1 Anafi-Wilson type airway wall Lambert model

- radius of airway lumen is determined by the transmural pressure P_{tm} given by Lambert

$$R\left(P_{tm}\right)=\begin{cases}\sqrt{R_i^2\left(1-\frac{P_{tm}}{P_1}\right)^{-n_1}}, & P_{tm}\leq 0\\ \sqrt{r_{imax}^2-\left(r_{imax}^2-R_i^2\right)\left(1-\frac{P_{tm}}{P_2}\right)^{-n_2}}, & P_{tm}\geq 0\end{cases}$$

  where r_{imax} is the maximal radius, R_i is the radius at $P_{tm}=0$. the parameters n_1, n_2 and P_1 are all dependent on the airway order and P_2 is calculated explicitly from r_{imax}, R_i, n_1, n_2 and P_1.

- 1st order relaxation dynamics toward the static equilibria when $\rho>0$,

$$\frac{dr}{dt}=\rho\left[R\left(P_{tm}\right)-r\right]$$

- The effective transmural pressure P_{tm} of the coupled system can be written as a balance between the imposed transmural pressure P_0, the constricting pressure of the ASM and the parenchymal tethering stress P_τ resulting from the pleural pressure

$$P_{tm}=P_0-\frac{\kappa * F_{ASM}}{r}+P_\tau$$

  F_{ASM} represents the contractile force of the ASM.

- We consider the airway wall model of Lambert with airflow modelled as done by AW

$$R_{aw}=\frac{12l\mu}{\pi r^4}$$

  where r is the time-dependent radius of the airway lumen.

- We consider the imposed transmural pressure P_0 as being the difference between the inter-lumen pressure (P_{lumen}) and the pressure in the acinus (P_A). i.e $P_0=P_{lumen}-P_A$ for which

$$P_{lumen}=(P_{aw}+P_A)/2$$

  and P_{aw} and P_A are the airway and acinar air pressures respectively.

2 Flexible Lung with gas exchange

- Ignoring intertia forces and incompressibility of the air, we can model the average alveolar pressure, P_A via

$$\frac{dP_A}{dt}=\frac{P_{aw}E}{P_A}Q_A+\frac{dP_L}{dt}$$

- airflow is modeled by

$$q = \frac{P_{aw} - P_A}{R_{aw}}$$

- The net flux of gas into the alveoli is given by

$$Q_A = q + D_c\,(p_c - p_{ac}) + D_o\,(p_o - p_{ao})$$

  where D_o, D_c represent the diffusion capacities a of oxygen and carbon dioxide resperctively. p_o and p_c are the blood partial pressures of oxygen and CO2, where p_{ao} and p_{ac} are the alveolar partial pressure of O2 and CO2.

- $f_o$and f_c are the rate of changes of the conc of O2 and CO2. f_{oi} and f_{ci} are the conc of inspired O2 and CO2. f_{om}: concentration of oxygen in the mouth. f_{cm}: conc of CO2 in the mouth.

3 System of Equations

- Hai-Murphy ASM ODE 4 state model

$$\begin{aligned}
\frac{dM}{dt} &= -k_1 M + k_2 M_p + k_7 AM \\
\frac{dM_p}{dt} &= k_4 AM_p + k_1 M - (k_2 + k_3) M_p \\
\frac{dAM_p}{dt} &= k_3 M_p + k_6 AM - (k_5 + k_4) AM_p \\
\frac{dAM}{dt} &= k_5 AM_p - (k_6 + k_7) AM
\end{aligned}$$

$$k_1 = \begin{cases} 0.55 & if\ t \geq 0\,\&\,t < 5 \\ 0.3 & otherwise \end{cases}$$

