Finite Element Modeling of Vasoreactivity Using COMSOL Multiphysics® Software

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Introduction:

- Vasoreactivity i.e. regulation of vessel tone and blood flow in microcirculation; is regulated via numerous signaling pathways acting at different spatial and temporal scales.
- Integrated spatiotemporal analysis is needed to relate macroscale responses to underlying cellular signaling and to examine commonly observed disease of vascular hyper reactivity (hypertension)
- Ca^{2+} levels in the Smooth muscle cell (SMC) determine its constriction and ultimately vessel tone. The Ca^{2+} levels in the SMC are modulated by the endothelial cell (EC through release of endothelium derived relaxing and hyperpolarizing factors (EDHF and EDRF).
- Several mathematical compartmental models have been developed to examine Ca^{2+} dynamics in SMC [1].

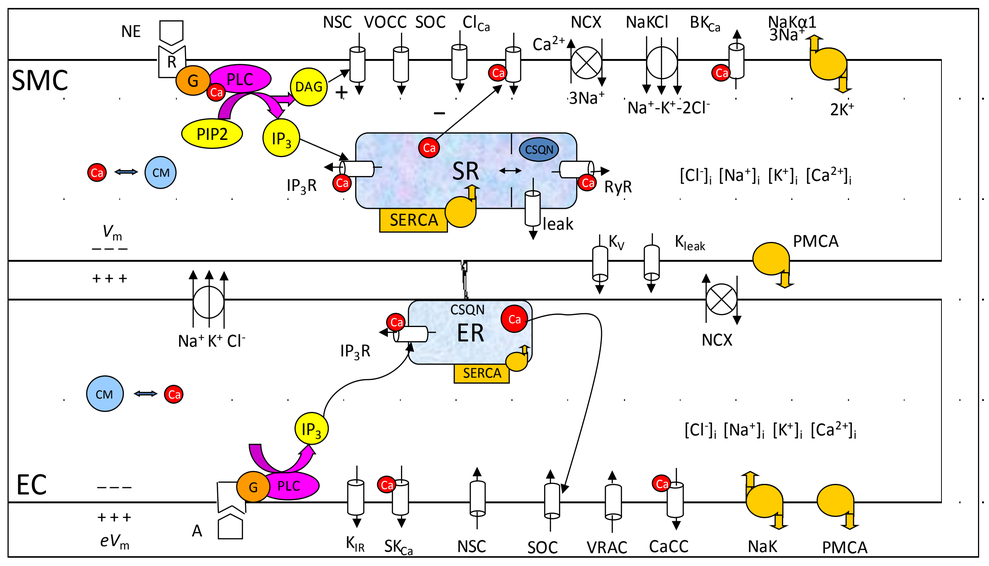

Figure 1. Schematic of the cellular components and signaling pathways regulating SMC and EC Ca^{2+} and V_m dynamics

Computational Methods:

- 2-D models (Fig. 2) were developed to study localized Ca^{2+} events, role of signaling microdomains, myoendothelial communication in modulation of vessel tone.
- Membrane potential and concentration gradients modulate the transport of ionic species (Ca^{2+}, K^+, Cl^- and Na^+) in EC and SMC and was implemented using the Nernst-Planck electrodiffusion equation (Eq. 1) (COMSOL Chemical Engineering module)

$$\delta_{buff}\frac{\partial [S]_i}{\partial t} = \nabla.\left(D_S \nabla [S]_i + Z_s F u_{ms} [S]_i \nabla V_i\right) - R_s \quad \text{Eq. 1}$$

- Transmembrane currents were implemented as boundary conditions.

