A detailed cardiopulmonary for dynamic simulation of their interaction

K. Hemalatha¹, and M. Manivannan²
¹,² Indian Institute of Technology Madras/Applied Mechanics, Chennai, India
Email: hema75@gmail.com, mani@iitm.ac.in

Abstract—A comprehensive lumped parameter electrical analog model of cardiopulmonary (CP) system to study the interaction between cardiovascular and respiratory system is presented. This model consists of 1) cardiovascular model integrates four cardiac chambers with valves, pulmonary and systemic circulation, septal and pericardial coupling, and baroreflex control 2) respiratory system with lung mechanics and gas transport at alveolar-capillary membrane. The cardiopulmonary interaction is realized by intrapleural pressure (Ppl). The governing equations for pressure, volume and flow in each vascular and respiratory compartment are derived from mass balance and continuity principles. Computer simulations are accomplished by numerically integrating the differential equations. Parameters of this combined model were adjusted to fit nominal data, yielding accurate hemodynamic waveforms and validated with literature data. Sensitivity analysis is also performed to individual model parameters. The respiratory influence on aortic pressure is presented for quite breathing and Valsalvamuever. In summary, this model can be used to analyze cardiopulmonary interactions in normal and pathological states of both the system.

I. INTRODUCTION

Cardiopulmonary (CP) diseases need better understanding of their interactions for diagnosis and treatment [1]. Mathematical models can provide more information regarding both invasive and non-invasive parameters related to cardiovascular and respiratory system. Our objective is to develop a detail model of CP with the facility of simulating all kinds of diseases related to both the systems and their influence on each other. This model integrates two distinct models, heart with closed loop circulation [2], respiratory system with lung mechanics [3] and gas exchange [4]. A comprehensive survey of mathematical models to study the interaction of cardiovascular and respiratory system vary significantly in their complexity, assumption and objectives [5,6]. Many authors have constructed separate models to explain cardiovascular system behavior in normal as well as pathophysiological conditions [6] and respiratory systems [7]. The interaction between cardiovascular and respiratory model are incorporated in many models only by modulating intrathoracic pressure in terms of respiratory frequency [8,2] without coupling detailed respiratory model. A comprehensive cardiopulmonary model with detailed circulatory model, lung mechanics and gas exchange has been reported in [9]. However, in their model, the cardiac valves are discrete in nature which has only two states either fully opened or closed. Therefore their model is unable to generate the actual hemodynamics of valves and to simulate valvular diseases which are the most common cardiac diseases. The pericardial coupling between heart chambers is also not addressed in their model and pulmonary vascular elastances are kept as constant, where as time varying elastances is important for studying cardiopulmonary interactions. Our model includes 1) cardiovascular model of four cardiac chambers with proportional valves, pulmonary and systemic circulation, pericardium, septum and baroreflex control, 2) respiratory system with lung mechanics and gas exchange. Our model therefore has the advantages of simulating normal and pathological conditions of both the systems and also their interaction in above said conditions.

II. MODEL FORMULATION

A. Cardiovascular Model

The general form of the cardiovascular model is based on the work reported in [2]. With the focus of our objective the base has been modified. Fig.1 shows the electrical analog of cardiovascular model.

Heart Model: It includes four cardiac chambers with four heart valves. The viscoelastic nature of the heart tissue is modeled by a time varying elastance as given below [10].

For Left Ventricle (LV)

\[
\begin{align*}
& f_c = \begin{cases} 
F_f & \text{for } 0.5 \cdot (1 - \cos (\pi t / t_{ec})) + \frac{F_{max}}{F_f} \\
F_f & \text{for } 0.5 \cdot (1 + \cos (\pi t / t_{ec})) + \frac{F_{max}}{F_f}
\end{cases} \quad 0 \leq t \leq t_{ec} \\
& F_f = 1 - \left(\frac{P_{av}}{P_{max}}\right)
\end{align*}
\]

