Airway Functional Tissue Unit (FTU)

Airway wall and smooth muscle layer:

In order to devlop a rudimentry model for the airway FTU, we considered a system of 3 branched conducting airways (Donovan 2016). This system consists of a parent airway of order 2 (max. radius $0.318mm$) and branched child airways of order 1 (max. radii $0.296mm$). Airway-airway coupling via flow through the conducting airway tree is incorporated such that at the junction conservation of flow

$$q_m = q_{c1} + q_{c2} \tag{1}$$

is maintained. Here q_m references the parent airway and $q_{C1}$and q_{c2} references the 2 children airways. In each airway we assume Poiseuille flow

$$\Delta p_i = \alpha_i r_i^{-4} q_i \tag{2}$$

where Δp_i is the pressure difference from the top to the bottom of the i^{th} airway, α_i represents the compact form of the Poiseuille flow co-efficients and r_i is the airway luminal radius. We treat the airway wall and surrounding airway smooth muscle as separate layers. Passive properties of the airway wall determine the lumen radius in response to tramsmural pressure P_{tm}, while the active force generated by the airway smooth muscle layer contributes to the pressure across the aiway wall (Politi et. al 2010).

$$P_{tm} = P_i + P_w \tag{3}$$

where P_i and P_w are the pressures on the luminal and adventitial side of the airway wall. The pressure P_w at the interface between the airway wall and the smooth muscle layer is computed from the pressure exerted by the SMC and the parenchymal layer is then given by

$$P_w = P_m - f\frac{R_m - R_w}{r_s} \tag{4}$$

where f is the active circumferential stress exerted by the SMC, P_m is the pressure at the SMC-parenchyma interface, $r_s = (r_w + r_w)/2$ is the mean SMC radius, and $R_m - R_w$ is the order dependent SMC layer thickness at $P_{tm} = 0$.

We consider for each airway two regions of parenchyma: the parenchymal continuum, in the organ-level model, and a layer of parenchya local to each airway, located between r_m and r_t.

The pressure P_t is calculated from the organ level model and the loacl parenchymal layer is used to calculate the local increase in tethering force due to airway constriction yielding the pressure P_m. To account for additional local non-linear effects caused by airway contraction, we find P_m via

$$P_m = 2\mu\left[\Delta R_m + \nu\left(\Delta R_m\right)^2\right] + P_t \tag{5}$$

where

$$\Delta R_m = \left(\bar{R_m} - r_m\right)/\bar{R_m} \tag{6}$$

The relation between isometric force and length is characterised by a force-length curve. We take the SMC tension as $f = f_L f_a$ where

$$f_a = \kappa \int_{-\infty}^{\infty} x\left(AM + AMp\right) \tag{7}$$

and f_L represents the approximation of expeimental data

$$f_L = \begin{cases} sin\left(\frac{\pi r_s}{2r_{smax}}\right)^3 & if \quad r_s \leq 2r_{rsmax} \\ 0 & otherwise \end{cases} . \tag{8}$$

The thickness of of the SMC layer and the airway wall are defined by $\epsilon_w = (R_w - R_i)/R_i$ and $\epsilon_m = (R_m - R_w)/R_i$ in the unstressed state ($P_{tm} = 0$) respectively, with the radii of the of the different layers

$$r_w = R_i\sqrt{(1+\epsilon_w)^2 + \left(\frac{r_i}{R_i}\right)^2 - 1}$$
$$r_m = R_i\sqrt{(\epsilon_m + \epsilon_w + 1)^2 + \left(\frac{r_i}{R_i}\right)^2 - 1}.$$

The radial and hoop stress for the SMC layer can then be given by

$$P_m = \sigma_{rr_m} = 2\mu\left(\Delta R_m + \nu\left(\Delta R_m\right)^2\right) + P_t$$
$$\sigma_{\theta\theta_m} = \sigma_{rr_m} + f_a\left(\frac{R_m - R_w}{r_m + r_w}\right)$$

and that for the airway wall is

$$P_w = \sigma_{rr_w} = \sigma_{rr_m} - f_a\left(\frac{R_m - R_w}{r_s}\right)$$
$$\sigma_{\theta\theta_w} = \sigma_{rr_w} + f_a\left(\frac{R_m - R_w}{r_m + r_w}\right)$$

