Optimal Determination of Respiratory Airflow Patterns using a Nonlinear Multi-Compartment Model for a Lung-Rib-Cage System

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Abstract— In this paper, we develop optimal respiratory airflow patterns using a nonlinear multi-compartment model for a lung-rib-cage system. Specifically, we use classical calculus of variations minimization techniques to derive an optimal airflow pattern for inspiratory and expiratory breathing cycles. The physiological interpretation of the optimality criteria used involve the minimization of work of breathing and lung volume acceleration for the inspiratory phase, and the minimization of the elastic potential energy and rapid airflow rate changes for the expiratory phase. Finally, we numerically integrate the resulting nonlinear two-point boundary value problems to determine the optimal airflow patterns over the inspiratory and expiratory breathing cycles.

I. INTRODUCTION

Respiratory failure, the inadequate exchange of carbon dioxide and oxygen by the lungs, is a common clinical problem in critical care medicine, and patients with respiratory failure frequently require support with mechanical ventilation while the underlying cause is identified and treated. The goal of mechanical ventilation is to ensure adequate ventilation, which involves a magnitude of gas exchange that leads to the desired blood level of carbon dioxide, and adequate oxygenation, which involves a blood concentration of oxygen that will ensure organ function. Achieving these goals is complicated by the fact that mechanical ventilation can actually cause acute lung injury, either by inflating the lungs to excessive volumes or by using excessive pressures to inflate the lungs. The challenge to mechanical ventilation is to produce the desired blood levels of carbon dioxide and oxygen without causing further acute lung injury.

With the increasing availability of micro-chip technology, it has been possible to design partially automated mechanical ventilators with control algorithms for providing volume or pressure control [1–4]. More sophisticated fully automated model reference adaptive control algorithms for mechanical ventilation have also been recently developed [5], [6]. These algorithms require a reference model for identifying a clinically plausible breathing pattern. However, the respiratory lung models that have been presented in the medical and scientific literature have typically assumed homogenous lung function. For example, in analogy to a simple electrical circuit, the most common model has assumed that the lungs can be viewed as a single compartment characterized by its compliance (the ratio of compartment volume to pressure) and the resistance to air flow into the compartment [7–9]. While a few investigators have considered two compartment models, reflecting the fact that there are two lungs (right and left), there has been little interest in more detailed models [10–12].

Early work on the optimality of respiratory control mechanisms using simple homogenous lung models dealt with the frequency of breathing. In particular, the authors in [13], [14] predicted the frequency of breathing by using a minimum work-rate criterion. This work involves a static optimization problem and assumes that the airflow pattern is a fixed sinusoidal function. The authors in [14], [15] developed optimality criteria for the prediction of the respiratory airflow pattern with fixed inspiratory and expiratory phases of a breathing cycle.

Although the problem for identifying optimal respiratory patterns has been addressed in the literature (see [13–16] and the references therein), the models on which these respiratory control mechanisms have been identified are predicated on a single compartment lung model with constant respiratory parameters. However, the lungs, especially diseased lungs, are heterogeneous, both functionally and anatomically, and are comprised of many subunits, or compartments, that differ in their capacities for gas exchange. Realistic models should take this heterogeneity into account. In addition, the resistance to gas flow and the compliance of the lung units are not constant but rather vary with lung volume. This is particularly true for compliance. While more sophisticated models entail greater complexity, since the models are readily presented in the context of dynamical systems theory, sophisticated mathematical tools can be applied to their analysis. Compartmental lung models are described by a state vector, whose components are the volumes of the individual compartments.

In this paper, we extend the work of [14], [15] to develop optimal respiratory airflow patterns using a nonlinear multi-compartment model for a lung-rib-cage system. Specifically, we extend the linear multi-compartment lung model given in [5] to address system model nonlinearities. Then, we extend the performance functionals developed in [14], [15] for the inspiratory and expiratory breathing cycles to derive an optimal airflow pattern using classical calculus of variations techniques. In particular, the physiological interpretation of the optimality criteria involve the minimization of work of breathing and lung volume acceleration for the inspiratory breathing phase, and the minimization of the elastic potential energy and rapid airflow rate changes for the expiratory breathing phase. Finally, we numerically integrate the resulting nonlinear two-point boundary value problems to determine the optimal airflow patterns over the inspiratory and expiratory breathing cycles.

The notation used in this paper is fairly standard. Specifically, $\mathbb{R}^n$ denotes the set of $n \times 1$ real column vectors and $\mathbb{R}^{n \times m}$ denotes the set of $n \times m$ real matrices. For $x \in \mathbb{R}^n$ we write $x \geq\geq 0$ (resp., $x >> 0$) to indicate that every component of x is nonnegative (resp., positive). In this case, we say that x is *nonnegative* or *positive*, respectively. Likewise, $A \in \mathbb{R}^{n \times m}$ is *nonnegative* or *positive* if every entry of A is nonnegative or positive. Furthermore, let $\overline{\mathbb{R}}_+^n$ and $\mathbb{R}_+^n$ denote the nonnegative and positive orthants of $\mathbb{R}^n$, that is, if $x \in \mathbb{R}^n$, then $x \in \overline{\mathbb{R}}_+^n$ and $x \in \mathbb{R}_+^n$ are equivalent, respectively, to $x \geq\geq 0$ and $x >> 0$. Finally, we write $(\cdot)^{\mathrm{T}}$

to denote transpose, $(\cdot)'$ to denote Frèchet derivative, and δx to denote the first variation of the function x.

II. A NONLINEAR MULTI-COMPARTMENT MODEL FOR RESPIRATORY DYNAMICS

In this section, we extend the linear multi-compartment lung model of [5] to develop a nonlinear model for the dynamic behavior of a multi-compartment respiratory system in response to an arbitrary applied inspiratory pressure. Here, we assume that the bronchial tree has a dichotomy architecture [17]; that is, in every generation each airway unit branches into two airway units of the subsequent generation. In addition, we assume that the lung compliance is a nonlinear function of lung volume. First, for simplicity of exposition, we consider a single-compartment lung model. In this model, the lungs are represented as a single lung unit with nonlinear compliance $c(x)$ connected to a pressure source by an airway unit with resistance (to air flow) of R. At time $t = 0$, a driving pressure $p_{\text{in}}(t)$ is applied to the opening of the parent airway, where $p_{\text{in}}(t)$ is generated by the respiratory muscles or a mechanical ventilator. This pressure is applied over the time interval $0 \leq t \leq T_{\text{in}}$, which is the inspiratory part of the breathing cycle. At time $t = T_{\text{in}}$, the applied airway pressure is released and expiration takes place passively, that is, the external pressure is only the atmospheric pressure $p_{\text{ex}}(t)$ during the time interval $T_{\text{in}} \leq t \leq T_{\text{in}} + T_{\text{ex}}$, where T_{ex} is the duration of expiration.