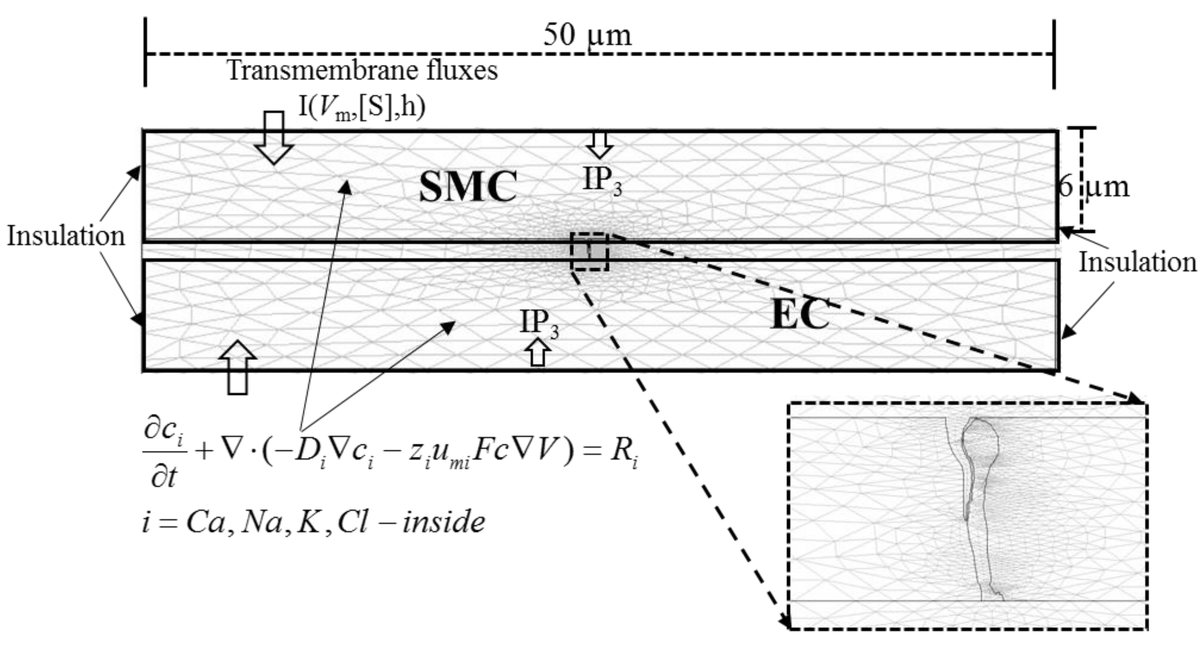

Figure 2. 2D EC-SMC model with microprojections

Results:

- MP provide few mV feedback during SMC stimulation.
- The feedback is through localized Ca^{2+} increase in the EC projections during SMC stimulation

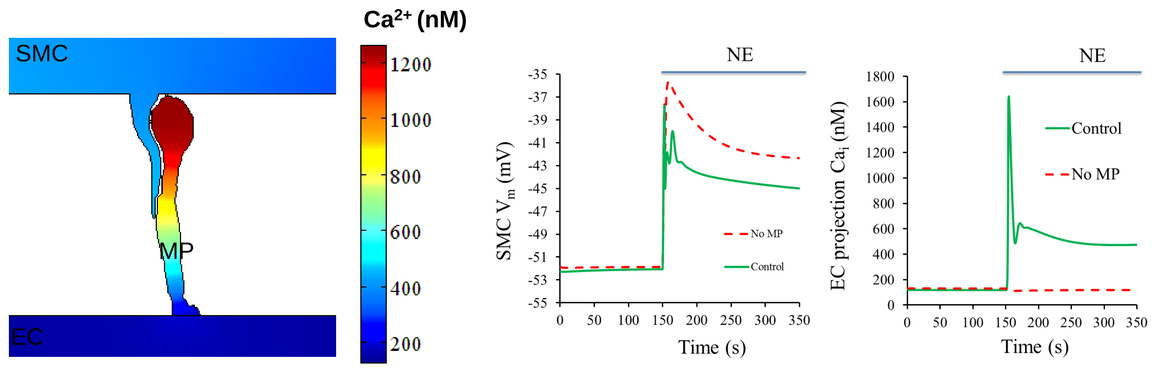

Figure 3: Role of MP in feedback response during SMC stimulation

- Localized calcium increase in μM range is observed through a single TRPV4 channel opening.
- The localized increase results in SMC hyperpolarization and vessel dilation through activation of localized channels in the projections

