Vascular Smooth Muscle FTU

This model is largely derived from the works of Yang et al,2003,Hai and Murphy,1988 and Wang et al,2010. This model considers the activation of soluble guanylate cyclase (sGC) which subsequently increases the intracellular cGMP production from GTP. We also include Ca2+ and cGMP comediated MLC phosphorylation and cross-bridge attachment.

sGC activation by Nitric Oxide

The first step in Nitric Oxide binding to sGC is expressed as a reversible biochemical reaction process

$$E_b + NO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E_{6c} \tag{1}$$

where E_b and E_{6c} represents sGC in the basal and intermediate forms.
The transition between from E_{6c} to E_{5c} (fully activated 5c complex) occurs via two parallel pathways: NO-dependent and NO-independent pathways.

- $E_{6c} \xrightarrow{k_2} E_{5c}$
- $E_{6c} + NO \xrightarrow{k_3} E_{5c} + NO$

The deactivation of E5c and the recovery of the basal sGC condition can be described according to

$$E_{5c} \xrightarrow{k_4} E_b + NO \tag{2}$$

The above sGC kinetics can be represented via the differential equations

$$\begin{aligned}
\frac{dE_b}{dt} &= -k_1 E_b[NO] + k_{-1} E_{6c} + k_4 E_{5c} \\
\frac{dE_{6c}}{dt} &= k_1 E_b[NO] - k_{-1} E_{6c} - k_2 E_{6c} - k_3 E_{6c}[NO] \\
\frac{dE_{5c}}{dt} &= k_3 E_{6c}[NO] + k_2 E_{6c} - k_4 E_{5c}
\end{aligned}$$

Conservation of total sGC concentration is assumed via $E_b + E_{6c} + E_{5c} = 1$. Total NO consumption rate is modeled via a first order kinetics

$$\frac{d[NO]}{dt} = J_{no} - k_{dno}[NO] \tag{3}$$

where J_{no} is the endogenenous or exogenous NO influx . k_{dno} denotes the lumped NO consumption rate constant that reflects the activity of NO scavengers.

cGMP production and degredation

The production and degradation of cGMP can both be modeled with Michaelis-Menten kinetics:

$$\begin{aligned}
GTP + E5c &\rightleftharpoons GTP \cdot E_{5c} \rightarrow cGMP + E_{5c} \\
cGMP + PDE &\rightleftharpoons cGMP \cdot PDE \rightarrow GMP + PDE
\end{aligned}$$

Assuming that the presence of GTP is abundant, cGMP production kinetics mainly depends on the sGC concentration. PDE (cyclic nucleotide phosphodiesterase) is assumed to have a constant intracellular concentration. Thus the balance equation for cGMP is

$$\frac{d[cGMP]}{dt} = V_{max,sGC} E_{5c} - \frac{[cGMP] V_{max,pde}}{K_{m,pde} + [cGMP]} \tag{4}$$

where $V_{max,sGC}$ represents the maximal rtate of cGMP production when $E_{5c} = 1$ and $V_{max,pde}$ is the maximum cGMP hydrolysis rate.

Ca2+ desenitization of MLC phosphorylation

The MLC (myosin light chain) phosphorylation rate constant is associated with cGMP concentration to model the cGMP effect on MLC activity via

$$k_{mlcp} = k^b_{mlcp} + \frac{k^c_{mlcp}[cGMP]^{n_{H,mlcp}}}{[cGMP]^{n_{H,mlcp}} + K_m^{n_{H,mlcp}}} \tag{5}$$

where k^b_{mlcp} is the basal MLC dephosphorylation rate constant, k^c_{mlcp} is the first-order rate constant for cGMP-regulated MLC dephosphrylation.