- Lambert mo

$$R\left(P_{tm}\right)=\begin{cases}\sqrt{R_i^2\left(1-\frac{P_{tm}}{P_1}\right)^{-n_1}}, & P_{tm}\leq 0\\ \sqrt{r_{imax}^2-\left(r_{imax}^2-R_i^2\right)\left(1-\frac{P_{tm}}{P_2}\right)^{-n_2}}, & P_{tm}\geq 0\end{cases}$$

$$\frac{dr}{dt}=\rho\left[R\left(P_{tm}\right)-r\right]$$

$$P_{tm}=P_{lumen}-\frac{\kappa * F_{ASM}}{r}+P_\tau$$

$$P_{lumen}=(P_{aw}+P_A)/2$$

$$R_{aw}=\frac{12l\mu}{\pi r^4}$$

$$P_\tau=2moo\left(\left(\frac{R_{ref}-r_i}{R_{ref}}\right)+1.5\left(\frac{R_{ref}-r_i}{R_{ref}}\right)^2\right)$$

$$x=1-\left(r/v^{1/3}\right)$$

$$v=0.2+0.04P_A$$

$$P_{aw}=P_0 sin(2\pi ft)+P_{min}$$

$$P_{ab}=\frac{P_0E}{\sqrt{E^2+(2\pi fR_{aw})^2}}$$

- Lung mechanics model (Ben Tal)

$$\frac{dP_A}{dt}=\frac{P_{ab}EQ_A}{P_A}+\frac{dP_\tau}{dt}$$

$$\frac{dV_A}{dt}=\frac{P_{ab}-P_\tau-V_AE}{R_{aw}}$$

$$q=\frac{P_{ab}-P_A}{R_{aw}}$$

$$\frac{dP_\tau}{dt}=2m\left(-\frac{3(r_{max}-r(t))\frac{dr}{dt}}{r_{max}^2}-\frac{\frac{dr}{dt}}{r_{max}}\right)$$

- Gas Exhange (Ben Tal)

$$p_{a0}=f_o(P_A-P_{aw})$$

$$p_{ac}=f_c(P_A-P_{aw})$$

$$Q_A=q+D_c(p_c-p_{ac})+D_o(p_o-p_{ao})$$

$$\frac{df_o}{dt}=\frac{1}{V_A}\left(D_o(p_o-p_{ao})+(f_{oi}-f_o)q-f_o(D_c(p_c-p_{ac})+D_o(p_op_{ao}))\right)$$

$$\frac{df_c}{dt}=\frac{1}{V_A}\left(D_c(p_c-p_{ac})+(f_{ci}-f_c)q-f_c(D_o(p_o-p_{ao})+D_c(p_cp_{ac}))\right)$$

$$f_{oi} = \begin{cases} \frac{f_o V_D + f_{om}(V_T - V_D)}{V_T} & if\ V_T \geq V_D \\ f_o & otherwise \end{cases}$$

$$f_{ci} = \begin{cases} \frac{f_c V_D + f_{cm}(V_T - V_D)}{V_T} & if\ V_T \geq V_D \\ f_c & otherwise \end{cases}$$

- Gas Transport (Ben Tal)

$$\frac{dp_o}{dt} = \frac{D_o}{\sigma V_c}\left(1 + \frac{4T_h}{\sigma} df_{satdp}\right)^{-1}(f_o(P_A - P_{aw}) - p_o)$$

$$\frac{dp_c}{dt} = \frac{D_c}{\sigma_c V_c}(p_{ac} - p_c) + \frac{\delta l_2}{\sigma_c} hz - \delta r_2 p_c$$

$$\frac{dz}{dt} = \delta r_2 \sigma_2 p_c - \delta l_2 hz$$

  Current issue lies in the form of the PA coupling, alongside parenchymal tethering. As it stands now, Ptm is too large and the airway is stuck in an open state. Perhaps i should consider a fluid dynamics type approach? I need to step back and consider the full model being modelled and keep everything to cmH2O, unit check everything and find valuable parameters. Remember the big picture is to develop a realistic simplified model that can represent a multitude of macroscopic lund characteristics. Can we build imaging along side this? What clinical measurements are taken by a physician?