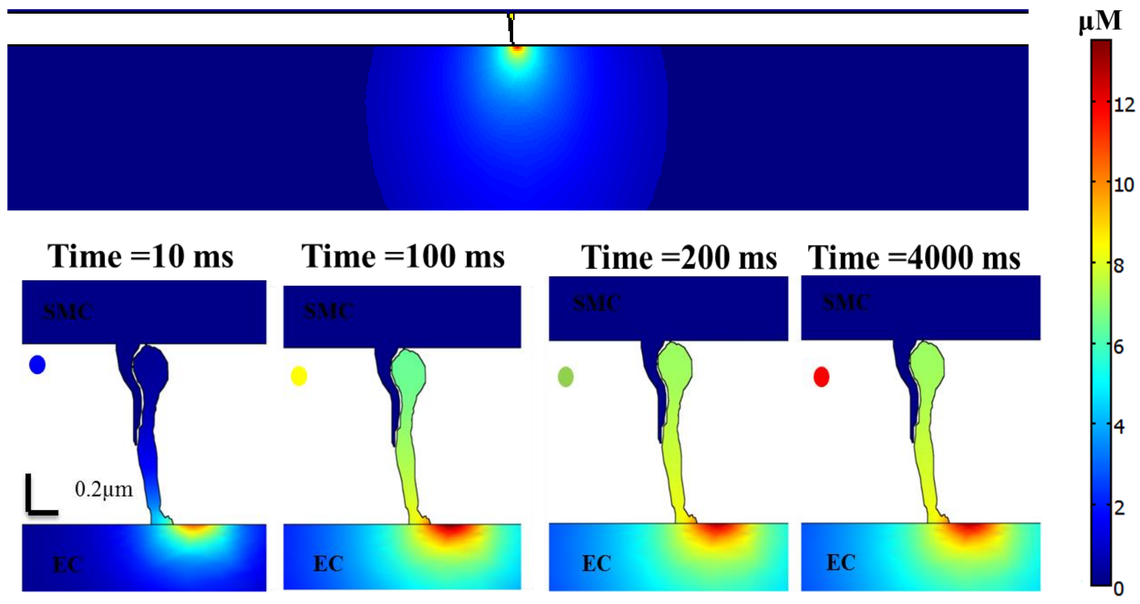

Figure 4: Spatial Ca^{2+} profiles on activation of a single TRPV4 channel

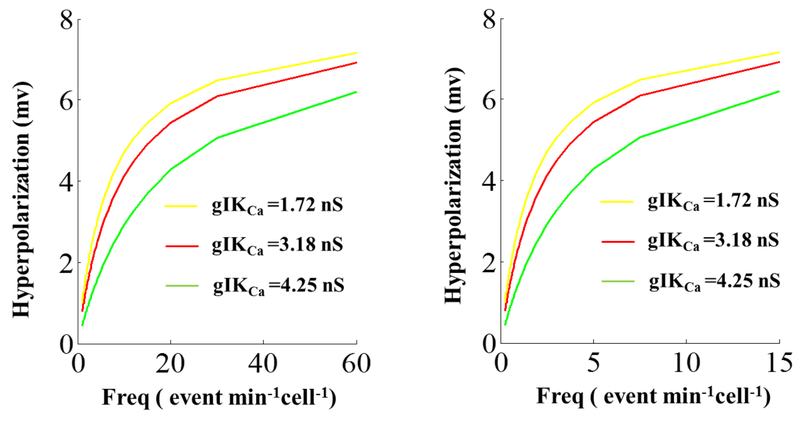

Figure 5. Predicted SMC hyperopolarization from single TRPV4 channel activation

Conclusions:

- We were able to develop FEM models of EC-SMC providing the spatiotemporal changes in Ca2+ and Vm levels similar to as observed in experiments.
- The model will
  - Help analyze and validate the experiments,
  - Provide quanitifcation of localized and global Ca^{2+} events and further out understanding of the role of these events and signaling microdomains in the regulation of vessel tone

References:

1. Tsoukias NM. Calcium dynamics and signaling in vascular regulation: computational models. Wiley Interdiscip Rev Syst Biol Med 3: 93-106, 2011.

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