Crossbridge model and contraction velocity

We describe here briefly the kinetic model for the 4 state ODE actin-myosin muscle contraction model as developed my Hai and Murphy 1988

$$\frac{dM}{dt} = -K_1(c)M + K_2(c)M_p + K_7AM$$
$$\frac{dM_p}{dt} = K_4AM_p + K_1(c)M - \left(K_2(c) + K_3\right)M_p$$
$$\frac{dAM_p}{dt} = K_3M_p + K_6AM - \left(K_4 + K_5\right)AM_p$$
$$\frac{dAM}{dt} = K_5AM_p - \left(K_7 + K_6\right)AM$$

where M, M_p represents unphosphorylated, phosphorylated myosin and AM, $AM_p$are the actin-myosin bound unphophorylated and phosphorylated population respectively. This is subject to the constraint $M + M_p + AM_p + AM = 1$. Here the rate of the regulatory light chain of myosin phosphorylation and dephosphorylation of myosin light chain kinease (MLCK) $K_1(c)$ are controlled by Ca2+ concentration (c) and agonist (a),

$$K_1 = \frac{k_{1a}c^4}{k_{1b}^4 + c^4} \tag{9}$$

Thus MLCK is activateted by an increase in calcium concentration. The dephosphorylation rate depends on both Ca2+ and agonist concentration (a) (Wang et al 2010):

$$\tau_p\frac{dP}{dt} = k_{on}(c)(1-P) - k_{off}(a)P$$
$$K_2 = \bar{k_2}P^2$$
$$k_{on}(c) = k_{on1} + \frac{c^2}{k_{on2}^2 + c^2}$$
$$k_{off}(a) = k_{off1} + \frac{k_{off}a}{1+a}$$

where P is the fraction of activated MLCP and τ_p is a time constant.

The calcium dynamics model used is the model of Wang et al 2010 as described below:

$$\begin{aligned}
\frac{dc}{dt} &= J_{release} - J_{serca} + \delta\left(J_{in} - J_{pm}\right) \\
\frac{dc_s}{dt} &= \gamma\left(J_{serca} - J_{release}\right) \\
\frac{dy}{dt} &= \Phi_1(1-y) - \Phi_2 y
\end{aligned}$$

where

$$\begin{aligned}
J_{release} &= \left(k_{IPR}P_{IPR} + k_{RyR}P_{RyR} + J_{er}\right)(c_s - c) \\
J_{in} &= \alpha_0 - \alpha_1\frac{I_{ca}}{2F} + \alpha_2 p \\
J_{serca} &= \frac{V_e c^2}{K_e^2 + c^2} \\
J_{pm} &= \frac{V_p c^4}{K_p^4 + c^4} \\
P_{IPR} &= \left(\frac{pc(1-y)}{(p+K_1)(c+K_5)}\right)^3 \\
\Phi_1 &= \frac{\left(k_{-4}K_2K_1 + k_{-2}K_4 p\right)c}{K_4K_2\left(K_1 + p\right)} \\
\Phi_2 &= \frac{k_{-2}p + k_{-4}K_3}{K_3 + p} \\
P_{RyR} &= \left(k_{ryr0} + \frac{k_{ryr1}c^3}{k_{ryr2}^3 + c^3}\right)\left(\frac{c_s^4}{k_{ryr3}^4 + c_s^4}\right) \\
I_{ca} &= g_{ca}m^2 V_{ca} \\
m &= \frac{1}{1 + c^{-(V - V_m)/k_m}} \\
V_{ca} &= \frac{V\left(c - c_e e^{\frac{-2VF}{RT}}\right)}{1 - e^{\frac{-2VF}{RT}}}
\end{aligned}$$

Parameter values are the same as Wang et al 2010.