Fig 1. Electrical analog of cardiovascular system

Where \(\sigma_{10} \text{ [mmHg•ml⁻¹]}\) represent the time varying elastance of the left ventricle free wall, \(t_{ec} \text{ [0.3 sec]}\) indicate a cardiac cycle and end ejection time, respectively. \(F_f\) is a scaling factor that characterizes the nonlinear property of the starling law and the dependence of the time-variant elastance on the volume of the left ventricle.
where \( v_{\text{max}} \) is the maximum cardiac fluid volume of normal human (900ml). In similar way right ventricle elastance can also be written. The corresponding parameter values are given in Fig.1. The coupling septal wall offers direct pressure coupling between left and right ventricles through its constant elastance \( (E_v) \). Hence the functional elastance of both ventricles are given as

\[
E_{\text{ref}} = \left( \frac{E_v}{(\epsilon_{\text{ref}} + E_v)} \right)
\]

Because of the pressure coupling, the net pressure of each ventricles depends not only their volume and elastance but also the coupling pressure from right ventricle.

\[
P_{\text{LV}} = E_{\text{ref}} \cdot v_{\text{LV}} + \frac{\epsilon_{\text{LV}}}{(\epsilon_{\text{L}} + E_v)}
\]

Similar way right ventricle pressure also can be formulated. But the atrium septum is assumed to be rigid i.e the atria are uncoupled and have no direct influence on each other. So the free walls of the atriums are characterized by a time varying elastance as given below. For Left Atrium (LA)

\[
e_{\text{at}} = \left\{ \begin{array}{ll}
e_{\text{at}} & 0.5 \cdot (1 - \cos(\pi \cdot (t - t_a) / t_{\text{ur}})) + e_{\text{at}} \quad t_a \leq t \leq t_u \\
e_{\text{at}} & 0.5 \cdot (1 + \cos(\pi \cdot (t - t_u) / t_{\text{ur}})) + e_{\text{at}} \quad t_u \leq t \leq (t_u + t_a)
\end{array} \right.
\]

Where \( e_{\text{at}} \) [mmHg*ml–1] represent the elastance of the atrium, respectively; \( t_r \) [0.855 sec] indicate a cardiac cycle, \( t_{\text{ur}} \) [0.696 sec] refers to the time when the atrium begins to contract and \( t_{\text{ur}} \) [0.835 sec] indicates the time when the atrium begins to relax. Right heart chambers elastance can be written in the same manner. Hence \( p_{\text{a}} \) can be given as follows

\[
p_{\text{a}} = e_{\text{at}} \cdot v_{\text{a}}
\]

Heart Valves: The heart valves nonlinear time dependent behavior is addressed by modeling them with three elements based on. The pressure-flow relationship across the valves are realized by Bernoulli’s resistance (S), which states that the pressure drop caused by flow separations at the exit of the valve is proportional to the square of flow \( \frac{v^2}{S} \), the inertial (L) term related to the acceleration and deceleration of flow and the viscous resistance (R).

Systemic and Pulmonary Circulation: The systemic circulation is modeled with simple capacitive where as an exponential P-V relationship [11] is adapted for pulmonary circulation in order to achieve effective coupling between respiratory and CV systems. The P-V relationship is given below

\[
p = E_0 \left( e^{v/s} \right) Z
\]

where \( E_0 \) (mmHg*ml–1) denotes the zero-volume elastance, \( Z \) (ml) refers to the volume constant, and \( v \) [ml] indicates the blood volume contained in pulmonary circulatory unit (artery/vein).

Pericardium: The volume coupling between two ventricles (left/right) is offered by the pericardium all chapers in the pericardial cavity [2]. Pericardium gives a significant constraint on the filling capabilities of the heart chambers[12]. So the total fluid volume includes not only the four chamber blood volume but also the pericardial fluid volume \( (V_{pc}) \).

\[
V_{pc} = v_{la} + v_{ra} + v_{lu} + v_{lu} + v_{pr}
\]

Baroreflux Control: A simple approximated first order relationship is used in this model to control heart rate based on Systolic peak pressure of aorta \( (P_{\text{a0}}) \) which is given as follows,

\[
HR = \frac{K_{\text{bar}}}{(P_{\text{a0}} - 120)} + HR_0
\]

where \( K_{\text{bar}} \) is 188.68 based on [13] and HR_0 is 70 beats/min.

