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Multi-Scale FEM Modeling of Vascular Tone: From Membrane Currents to Vessel Mechanics

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Abstract

Regulation of vascular tone is a complex process that remains poorly understood. Here we present our recent efforts for the development of physiologically realistic models of arterial segments for the analysis of vasoreactivity in health and disease. Multi-scale modeling integrates intracellular and cell membrane components into whole-cell models of calcium and membrane potential dynamics. Single-cell models of vascular cells are combined into a multicellular model of the vascular wall, and vessel wall biomechanics are integrated with calcium dynamics in the smooth muscle layer. At each scale, continuum models using finite element method can account for spatial heterogeneity in calcium signaling and for nonuniform deformations of a vessel segment. The outlined approach can be used to investigate cellular mechanisms underlying altered vasoreactivity in hypertension.

Index Terms

calcium oscillations; microcirculation; nonlinear mechanics; vasoconstriction

I. INTRODUCTION

Vascular tone and thus blood flow in the microcirculation is regulated by numerous signaling pathways, acting at different spatial and temporal scales, that create complex dynamic feedback loops. Intra- and intercellular concentration gradients, radial and axial diffusion of vasoactive substances, oscillatory behavior and waves contribute to this complexity. Integrated spatiotemporal analysis at different scales is needed to relate macroscale responses to the underlying cellular signaling and to elucidate common but poorly controlled diseases associated with vascular hyperreactivity.

Calcium (Ca^{2+}) controls directly or indirectly short and long term responses in vascular cells, including release of endothelium derived hyperpolarizing and relaxing factors (EDHF and EDRF), smooth muscle cell (SMC) contraction, channel expression, and cell proliferation. Ca^{2+} is closely regulated by membrane potential (V_m), which is also an important intercellular signal in conducted responses, vasomotion and endothelium dependent relaxation. Furthermore, changes in vessel diameter feed back on Ca^{2+} through mechanosensitive and shear-stress sensitive membrane channels in SMCs and endothelial cells (ECs). Therefore, integrated Ca^{2+} and V_m dynamics is a central aspect of microcirculatory function and modeling.

In this paper, we propose a multi-scale modeling framework for integrating and analyzing multitude of microcirculatory experimental data from various electrophysiological and reactivity studies, that would be otherwise difficult to combine. Novel cellular modeling

based on a continuum approach is described as an extension of traditional compartmental models. We emphasize the physiological relevance, advantages and limitations of certain choices in model development, and we present as a paradigm the application of the model for the analysis of altered vasoreactivity in a hypertension.

II. SUBCELLULAR COMPONENTS

Ca^{2+} homeostasis depends on number of Ca^{2+} channels, pumps, and exchangers expressed in the cell membrane and on internal stores (i.e., the sarcoplasmic/endoplasmic reticulum (SR/ER)). Transmembrane Ca^{2+} fluxes depend on electrochemical gradients and thus cytosolic Ca^{2+} levels also depend on V_m and intra- and extra-cellular ionic concentrations. V_m is determined mostly by Na^+ , K^+ and Cl^- conductances, and these are modulated directly or indirectly by Ca^{2+} . Therefore, developing physiologically relevant models requires integrating Ca^{2+} and V_m dynamics.

A. Cell membrane channels

A large number of electrophysiological and gene expression studies revealed that vascular SMCs and ECs express a significant amount of membrane channels with varying characteristics between vascular beds and species. It is therefore critical that tissue specific data be utilized for model development whenever available. The formulations of ionic fluxes through membrane channels and pumps can be based on whole cell and single channel patch clamp data, and typically use the linear or Goldman-Hodgkin-Katz (GHK) equations. Extracellular accumulation of ions can play a role in vascular physiology, thus descriptions of membrane currents should depend on intracellular and extracellular ionic concentrations (i.e., concentrations are accounted directly in GHK equations, or through their effect on Nernst potential in the linear formulation). GHK equations are more adequate for nonselective channels when absolute or relative permeabilities for individual ionic species are given.

