Finite Element Modeling of Vasoreactivity Using COMSOL Multiphysics®

J. B. Parikh[1*], A. Kapela[1], N. M. Tsoukias[1]
[1]Florida International University, Department of Biomedical Engineering,
*Corresponding author: 10555 W Flagler Street, EC 2614, Miami, FL, 33174. jpari004@fiu.edu

Abstract: Localized calcium events in the endothelial cells (EC) can modulate smooth muscle cell (SMC) calcium (Ca^{2+}) and membrane potential dynamics through release of endothelium derived hyperpolarizing and relaxing factors. Ca^{2+} levels in the smooth muscle cell (SMC) determine its contractile state. The underlying complex mechanism regulating the SMC Ca^{2+} levels and ultimately vessel tone remains poorly understood. We developed coupled EC-SMC continuum models to describe function at macro-scale level by integrating mechanisms at the subcellular/ molecular level. Cellular models were coupled through diffusion of ions and second messengers. The models allows introduction of spatial distribution of cellular components and micro domains. The model will provide quantification and better understanding of localized events in the EC and its modulation of the vessel tone.
Keywords: endothelial cell, smooth muscle cell, calcium, vessel tone.

1. Introduction

Endothelial cell (EC) form the inner lining of the blood vessels. They modulate the vascular tone (vasoreactivity) through regulation of contractility of surrounding blood vessel smooth muscle cells (SMCs). EC Ca^{2+} increase can induce Ca^{2+} dependent hyperpolarizing signals such as endothelium derived hyperpolarizing factors (EDHF) [1, 2] and synthesis of vasorelaxing mediators such as nitric oxide (NO) [3] and prostacyclin (PGI_2) [4] to modulate the vessel tone. EC extensions over the internal elastic lamina towards SMC, termed myoendothelial projections (MPs), have been observed in small diameter vessels [5, 6] and can play a role in the modulation of vessel tone [7]. Recent work have demonstrated spontaneous local Ca^{2+} events through transmembrane calcium influx (TRPV4 sparklets [8-10]) and intracellular store calcium release ('pulsars'[11] and 'wavelets'[12]) in the vicinity of the MPs and suggested their role in the regulation of the vessel tone.

Mathematical modeling can provide quantification of the localized events and further the analysis of experiments. Integrated spatiotemporal analysis is needed to relate macro scale responses to underlying cellular signaling. In this study, we develop finite element models (FEM) using COMSOL multiphysics to examine the localized Ca^{2+} in the vicinity of the MPs and induced vasoreactivity.

2. Methods

We have previously developed detailed compartmental models of integrated Ca^{2+} and V_m dynamics in isolated EC and SMC [13, 14], based primarily on data from RMA. The isolated models were combined into a two-cell (EC-SMC) and multicellular compartmental models to investigate the myoendothelial communication and conducted vasoreactivity respectively [15, 16]. Here, we updated the compartmental models to capture the spatiotemporal nature of Ca^{2+} mobilization through the development of continuum EC–SMC model, incorporated with the accurate MP geometry from experimental studies. We examined the role of MP and the localized Ca^{2+} events in the vicinity of the MP, in the modulation of SMC Ca^{2+} and membrane potential (V_m) dynamics and ultimately the regulation of the vascular tone. Figure.1 illustrates the cellular components and signaling pathways implemented in the model. All the parameter values and current descriptions are similar to our previous models [13-16].

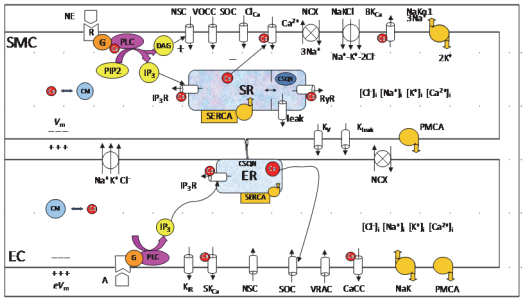

Figure 1. Schematic of the cellular components and signaling pathways regulating SMC and EC Ca^{2+} and V_m dynamics.