Coupled airways

In order to model for a system of 3 coupled airways, we adopted the method used in Donovan 2016, where the author developed a model which incorporates a conducting airway tree (with arbitrary geometry of N airways and M junctions.) We summarize the system below:

- The compact form of the Poiseulle flow constants for each airway is given by

$$\alpha_{r_i} = \frac{8a\mu L_{r_i}}{\pi} \tag{10}$$

  where $i = p$ for the parent airway, and $i = r1, r2$ for the child airways.

- two types of boundary conditions are assumed:
  - pressure-controlled b.c. prescribe both p_{top} and p_{bot}. Narrowing of the airways by stimulating ASM will reduce airflow.

– Flow-controlled b.c. prescribe p_{top} and $q_{top} = \hat{q}$ allowing p_{bot} to vary in order to maintain the flow despite airway narrowing.

(p_{top} and p_{bot} represents the pressure at the top and bottom of the airway tree respectively)

- We define the pressure difference from the top to the bottom of wach airway by

$$\begin{aligned} \Delta p_{r_p} &= p_{top} - p \\ \Delta p_{r1} = \Delta p_{r1} &= p - p_{bot} \end{aligned}$$

where p represents the pressure within each airway. p is defined as

$$p = \frac{\hat{q} - p_{top} D_{\alpha_{r_p}}}{W\Lambda} \tag{11}$$

where

$$\begin{aligned} D_{\alpha_{rp}} &= \frac{r_p^4}{\alpha_{r_p}} \\ W &= -\sum_{ri} D_{\alpha_{ri}} \\ \Lambda &= 1 - temp \end{aligned}$$

for

$$temp = \frac{-\left(2\left(D_{\alpha_{r1}}^2 + D_{\alpha_{r2}}^2\right)\right) W^{-1}}{\lambda} \tag{12}$$

where $\lambda = D_{\alpha_{r1}} + D_{\alpha_{r2}}$. The pressure at the bottom of the airway tree, p_{bot} is given by

$$p_{bot} = \frac{\lambda p - \hat{q}}{\lambda}. \tag{13}$$

The airflow, q, through each airway can be calculated via

$$\begin{aligned} q_p &= p_{top} - D_{\alpha_{r_p}} p \\ q_{r1} &= D_{\alpha_{r1}} p - p_{bot} \\ q_{r2} &= q_p - q_{r1}. \end{aligned}$$

Airway Dynamics

The equilibria for radii of the airway lumen can be found following the modified form of Lambert et al 1982 as described in Politi et al 2010. Here the airway radius is modeled as a function of transmural pressure P_{tm}, where first order dynamics apply.

$$R\left(P_{tm}\right) = \begin{cases} \sqrt{R_i^2 \left(1 - P_{tm}/P_A\right)^{-nA}} & P_{tm} \leq 0 \\ \sqrt{r_{imax}^2 - \left(r_{imax}^2 - R_i^2\right)\left(1 - P_{tm}/P_B\right)^{-nB}} & P_{tm} > 0 \end{cases} \tag{14}$$

where

$$P_{tm}\left(r_i\right) = p_{mid_i} - \frac{f_a R_{ref}}{r_i} + \tau\left(r_i\right). \tag{15}$$

The mid-away pressure P_{mid} is obtained for each airway is given by

$$\begin{aligned} p_{mid_p} &= \frac{p_{top} - p}{2} \\ p_{mid_{r1}} = &p_{mid_{r2}} = \frac{p_{bot} + p}{2}. \end{aligned}$$

Finally, τ represents the parenchymal tethering pressure, which arises from the restoring forces generated by the parenchymal tissue surrounding the airway, and is described by

$$\tau\left(r_i\right) = 2\mu\left(\frac{R_{ref-r_i}}{R_{ref}} + 1.5\left(\frac{R_{ref-r_i}}{R_{ref}}\right)^2\right) \tag{16}$$

according to Lai-Fook 1979. Here for the respiratory bronchioles, as in Donovan and Kritter (2015) we use the local effect that the shear modulus is a function of the local inflation via mean local flow, so that

$$2\mu_i = 0.7 \times \frac{A}{3}\left(|q_p| + |q_{r2}| + |q_{r2}|\right) \tag{17}$$

where the parameter A represents the coupling strength.