B. Respiratory Model:

The basics of the respiratory model consists of lung mechanics model based on [2] and gas exchange model based on [4,9] with some modifications (Fig.2). In general gas transport occurs at two sites 1) between alveoli air and pulmonary capillary blood and 2) between systemic capillary blood and cellular fluid. Our gas exchange model is limited to characterize gas transport only between blood and air at alveoli (lung gas exchange) not at tissue level (between blood and cellular fluid).

Lung Mechanics: In our lung mechanics model airway path of the respiratory system is subdivided as peripheral airways (small airways), collapsible airway region and upper airway region. Peripheral airways is lumped as a single unit and termed as small airway and is characterized by a resistance (Rs) that was inversely proportional to VA [14,15]. The Collapsible airway region of volume VC has been characterized in terms of a volume-dependent resistance and the upper airway region is also by a nonlinear, volume-dependent resistance. Alveolar region (of volume VA) is assumed to exhibit nonlinear, time-varying viscoelastic behavior [16].

The viscoelastic property of the lung tissue is modeled by two element Kelvin body which incorporates capacitance to represent elastic nature and a lung tissue resistance to characterize viscous dissipative property. The lung and airways are assumed to be enclosed within a rigid-walled thoracic cage, with the airways open to the atmosphere. The intrapleural space is assumed to be subject to a time-varying, spatially averaged driving intrapleural pressure which is assumed to be equivalent to the average pressure in the pleural space acting on the

Table.1 Model Parameters for Respiratory system

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_s )</td>
<td>1.5x10^4 mmHg/ml·s⁻¹</td>
<td>( K_i )</td>
<td>0.001 mmHg/ml·s⁻¹</td>
</tr>
<tr>
<td>( R_l )</td>
<td>0 mmHg/ml</td>
<td>( A_i )</td>
<td>0.368 mmHg</td>
</tr>
<tr>
<td>( V_{\text{max}} )</td>
<td>27.43 mmHg</td>
<td>( A_s )</td>
<td>5.21 mmHg</td>
</tr>
<tr>
<td>( V_{\text{air}} )</td>
<td>185 ml</td>
<td>( C_s )</td>
<td>2.74 mmHg</td>
</tr>
<tr>
<td>( V_{\text{cap}} )</td>
<td>6.6x10⁻³ mmHg/ml·s⁻¹</td>
<td>( L_s )</td>
<td>680 ml/mmHg</td>
</tr>
<tr>
<td>( K_s )</td>
<td>10.9 mmHg</td>
<td>( F_{\text{air}} )</td>
<td>7.3x10⁴ mmHg/ml·s⁻²</td>
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<tr>
<td>( V_{\text{RV}} )</td>
<td>1650 ml</td>
<td>( F_{\text{eff}} )</td>
<td>0 mmHg</td>
</tr>
<tr>
<td>( V_{\text{LV}} )</td>
<td>5300 ml</td>
<td>( P_{\text{eff}} )</td>
<td>760 mmHg</td>
</tr>
<tr>
<td>( A_r )</td>
<td>2.5x10⁻³ mmHg/ml·s⁻¹</td>
<td>( H_{\text{air}} )</td>
<td>0.45</td>
</tr>
<tr>
<td>( K_r )</td>
<td>3.3x10⁻³ mmHg/ml·s⁻¹</td>
<td>( T_{\text{eff}} )</td>
<td>300 K</td>
</tr>
<tr>
<td>( A_t )</td>
<td>0.147 mmHg</td>
<td>( C_H )</td>
<td>2x10⁸</td>
</tr>
</tbody>
</table>

Fig.1: Lung and respiratory system diagram
lungs and produced by the muscles of respiration. Excursion in pleural pressure is dictated by the effort generated by the subject. So the source for the respiratory model is the time varying intrapleural pressure.

Gas exchange model: Gas exchange between blood and air occurs across the alveolar – capillary membrane. The following assumptions are made in our model 1) Inspired air was instantaneously warmed to body temperature (typically 300K) and fully saturated with water vapor, 2) The gaseous mixture obeys the ideal gas law, 3) Blood is considered as a uniform homogeneous medium (plasma and erythrocytes are lumped together), 4) within a control volume, the instantaneous specific reactions were then considered to be at equilibrium, 5) Diffusion in radial and axial directions are not considered [17], so bulk gas transport occurs only in axial direction, 6) Diffusion is the sole cause of gas transport and its rate depends on lung diffusion capacity(DL_{a}) for the particular species (O_{2} and CO_{2}), 7) One directional diffusion is possible (O_{2} from air to blood and CO_{2} from blood to air). 8) N_{2} diffusion is neglected which has either way diffusion.

