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Modeling and Experimental Identification of Airway Oxygen Transport Dynamics During Mechanical Ventilation

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Abstract: This paper examines the problem of modeling the dynamics of oxygen transport through the endotracheal tube of a mechanical ventilator. Such modeling can be potentially valuable for ventilator control, patient monitoring, and estimating airway oxygen transport during experimental studies on hypoxia. The paper presents an airway sensing package that provides collocated measurements of oxygen concentration and total gas flow rate. In theory, multiplying these two measurements can provide an estimate of tracheal oxygen flow rate. Unfortunately, substantial differences in dynamics between the above two sensors necessitate a more sophisticated modeling and estimation approach. Towards this goal, the paper presents a dynamic model of advective tracheal oxygen transport that accounts for measurement dynamics and delays. Parameters of this model are estimated from a hypoxia experiment on a Yorkshire swine, leading to good fitting accuracy for oxygen concentration measurements.

Keywords: Mechanical ventilation; system identification; advection modeling.

1. INTRODUCTION

This paper examines the problem of modeling the dynamics of oxygen flow in a mechanical ventilator's endotracheal (or "breathing") tube. This problem is motivated by the grand challenge of providing life support for respiratory failure patients. The COVID-19 pandemic brought this challenge to the forefront of societal awareness by causing millions of deaths worldwide (Taylor (2022)). Moreover, even before the pandemic, more than 1.1 million respiratory failure patients were hospitalized annually in the U.S. alone, with the average hospitalization lasting 10 days and costing more than $150,000 (Kempker et al. (2020)).

Mechanical ventilation is the most prevalent respiratory support technology today. It involves supplying inhaled gas at elevated pressures and oxygen concentrations compared to spontaneous breathing. Unfortunately, such aggressive *pulmonary* support has the potential to cause *ventilator-induced lung injury* (VILI): a condition that worsens ventilation effectiveness, and can be life threatening (Anzueto et al. (2004)). When mechanical ventilation is no longer viable due to VILI, severe lung parenchyma disease, etc., the only alternative is to support the patient in an *extra-pulmonary* manner. This can be achieved through *extra-corporeal membrane oxygenation* (ECMO), where blood is oxygenated using a gas exchange membrane extracorporeally, then returned to the patient (Marasco et al. (2008)). ECMO is highly effective, but it comes with significant complexity, cost, and safety risks (Murphy et al. (2015)). These factors have motivated research on extra-pulmonary interventions where oxygen carriers are circulated through a body cavity such as the abdomen or large intestine. The idea is to enable diffusion-based oxygen transport into the bloodstream, thereby employing the above body cavities as "third lungs" (Carr et al. (2006); Feshitan et al. (2014); Okabe et al. (2021)).

Modeling the dynamics of endotracheal oxygen transport is important because it can enable: *(i)* mechanical ventilator control; *(ii)* patient monitoring; and *(iii)* pulmonary oxygen intake estimation. Estimating pulmonary oxygen intake is particularly valuable during laboratory animal experiments on respiratory failure. One possible protocol for such experiments involves using a mechanical ventilator to induce either *hypoxia* (i.e., oxygen deprivation) or *hypercarbia* (i.e., excessive CO_2 in the bloodstream) by curtailing either inspired oxygen concentration or ventilation rate, respectively (KadkhodaeiElyaderani et al. (2023)). Researchers can then examine the physiological impacts of hypoxia/hypercarbia, as well as the degree to which different extra-pulmonary life support technologies can help mitigate respiratory failure.

In theory, estimating the rate of endotracheal oxygen flow is a three-step process. One needs to measure *(i)* endotracheal oxygen concentration and *(ii)* total airway flow rate, then simply *(iii)* multiply these two signals. Unfor-

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tunately, the sensors typically employed for the above two measurements in clinical settings often have significantly different dynamics and communication delays. This can induce sizable estimation errors, especially if the difference in overall measurement lag between the two sensors is non-trivial compared to the duration/period of a single breath. Instantaneous tracheal oxygen flow rate estimation is, therefore, quite challenging in practice, even if it appears straightforward in theory.