- Parameters

Symbol	Meaning	Initial value
AM_p	phosphorylated bound crossbridge	0
AM	unphosohorylated bound crossbridge	0
M_p	phosphorylated myosin	0
M	unphosporylated myosin	1
k_2, k_5	phosphorylation rate	$0.5s^{-1}$
k_3	binding rate	$0.4s^{-1}$
k_4	unbinding rate	$0.1s^{-1}$
k_7	slow unbinding rate	$0.01s^{-1}$
$R(P_{tm})$	radius of airway lumen	
R_i^2	radius at P_{tm}	0.0174 mm^2
P_{tm}	transmural pressure	
P_1		0.295768328 mmHg
r_{imax}	maximum airway	0.4450 mm
P_2		-24.52310023 mmHg
n_1		1
n_2		8
r	time-dependent airway radius	0.4450 mm
ρ		1
P_{lumen}	airway lumen pressure	mmHg
κ	ASM force activation parameter	
F_{ASM}	ASM force	
P_τ	parenchymal pressure (due to pleural pressure?)	mmHg
P_{aw}	Airway pressure	10mmHg
P_A	acinar pressure	mmHg
R_{aw}	Resistance of airway	
L	airway length	2.6mm
μ	gas viscosity	1.9008e-8$kgm^{-1}s^{-1}$
x		

Symbol	Meaning	Initial value
v		
P_0	Amplitude of breathing	10mmHg
P_{min}	Minimum basal airway pressure	mmHg
E	Acinar elastance	186 mmHg/ml
f	frequency of breathing	$0.25Hz$
Q_A	Net flux of air into the alveoli	ls^{-1}
V_A	lung volume (Ben Tal model)	l
q	Air flow to and from the lung	ls^{-1}
p_{ao}	Alveolar partial pressure of O_2	mmHg
f_o	Concentration of O_2 in alveoli	0.1368
P_w	Vapor pressure of water at 37^oC	60 mmHg
p_{ac}	Alveolar partial pressure of CO_2	mmHg
f_c	Concentration of CO_2 in alveoli	0.05263
D_c	Diffusion capacity of CO_2	0.0000316 $mols^{-1}mmHg^{-1}$
D_o	Diffusion capacity of O_2	0.0000156 $mols^{-1}mmHg^{-1}$
f_{oi}	Concentration of inspired O_2	
f_{ci}	Concentration of inspired CO_2	
V_T	Lung tidal volume	$0.41l$
V_D	Lung dead space	$0.151l$
f_{om}	Concentration of O_2 in the mouth	
V_c	Volume of capillaries	$0.071l$
T_h	Concentration of hemoglobin molecule	0.002 $mol\,l^{-1}$
σ,σ_2	Solubility of O_2in plasma	$mol\,l^{-1}\,mmHg^{-1}$
df_{satdp}	saturation function	
δ	Acceleration rate	$10^{1.9}$
l_2	Hydration reaction rate	164000
h	Concentration of H^+	$mol\,l^{-1}$
z	Concentration of HCO_3^-	
r_2	Dehydration reaction rate	$0.12s^{-1}$

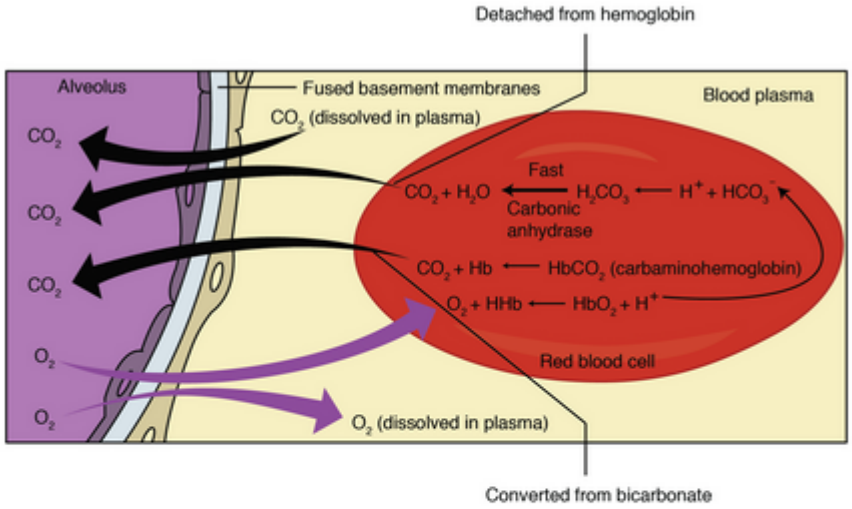

Figure 3. External Respiration. In external respiration, oxygen diffuses across the respiratory membrane from the alveolus to the capillary, whereas carbon dioxide diffuses out of the capillary into the alveolus.