The state equation for inspiration (inflation of lung) is given by

$$R_{\text{in}}\dot{x}(t) + \frac{1}{c_{\text{in}}(x)}x(t) = p_{\text{in}}(t), \ x(0) = x_0^{\text{in}}, \ 0 \leq t \leq T_{\text{in}}, \tag{1}$$

where $x(t) \in \mathbb{R}$, $t \geq 0$, is the lung volume, $R_{\text{in}} \in \mathbb{R}$ is the resistance to air flow during the inspiration period, $c_{\text{in}} : \mathbb{R} \to \mathbb{R}_+$ is a nonlinear function defining the lung compliance at inspiration, $x_0^{\text{in}} \in \mathbb{R}_+$ is the lung volume at the start of the inspiration and serves as the system initial condition. Equation (1) is simply a pressure balance equation where the driving pressure $p_{\text{in}}(t), 0 \leq t \leq T_{\text{in}}$, applied to the compartment is proportional to the volume of the compartment via the compliance and the rate of change of the compartmental volume via the resistance. We assume that expiration is passive due to the elastic stretch of the lung unit. During the expiration process, the state equation is given by

$$R_{\text{ex}}\dot{x}(t) + \frac{1}{c_{\text{ex}}(x)}x(t) = p_{\text{ex}}(t), \quad x(T_{\text{in}}) = x_0^{\text{ex}},$$
$$T_{\text{in}} \leq t \leq T_{\text{in}} + T_{\text{ex}}, \tag{2}$$

where $x(t) \in \mathbb{R}$, $t \geq 0$, is the lung volume, $R_{\text{ex}} \in \mathbb{R}$ is the resistance to air flow during the expiration period, $c_{\text{ex}} : \mathbb{R} \to \mathbb{R}_+$ is a nonlinear function defining the lung compliance at expiration, and $x_0^{\text{ex}} \in \mathbb{R}_+$ is the lung volume at the start of expiration.

Next, we develop the state equations for inspiration and expiration for a 2^n-compartment model, where $n \geq 0$. In this model, the lungs are represented as 2^n lung units which are connected to the pressure source by n generations of airway units, where each airway is divided into two airways of the subsequent generation leading to 2^n compartments.

Let x_i, $i = 1, 2, \ldots, 2^n$, denote the lung volume in the ith compartment, $c_i^{\text{in}}(x_i)$ (resp., $c_i^{\text{ex}}(x_i)$), $i = 1, 2, \ldots, 2^n$, denote the compliance at inspiration (resp., expiration) of each compartment as a nonlinear function of the volume of ith compartment, and let $R_{j,i}^{\text{in}}$ (resp., $R_{j,i}^{\text{ex}}$), $i = 1, 2, \ldots, 2^j$, $j =$

$0, \ldots, n$, denote the resistance (to air flow) of the ith airway in the jth generation during the inspiration (resp., expiration) period with R_{01}^{in} (resp., R_{01}^{ex}) denoting the inspiration (resp., expiration) of the *parent* (i.e., 0th generation) airway. As in the single-compartment model we assume that a pressure of $p_{\text{in}}(t), t \geq 0$, is generated (by the inspiratory muscles) or applied (by a mechanical ventilator) during inspiration.

Now, the state equations for inspiration are given by

$$R_{n,i}^{\text{in}}\dot{x}_i(t) + \frac{1}{c_i^{\text{in}}(x_i(t))}x_i(t)$$
$$+ \sum_{j=0}^{n-1} R_{j,k_j}^{\text{in}} \sum_{l=(k_j-1)2^{n-j}+1}^{k_j 2^{n-j}} \dot{x}_l(t) = p_{\text{in}}(t),$$
$$x_i(0) = x_{i0}^{\text{in}}, \quad 0 \leq t \leq T_{\text{in}}, \quad i = 1, 2, \ldots, 2^n, \tag{3}$$

where $c_i^{\text{in}}(x_i)$, $i = 1, 2, \ldots, 2^n$, are nonlinear functions of x_i, $i = 1, 2, \ldots, 2^n$, given by ([18])

$$c_i^{\text{in}}(x_i) \triangleq \begin{cases} a_{i_1}^{\text{in}} + b_{i_1}^{\text{in}}x_i, & \text{if } V_{i_0} \leq x_i \leq x_{i_1}^{\text{in}}, \\ a_{i_2}^{\text{in}}, & \text{if } x_{i_1}^{\text{in}} \leq x_i \leq x_{i_2}^{\text{in}}, i = 1, \ldots, 2^n, \\ a_{i_3}^{\text{in}} + b_{i_3}^{\text{in}}x_i, & \text{if } x_{i_2}^{\text{in}} \leq x_i \leq V_{i_0} + V_{T_i}, \end{cases} \tag{4}$$

where $a_{i_j}^{\text{in}}$, $j = 1, 2, 3$, and $b_{i_j}^{\text{in}}$, $j = 1, 3$, are model parameters with $b_{i_1}^{\text{in}} > 0$ and $b_{i_3}^{\text{in}} < 0$, $x_{i_j}^{\text{in}}$, $j = 1, 2$, are volume ranges wherein the compliance is constant, V_{i_0} denotes the end expiratory volume, V_{T_i} denotes tidal volume, and

$$k_j = \lfloor \frac{k_{j+1} - 1}{2} \rfloor + 1, \quad j = 0, \ldots, n-1, \quad k_n = i, \tag{5}$$

where $\lfloor q \rfloor$ denotes the *floor function* which gives the largest integer less than or equal to the positive number q.

