FIU Biomedical Engineering
Florida International University

Finite Element Modeling of Vasoreactivity Using COMSOL Multiphysics® Software

Jaimit Parikh, Adam Kapela and Nikolaos Tsoukias

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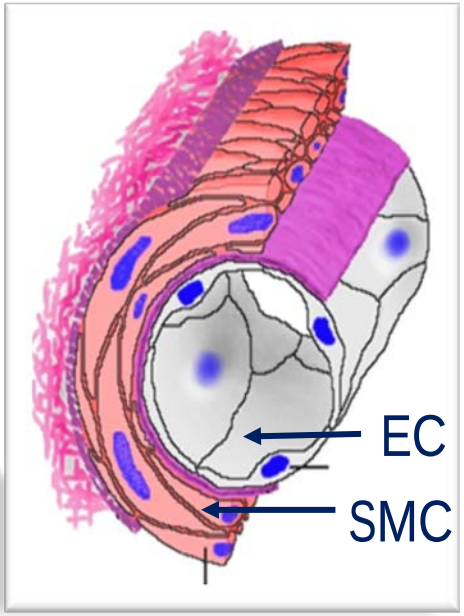
INTRODUCTION

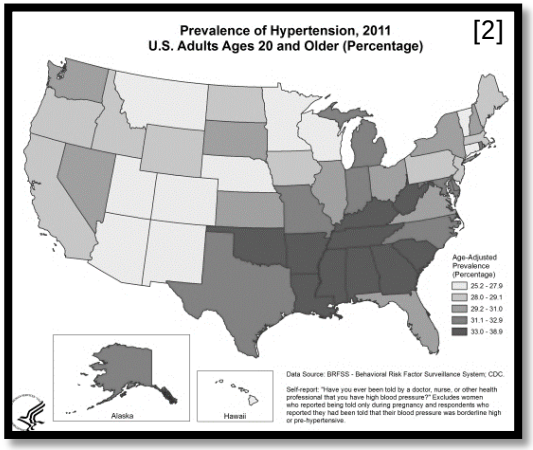
- Microvasculature: Blood vessels < 150 μM
- Longitudinally arranged single layer of ECs surrounded by perpendicular arrangement of one or many layers of SMCs
- Role of Microcirculation:
  - Regulate blood flow
  - Tissue perfusion
  - Regulates blood pressure and responses to inflammation

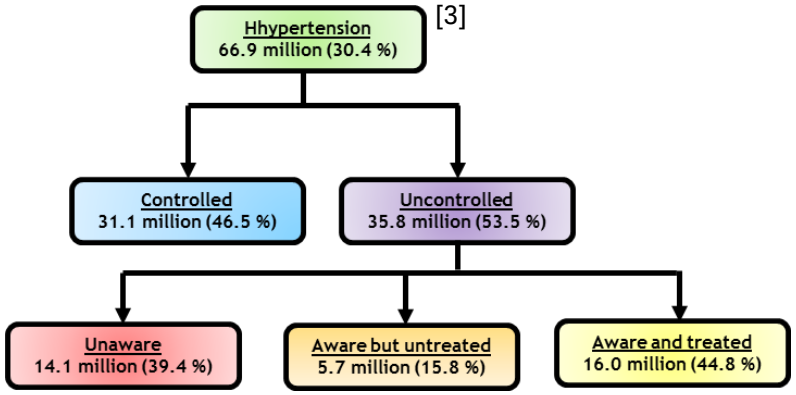


Microcirculation

SIGNIFICANCE

- High blood pressure: 1 in 3 adults in US. [1]
- Almost 3 of 4 patients that experience their first heart attack or stroke are hypertensive. [1]
- Peripheral vascular resistance is increased in virtually all models of hypertension and altered arteriolar tone can affect renal function and the ability of the kidneys to regulate blood pressure.