**Ppl mediated CP interaction:** The interactions between cardiovascular and respiratory system could be incorporated in variety of forms. To study the interaction between two subsystems, generally one subsystem is perturbed and the other subsystem parameters are monitored. In our model the driving pressure of the respiratory system (Ppl) is perturbed and the radial artery pulse of cardiovascular system is monitored. This is achieved by incorporating the pleural pressure variations in the CV system directly to all compartments in the thorax, which includes vena cava, right heart, pulmonary circulation, left heart, and aorta[2,9].

### III. RESULTS AND DISCUSSION

#### A. Numerical methods and Parameters

In our cardiovascular model, Elastance or capacitance nodes are considered for formulating volume equations according to mass balance principles and for flow equations are formulated for inertia nodes based on continuity equations. Totally 25 (Fig.1) first order state equations are written for CV model.

In respiratory model in similar way, volume (elastance or capacitance) and flow equations ( thro’ airway resistances) equations are written. The partial pressure equations of O_{2} and CO_{2} in blood and air are formulated based on ideal gas law. The state equations are given in

#### APPENDIX. Fourth order Runge-Kutta numerical method is used to solve the state equation for a time step of 10ms. The model simulation software is return using MATLAB. Two step model parameter identification procedure is adapted. Initially they are roughly taken from physiological ranges reported in literature based on experimental works and then fine tuned based on to yield accurate hemodynamic waveforms. The turned model parameters for CV system is given in Fig.1 and Table.1 gives model parameters of respiratory system. The sensitivity of each parameter of the CV model to important hemodynamic parameter has been analyzed. The sensitivity is quantified by computing a gain factor which is the ratio of percent change of affected (important hemodynamic) parameter and percent change of affecting model parameter. Each model parameter is perturbed by a 10% increase from its control value. The simulation is run for few cardiac cycles (10 cycles) to settle from the initial transients. From the settled response the sensitivity gain is calculated for each parameter. The parameter for which the sensitivity gain ≥0.1 is considered and tabulated in Table.2, the remaining parameters are considered as insensitive which are not given in the table. Systemic after load resistance (Ra) and aortic valve resistance (Rav) and Venous compliances (Cven) are sensitive which are major determinants of cardiac output and aortic pressure. All hemodynamics are more sensitive to ventricular elastances which are main source of pumping action of the model (source). Intrapleural pressure (Ppl) has good sensitivity, may be due to it’s direct influence on aortic pressure. The septum and pericardium sensitivity is studied by removing them from the simulation. The qualitative sensitivity of respiratory system can be analyzed by changing the functional description of resistances and compliances which is well explored in [4].

#### B. Hemodynamic waveforms of CV model

Fig.3 shows the elastance and corresponding pressure plots for right and left heart. The elastance varies from their respective minimum diastolic value to their respective maximum end systolic (end of ejection) value and vice versa from early diastolic relaxation to minimum diastolic value in one cardiac cycle based on cosine function and the data are compared with the experimental results reported in [18]. The arterial pressure has two

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>LVV</th>
<th>Vpua</th>
<th>Vvc</th>
<th>MAP</th>
<th>Ppl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ra</td>
<td>-0.1</td>
<td>-0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Epua0</td>
<td>-0.1</td>
<td>-0.3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Erva</td>
<td>-0.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Erab</td>
<td>NS</td>
<td>NS</td>
<td>0.1</td>
<td>NS</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Elaa</td>
<td>0.1</td>
<td>0.1</td>
<td>NS</td>
<td>NS</td>
<td>0.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>Elab</td>
<td>NS</td>
<td>NS</td>
<td>0.1</td>
<td>NS</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Elva</td>
<td>-0.1</td>
<td>NS</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>-0.2</td>
</tr>
<tr>
<td>Elvb</td>
<td>-0.2</td>
<td>-0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Vpco</td>
<td>-0.2</td>
<td>0.1</td>
<td>NS</td>
<td>0.2</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Ppl</td>
<td>-0.3</td>
<td>0.1</td>
<td>NS</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Cvc</td>
<td>0.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cart</td>
<td>0.1</td>
<td>NS</td>
<td>-0.1</td>
<td>0.1</td>
<td>NS</td>
<td>0.1</td>
</tr>
</tbody>
</table>