Next, we consider the state equation for the expiration process. As in the single-compartment model we assume that the expiration process is passive and the external pressure applied is $p_{\text{ex}}(t), t \geq 0$. Following an identical procedure as in the inspiration case, we obtain the state equation for expiration as

$$R_{n,i}^{\text{ex}}\dot{x}_i(t) + \sum_{j=0}^{n-1} R_{j,k_j}^{\text{ex}} \sum_{l=(k_j-1)2^{n-j}+1}^{k_j 2^{n-j}} \dot{x}_l(t)$$
$$+ \frac{1}{c_i^{\text{ex}}(x_i(t))}x_i(t) = p_{\text{ex}}(t),$$
$$x_i(T_{\text{in}}) = x_{i_0}^{\text{ex}}, \quad T_{\text{in}} \leq t \leq T_{\text{ex}} + T_{\text{in}}, \quad i = 1, 2, \ldots, 2^n, \tag{6}$$

where

$$c_i^{\text{ex}}(x_i) \triangleq \begin{cases} a_{i_1}^{\text{ex}} + b_{i_1}^{\text{ex}}x_i, & \text{if } V_{i_0} \leq x_i \leq x_{i_1}^{\text{ex}}, \\ a_{i_2}^{\text{ex}}, & \text{if } x_{i_1}^{\text{ex}} \leq x_i \leq x_{i_2}^{\text{ex}}, i = 1, \ldots, 2^n, \\ a_{i_3}^{\text{ex}} + b_{i_3}^{\text{ex}}x_i, & \text{if } x_{i_2}^{\text{ex}} \leq x_i \leq V_{i_0} + V_{T_i}, \end{cases} \tag{7}$$

$a_{i_j}^{\text{ex}}$, $j = 1, 2, 3$, and $b_{i_j}^{\text{ex}}$, $j = 1, 3$, are model parameters with $b_{i_1}^{\text{ex}} > 0$ and $b_{i_3}^{\text{ex}} < 0$, $x_{i_j}^{\text{ex}}$, $j = 1, 2$, are volume ranges wherein the compliance is constant, and k_j is given by (5).

Next, we provide a smooth (i.e., C^∞) characterization of the nonlinear compliance using sigmoidal functions [19]. Specifically, for inspiration, $c_i^{\text{in}}(x_i)$ can be approximated as

$$c_i^{\text{in}}(x_i) \approx a_{i_2}^{\text{in}} \left(S_{a,b}^{(\beta)}(x_i) - S_{c,d}^{(\beta)}(x_i) \right), \ i = 1, \ldots, 2^n, \tag{8}$$

where $a = -\frac{a_{i_1}^{\text{in}}}{b_{i_1}^{\text{in}}}$, $b = \frac{a_{i_2}^{\text{in}}}{b_{i_1}^{\text{in}}} + a$, $c = -\frac{a_{i_3}^{\text{in}}}{b_{i_3}^{\text{in}}}$, $d = \frac{a_{i_2}^{\text{in}}}{b_{i_3}^{\text{in}}} + c$, $S_{a,b}^{(\beta)}(x_i) \triangleq \frac{1}{b-a} \ln \left(\frac{\sigma_b^{(-\beta)}(x_i)}{\sigma_a^{(-\beta)}(x_i)} \right)^{1/\beta}$ with $\sigma_b^{(-\beta)}(x_i) \triangleq \frac{1}{1+e^{-\beta(x_i-a)}}$, and $\beta > 0$ is an approximation parameter. A similar approximation holds for $c_i^{\text{ex}}(x_i), i = 1, \ldots, 2^n$.

Finally, we rewrite the state equations (3) and (6) for inspiration and expiration, respectively, in vector-matrix state space form. Specifically, define the state vector $x \triangleq [x_1, x_2, \ldots, x_{2^n}]^{\text{T}}$, where x_i denotes the lung volume of the ith compartment. Now, the state equation (3) for inspiration can be rewritten as

$$R_{\text{in}}\dot{x}(t) + C_{\text{in}}(x(t))x(t) = p_{\text{in}}(t)\mathbf{e}, \ x(0) = x_0^{\text{in}},$$
$$0 \leq t \leq T_{\text{in}}, \quad (9)$$

where $\mathbf{e} \triangleq [1, \ldots, 1]^{\text{T}}$ denotes the ones vector of order 2^n,

$$C_{\text{in}}(x) \triangleq \text{diag}\left[\frac{1}{c_1^{\text{in}}(x_1)}, \cdots, \frac{1}{c_{2^n}^{\text{in}}(x_{2^n})} \right], \quad (10)$$

$$R_{\text{in}} \triangleq \sum_{j=0}^{n} \sum_{k=1}^{2^j} R_{j,k}^{\text{in}} Z_{j,k} Z_{j,k}^{\text{T}}, \quad (11)$$

where $Z_{j,k} \in \mathbb{R}^{2^n}$ is such that the l-th element of $Z_{j,k}$ is 1 for all $l = (k-1)2^{n-j}+1, (k-1)2^{n-j}+2, \ldots, k2^{n-j}, k = 1, \ldots, 2^j, j = 0, 1, \ldots, n$, and zero elsewhere.

Similarly, the state equation (6) for expiration can be rewritten as

$$R_{\text{ex}}\dot{x}(t) + C_{\text{ex}}(x(t))x(t) = p_{\text{ex}}(t)\mathbf{e}, \ x(T_{\text{in}}) = x_0^{\text{ex}},$$
$$T_{\text{in}} \leq t \leq T_{\text{ex}} + T_{\text{in}}, \quad (12)$$

where

$$C_{\text{ex}}(x) \triangleq \text{diag}\left[\frac{1}{c_1^{\text{ex}}(x_1)}, \cdots, \frac{1}{c_{2^n}^{\text{ex}}(x_{2^n})} \right], \quad (13)$$

$$R_{\text{ex}} \triangleq \sum_{j=0}^{n} \sum_{k=1}^{2^j} R_{j,k}^{\text{ex}} Z_{j,k} Z_{j,k}^{\text{T}}. \quad (14)$$

Finally, it follows from Proposition 4.1 of [5] that R_{in} and R_{ex} are positive-definite and, hence, R_{in} and R_{ex} are invertible matrices.