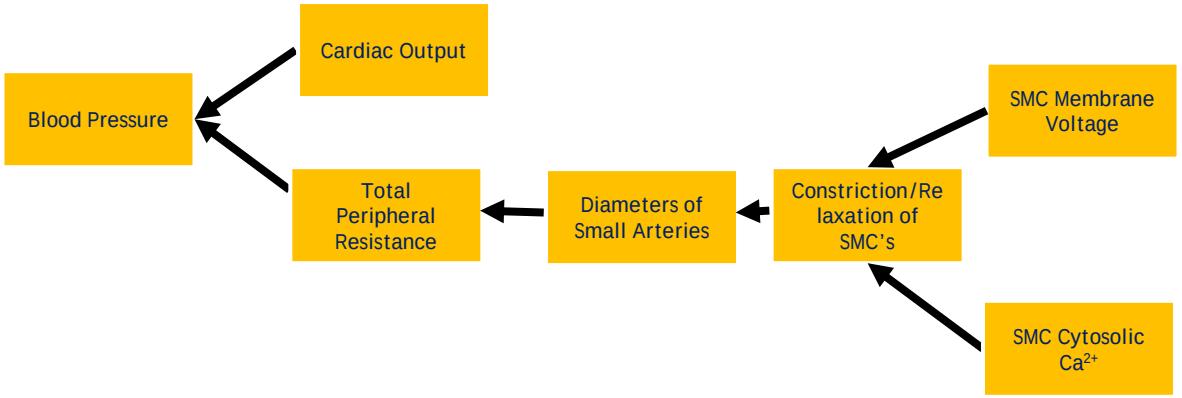


GOAL

Complex mechanisms at the molecular, cellular levels participate in the regulation of vascular resistance and hence the vessel tone.

Develop theoretical models to better understand *mechanisms modulating* Ca^{2+} *and* V_m *dynamics that regulate vascular resistance, blood flow and pressure in health and in hypertension*

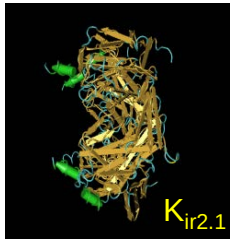
In particular: Quantification and role localized Ca^{2+} *signals via TRPV4 channels and localized NO signaling in vessel tone modulation*

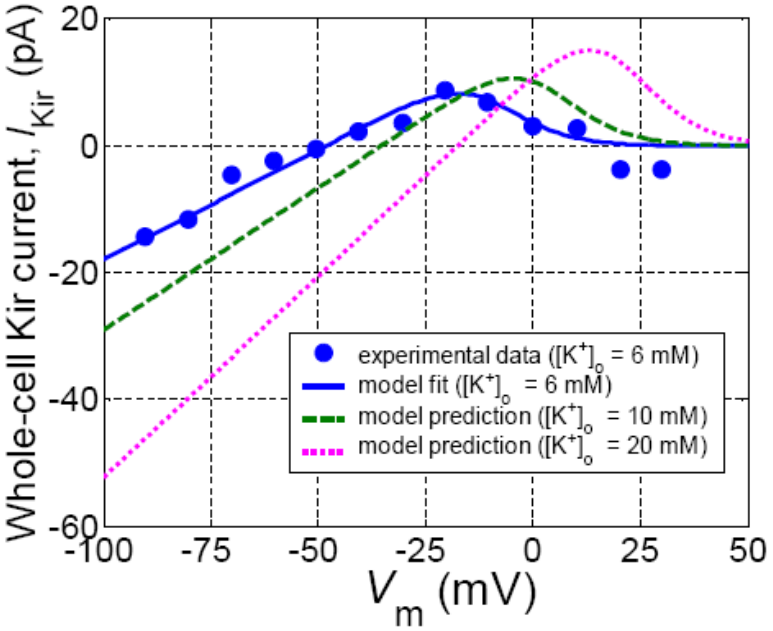


METHODS

STEP 1: Ion Channels

Fitting of current-voltage data for the individual channel provides a mathematical description for each channel





$$I_{\mathrm{Kir}} = \frac{G_{\mathrm{Kir,max}}\left(V_{\mathrm{m}} - E_{\mathrm{K}}\right)}{1 + e^{\frac{\Delta V - \Delta V_{\mathrm{Kir,h}}}{\upsilon_{\mathrm{Kir}}}}}$$