B. Intracellular species

In addition to membrane fluxes, cytosolic Ca^{2+} depends on Ca^{2+} diffusivity, buffering, and release and uptake of Ca^{2+} by the intracellular stores. Numerous functional studies with inhibition of ryanodine receptors (RyRs), inositol trisphosphate receptors (IP_3Rs), and SR/ER Ca^{2+} pump (SERCA) have demonstrated an important role of SR/ER. However, quantitative characteristics of store Ca^{2+} release are difficult to obtain experimentally, and generic models of RyRs and IP_3Rs are typically used. IP_3 activates IP_3Rs and Ca^{2+} release, and is generated by plasma membrane phospholipase C (PLC) following activation by various membrane receptors in SMCs (e.g., α_1 -adrenoceptor) and ECs. IP_3 balance is likely to be important also in multicellular coordination due to its diffusion through homo- and heterocellular gap junctions with significant consequences for Ca^{2+} regulation.

III. SINGLE CELL MODELS

A. Well-mixed models

Direct formulation, implementation, and validation of a continuum cell model may be complicated, and it is easier to start from well-mixed, compartmental models. Fig. 1a shows schematic diagram of our EC and SMC models based on data from rat mesenteric resistance arteries [1, 2]. The models assume that the cytosol and SR/ER are well-mixed compartments with uniform concentration of various ionic and signaling species. However, experiments suggest presence of functional microdomains in ECs and SMCs with channels and signaling pathways distinct from the bulk cytosol. Compartmental models can simulate discrete microdomains and have been used to study pharmacological modulation of Ca^{2+} stores and

signaling [3], to examine the role of myoendothelial projections in myoendothelial communication, or the contribution of K^+ accumulation in extracellular clefts in EDHF response. Compartmentalization of the cytosol was also applied to study 1D Ca^{2+} waves and their synchronization in SMCs [4].

Compartmental models can be implemented as systems of ordinary differential equations (ODEs). ODE solvers for stiff systems are adequate for single and multicellular problems. Recently, we have also implemented the EC-SMC models in JSIM. JSIM is a Java-based simulation system for solving numerical models, developed by the National Simulation Resource at the University of Washington, Department of Bioengineering. Our codes together with JSIM software can be downloaded freely from <http://nsr.bioeng.washington.edu/>.

B. FEM models

Continuous 2D spatial resolution within cytosol and microdomains can be achieved with the finite element method (FEM) approach. FEM models will enable us to study localized events such as Ca^{2+} sparks and puffs or intra- and inter-cellular Ca^{2+} waves, which are now recognized as important aspects of Ca^{2+} signaling. Based on the compartmental models, we have implemented EC and SMC models on 2D rectangular domains and cylindrical domain with 2D axial symmetry using Comsol Multiphysics software. The intracellular and extracellular concentrations of ionic species $S = Ca^{2+}, Na^+, K^+, Cl^-$ were calculated with time-dependent electrodiffusion equations with the electroneutrality condition, implemented in the Chemical Engineering module. In the cytosol,

$$\delta_{ts} \frac{\partial [S]_i}{\partial t} + \nabla \cdot (-D_s \nabla [S]_i - z_s u_{ms} F [S]_i \nabla V_i) = R_s, \quad (1)$$

where, D_s is the diffusion coefficient, u_{ms} is the ionic mobility, z_s gives the charge number of S , F refers to Faraday's constant, and V_i denotes intracellular electrical potential. Unspecified anions X are introduced to ensure the electroneutrality condition in every volume in the solution:

$$z_X [X]_i + \sum z_s [S]_i = 0. \quad (2)$$

This gives the conservation of the electric charge equation:

$$\nabla \cdot \mathbf{i} = \nabla \cdot (F z_X (-D_X \nabla [X]_i - z_X u_{mX} F [X]_i \nabla V_i) + F \sum z_s (-D_s \nabla [S]_i - z_s u_{ms} F [S]_i \nabla V_i)) = F z_{Ca} R_{Ca}. \quad (3)$$