We implemented both the EC and SMC as simple rectangular domains with dimensions shown in Figure 2. Moreover we implemented only half of the EC and SMC assuming symmetry for the other half. We incorporated the accurate MP geometry from experimental studies and spatial localization of K_{Ca} (Ca^{2+} activated potassium channels), IP_3Rs (Inositol triphosphate receptors) within the MP. A single TRPV4 (Transient receptor potential vanilloid 4) channel was also considered in the vicinity of the MP. The transport for individual ionic species in EC, MP, and SMC is influenced by both electrical and concentration gradients, hence was described using the Nernst-Planck electrodiffusion equation (Eq. 1) built in the chemical engineering module of COMSOL mulphysics.

$$\delta_{buff}\frac{\partial[S]_i}{\partial t} = \nabla.\left(D_S\nabla[S]_i + Z_s F u_{ms}[S]_i\nabla V_i\right) - R_s$$

Eq. 1

where S=Na^+, K^+, Cl^-, Ca^{2+}, D_S is the diffusion coefficient of ionic species S (Table 1), u_{mS} is the ionic mobility, Z_s is the valence of ionic species S, ∇V is the electrical gradient and F is the Faraday constant. The source/sink term, R_s, includes expressions for Ca^{2+} release/uptake from the ER/SR and Ca^{2+} buffering in EC bulk and MP. The fast Ca^{2+} buffering is represented by the Ca^{2+}-dependent function δ_{buff}.

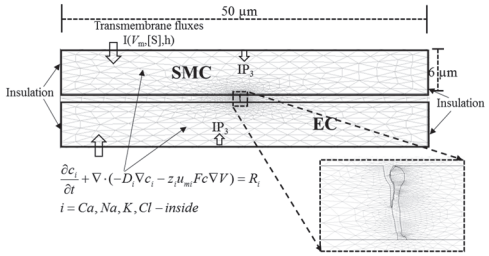

Figure 2. Schematic of 2D FEM EC-SMC model with MP.

The membrane currents were defined as boundary fluxes (Eq. 2) across the top and bottom boundaries of EC, SMC and all boundaries of the MP. The current were scaled according to volumes of MP and bulk cytosol.

$$-n.N_S = \frac{1}{z_S F}\sum_K I_{S,K}$$

Eq. 2

where n is the normal to surface vector and N_s the membrane flux of species S given by summation of all the membrane currents ($I_{S,k}$) of species S. A single TRPV4 channel was introduced in the model on the EC boundary in the vicinity of the MP. Flux ($I_{TRPV4,S}$) of individual ions S, through single TRPV4 channel was implemented using a GHK equation (Eq. 3).

$$I_{TRPV4,S}(t,V_m,S_i) = P_{TRPV4,S}C_m\frac{z_s^2F^2}{RT}V_m\frac{S_i - S_0 e^{\frac{-z_sV_mF}{RT}}}{1-e^{\frac{-z_sV_mF}{RT}}}$$

Eq.3

where S_i is the concentration of Ca^{2+}, K^+, Na^+ inside the endothelial cell, S_o is the concentration of the species outside the cell, F is faradays constant, $P_{TRPV4,S}$ is the permeability of species S through a TRPV4 channels, C_m is the membrane capacitance, V_m *is* the membrane potential, R is the gas constant and T is the absolute temperature.

Table 1: Parameter Values

Parameter	Value	Units
D_{Na} , D_K, D_{Ca}, D_{Cl}	505, 744, 300, 900	$\mu m^2 s^{-1}$
C_m	17	pF
F	96487	$Cmol^{-1}$
T	293	K
R	8341	mJ $(molK)^{-1}$
$P_{TRPV,Ca}$	$6.25x10^{-8}$	cms^{-1}
$P_{TRPV,Na}$	$9.05x10^{-9}$	cms^{-1}
$P_{TRPV,K}$	$1.22x10^{-8}$	cms^{-1}
Z_K, Z_{Na}, Z_{Ca}, Z_{Cl}	1, 1, 2, -1	

3. Results

SMC stimulation in the model with NE (1μM) resulted in transient Ca^{2+} increase via CICR (calcium induced calcium release) from IP_3Rs localized in the EC MP (Figure.3A green line), mediated through IP_3 diffusion from the SMC to the EC MP. The spatial Ca^{2+} profile obtained in a region in close proximity of the MP after 200s of NE stimulation is shown in Figure.4. The amplitude of Ca^{2+} increase in the MP was around 1μM. We observed no significant increase in the EC bulk Ca^{2+} levels (Figure.4) during NE stimulation. Hence, the lack of the MP in the model resulted in absence of EC Ca^{2+} increase (Figure.3A red line). The transient increase of Ca^{2+} in the MP activated localized K_{Ca} channels in the projections to result in EC hyperpolarization. The hyperpolarization spreads to adjacent SMC cell through the gap junctions to result in reduction of the SMC depolarization induced by NE stimulation. We observed feedback of ~4 mV in the presence of the MP during the SMC stimulation as shown in Figure.3B (Resting SMC V_m is -52 mV).