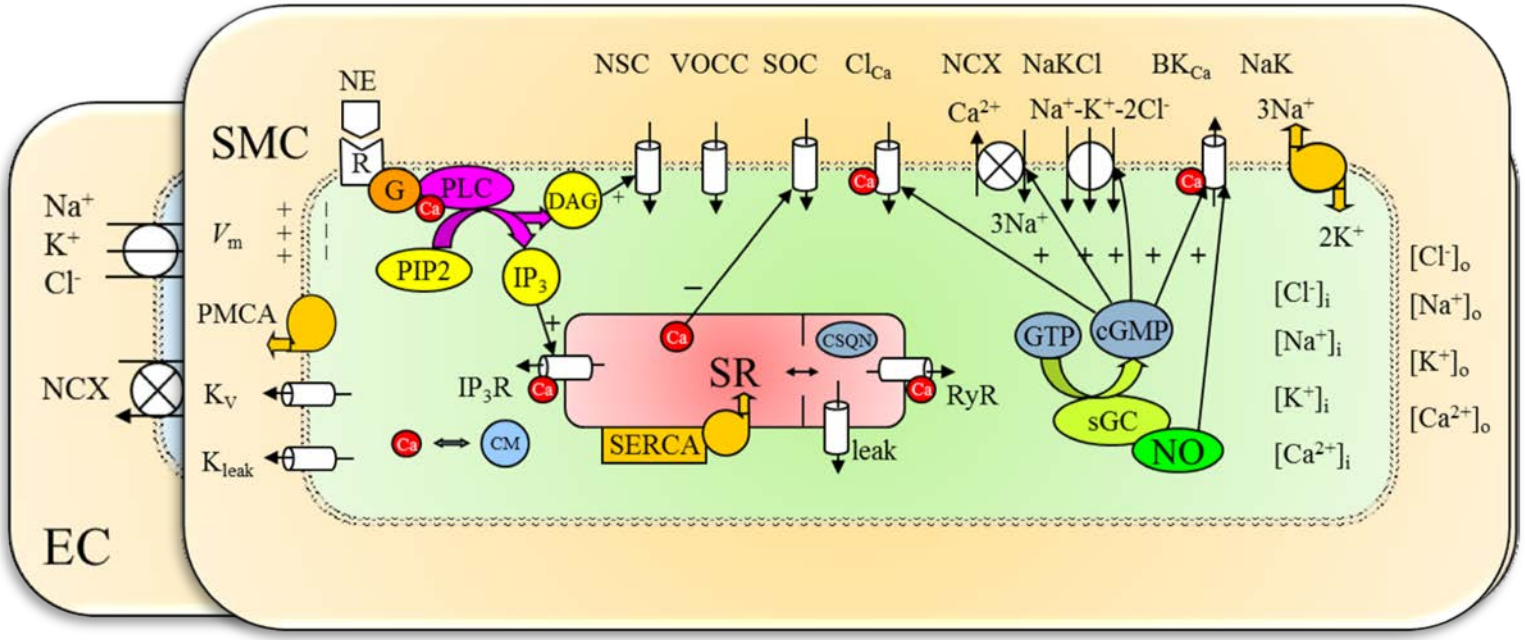
$$G_{\mathrm{Kir,max}} = \mathrm{G}_{\mathrm{Kir}}\left([\mathrm{K}^+]_{\mathrm{o}}\right)^{\mathrm{n}_{\mathrm{Kir}}}$$

$$\Delta V = V_{\mathrm{m}} - E_{\mathrm{K}}$$

METHODS

STEP 2:Single Cell Models

Incorporates major channels, pumps and accounts for balance of Ca^{2+}, Na^{+}, K^{+}, Cl^{-}, and IP_3



Smooth Muscle Cell Model: 26 ODEs solved using Gear's backward differential formula method for stiff systems

Endothelial Cell Model: 11 ODEs solved using Gear's backward differential formula method for stiff systems