Although the cytosol is largely isopotential, in some microdomains with possibly limited diffusivity to the bulk cytosol (e.g., microprojections), the isopotentiality may not be guaranteed and this heterogeneity may have functional significance. Furthermore, the use of electrodiffusion equations, rather than diffusion equations, allows simple implementation of intercellular coupling as ionic fluxes proportional to electrochemical gradients, and voltage and concentration dependent membrane currents as boundary conditions:

$$-\mathbf{n} \cdot \mathbf{i} = \sum_k I_k (V_m, [S]_i, [S]_e, \mathbf{h}_k), \quad (4)$$

where k refers to all membrane channels shown in Fig. 1, $\mathbf{h}_k$ represents gating variables for channel k , e denotes extracellular domain, and $V_m = V_i - V_e$. The molar fluxes on the boundary are calculated for each ionic species S from the sum of corresponding currents:

$$-\mathbf{n} \cdot \mathbf{N}_s = \frac{1}{z_s F} \sum_k I_{s,k}, \quad (5)$$

Receptor activation and channel gating were defined only on the boundaries and implemented as ODEs in weak form. Uncharged species and Ca^{2+} in SR were calculated with time-dependent diffusion equations. The SR/ER can be homogenized throughout the cytosol and the Ca^{2+} release/uptake is introduced into the electrodiffusion equations through a source term R_{Ca} (Fig. 2a). SR can be also implemented as a discrete domain inside the cytosol with Ca^{2+} release as its boundary flux (Fig. 2c). Ca^{2+} buffering in the cytosol and SR can be accounted for by the time-scaling coefficient δ_{ts} or source term R^{Ca} . In the well-mixed SMC model, Ca^{2+} oscillations can be generated by modifying SR leak and uptake parameters [1]. Oscillations with similar period and amplitude were also generated in the FEM version of the model. Fig. 2b shows a snapshot of intracellular Ca^{2+} and electrical potential during oscillations.

IV. MULTICELLULAR MODELS

In many vessel types, ECs are coupled with SMCs through nonselective myoendothelial gap junctions. This heterocellular coupling allows transmission of hyperpolarizing current from ECs to SMCs (EDHF) during EC stimulation, and diffusion of IP_3 and/or Ca^{2+} from SMCs to ECs during SM stimulation. SMCs and ECs are also coupled by homocellular gap junctions, which play a role during conducted responses and vasomotion. In microcirculation, local stimuli can induce spreading (or conducted) responses to distant sites to coordinate blood flow. The signaling pathways that mediate the distant responses remain unclear. Vasomotion (i.e., macroscopic variations in vessel diameter that are believed to improve blood flow and oxygenation) results from coordinated contraction of many SMCs, but the mechanism of synchronization also remains elusive.

To study such coordinated responses, multicellular models were formulated as systems of ODEs [5]. In FEM modeling, cells can be coupled by common domain with active IP_3 and ionic electrodiffusion equations. Proper intercellular resistance can be obtained by setting intercellular diffusivity coefficient to:

$$D_{\text{gj},S} = D_{\text{gj},\text{IP}_3} = (L/A) \times RT / \left(F^2 R_{\text{gj}} \sum z_s^2 [S]_i \right), \quad (6)$$

where L and A are the length and area of the coupling domain (Fig. 2c), R is the gas constant, T is temperature, and R_{gj} denotes the gap junction resistance [6].

V. BIOMECHANICS

A. 1D models

Although the vascular tone is regulated by SM Ca^{2+} , predicting the diameter of pressurized vessel relative to its fully relaxed state requires knowledge of Ca^{2+} -dependent active stress, stress/strain effect on SM Ca^{2+} , and material properties of the vascular wall [7]. In 1D scenario, uniform changes of the vessel radius (r) can be calculated from the Laplace law:

$$\eta \frac{dr}{dt} + \sigma_p + \sigma_a = \frac{pr}{h}, \quad (7)$$

where η – is the wall viscosity coefficient, σ_p – passive stress described by an exponential function of r , σ_a – active stress expressed as a product of SM Ca^{2+} -dependent sigmoidal

function and r -dependent Gaussian function obtained by fitting pressure and wire myography data. Changes in tone can feed back on the SM Ca^{2+} through activation of mechanosensitive channels in SMCs and/or ECs. It remains unclear whether these channels are sensitive to wall strain or stress. In [8], we assumed that DAG-dependent NSC channels in SMCs are activated by vessel strain $\epsilon = (r - r_0)/r_0$:

$$P_{\text{NSC}} = (k\epsilon^3 + [\text{DAG}]) / (k\epsilon^3 + [\text{DAG}] + K_{\text{NSC}}). \quad (8)$$