There is a significant literature on endotracheal oxygen intake modeling and estimation. Schena et al. (2015) and Breen and Rosenbaum (2013) survey the ideas and technologies employed for such estimation. Airway oxygen flow estimation is recognized as being quite difficult in this literature, with at least one study reporting failure to achieve such estimation (Vincent et al. (2016)). The literature identifies sensor time delay as being a major contributor to this difficulty, for both O_2 and CO_2 flow rate estimation (Breen et al. (1992); Chen and Chen (2019)). The literature also recognizes the importance of accounting for the multiplicity of time constants and/or delays for a given gas concentration sensor (Vincent et al. (2014)). Correcting concentration and flow rate sensor measurements for different humidity levels and temperatures is also recognized as important for overall estimation accuracy (Breen (2000)). Different innovations in estimation algorithms and measurement hardware are proposed for addressing these challenges (e.g., Rosenbaum et al. (2007)). This includes the design of closed-loop ventilation circuits where aggressive CO_2 purging, coupled with measurements of total gas volume change, enables the estimation of oxygen intake rate (Hirschl et al. (1993)). The literature also presents the development of testing hardware for evaluating different respiratory gas flow rate measurement and estimation systems (Helwig et al. (2014)).

The above literature, while valuable, focuses predominantly on correcting tracheal oxygen flow estimates for measurement errors, dynamics, and time delays. While such correction is valuable, at least one other factor has a non-trivial effect on the accuracy of instantaneous pulmonary oxygen intake estimation - namely, tracheal advection. The endotracheal tube, together with the hardware attached to it such as water traps, filters, etc., essentially serves as a dead volume. Modeling the impact of this dead volume on overall pulmonary gas transport dynamics is important - and, to the best of our knowledge, relatively unexplored in the literature.

The remainder of this paper addresses the above research gap by presenting: *(i)* a sensor package for pulmonary oxygen flow rate estimation; plus *(ii)* an integrated model of the tracheal advection and sensor dynamics associated with this package. To the best of our knowledge, this integrated model as well as its experimental parameterization is a novel and important addition to the literature. The remainder of the paper presents the sensor package (Section 2), its initial bench-top characterization (Section 2), the proposed model (Section 3), and its parameterization using laboratory hypoxia experiments on a Yorkshire swine (Section 3). As discussed in Section 3, the proposed model estimates tracheal oxygen concentration measurements accurately. This provides confidence in its suitability for pulmonary oxygen intake estimation in future research.

2. SENSOR PACKAGE AND BENCHTOP CHARACTERIZATION

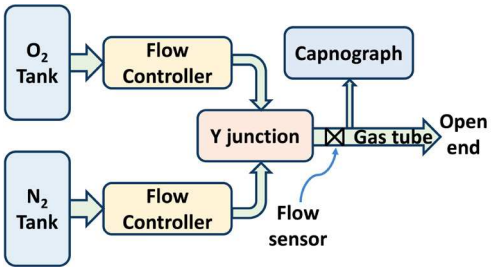

Fig. 1. Sensor package and characterization setup

Figure 1 provides a schematic of this paper's sensor package, as well as the benchtop setup used for its preliminary characterization. The sensor package measures oxygen concentration and total gas flow rate in a gas tube. One end of the gas tube is open to the atmosphere. The other end receives an adjustable mixture of O_2 and N_2 from a characterization setup consisting of two gas tanks plus two mass flow controllers. The sensor package uses an inline sensor (SFM3200-AW, Sensirion AG) for obtaining bidirectional flow rate measurements in the gas tube. A clip-on cap/cable evaluation kit (SEK-SFM3xxx-AW/D, Sensirion AG), which includes a built-in pressure sensor, is attached to the flow sensor. Both sensors communicate via the I2C protocol, which the clip-on cap converts to RS-232. Moreover, the clip-on cap's 0.5 W built-in heater is continuously activated to prevent moisture accumulation on the sensor. The RS-232 signals are converted to TTL and read by a microcontroller development board (Teensy 4.1), which then converts the measurement data into analog signals using two DAC converters (Adafruit AD5693R, Analog Devices) at a rate of 2 kHz. A small portion of total gas flow (namely, 200 mL/min) is sampled and routed into a clinical capnograph (Datex-Ohmeda Capnomac Ultima) for oxygen concentration measurement. Analog oxygen concentration and gas flow rate measurements are finally read by a data acquisition board (dSpace MicroLabBox-II) at a 100Hz sampling rate.

Every sensor and actuator in the above setup has inherent dynamics and delays. Recognizing this, one can perhaps design a separate setup for characterizing each sensor and actuator independently. However, doing so is unnecessary for accurate tracheal oxygen flow estimation, because the accuracy of such estimation depends on the ability to characterize the *difference* in dynamics and delays between the setup's two sensors. The purpose of the above setup is to provide an initial characterization of this difference.