III. OPTIMAL DETERMINATION OF INSPIRATORY AND EXPIRATORY AIRFLOW IN BREATHING

In this section, we use the respiratory dynamical system characterized by (9) and (12) to develop an optimal model for predicting airflow patterns in breathing. The optimization criteria used allows for the minimization of oxygen expenditure of the respiratory muscles as well as rapid changes in the lung volume flow rate. The oxygen consumption of the lung muscles is mainly due to the work carried out by the respiratory muscles to overcome the resistive forces and stretch the lung and chest wall. In [20], this work is defined as PV, where P is the pressure driving inflation and V is the lung unit volume. The efficiency of gas exchange in the lungs is related to the volume acceleration, since rapid changes in lung volume can cause discomfort and inefficacy of muscular contraction and control. Moreover, high volume acceleration can result in overexpansion of the lung resulting in lung tissue rupture as well as excessive work of breathing with subsequent ventilatory muscle fatigue.

In the ensuing discussion, we assume that the inspiration process starts from a given initial state x_0^{in} and is followed by the expiration process where its initial state will be the final state of the inspiration. An inspiration followed by an expiration is called a single *breathing cycle*. Furthermore, we assume that each breathing cycle is followed by another breathing cycle where the initial condition for the latter breathing cycle is the final state of the former breathing cycle. Since the respiratory process is periodic, we need only focus on one breathing cycle.

The next result gives the optimal solution $x^*(t), 0 \leq t \leq T_{\text{in}}$, for the inspiratory airflow breathing pattern using classical calculus of variations techniques.

Theorem 3.1: Consider the system model for inspiration given by (9). Let the optimal air volume $x^*(t), 0 \leq t \leq T_{\text{in}}$, be given by the solution to the minimization problem

$$\mathcal{J}_{\text{in}}(x) = \int_0^{T_{\text{in}}} \left[\ddot{x}^{\text{T}}(t)\ddot{x}(t) + \alpha_1 p_{\text{in}}(t)\mathbf{e}^{\text{T}}\dot{x}(t) \right] \text{d}t,$$
$$\alpha_1 \geq 0, \quad (15)$$

subject to the natural boundary conditions

$$x(0) = V_0, \quad \dot{x}(0) = 0, \quad (16)$$
$$x(T_{\text{in}}) = V_0 + V_{\text{T}}, \quad \dot{x}(T_{\text{in}}) = 0, \quad (17)$$

where $V_0 \in \mathbb{R}^{2^n}$ is the end expiratory volume and $V_{\text{T}} \in \mathbb{R}^{2^n}$ is the tidal volume. If $\alpha_1 > 0$, then $x^*(t), 0 \leq t \leq T_{\text{in}}$, is given by

$$x^*(t) = d_1 + d_2 t + \exp(\sqrt{\alpha_1}R_{\text{in}}^{1/2}t)d_3$$
$$+ \exp(-\sqrt{\alpha_1}R_{\text{in}}^{1/2}t)d_4, \quad t \geq 0, \quad (18)$$

and if $\alpha_1 = 0$, then

$$x^*(t) = d_1 + d_2 t + d_3 t^2 + d_4 t^3, \quad t \geq 0, \quad (19)$$

where d_1, d_2, d_3, and $d_4 \in \mathbb{R}^{2^n}$ are constant vectors determined by the boundary conditions (16) and (17), and $R_{\text{in}}^{1/2}$ denotes the (unique) positive-definite square root of R_{in}.

Proof: First, note that $p_{\text{in}}(t)\mathbf{e}, 0 \leq t \leq T_{\text{in}}$, in (15) can be eliminated using the state equation (9). Thus, the integrand of the performance criterion (15) can be written as

$$L_{\text{in}}(x(t), \dot{x}(t), \ddot{x}(t))$$
$$= \ddot{x}^{\text{T}}(t)\ddot{x}(t) + \alpha_1 \left[R_{\text{in}}\dot{x}(t) + C_{\text{in}}(x(t))x(t) \right]^{\text{T}} \dot{x}(t)$$
$$= \ddot{x}^{\text{T}}(t)\ddot{x}(t) + \alpha_1 \left[\dot{x}^{\text{T}}(t)R_{\text{in}}\dot{x}(t) + x^{\text{T}}(t)C_{\text{in}}(x)\dot{x}(t) \right],$$
$$\alpha_1 \geq 0. \quad (20)$$

The first variation of the performance criterion $\mathcal{J}_{\text{in}}(x)$ is given by

$$\delta \mathcal{J}_{\text{in}}(x^*, \delta x)$$
$$= \int_0^{T_{\text{in}}} \delta L_{\text{in}}(x^*(t), \dot{x}^*(t), \ddot{x}^*(t))\text{d}t$$
$$= \int_0^{T_{\text{in}}} \left\{ \left(\frac{\partial L_{\text{in}}}{\partial x} \right) \delta x(t) + \left(\frac{\partial L_{\text{in}}}{\partial \dot{x}} \right) \delta \dot{x}(t) \right.$$
$$\left. + \left(\frac{\partial L_{\text{in}}}{\partial \ddot{x}} \right) \delta \ddot{x}(t) \right\} \text{d}t$$
$$= \left[\frac{\partial L_{\text{in}}}{\partial \ddot{x}}\delta \dot{x} + \left(\frac{\partial L_{\text{in}}}{\partial \dot{x}} - \frac{\text{d}^2}{\text{d}t^2}\frac{\partial L_{\text{in}}}{\partial \ddot{x}} \right) \delta x \right]_0^{T_{\text{in}}}$$
$$+ \int_0^{T_{\text{in}}} \left\{ \left(\frac{\partial L_{\text{in}}}{\partial x} \right) - \frac{\text{d}}{\text{d}t}\left(\frac{\partial L_{\text{in}}}{\partial \dot{x}} \right) \right.$$
$$\left. + \frac{\text{d}}{\text{d}t}\left(\frac{\partial L_{\text{in}}}{\partial \ddot{x}} \right) \right\} \delta x(t)\text{d}t. \quad (21)$$

