "Review of ecmo (extra corporeal membrane oxygenation) support in critically ill adult patients," *Heart, Lung and Circulation*, vol. 17, pp. S41–S47, 2008.

[4] D. A. Murphy, L. E. Hockings, R. K. Andrews, C. Aubron, E. E. Gardiner, V. A. Pellegrino, and A. K. Davis, "Extracorporeal membrane oxygenation—hemostatic complications," *Transfusion medicine reviews*, vol. 29, no. 2, pp. 90–101, 2015.

[5] J. G. Riess, "Understanding the fundamentals of perfluorocarbons and perfluorocarbon emulsions relevant to in vivo oxygen delivery," *Artificial cells, blood substitutes, and biotechnology*, vol. 33, no. 1, pp. 47–63, 2005.

[6] C. I. Castro and J. C. Briceno, "Perfluorocarbon-based oxygen carriers: review of products and trials," *Artificial organs*, vol. 34, no. 8, pp. 622–634, 2010.

[7] G. P. Biro, P. Blais, and A. L. Rosen, "Perfluorocarbon blood substitutes," *Critical reviews in oncology/hematology*, vol. 6, no. 4, pp. 311–374, 1987.

[8] S. G. Kramer, D. Hwang, G. A. Peyman, J. A. Schulman, and B. Sullivan, "Perfluorocarbon liquids in ophthalmology," *Survey of ophthalmology*, vol. 39, no. 5, pp. 375–395, 1995.

[9] M. R. Wolfson and T. H. Shaffer, "Liquid ventilation: an adjunct for respiratory management," *Pediatric Anesthesia*, vol. 14, no. 1, pp. 15–23, 2004.

[10] N. Faithfull, J. Klein, H. Vanderzee, and P. Salt, "Whole body oxygenation using intraperitoneal perfusion of fluorocarbons," *British journal of anaesthesia*, vol. 56, no. 8, pp. 867–872, 1984.

[11] S. R. Carr, J. P. Cantor, A. S. Rao, T. V. Lakshman, J. E. Collins, and J. S. Friedberg, "Peritoneal perfusion with oxygenated perfluorocarbon augments systemic oxygenation," *Chest*, vol. 130, no. 2, pp. 402–411, 2006.

[12] R. Okabe, T. F. Chen-Yoshikawa, Y. Yoneyama, Y. Yokoyama, S. Tanaka, A. Yoshizawa, W. L. Thompson, G. Kannan, E. Kobayashi, H. Date, *et al.*, "Mammalian enteral ventilation ameliorates respiratory failure," *Med*, vol. 2, no. 6, pp. 773–783, 2021.

[13] N. Legband, L. Hatoum, A. Thomas, C. Kreikemeier-Bower, D. Hostetler, K. Buesing, M. Borden, and B. Terry, "Peritoneal membrane oxygenation therapy for rats with acute respiratory distress syndrome," *Journal of Medical Devices*, vol. 10, no. 2, 2016.

[14] A. Ben-Tal, "Simplified models for gas exchange in the human lungs," *Journal of theoretical biology*, vol. 238, no. 2, pp. 474–495, 2006.

[15] M. Khoo, R. E. Kronauer, K. P. Strohl, and A. S. Slutsky, "Factors inducing periodic breathing in humans: a general model," *Journal of applied physiology*, vol. 53, no. 3, pp. 644–659, 1982.

[16] M. Khoo and R. Kronauer, "Estimation of cardiopulmonary parameters using quasi-optimal inputs," in *1983 American Control Conference*. IEEE, 1983, pp. 46–51.

[17] J. J. Batzel, F. Kappel, D. Schneditz, and H. T. Tran, *Cardiovascular and respiratory systems: modeling, analysis, and control*. SIAM, 2007.

[18] A. ElHefnawy, G. M. Saidel, and E. N. Bruce, "co_2 control of the respiratory system: plant dynamics and stability analysis," *Annals of biomedical engineering*, vol. 16, no. 5, pp. 445–461, 1988.

[19] L. Hatoum, "Diffusion modeling and device development for peritoneal membrane oxygenation," 2016.

[20] E. Seames, J. Moncrief, and R. Popovich, "A distributed model of fluid and mass transfer in peritoneal dialysis," *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 258, no. 4, pp. R958–R972, 1990.

[21] C.-S. Kim, J. M. Ansermino, and J.-O. Hahn, "A comparative data-based modeling study on respiratory co_2 gas exchange during mechanical ventilation," *Frontiers in bioengineering and biotechnology*, vol. 4, p. 8, 2016.

[22] M. Schmal, J. Haueisen, G. Männel, P. Rostalski, M. Kircher, T. Bluth, M. G. de Abreu, and B. Stender, "Robust predictive control for respiratory co_2 gas removal in closed-loop mechanical ventilation: An in-silico study," *Current Directions in Biomedical Engineering*, vol. 6, no. 3, pp. 311–314, 2020.

[23] J.-O. Hahn, G. A. Dumont, and J. M. Ansermino, "System identification and closed-loop control of end-tidal co_2 in mechanically ventilated patients," *IEEE Transactions on Information Technology in Biomedicine*, vol. 16, no. 6, pp. 1176–1184, 2012.

[24] M. Doosthosseini, K. R. Aroom, M. Aroom, M. Culligan, W. Naselsky, C. Thamire, H. W. Haslach Jr, S. A. Roller, J. R. Hughen, J. S. Friedberg, *et al.*, "Monitoring and control system development and experimental validation for a novel extrapulmonary respiratory support setup," *arXiv preprint arXiv:2107.02902*, 2021.