Figures 2 and 3 show the total gas flow rate measured during one of the benchtop characterization experiments. The commanded N_2 flow rate was 0.5 L/min throughout this experiment, but a step O_2 input was commanded, rising from zero to 4.5 L/min. The intent was to generate a rise in O_2 concentration from zero to 90%. The plot in Fig. 2 shows the *measured* total flow rate in the gas tube. The fact that this plot is not a perfect step function reflects the combined dynamics, delays, and errors associated with the gas flow controllers and flow rate sensor.

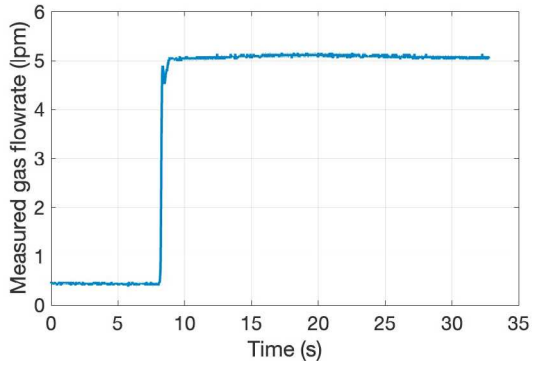

Fig. 2. Gas flow during benchtop characterization

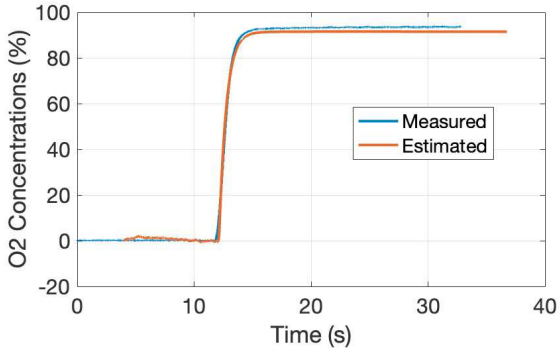

Fig. 3. Benchtop sensor characterization results

We characterized the difference in dynamics between the flow rate and oxygen concentration sensors by solving the following optimization problem:

$$\min_{\xi_1, q_{N_2}, \alpha, \tau} \sum_{i=501}^{N-500} (\xi_{i-\tau/\delta t} - \phi_i)^2$$
$$sub.\ to:\ \xi_i^* = \frac{q_i - q_{N_2}}{q_i},\ \frac{\xi_i - \xi_{i-1}}{\delta t} = \alpha(\xi_{i-1}^* - \xi_{i-1}) \quad (1)$$

In the above optimization problem, i represents a discrete-time sampling index, ϕ_i is a measurement of oxygen concentration (as a fraction), and q_i is a total flow rate measurement. A constant N_2 flow rate value of q_{N_2} is assumed at all moments in time. Therefore, the quantity ξ_i^* represents a flow rate measurement-based estimate of oxygen concentration. The dynamics of the actual measurement of oxygen concentration versus time are related to this flow rate measurement-based estimate through a first-order discrete-time filter whose dynamics are dictated by the constant α. Moreover, this measurement is assumed to go through a pure time delay equal to τ, corresponding to $\tau/\delta t$ samples, where $\delta t = 0.01$ seconds is the sampling time. If this number of samples is not an integer, linear interpolation is used for computing $\xi_{i-\tau/\delta t}$. The optimization objective represents the summed square error in predicting the oxygen sensor's concentration measurement. Because the time delay, τ, can be substantial, optimization is performed over a shortened time window compared to the full experiment, starting 5 seconds after the beginning of the experiment and ending 5 seconds before its completion. The optimized parameters are the initial oxygen concentration estimate, ξ_1, the constant nitrogen flow rate, q_{N_2}, the constant α representing sensor dynamics, and the sensor delay τ. Please note that while the commanded N_2 flow rate is known, optimizing an estimated N_2 flow rate, q_{N_2}, makes it possible to correct for at least one possible cause of experimental error (namely, N_2 flow command execution error). This optimization problem was solved using the *particleswarm* function in *Matlab*.