METHODS

EC MODEL SET OF ODEs

$$\frac{dV_m}{dt} = -\frac{1}{C_m}(I_{SOC} + I_{NSC} + I_{VRAC} + I_{CaCC} + I_{K_{ir}} + I_{IK_{Ca}} + I_{SK_{Ca}} + I_{NaK} + I_{NCX} + I_{PMCA})$$

$$\frac{dCa_i}{dt} = -\frac{I_{SOC,Ca} - 2I_{NCX} + I_{CaP} + I_{NSC,Ca} + I_{SERCA,S1} - I_{leak,S1} - I_{IP3R} + I_{SERCA,S2} - I_{CICR} - I_{leak,S2}}{2 \cdot F \cdot vol_{Ca}}$$

$$\frac{dCa_{S1}}{dt} = -\frac{I_{IP3R} - I_{SERCA,S1} + I_{leak,S1}}{2 \cdot F \cdot vol_{S1}}$$

$$\frac{dCa_{S2}}{dt} = -\frac{I_{CICR} - I_{SERCA,S2} + I_{leak,S2}}{2 \cdot F \cdot vol_{S2}}$$

$$\frac{dCa_B}{dt} = kB_{on} \cdot Ca_i \cdot (B_T - Ca_B) - kB_{off} \cdot Ca_B$$

$$\frac{dNa_i}{dt} = -\frac{I_{SOC,Na} + 3I_{NCX} + I_{NSC,Na} + 3I_{NaK} - 0.5I_{NaKCl\_Cl}}{F \cdot vol_i}$$

$$\frac{dK_i}{dt} = -\frac{I_{SKCa} + I_{IKCa} + I_{Kir} + I_{NSC,K} - 2I_{NaK} - 0.5I_{NaKCl\_Cl}}{F \cdot vol_i}$$

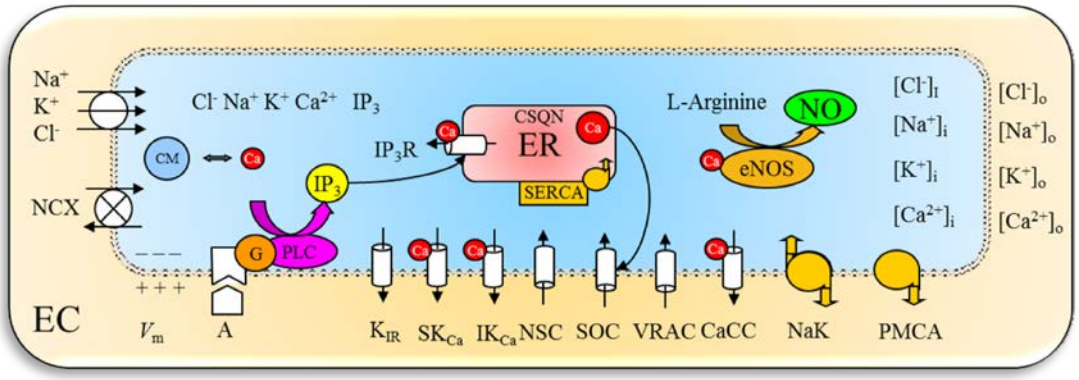
$$\frac{dCl_i}{dt} = -\frac{I_{NaKCl\_Cl} + I_{VRAC} + I_{CaCC}}{-1 \cdot F \cdot vol_i}$$

$$\frac{dIP_3}{dt} = Q_{GIP3} - k_{DIP3} \cdot IP_3$$

$$\frac{dQ_{GIP3}}{dt} = \frac{Q_{GIP3,SS} - Q_{GIP3}}{\tau_{IP_3}}$$

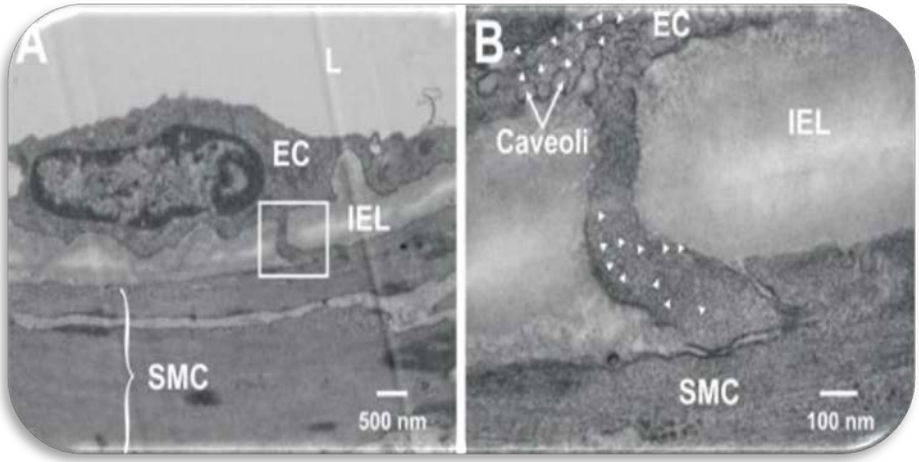
$$\frac{dP_{O,CaCC}(t)}{dt} = \frac{P_{O,CaCC,SS} - P_{O,CaCC}(t)}{\tau_{CaCC}}$$