Using the boundary conditions (16) and (17) it follows that $\delta x(0) = \delta x(T_{\text{in}}) = \delta\dot{x}(0) = \delta\dot{x}(T_{\text{in}}) = 0$. Now, since T_{in} is fixed, it follows from the fundamental theorem of the calculus of variations that the variation of $\mathcal{J}_{\text{in}}(x)$ must vanish on x^*; that is, the extremals optimizing the performance criterion $\mathcal{J}_{\text{in}}(x)$ satisfy the Euler-Lagrange equation

$$\left(\frac{\partial L_{\text{in}}}{\partial x}\right)^{\text{T}} - \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial L_{\text{in}}}{\partial \dot{x}}\right)^{\text{T}} + \frac{\mathrm{d}^2}{\mathrm{d}t^2}\left(\frac{\partial L_{\text{in}}}{\partial \ddot{x}}\right)^{\text{T}} = 0. \quad (22)$$

Next, using $C_{\text{in}}(x)$ given by (10),

$$\left(\frac{\partial L_{\text{in}}}{\partial x}\right)^{\text{T}} = \alpha_1 C_{\text{in}}(x(t))\dot{x}(t) + \alpha_1 C'_{\text{in}}(x(t))\dot{X}(t)x(t), (23)$$

$$\left(\frac{\partial L_{\text{in}}}{\partial \dot{x}}\right)^{\text{T}} = 2\alpha_1 R_{\text{in}}\dot{x}(t) + \alpha_1 C_{\text{in}}(x(t))x(t), \quad (24)$$

$$\left(\frac{\partial L_{\text{in}}}{\partial \ddot{x}}\right)^{\text{T}} = 2\ddot{x}(t), \ \ 0 \le t \le T_{\text{in}}, \quad (25)$$

where $C'_{\text{in}}(x(t)) \triangleq \text{diag}\left[\frac{\partial}{\partial x_i}\left(\frac{1}{c_i^{\text{in}}(x_i(t))}\right)\right]$ and $\dot{X}(t) \triangleq \text{diag}\left[\dot{x}_i(t)\right], i = 1, \ldots, 2^n$. Thus, (22) yields the fourth-order differential equation

$$x^{(4)}(t) - \alpha_1 R_{\text{in}}x^{(2)}(t) = 0, \quad 0 \le t \le T_{\text{in}}, \quad (26)$$

where $x^{(n)}(t) \triangleq \frac{\mathrm{d}^n x(t)}{\mathrm{d}t^n}$, with boundary conditions given in (16) and (17). Now, using standard analysis techniques, the solution $x(t), 0 \le t \le T_{\text{in}}$, to (26) satisfies (18) if $\alpha_1 > 0$ and (19) if $\alpha_1 = 0$. ∎

Remark 3.1: The vectors d_1, d_2, d_3, and d_4 in Theorem 3.1 can be uniquely determined using the four boundary conditions given by (16) and (17). Specifically, if $\alpha_1 = 0$, it can be shown that $d_1 = V_0$, $d_2 = 0$, $d_3 = \frac{3}{T_{\text{in}}^2}V_{\text{T}}$, and $d_4 = -\frac{2}{T_{\text{in}}^3}V_{\text{T}}$. Hence, in this case, $\dot{x}(t) = d_2 + 2d_3 t + 3d_4 t^2 = \frac{6t}{T_{\text{in}}^2}V_{\text{T}}(1 - \frac{t}{T_{\text{in}}}) \ge\ge 0, 0 \le t \le T_{\text{in}}$, which implies that the solution $x^*(t), 0 \le t \le T_{\text{in}}$, to (26) is increasing during inspiration, and hence, $V_{0_i} \le x_i^*(t) \le V_{0_i} + V_{\text{T}_i}, i = 1, \ldots, 2^n$, where $V_{0_i}, x_i(t)$, and V_{T_i} are the ith components of $V_0, x(t)$, and V_{T}, respectively. A similar result holds for the case where $\alpha_1 > 0$.

Next, we give the optimal solution $x^*(t), T_{\text{in}} \le t \le T_{\text{in}} + T_{\text{ex}}$, for the expiratory airflow breathing pattern.

Theorem 3.2: Consider the system model for expiration given by (12). Let the optimal solution $x^*(t), T_{\text{in}} \le t \le T_{\text{in}} + T_{\text{ex}}$, be given by the solution to the minimization problem

$$\mathcal{J}_{\text{ex}}(x) = \int_{T_{\text{in}}}^{T_{\text{in}}+T_{\text{ex}}} \left[\ddot{x}^{\text{T}}(t)\ddot{x}(t) + \alpha_2 p_{\text{ex}}^2(t)\mathbf{e}^{\text{T}}\mathbf{e}\right]\mathrm{d}t,$$
$$\alpha_2 \ge 0, \quad (27)$$

subject to the natural boundary conditions

$$x(T_{\text{in}}) = V_0 + V_{\text{T}}, \quad \dot{x}(T_{\text{in}}) = 0, \quad (28)$$
$$x(T_{\text{in}} + T_{\text{ex}}) = V_0, \quad \dot{x}(T_{\text{in}} + T_{\text{ex}}) = 0. \quad (29)$$

If $\alpha_2 > 0$, then $x^*(t), T_{\text{in}} \le t \le T_{\text{in}} + T_{\text{ex}}$, satisfies

$$x^{(4)}(t) - \alpha_2 R_{\text{ex}}^2 x^{(2)}(t) + \alpha_2 C_{\text{ex}}^2(x)x(t)$$
$$+ \alpha_2 \left[C_{\text{ex}}(x)R_{\text{ex}}\dot{x}(t) - R_{\text{ex}}C_{\text{ex}}(x)\dot{x}(t)\right.$$
$$+ X(t)C'_{\text{ex}}(x)R_{\text{ex}}\dot{x}(t) - R_{\text{ex}}C'_{\text{ex}}(x)X(t)\dot{x}(t)$$
$$+ \left. X(t)C'_{\text{ex}}(x)C_{\text{ex}}(x)x(t)\right] = 0, \quad (30)$$

where $X(t) \triangleq \text{diag}\left[x_i(t)\right]$ and $C'_{\text{ex}}(x) \triangleq \text{diag}\left[\frac{\partial}{\partial x_i}\left(\frac{1}{c_i^{\text{ex}}(x_i)}\right)\right], i = 1, \ldots, 2^n$, and if $\alpha_2 = 0$, then

$$x^*(t) = d_1 + d_2 t + d_3 t^2 + d_4 t^3, \quad t \ge 0, \quad (31)$$

where d_1, d_2, d_3, and $d_4 \in \mathbb{R}^{2^n}$ are constant vectors determined by the four boundary conditions (28) and (29).