Figure 3 plots the time-shifted estimate of oxygen concentration measurement versus the actual measurement. An excellent quality of fit is obtained, with a root mean square concentration percentage error of 1.70%. The optimal parameter estimates are $\xi_1 = 0$, $q_{N_2} = 0.434L/min.$, $\alpha = 1.65s^{-1}$, and $\tau = 3.95s$. These values reflect the facts that the initial gas tube oxygen concentration is zero, the gas flow controllers are imperfect, and the oxygen sensor has non-trivial measurement dynamics/delay. The estimated value of τ is particularly important because it is comparable in magnitude to the duration of a typical breath. This is a massive time delay, one that is guaranteed to jeopardize tracheal oxygen intake estimation accuracy if it is not accounted/corrected for. To complicate matters further, the value of this delay is not guaranteed to remain the same as one migrates from benchtop to animal experiments. A portion of this delay, for instance, is likely to depend on the length of the tubing used for providing sampled gas to the capnograph. This tubing is often replaced between experiments, and its length is not guaranteed to remain precisely the same from one experiment to another.

3. ADVECTION MODEL DEVELOPMENT AND IDENTIFICATION

Sensor dynamics and delays are not the only factors affecting the accuracy of oxygen intake estimation. The dead volume of the endotracheal tube and its attachments is also very important to model. To see this, consider a hypoxia experiment where tidal volume and respiratory rate are set to 500 mL/breath and 20 breaths/minute, respectively. Moreover, suppose that the inspired (i.e., inhaled) and expired (i.e., exhaled) oxygen concentrations in this experiment are 20% and 15%, respectively. If one neglects endotracheal tube volume, it is reasonable to estimate a net/average pulmonary oxygen transport rate of $20 \times 500 \times (0.2 - 0.15) = 500$ mL/min. Now suppose that the endotracheal tube has a total volume of 100 mL. This implies that during every breath, while the mechanical ventilator provides 500 mL of inspired air, 20% of this air fills the endotracheal tube, and only 80% reaches the lungs. A similar calculation can be employed during exhalation, the conclusion being that the true pulmonary oxygen transport rate is only 400 mL/min. This simple example illustrates the fact that the larger the volume of the tracheal tube, the more important it is to take into account when computing pulmonary gas transport rates. In fact, in the limit as the tracheal tube's volume becomes equal to (or greater than) tidal volume, net endotracheal gas transport rates will approach zero. Endotracheal tubes, in and of themselves, tend to be small in volume. However, once these tubes are equipped with additional devices (e.g., filters, water traps, etc.), their effective volumes

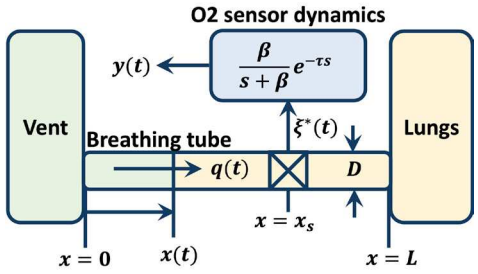

Fig. 4. Advection model schematic

increase, with the 100 mL volume used in this illustrative example being plausible in practical hypoxia experiments.

This paper addresses the above insights by proposing a novel model capturing both *(i)* the dynamics of endotracheal gas transport and *(ii)* the difference in dynamics between airway flow rate and concentration sensors. As shown in Fig. 4, the model treats the endotracheal tube as a purely advective transport channel connecting two well-mixed chambers representing a mechanical ventilator and the lungs, respectively. The assumption that these two chambers are well-mixed means that at every moment in time, there will exist two bodies of gas in the endotracheal tube, each body containing a spatially uniform gas concentration equal to either inspired or expired gas concentration. This simplifies the advection modeling problem by eliminating the need for solving an advection partial differential equation (PDE). Instead, one can simply employ an ordinary differential equation (ODE) model, such as the one shown below:

$$\begin{aligned} \dot{x} &= \frac{q(t)}{\pi \frac{D^2}{4}} \left(1 - \mathcal{U}(-x) - \mathcal{U}(x - L)\right) \\ \xi^*(t) &= c_{et}(t) + (c_i(t) - c_{et}(t))\mathcal{U}(x(t) - x_s) \\ \dot{\xi} &= \beta(\xi^*(t) - \xi(t)),\ y(t) = \xi(t - \tau) \end{aligned} \tag{2}$$