- 11 Nonlinear ODE
- ~ 60 Model parameters
- Values acquired from RMA-EC, other EC, other cell types

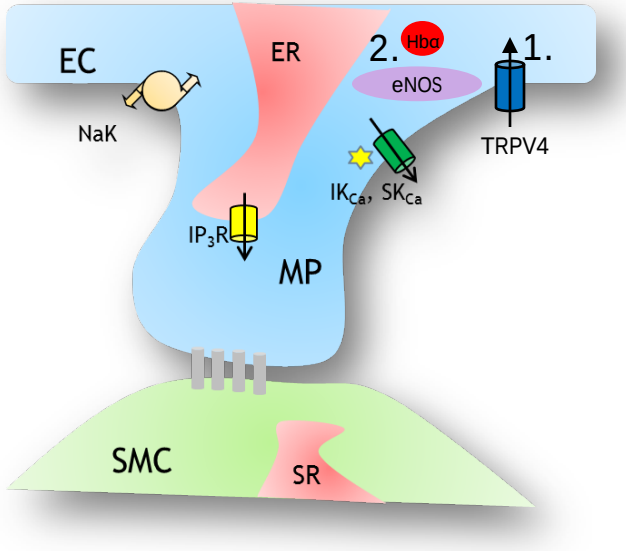


MICROPROPJECTIONS

Traditional transmission electron photomicrograph (×15,000) of the arterial wall [5]



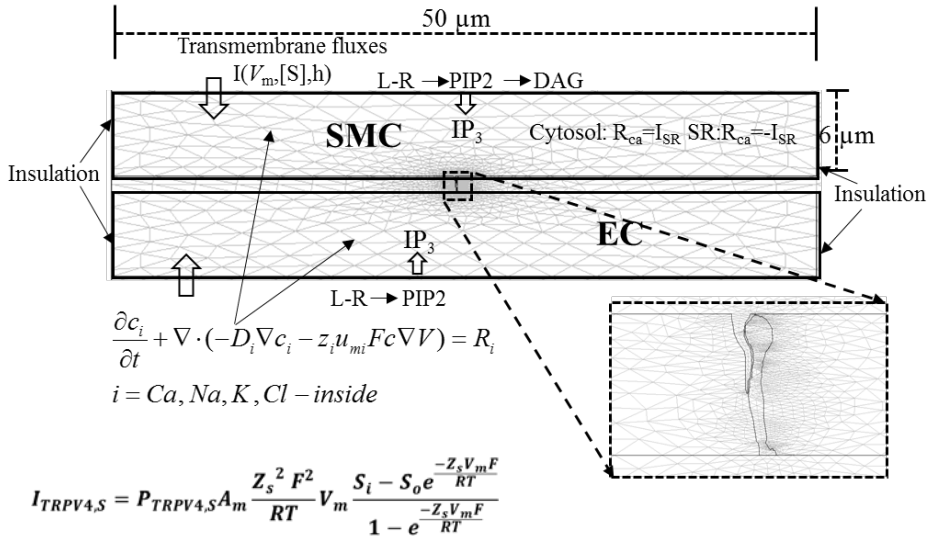
Schematic of channels and cellular components localized in the microprojections