![Table 2. Sensitivity analysis in terms of gain for CV model simulation](image-url)
positive deflections: the a wave reflects atrium contraction at the end of diastole, and the v wave represents passive filling of the atrium during systole when the tricuspid valve is closed. The negative deflection follows the c wave is known as the x descent and v wave following negative deflection is y descent [18]. The ventricular volume plots (Fig.4) show ventricular filling (phase a; diastole), isovolumetric contraction (phase b), ejection (phase c), and isovolumetric relaxation (phase d) clearly [19]. Tricuspid and mitral valves flow (Fig.4) show Normal flow across the atria-ventricular valves is which characterized by initial rapid early flow (E-wave) and a smaller, late atrial kick (A-wave) as reported in [20]. Vena cava and pulmonary vein flow pattern [19] show (Fig.5) R wave which represents reverse flow, S wave represents systolic forward flow and D wave represents diastolic forward flow. Arterial pressure waveform has distinct peak systolic pressure (PSP), dicrotic notch(DN), aortic valve opens (AVO) and aortic end-diastolic pressure (AEDP) phases.

D. CP interaction

Fig.10 shows the effect of spiratory induced variation in aortic pressure (Pao) for quite breathing and valsalva maneuver condition. Valsalva maneuver condition is simulated by keeping Ppl as high positive pressure (30 mmHg). Pao show four distinct phase, the phase I transient increase, the phase II suppressed pulses, the phase III transient decrease and phase IV bradycardia as reported in [23].

C. Dynamics of Respiratory model

The time varying pleural pressure (Ppl) is the driving force for the respiratory model. Simulation is done for quite breathing condition in which Ppl (Fig.6) is less negative during expiration and more negative during inspiration. The simulation is stated form start of inspiration (or end of expiration). During inspiration more negative Ppl pressure makes alveolar pressure (PA) as negative compared to atmospheric pressure (P atm =0 mmHg) and sucks air from atmosphere. This increases lung recoil pressure and compensates PA and makes it equal to Patm and ends inspiration phase. The reverse process occurs during expiration. Fig.7 shows corresponding changes in dead space volume and alveolar volume during respiratory cycles [21].

Gas exchange occurs at the alveolar- capillary membrane due to partial pressure. Fig.8 shows partial pressure of O2 and CO2 in upper air way (Dead space) and Fig.9 for alveolar region [22]. During inspiration through upper airway O2 rich atmospheric air enters alveolar region which increases partial pressure of O2 both in alveoli and in dead space and reduces CO2 partial pressure and vice versa during expiration. The slope of the partial pressure plots for both O2 and CO2 space is high (more changes in P O2 and P CO2) compared to alveolar P O2 and P CO2 (less changes), this implies alveolar P O2 and P CO2 is maintained more or less constant to facilitate continuous gas transfer between alveoli and capillary. The constant maintenance of P O2 and P CO2 is achieved by mixing of inhaled air with residual air at alveoli. The high frequency variations in alveoli P O2 and P CO2 represents cardiac influences (cardiac frequency).

Figure 3. Elastance and Pressure waveforms of cardiac chambers
Figure 4. Cardiac chambers volume and Heart valves flow (AV-Aortic Valve, MV-Mitral Valve, PV-Pulmonary Valve and TV-Tricuspid Valve)
Figure 5. Flow waveforms of systemic and pulmonary circulation
Figure 6. Pleural pressure and Alveolar Pressure
Figure 7. Alveolar and Dead space volume
D. Model limitations and extension

As in any physical model, our model also has some limitations. 1) The pulse wave propagation phenomena is not addressed. 2) ANS mediated reflex activities such as cardiopulmonary reflex, chemoreflex are not considered. 3) Whole alveolar units are lumped as a single unit in respiratory model and upper airway bifurcations are not considered, 4) It’s a supine human model, so average Ppl is applied to all CV segments lie in intrathoracic cavity. 5) Coronary circulation is omitted and also not possible to simulate regional disease. However this model has freedom to extent in order to address the above mentioned limitations. This model also has the advantages of simulating the cardio-pulmonary diseases such as Mitral valve stenosis (MS), mitral regurgitation, left heart failure, right heart failure, cardiac tamponade, pulsus paradoxus, asthma, sleep apnea, emphysema and influence of one system pathophysiology on other system.