Crossbridge model and contraction velocity

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

$$\begin{aligned}
\frac{dM}{dt} &= -K_1(c)M + K_2(c)M_p + K_7 AM \\
\frac{dM_p}{dt} &= K_4 AM_p + K_1(c)M - (K_2(c) + K_3)\, M_p \\
\frac{dAM_p}{dt} &= K_3 M_p + K_6 AM - (K_4 + K_5)\, AM_p \\
\frac{dAM}{dt} &= K_5 AM_p - (K_7 + K_6)\, AM
\end{aligned}$$

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),

$$K_1 = \frac{k_{1a}c^4}{k_{1b}^4 + c^4} \tag{6}$$

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

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

where P is the fraction of activated MLCP and τ_p is a time constant. Where we considered a linear relationship for the inclusion of cGMP regulation.

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

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

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.

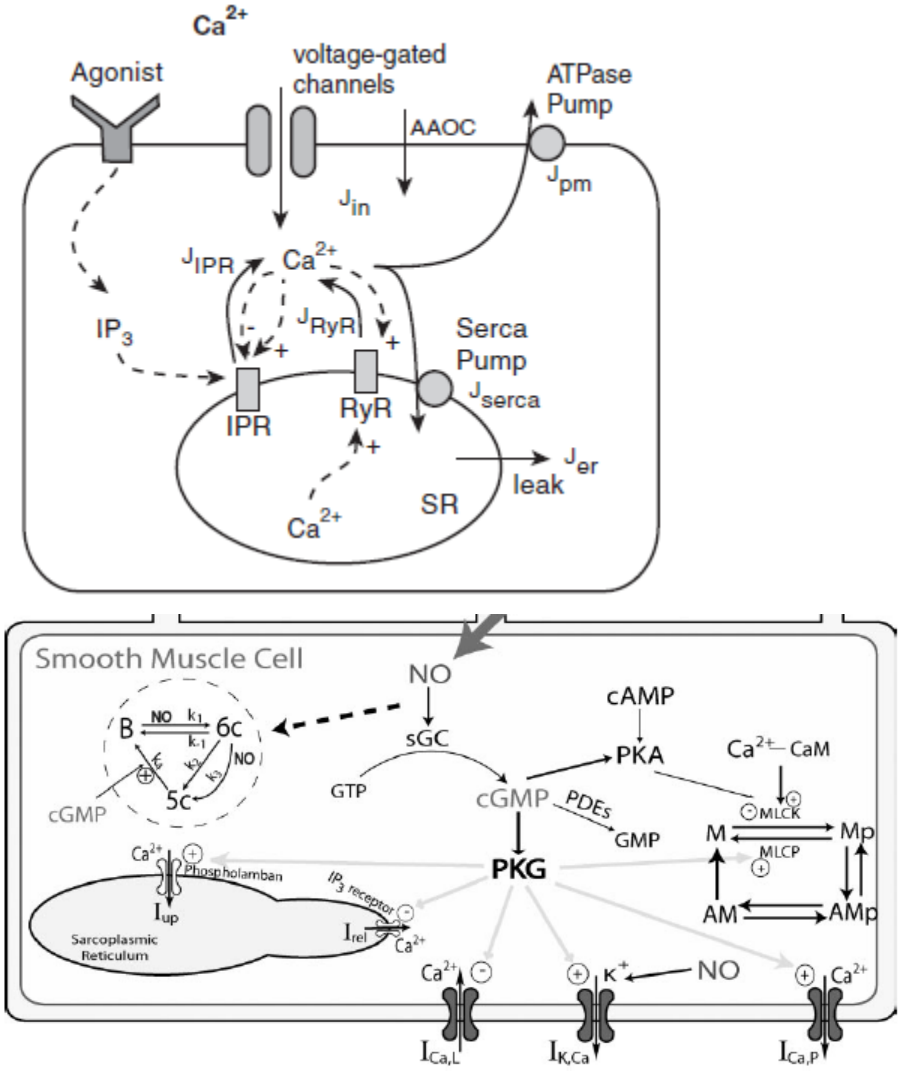

Figure 1: Original diagrams of Wang et al,2010 and Yang et al,2003

References

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