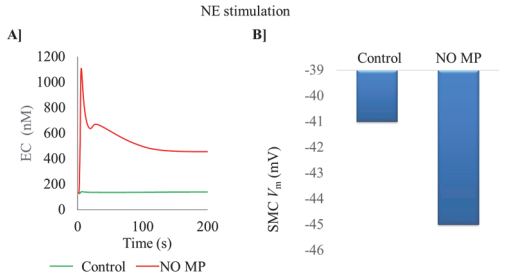

Figure 3. NE (1μM) stimulation of the SMC cell. A) SMC Ca^{2+} concentrations in the presence and absence of the MP. B) Observed SMC V_m changes in the presence and absence of the MP.

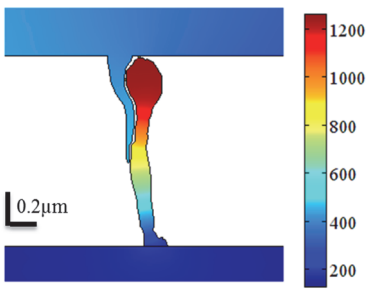

Figure 4. Spatial Ca^{2+} profile in the vicinity of the MP after 200s NE stimulation of the SMC.

Opening of a single TRPV4 channel incorporated on the EC boundary close to the MP in the model resulted in μM Ca^{2+} release in a region close to the channel (Figure.5). The high Ca^{2+} concentration lasted for the duration of the channel open time after which they dropped back to resting levels through scavenging by the Ca^{2+} buffers in the EC and its removal through membrane and store pumps.

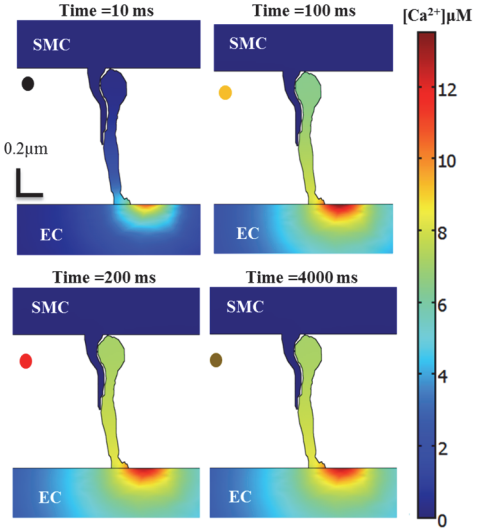

Figure 5. Spatial Ca^{2+} profiles in a region close to the MP on opening of single TRPV4 channel for 10,100, 200 and 4000 ms.

We plotted 700 nM contours (half activation of the Kca channels) to define the Ca^{2+} spread for different duration of channel opening and observed enhanced Ca^{2+} spread with increase in duration of the TRPV4 channel openings (Figure 6).

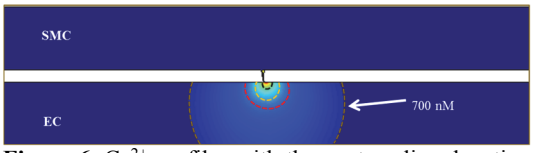

Figure 6. Ca^{2+} profiles with the contour line denoting 700nM Ca^{2+} levels on opening of single TRPV4 channel for 10 (black), 100(orange), 200 (red) and 4000 (brown) ms.

Localized Ca^{2+} increase from the opening of a single TRPV4 channel in the vicinity of the MP can activate the K_{Ca} channels localized in the MP to result in the SMC hyperpolarization. However the sustained vessel hyperpolarization necessitate the spread of induced hyperpolarization in the SMC to longer distances. We observed the vessel

hyperpolarization arising from a single TRPV4 channel opening for 1 and 5 sec durations using an electrical equivalent for a multicellular vessel model. The observed vessel hyperpolarization increases exponentially with increase in the frequency of TRPV4 channels opening as shown in Figure 6.

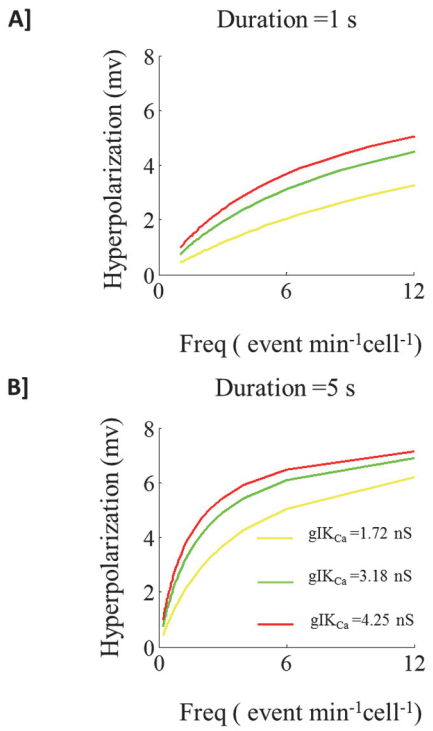

Figure 6. A single TRPV4 channel opening induced vessel hyperpolarization. A] TRPV4 channel open duration is 1s B] channel open duration is 4 sec. Spatial Ca^{2+} profiles in a region close to the MP on opening of single TRPV4 channel for 10,100, 200 and 4000 ms.