IV. CONCLUSION

Our model of the human cardiopulmonary system combines the advantages of several component models previously reported in literature. The parameters of the model are tuned to match literature data of cardiovascular and respiratory systems. The model simulated basic hemodynamic waveform (pressure, flow and volume) and respiratory system responses (pressure, flow, volume and partial pressure of gas species) are fit reasonable with literature data for normal human subjects. The interaction between CV and respiratory system is simulated for quite breathing and Valsalva maneuver (VM) conditions. The aortic pressure is modulated with respiratory frequency and it shows four distinct phases in VM. Our model has the freedom of simulating all kinds of cardiac and respiratory pathophysiological conditions. Therefore with this model the CP interactions study can be extended to both the system diseases. ANS control over CP can also be implemented in this model.

APPENDIX A  CARDIOVASCULAR MODEL

The dynamics of cardiovascular system is defined by following 24 state equations.

\[
\begin{align*}
\frac{d\text{waven}}{dt} &= q_{\text{cap}} - q_{\text{ven}}, \\
\frac{d\text{pp}}{dt} &= q_{\text{ven}} - q_{\text{oc}}, \\
\frac{d\text{pnu}}{dt} &= q_{\text{oc}} - q_{\text{pv}}, \\
\frac{d\text{pnu}}{dt} &= q_{\text{pv}} - q_{\text{pmu}}, \\
\frac{d\text{pcap}}{dt} &= q_{\text{pmu}} + q_{\text{pm}} + q_{\text{pm}} - q_{\text{pm}}.
\end{align*}
\]

\[
\frac{d\text{qcap}}{dt} = \frac{\nu_{\text{ven}}}{C_{\text{ven}}} + \frac{S_{\text{ven}}}{C_{\text{ven}}} - R_{\text{ven}}q_{\text{ven}} - \frac{\nu_{\text{oc}}}{C_{\text{oc}}} - \frac{S_{\text{oc}}}{C_{\text{oc}}}/q_{\text{oc}}.
\]

\[
\frac{d\text{qpmu}}{dt} = \frac{\nu_{\text{pmu}}}{C_{\text{pmu}}} + \frac{S_{\text{pmu}}}{C_{\text{pmu}}} - R_{\text{pmu}}q_{\text{pmu}} + \frac{\nu_{\text{pm}}}{C_{\text{pm}}} - \frac{S_{\text{pm}}}{C_{\text{pm}}} + \frac{\nu_{\text{pmu}}}{C_{\text{pmu}}} - \frac{S_{\text{pmu}}}{C_{\text{pmu}}} + \frac{\nu_{\text{pm}}}{C_{\text{pm}}} - \frac{S_{\text{pm}}}{C_{\text{pm}}} + \frac{p_{\text{pl}}}{C_{\text{pmu}}}.
\]

\[
\frac{d\text{qpm}}{dt} = \left\{ \begin{array}{ll}
(P_{\text{pl}} - q_{\text{pm}}/C_{\text{pm}} - R_{\text{pm}}q_{\text{pm}} - b_{\text{pm}}q_{\text{pm}}) + S_{\text{pm}} & , \text{if } A_{\text{pm}} > 0 \\
0 & , \text{otherwise}.
\end{array} \right.
\]

\[
\frac{d\text{qpl}}{dt} = \left\{ \begin{array}{ll}
(e_{\text{pl}}q_{\text{pl}} - R_{\text{pm}}q_{\text{pm}} - b_{\text{pm}}q_{\text{pm}}) & , \text{if } A_{\text{pm}} > 0 \\
0 & , \text{otherwise}.
\end{array} \right.
\]