Proof: Using (12), the integrand of the performance criterion (27) can be written as

$$L_{\text{ex}}(x(t), \dot{x}(t), \ddot{x}(t))$$
$$= \ddot{x}^{\text{T}}(t)\ddot{x}(t) + \alpha_2 \left(p_{\text{ex}}(t)\mathbf{e}\right)^{\text{T}}\left(p_{\text{ex}}(t)\mathbf{e}\right)$$
$$= \ddot{x}^{\text{T}}(t)\ddot{x}(t) + \alpha_2 \left[R_{\text{ex}}\dot{x}(t) + C_{\text{ex}}(x(t))x(t)\right]^{\text{T}}$$
$$\quad \left[R_{\text{ex}}\dot{x}(t) + C_{\text{ex}}(x(t))x(t)\right],$$
$$= \ddot{x}^{\text{T}}(t)\ddot{x}(t) + \alpha_2 \left[\dot{x}^{\text{T}}(t)R_{\text{ex}}^2\dot{x}(t)\right.$$
$$\quad \left. + x^{\text{T}}(t)C_{\text{ex}}^2(x(t))x(t) + 2\dot{x}^{\text{T}}(t)R_{\text{ex}}C_{\text{ex}}(x(t))x(t)\right],$$
$$\alpha_2 > 0. \quad (32)$$

Thus, the variation of $\mathcal{J}_{\text{ex}}(x)$ on an extremal solution gives

$$\delta\mathcal{J}_{\text{ex}}(x^*, \delta x)$$
$$= \int_{T_{\text{in}}}^{T_{\text{in}}+T_{\text{ex}}} \delta L_{\text{ex}}(x^*(t), \dot{x}^*(t), \ddot{x}^*(t))\mathrm{d}t$$
$$= \int_{T_{\text{in}}}^{T_{\text{in}}+T_{\text{ex}}} \left\{\left(\frac{\partial L_{\text{ex}}}{\partial x}\right)\delta x(t) + \left(\frac{\partial L_{\text{ex}}}{\partial \dot{x}}\right)\delta\dot{x}(t)\right.$$
$$\quad \left. + \left(\frac{\partial L_{\text{ex}}}{\partial \ddot{x}}\right)\delta\ddot{x}(t)\right\}\mathrm{d}t$$
$$= \left[\frac{\partial L_{\text{ex}}}{\partial \ddot{x}}\delta\dot{x} + \left(\frac{\partial L_{\text{ex}}}{\partial \dot{x}} - \frac{\mathrm{d}}{\mathrm{d}t}\frac{\partial L_{\text{ex}}}{\partial \ddot{x}}\right)\delta x\right]_{T_{\text{in}}}^{T_{\text{in}}+T_{\text{ex}}}$$
$$\quad + \int_0^{T_{\text{ex}}} \left\{\left(\frac{\partial L_{\text{ex}}}{\partial x}\right) - \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial L_{\text{ex}}}{\partial \dot{x}}\right)\right.$$
$$\quad \left. + \frac{\mathrm{d}^2}{\mathrm{d}t^2}\left(\frac{\partial L_{\text{ex}}}{\partial \ddot{x}}\right)\right\}\delta x(t)\mathrm{d}t$$
$$= 0. \quad (33)$$

Using the boundary conditions (28) and (29) it follows that $\delta x(T_{\text{in}}) = \delta x(T_{\text{in}} + T_{\text{ex}}) = \delta\dot{x}(T_{\text{in}}) = \delta\dot{x}(T_{\text{in}} + T_{\text{ex}}) = 0$. Hence, the extremals optimizing the performance criterion $\mathcal{J}_{\text{ex}}(x)$ satisfy the Euler-Lagrange equation

$$\left(\frac{\partial L_{\text{ex}}}{\partial x}\right)^{\text{T}} - \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial L_{\text{ex}}}{\partial \dot{x}}\right)^{\text{T}} + \frac{\mathrm{d}^2}{\mathrm{d}t^2}\left(\frac{\partial L_{\text{ex}}}{\partial \ddot{x}}\right)^{\text{T}} = 0. \quad (34)$$

Now, using $C_{\text{ex}}(x)$ given by (13),

$$\left(\frac{\partial L_{\text{ex}}}{\partial x}\right)^{\text{T}} = \alpha_2 \left[2C_{\text{ex}}^2(x(t))x(t) + 2C_{\text{ex}}(x(t))R_{\text{ex}}\dot{x}(t)\right.$$
$$\quad + 2X(t)C'_{\text{ex}}(x(t))R_{\text{ex}}\dot{x}(t)$$
$$\quad \left. + 2X(t)C'_{\text{ex}}(x(t))C_{\text{ex}}(x(t))x(t)\right], \quad (35)$$

$$\left(\frac{\partial L_{\text{ex}}}{\partial \dot{x}}\right)^{\text{T}} = \alpha_2 \left[2R_{\text{ex}}^2\dot{x}(t) + 2R_{\text{ex}}C_{\text{ex}}(x(t))x(t)\right], \quad (36)$$

$$\left(\frac{\partial L_{\text{ex}}}{\partial \ddot{x}}\right)^{\text{T}} = 2\ddot{x}(t), \ \ T_{\text{in}} \le t \le T_{\text{in}} + T_{\text{ex}}, \quad (37)$$

which yields (30). Finally, in the case where $\alpha_2 = 0$, (30) collapses to $x^{(4)}(t) = 0, T_{\text{in}} \le t \le T_{\text{in}} + T_{\text{ex}}$, which satisfies (31). ∎