4. Conclusions

We were able to develop FEM models of coupled EC-SMC using COMSOL multiphysics providing the spatiotemporal changes in Ca^{2+} and V_m levels similar to those observed in the experiments. We showed a significant reduction in SMC depolarization and induced SMC hyperpolarization mediated by localized Ca^{2+} events during SMC stimulation and EC TRPV4 opening respectively, through the activation of the K_{Ca} channels in the vicinity of the endothelial projections. The developed model furthers our understanding of the role of these events and signaling micro domains in the regulation of vessel tone.

5. References

1. R. Busse, *et al.*, "EDHF: bringing the concepts together," *Trends Pharmacol Sci,* **vol. 23**, pp. 374-80 (2002)
2. G. Edwards, *et al.*, "Endothelium-derived hyperpolarising factors and associated pathways: a synopsis," *Pflugers Arch,* **vol. 459**, pp. 863-79 (2010)
3. I. Fleming and R. Busse, "NO: the primary EDRF," *J Mol Cell Cardiol,* **vol. 31**, pp. 5-14 (Jan 1999)
4. N. V. Bogatcheva, *et al.*, "Arachidonic acid cascade in endothelial pathobiology," *Microvasc Res,* **vol. 69**, pp. 107-27(2005)
5. S. L. Sandow, *et al.*, "What's where and why at a vascular myoendothelial microdomain signalling complex," *Clin Exp Pharmacol Physiol,* **vol. 36**, pp. 67-76 (2009)
6. K. R. Heberlein, *et al.*, "The myoendothelial junction: breaking through the matrix?," *Microcirculation,* **vol. 16**, pp. 307-22 (2009)
7. P. M. Kerr, *et al.*, "Endothelial feedback and the myoendothelial projection," *Microcirculation,* **vol. 19**, pp. 416-22 (2012)
8. P. Bagher, *et al.*, "Low intravascular pressure activates endothelial cell TRPV4 channels, local Ca2+ events, and IKCa channels, reducing arteriolar tone," *Proc Natl Acad Sci U S A,* **vol. 109**, pp. 18174-9 (2012)
9. S. K. Sonkusare, *et al.*, "Elementary Ca2+ signals through endothelial TRPV4 channels regulate vascular function," *Science,* **vol. 336**, pp. 597-601 (2012)
10. S. K. Sonkusare, *et al.*, "AKAP150-dependent cooperative TRPV4 channel gating is central to endothelium-dependent vasodilation and is disrupted in hypertension," *Sci Signal,* **vol. 7**, p. ra66 (2014)
11. J. Ledoux, *et al.*, "Functional architecture of inositol 1,4,5-trisphosphate signaling in restricted spaces of myoendothelial projections," *Proc Natl Acad Sci U S A,* **vol. 105**, pp. 9627-32 (2008)
12. C. H. Tran, *et al.*, "Endothelial Ca2+ wavelets and the induction of myoendothelial feedback," *Am J Physiol Cell Physiol,* **vol. 302**, pp. C1226-42 (2012)
13. A. Kapela, *et al.*, "A mathematical model of Ca2+ dynamics in rat mesenteric smooth muscle

cell: agonist and NO stimulation," *J Theor Biol,* **vol. 253**, pp. 238-60 (2008)
14. H. S. Silva*, et al.*, "A mathematical model of plasma membrane electrophysiology and calcium dynamics in vascular endothelial cells," *Am J Physiol Cell Physiol,* **vol. 293**, pp. C277-93 (2007)
15. A. Kapela*, et al.*, "A mathematical model of vasoreactivity in rat mesenteric arterioles: I. Myoendothelial communication," *Microcirculation,* **vol. 16**, pp. 694-713 (2009)
16. A. Kapela*, et al.*, "A mathematical model of vasoreactivity in rat mesenteric arterioles. II. Conducted vasoreactivity," *Am J Physiol Heart Circ Physiol,* **vol. 298**, pp. H52-65 (2010)