Figure 1: External Respiration function

$mols^{-1}mmHg^{-1}$

4 Current status

I have developed a model that contains as its modules 1) ASM contraction via Hai-Murphy 4 state ODEs 2) Non-linear airway compliance via Lambert model 3) Anafi-Wilson type coupled system where the acinar pressure is modulated by the elastance of the acinar, resistance to airflow and amplitude of breathing. 4) Gas Transport and gas exchange between the capilaries and acinar is included in the model (needs further investigating), this modulates the acinar pressure.

4.1 External Respiration

The pulmonary artery carries deoxygenated blood into the lungs from the heart, where it branches and eventually becomes the capillary network composed of pulmonary capillaries. These pulmonary capillaries create the respiratory membrane with the alveoli (Figure 2). As the blood is pumped through this capillary

network, gas exchange occurs. Although a small amount of the oxygen is able to dissolve directly into plasma from the alveoli, most of the oxygen is picked up by erythrocytes (red blood cells) and binds to a protein called hemoglobin, a process described later in this chapter. Oxygenated hemoglobin is red, causing the overall appearance of bright red oxygenated blood, which returns to the heart through the pulmonary veins. Carbon dioxide is released in the opposite direction of oxygen, from the blood to the alveoli. Some of the carbon dioxide is returned on hemoglobin, but can also be dissolved in plasma or is present as a converted form, also explained in greater detail later in this chapter.

4.2 Ventilation and Perfusion

Two important aspects of gas exchange in the lung are ventilation and perfusion. Ventilation is the movement of air into and out of the lungs, and perfusion is the flow of blood in the pulmonary capillaries. For gas exchange to be efficient, the volumes involved in ventilation and perfusion should be compatible. However, factors such as regional gravity effects on blood, blocked alveolar ducts, or disease can cause ventilation and perfusion to be imbalanced.

The partial pressure of oxygen in alveolar air is about 104 mm Hg, whereas the partial pressure of the oxygenated pulmonary venous blood is about 100 mm Hg. When ventilation is sufficient, oxygen enters the alveoli at a high rate, and the partial pressure of oxygen in the alveoli remains high. In contrast, when ventilation is insufficient, the partial pressure of oxygen in the alveoli drops. Without the large difference in partial pressure between the alveoli and the blood, oxygen does not diffuse efficiently across the respiratory membrane. The body has mechanisms that counteract this problem. In cases when ventilation is not sufficient for an alveolus, the body redirects blood flow to alveoli that are receiving sufficient ventilation. This is achieved by constricting the pulmonary arterioles that serves the dysfunctional alveolus, which redirects blood to other alveoli that have sufficient ventilation. At the same time, the pulmonary arterioles that serve alveoli receiving sufficient ventilation vasodilate, which brings in greater blood flow. Factors such as carbon dioxide, oxygen, and pH levels can all serve as stimuli for adjusting blood flow in the capillary networks associated with the alveoli.

Ventilation is regulated by the diameter of the airways, whereas perfusion is regulated by the diameter of the blood vessels. The diameter of the bronchioles is sensitive to the partial pressure of carbon dioxide in the alveoli. A greater partial pressure of carbon dioxide in the alveoli causes the bronchioles to increase their diameter as will a decreased level of oxygen in the blood supply, allowing carbon dioxide to be exhaled from the body at a greater rate. As mentioned above, a greater partial pressure of oxygen in the alveoli causes the pulmonary arterioles to dilate, increasing blood flow.

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