\[
\frac{d\text{qpp}}{dt} = \left\{ \begin{array}{ll}
(P_{\text{pp}} - q_{\text{pp}}/C_{\text{pp}} - R_{\text{pp}}q_{\text{pp}} - b_{\text{pp}}q_{\text{pp}}) & , \text{if } A_{\text{pp}} > 0 \\
0 & , \text{otherwise}.
\end{array} \right.
\]

\[
\frac{d\text{qpv}}{dt} = \left\{ \begin{array}{ll}
(e_{\text{pv}}q_{\text{pv}} - R_{\text{pv}}q_{\text{pv}} - b_{\text{pv}}q_{\text{pv}}) & , \text{if } A_{\text{pv}} > 0 \\
0 & , \text{otherwise}.
\end{array} \right.
\]

\[
\frac{d\text{qoc}}{dt} = \left\{ \begin{array}{ll}
(e_{\text{oc}}q_{\text{oc}} - R_{\text{oc}}q_{\text{oc}} - b_{\text{oc}}q_{\text{oc}}) & , \text{if } A_{\text{oc}} > 0 \\
0 & , \text{otherwise}.
\end{array} \right.
\]

\[
\frac{d\text{qpm}}{dt} = \left\{ \begin{array}{ll}
(R_{\text{pm}}q_{\text{pm}} - R_{\text{pm}}q_{\text{pm}} - b_{\text{pm}}q_{\text{pm}}) & , \text{if } A_{\text{pm}} > 0 \\
0 & , \text{otherwise}.
\end{array} \right.
\]

\[
\frac{d\text{qpv}}{dt} = \left\{ \begin{array}{ll}
(R_{\text{pv}}q_{\text{pv}} - R_{\text{pv}}q_{\text{pv}} - b_{\text{pv}}q_{\text{pv}}) & , \text{if } A_{\text{pv}} > 0 \\
0 & , \text{otherwise}.
\end{array} \right.
\]

\[
\frac{d\text{qoc}}{dt} = \left\{ \begin{array}{ll}
(R_{\text{oc}}q_{\text{oc}} - R_{\text{oc}}q_{\text{oc}} - b_{\text{oc}}q_{\text{oc}}) & , \text{if } A_{\text{oc}} > 0 \\
0 & , \text{otherwise}.
\end{array} \right.
\]
APPENDIX B RESPIRATORY MODEL

The complete respiratory model equations are given here. The suffix means are given as: c- collapsible airway, s-small airway, u-upper airway, RV-residual volume, ve-lung recoil, w-chest wall, A-alveole, and Pb-partial pressure. Gas exchange equations are given only for O₂, similarly CO₂ equations can be written.

\[ R_c = \begin{cases} K_{c0} + R_{c0}Bc \left( \frac{V_c}{V_{cmax}} - 0.7 \right)^2 & V_c > V_{cmax} \\ K_{c0} \left( \frac{V_{cmax}}{V_c} \right)^2 + R_{c0} & V_c < V_{cmax} \end{cases} \]

\[ R_s = A_s \left( e^{\frac{V_s(V_{A-R})}{P_{A-R}}} \right) \]

\[ R_u = Au + Ku[Vc\cdotw] \]

\[ P_l = A_l e^{V_l[Vl\cdotw]} + B_l \]

\[ P_c = \begin{cases} \frac{A_c - B_c}{\left( \frac{V_c}{V_{cmax}} - 0.7 \right)^2} V_{cmax} & V_c > V_{cmax} \\ A_c - B_c(0.5 - 0.7)^2 - R_{c0} \log \left( \frac{V_{cmax}}{V_c} - 0.999 \right) \end{cases} \]

\[ PA = Ppl + Pve + PI = Pce \]

\[ Pve = Vve/Cve \]  \[ \phi_A = \frac{\Delta P_A}{\Delta V} \]  \[ Q_A = \frac{P_{ave} - P_{alve}}{\rho_s} \]  \[ Q_e = \frac{P_{ave} - P_{e}}{\rho_s} \]  \[ Q_w = \frac{P_{ave} - P_{e}}{\rho_s} \]

\[ \frac{dQ_H}{dt} = \frac{D_{O2}}{V_{P_{O2}}} = \frac{P_{O2} - P_{O2}}{V_{P_{O2}}} \]

REFERENCES