Remark 3.2: In the case where $\alpha_2 = 0$, the vectors d_1, d_2, d_3, and d_4 in Theorem 3.2 can be uniquely determined using the four boundary conditions (28) and (29). In particular, $d_1 = V_0 + V_T + 3\beta T_{\text{in}}^2 T_{\text{ex}} V_T + 2\beta T_{\text{in}}^3 V_T$, $d_2 = -\beta(6T_{\text{in}}^2 V_T + 6T_{\text{ex}}T_{\text{in}}V_T)$, $d_3 = \beta(3T_{\text{ex}}V_T + 6T_{\text{in}}V_T)$, and $d_4 = -2\beta V_T$, where $\beta = 1/(3T_{\text{ex}}^3 + 12T_{\text{in}}^2 T_{\text{in}} + 12T_{\text{ex}}T_{\text{in}}^2 + 4T_{\text{in}}^3)$. Hence, $\dot{x}(t) = d_2 + 2d_3 t + 3d_4 t^2 = -6\beta V_T t(T_{\text{in}} + T_{\text{ex}} - t) - 6\beta V_T t(t - T_{\text{in}}) \leq \leq 0$, $T_{\text{in}} \leq t \leq T_{\text{in}} + T_{\text{ex}}$, which implies that the solution $x^*(t)$, $T_{\text{in}} \leq t \leq T_{\text{in}} + T_{\text{ex}}$, is decreasing during expiration, and hence, $V_{0_i} \leq x_i^*(t) \leq V_{0_i} + V_{T_i}$, $i = 1, \ldots, 2^n$. The case where $\alpha_2 > 0$ involves the solution to (30), and hence, we have been unable to show that $x^*(t)$, $T_{\text{in}} \leq t \leq T_{\text{in}} + T_{\text{ex}}$, is decreasing during expiration analytically. However, this has been verified numerically.

The physiological interpretations of the performance criteria for inspiration and expiration used in Theorem 3.1 and 3.2 are slightly different. In particular, the inspiratory criterion $\mathcal{J}_{\text{in}}(x)$ involves a weighted sum of squares of the lung volume acceleration and the mechanical work performed by the inspiratory muscles. Alternatively, during the expiratory phase the respiratory muscles remain active in the beginning of expiration since they continue their action by opposing expiration, and hence, consume oxygen thereby performing negative work. Thus, mechanical work alone is not a satisfactory criterion for describing control of breathing at rest. As in [15], we assume that oxygen consumption of expiration correlates with the integral square of the driving pressure. This assumption is supported in [21] which shows that an index of average respiratory pressure can predict the total oxygen cost of breathing. Hence, instead of mechanical work, we use the integral square of the applied pressure in the expiratory criterion $\mathcal{J}_{\text{ex}}(x)$, which corresponds to minimizing the mean standard potential energy in the lung.

It can be seen that the optimal solutions $x^*(t)$, $t \geq 0$, depend on the variables T_{in}, T_{ex}, V_0, and V_T through the boundary conditions. Moreover, the nonlinearities in (30) are due to nonlinearities in the lung compliance $C_{\text{ex}}(x)$, which make analytical solutions to (30) difficult to obtain. It is interesting to note that although the optimal solutions $x^*(t)$, $T_{\text{in}} \leq t \leq T_{\text{in}} + T_{\text{ex}}$, to (30) during the expiration phase depend on the nonlinear compliance of $C_{\text{ex}}(x)$, the optimal solutions $x^*(t)$, $0 \leq t \leq T_{\text{in}}$, to (26) during the inspiration phase are independent of the nonlinear system compliance $C_{\text{in}}(x)$. In the case where $n = 0$ (i.e., a single lung compartment model), $x(t) \in \mathbb{R}$, $R_{\text{ex}} \in \mathbb{R}$, and $C_{\text{ex}}(x) = C_{\text{ex}}$ is a constant, and hence, (30) reduces to

$$x^{(4)}(t) - \alpha_2 R_{\text{ex}}^2 x^{(2)}(t) + \alpha_2 C_{\text{ex}}^2 x(t) = 0. \tag{38}$$

This case is extensively discussed in [22] wherein the authors characterize four different solutions to (38) corresponding to $\alpha_2 = 0$, $0 < \alpha_2 < 4C_{\text{ex}}^2/R_{\text{ex}}^4$, $\alpha_2 = 4C_{\text{ex}}^2/R_{\text{ex}}^4$, and $\alpha_2 > 4C_{\text{ex}}^2/R_{\text{ex}}^4$.

IV. NUMERICAL DETERMINATION OF OPTIMAL VOLUME TRAJECTORIES

The optimal volume trajectories formulated in Section III result in two-point nonlinear boundary-value problems. Numerical methods for solving such problems include shooting methods and steepest descent methods. In this section, we use the collocation method implemented by *bvp4c* in MATLAB® to numerically integrate the differential equations (26) and (30) to obtain the optimal volume trajectory $x^*(t)$, $t \geq 0$.

For our simulations we first consider a two-compartment lung model and use the values for the lung compliance found in [18]. In particular, we set $a_{i_1}^{\text{in}} = 0.018 \, \ell/\text{cm H}_2\text{O}$, $b_{i_1}^{\text{in}} = 0.0233$, $a_{i_2}^{\text{in}} = 0.025 \, \ell/\text{cm H}_2\text{O}$, $a_{i_3}^{\text{in}} = 0.2532 \, \ell/\text{cm}$

H_2O, $b_{i_3}^{\text{in}} = -0.01$, $x_{i_1}^{\text{in}} = 0.3 \, \ell$, $x_{i_2}^{\text{in}} = 0.48 \, \ell$, $a_{i_1}^{\text{ex}} = 0.02 \, \ell/\text{cm H}_2\text{O}$, $b_{i_1}^{\text{ex}} = 0.078$, $a_{i_2}^{\text{ex}} = 0.038 \, \ell/\text{cm H}_2\text{O}$, $a_{i_3}^{\text{ex}} = 0.1025 \, \ell/\text{cm H}_2\text{O}$, $b_{i_3}^{\text{ex}} = -0.15$, $x_{i_1}^{\text{ex}} = 0.23 \, \ell$, $x_{i_2}^{\text{ex}} = 0.43 \, \ell$, $i = 1, 2$. Here, we assume that the bronchial tree has a dichotomy structure (see Section II). The airway resistance varies with the branch generation and typical values can be found in [23]. Furthermore, the expiratory resistance will be higher than the inspiratory resistance by a factor 2 to 3. Here, we assume that the factor is 2.5.