The above model approximates the endotracheal tube as a cylinder of length L and diameter D. The model represents the ventilator and lungs as well-mixed chambers providing gas at the inspired and expired oxygen concentrations, $c_i(t)$ and $c_{et}(t)$, respectively. These concentrations are treated as inputs to the model, and their variations with time are assumed to be much slower than the duration of a single breath. The state variable $x(t)$ represents the axial location of a boundary separating these two gas concentrations. Total airway gas flow rate is denoted by $q(t)$, and treated as a model input. Dividing this flow rate by tube area furnishes a nominal velocity, $\dot{x}$ of the boundary point between the two gas concentrations. The terms $\mathcal{U}(-x)$ and $\mathcal{U}(x - L)$ correct this velocity term by preventing $x(t)$ from dropping below zero or exceeding L, respectively, with $\mathcal{U}$ being the unit step function. The constant parameter x_s represents the location of the oxygen sensor along the endotracheal tube. The gas concentration at this sensor, $\xi^*(t)$ equals $c_{et}(t)$ when $x(t) < x_s$, and equals $c_i(t)$ otherwise. The sensor is assumed to have continuous-time linear first-order dynamics with an eigenvalue $-\beta$, related to the discrete-time constant α and the time step δt from the benchtop characterization experiment by $\alpha = (1 - e^{-\beta \delta t})/\delta t$. Finally, the output measurement from the sensor, $y(t)$, is equal to the output of these first-order sensor dynamics with a time delay τ.

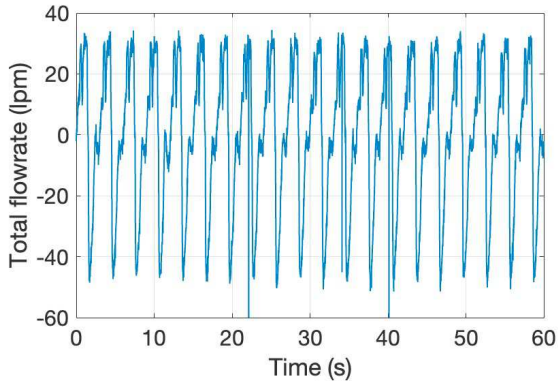

Fig. 5. Experimental results: measured total gas flow rate

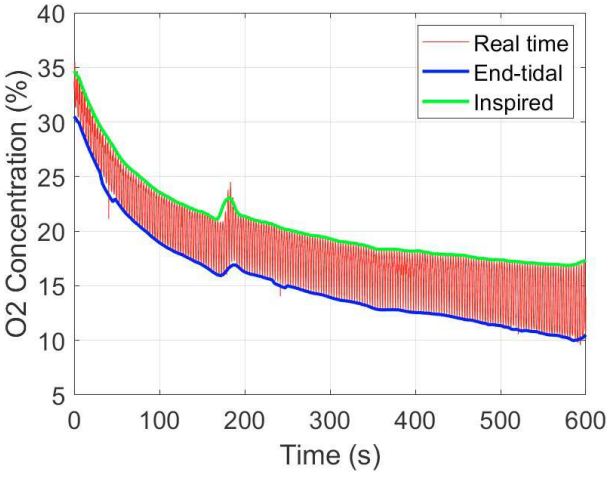

Fig. 6. Experimental results: O_2 concentration measurements

We parameterized the above model for an IACUC-approved hypoxia experiment conducted at Temple University on an adult Yorkshire swine. The experiment involved curtailing inspired oxygen concentration to induce hypoxia, using a recirculating mechanical ventilator capable of delivering inhaled anesthetics (AVS-Penlon). The ventilator settings were adjusted to provide a tidal volume of 500 mL/min, at a respiratory rate of 20 breaths/minute. A total of 550 seconds of experimental data were used for model parameterization, as discussed in more detail below.

Figure 5 shows the raw measurements of total gas flow rate in the endotracheal tube, for a representative portion (namely, the first 60 seconds) of the overall fitting dataset. The ventilator provides the animal with the requested respiratory rate. Moreover, in order to track the desired tidal volume command, the ventilator provides significant instantaneous gas flow rates, potentially as high as 30-40 liters per minute. Trapezoidal numerical integration of this signal with respect to time makes it possible to estimate total changes in lung volume versus time. This, in turn, makes it possible to correct small biases in the flow rate measurement signal (specifically, by adjusting the bias corrections to eliminate long-term drifts in lung volume estimates). Doing so furnishes the flow rate signal, $q(t)$, employed in the proposed advection model.

Figure 6 provides the real-time oxygen concentration measurements from our sensor package. Time-dependent upper and lower bounds of this measurement are obtained using a simple moving-horizon peak-finding algorithm, then smoothed using a moving-horizon average. This furnishes estimates of both inspired oxygen concentration, $c_i(t)$, and expired oxygen concentration, $c_{et}(t)$, that are subsequently used for fitting the proposed advection model. As shown in the figure, these concentrations vary slowly with time compared to the duration of a single breath, even in a transient hypoxia experiment. This supports one of the assumptions behind the proposed advection model - namely, that inspired and expired oxygen concentrations vary slowly compared to the time duration of one breath.