B. 2D axisymmetric models

1D models are adequate to analyze myogenic tone, but axial resolution is required to capture conducted responses, waves of vasomotion, and possible role of mechanical stress/strain in synchronization. In higher dimensions, blood vessels can be represented through continuum mechanics, but major difficulty arises due to large deformations involved and highly nonlinear stress-strain relationships. Large deformations of nonlinear material can be captured by hyperelastic material model, for which:

$$\mathbf{S} = \partial W / \partial \mathbf{E}, \quad (9)$$

where $\mathbf{S}$ is the 2nd Piola-Kirchhoff stress tensor, $\mathbf{E}$ – Green–Lagrange strain tensor, W – strain energy density function. For blood vessels, Fung [9] proposed the exponential strain energy function:

$$W = c(e^Q - 1)/2, \quad Q = c_1 E_{rr}^2 + c_2 E_{\theta\theta}^2 + c_3 E_{zz}^2 + c_4 E_{rr} E_{\theta\theta} + c_5 E_{zz} E_{\theta\theta} + c_6 E_{rr} E_{zz} + c_7 E_{rz}^2 \quad (10)$$

To simplify the numerical implementation and reduce the number of parameters, we assumed 2D axisymmetric and isotropic model. The implementation of passive Neo-Hookean material in Comsol Structural Mechanics module was adapted to incorporate the exponential strain energy function and circumferential active stress. The active stress was imported to Comsol from Fortran multicellular model having as input arguments local agonist concentration and vessel diameter. The computations were iterated until steady-state diameter was reached at constant pressure (Fig. 2d).

VI. PARAMETRIC STUDIES

A major limitation in the implementation of the models is a frequent lack of tissue specific parameter values. In many cases, values from other tissues have to be taken, or physiologically relevant values have to be assumed. Sensitivity analysis and parametric studies can examine the effect of parameter uncertainty on model predictions. Parametric studies can be also used to examine the effect of disease related changes on system responses. Based on literature, we have incorporated changes in channel expression identified in spontaneously hypertensive rats into the compartmental ECSMC model to examine their effect on Ca^{2+} responses [8]. Fig. 1 shows the upregulated and downregulated cellular components. Since the individual changes can have competing effects, their net result is difficult to predict without a detailed quantitative model. Simulations suggest that the effect of VOCC upregulation can be compensated by upregulation of large conductance Ca^{2+} activated K^+ channels (BK_{Ca}), and that the increased contractility in hypertensive rats may result from increased active stress in vessel wall. Another parametric analysis on the effect of ouabain in salt sensitive hypertension predicted increased reactivity of SMCs and impaired endothelium-dependent relaxation [10]. Similar perturbation analyses can be applied to the more detailed continuous FEM models to investigate intra- and inter-cellular

Ca²⁺ waves, Ca²⁺ synchronization in vasomotion and effect of wall mechanics on vascular tone regulation.

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Fig. 1. Example of fitting patch clamp data for voltage-operated Ca^{2+} channels (VOCC) with GHK equations, which are then integrated into wholecell SMC model. Single SMC and EC models are next coupled into multicellular vessel models. The upward and downward arrows indicate upregulation and downregulation, respectively, of corresponding components in the model of spontaneously hypertensive rat.

Fig. 2.

FEM models of Ca^{2+} dynamics and biomechanics. a) Intracellular and extracellular domains were implemented with time-dependent electrodiffusion equations, and membrane currents as boundary fluxes. b) An example of cytosolic Ca^{2+} profile and electrical potential during oscillations in 2D SMC model. c) (left) Integration of 2D axisymmetric SMC and EC models through myoendothelial microprojections and gap junctions. SMC SR is homogenized, while EC ER is implemented as discrete compartment. (right) Predicted Ca^{2+} increase in endothelial projection induced by SMC stimulation with norepinephrine (NE). d) Predicted spreading vasodilatation induced by local ECs stimulation with acetylcholine (Ach) in the presence of global NE. T_{act} – circumferential active stress.