For our simulation we assume that the inspiration time $T_{\text{in}} = 2$ sec and the expiration time $T_{\text{ex}} = 3$ sec. The two weighting parameters α_1 and α_2 differ from person to person. Nominal values for the weighting parameters are $\alpha_1 = 2.0l/\text{sec}^3$ cm H_2O and $\alpha_2 = 0.1l^2/\text{sec}^4$ cm H_2O, which correspond to spontaneous breathing at rest. Figure 1 shows the optimal air volume $x_1^*(t)$, $t \geq 0$, and the optimal airflow rate $\dot{x}_1^*(t)$, $t \geq 0$, for the first compartment given by the two-point nonlinear boundary-value problems (22) and (34). Note that the airflow curve for inspiration is symmetric since the nonlinearities in $C_{\text{in}}(x)$ do not appear in (26). However, $x^*(t)$, $t \geq 0$, obtained using (30) during expiration involves $C_{\text{ex}}(x)$, and hence, the airflow curve is asymmetric. Moreover, if we set the weighting parameter $\alpha_2 = 0$, it follows from (30) that the airflow curve for the expiration is given by a parabolic arc. See Figure 2.
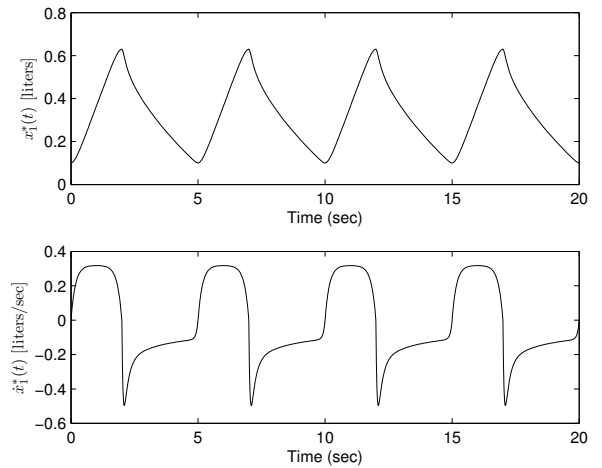

Fig. 1. Volume and airflow pattern for the first compartment.

Figure 3 shows the driving pressure generated by the respiratory muscles for the first compartment using the optimal air volume $x_1^*(t)$, $t \geq 0$. Figure 4 compares the optimal air volume trajectory $x_1^*(t)$, $t \geq 0$, with a non-optimal air volume trajectory $x_1(t)$, $t \geq 0$, generated by the linear pressure $p_{\text{in}}(t) = 20t + 5$ cm H_2O, $t \in [0, T_{\text{in}}]$, and $p_{\text{ex}}(t) = 0$ cm H_2O, $t \in [T_{\text{in}}, T_{\text{in}} + T_{\text{ex}}]$ [5]. Note that $x_1^*(t)$, $t \geq 0$, switches between the end expiratory level $V_{0_1} = 0.1l$ and the tidal volume $V_{T_1} = 0.53l$. Figure 5 shows the phase portrait of the optimal trajectories $x_1^*(t)$ and $x_2^*(t)$, and suboptimal trajectories $x_1(t)$ and $x_2(t)$. Note that both sets of trajectories asymptotically converge to a limit cycle, with the optimal solutions satisfying the boundary conditions given in (16), (17), (28), and (29).

Finally, Figure 6 shows the optimal air volume trajectories for a four-compartment model with each air volume trajectory satisfying the boundary conditions given in (16), (17), (28), and (29). For this simulation, the compliance parameters are taken to be identical to those used for the two-compartment model with $i = 1, 2, 3, 4$, and the values
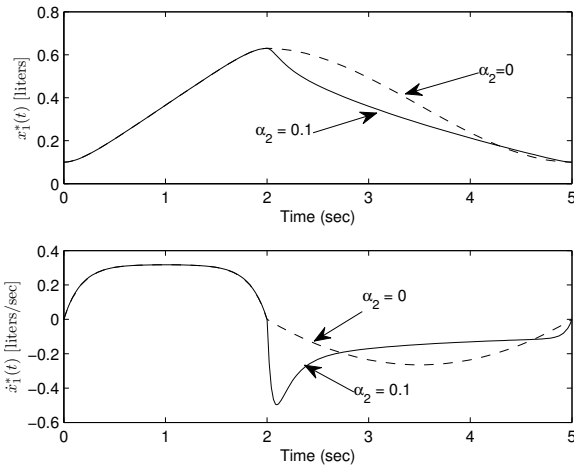
Fig. 2.   Volume and airflow pattern for $\alpha_2 = 0$ and $\alpha_2 = 0.1$.
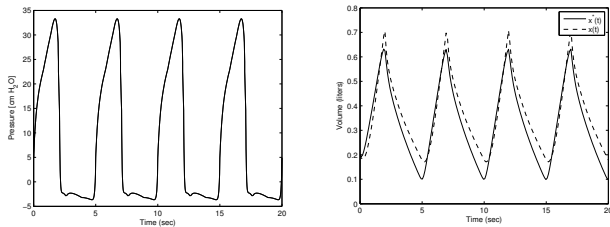

Fig. 3. Pressure generated by optimal solution.

Fig. 4.   Optimal volume $x^*(t)$ and nonoptimal volume $x(t)$ versus time.

for airway resistances are generated using the results of [23].

V. CONCLUSION

We developed an optimal respiratory air flow pattern using a nonlinear multi-compartment model for a lung-rib-cage system. The determination of the optimal air volume trajectories are derived using classical calculus of variations techniques and involve optimization criteria that account for oxygen expenditure of the respiratory lung muscles, lung volume acceleration, and elastic potential energy of the lung. Future work will include the development of adaptive control algorithms that will utilize these models within a model reference adaptive control architecture for fully automating mechanical ventilation to ensure adequate ventilation and oxygenation for critical care patients in intensive care units.

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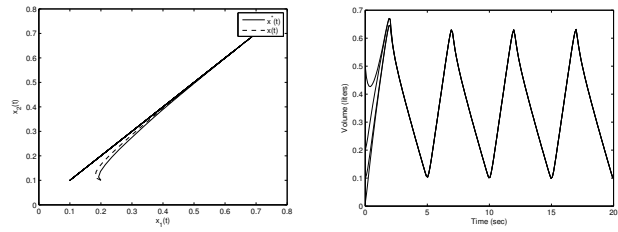
Fig. 5. Phase portrait for $x_1^*(t)$ versus $x_2^*(t)$ and $x_1(t)$ versus $x_2(t)$.

Fig. 6. Optimal volume $x^*(t)$ versus time for a four-compartmental model.

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