Given the above input signals, we used the *particleswarm* optimization routine in *Matlab* to minimize the root mean square deviation between predicted and measured oxygen concentrations. Optimization was performed with respect to seven model parameters, as shown below.

Table 1. Model parameterization results

Symbol	Meaning	Estimate	Units
D	Tube diameter	17.7	mm
L	Tube length	1.66	m
$x(0)$	Initial condition	1.66	m
x_s	Sensor location	0.37	m
$-\beta$	Sensor eigenvalue	-2.79	1/sec
$\xi(0)$	Initial condition	32.6	%
τ	Time delay	4.26	s

The above parameter values resulted in excellent predictions of oxygen concentration sensor measurements. Figures 7 and 8 highlight this by comparing the true oxygen sensor output versus the predicted sensor output for both the full fitting period and the first 60 seconds of this period, respectively. The root mean square error in predicting instantaneous oxygen concentration is 0.50%. This suggests that modeling endotracheal oxygen transport dynamics as being advective in nature is reasonable. It also suggests that the model parameters provide a good fit for the underlying dynamics.

At least two important observations can be made by examining the above model parameter values:

- First, while the optimal estimate of the endotracheal tube's diameter is reasonable, the optimal estimate of tube length is excessively large. In this paper's hypoxia experiment, the endotracheal tube consisted of multiple interconnected sections, ranging in diameter from 16 mm to 22 mm. The estimated diameter falls within this range. However, the total length of the endotracheal tube in the hypoxia experiment was significantly shorter than the optimal estimate. This discrepancy can be easily explained and justified by computing the estimate of the endotracheal tube's volume from the optimal estimates of its length and diameter - namely, 408 mL. While this is an unreasonable estimate of the volume of the endotracheal tube alone, it is a potentially plausible estimate of the volume of the tube plus the attached accessories (especially the water trap used for preventing moisture accumulation on the flow rate sensor). The magnitude of this "dead volume" is quite substantial compared to the ventilator's tidal volume setting, highlighting the great importance of modeling this dead volume prior to oxygen intake estimation.
- Second, while the estimated values of the sensor's time constant and delay are on the same order of magnitude as the outcomes of the benchtop experiment, there are non-trivial differences between those two sets of parameter estimates. These differences are to be expected, for a number of reasons, one of which is that variation in the length of the sampling tube used for capnography from one experiment to another. This observation underscores the importance of utilizing the proposed advection model, together with system identification, for experiment-specific characterization of airway oxygen transport dynamics.

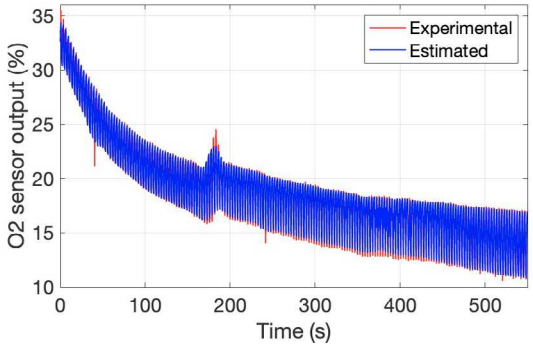

Fig. 7. Fitting results: full duration

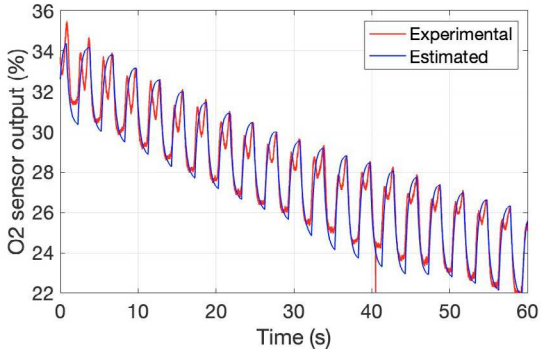

Fig. 8. Fitting results: first 60 seconds

4. CONCLUSIONS

The main conclusion of this paper is that modeling and parameterizing the dynamics of endotracheal gas transport and oxygen sensor dynamics/delays makes it possible to fit the real-time measurements of airway oxygen concentration with very high accuracy. A reasonable next step, to be explored in future research, is to validate the pulmonary oxygen intake estimates furnished by such modeling. This, in turn, has the potential to be quite valuable as an experimental tool for assessing and comparing different respiratory support technologies.

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