METHODS

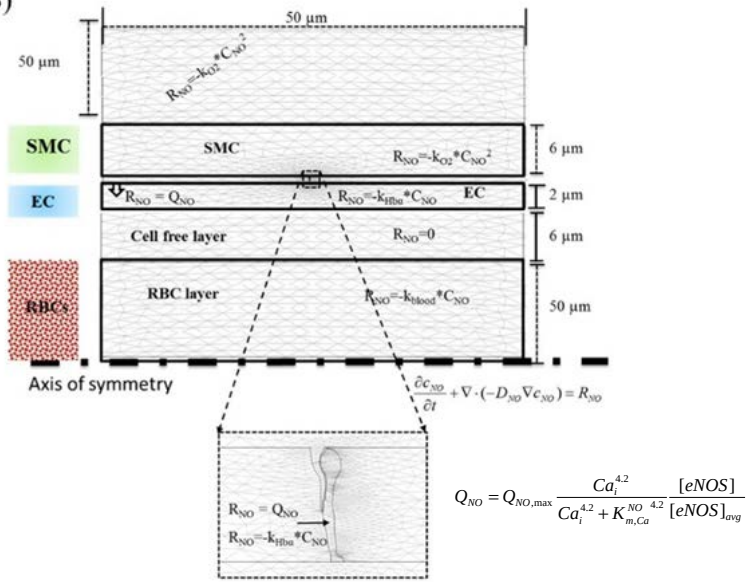
STEP 3: FINITE ELEMENT EC-SMC MODEL

A)



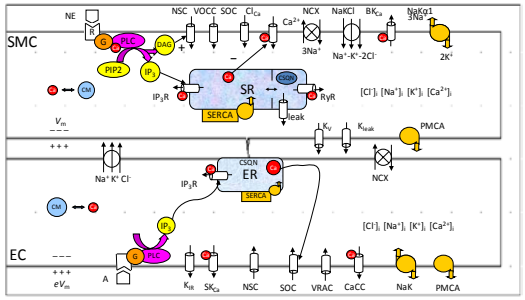
$$I_{TRPV4,S} = P_{TRPV4,S} A_m \frac{{Z_s}^2 F^2}{RT} V_m \frac{S_i - S_o e^{\frac{-Z_s V_m F}{RT}}}{1 - e^{\frac{-Z_s V_m F}{RT}}}$$

B)



$$Q_{NO} = Q_{NO,\max} \frac{Ca_i^{4.2}}{Ca_i^{4.2} + K_{m,Ca}^{NO\ 4.2}} \frac{[eNOS]}{[eNOS]_{avg}}$$

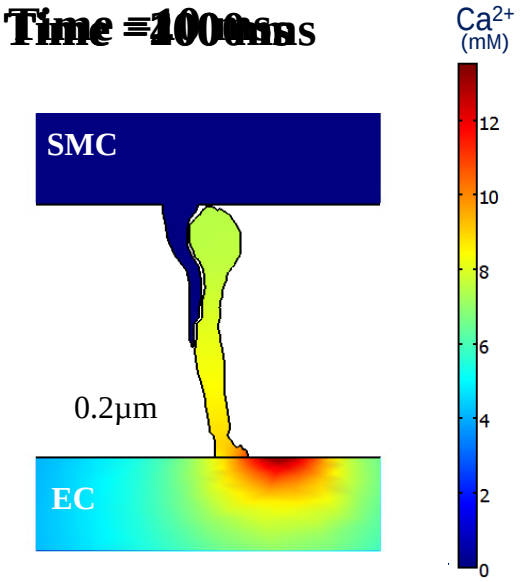
- Allow to examine spatiotemporal changes in Ca^{2+} and V_m dynamics.
- To incorporate exact geometries of microdomain structures like micorprojections and implement spatial localization of cellular components



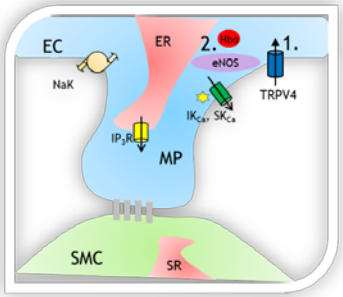
- COMSOL Multiphysics
- Membrane Currents implemented as boundary conditions $-n.N_S = \frac{1}{z_S F} \sum_K I_{S,K}$
- Electro-diffusion for ionic transport
- Diffusion for second messenger

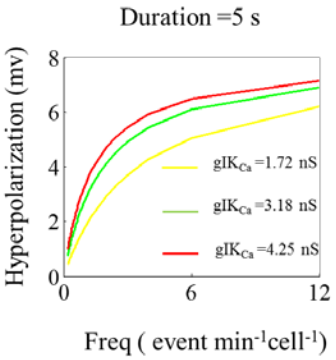
RESULTS

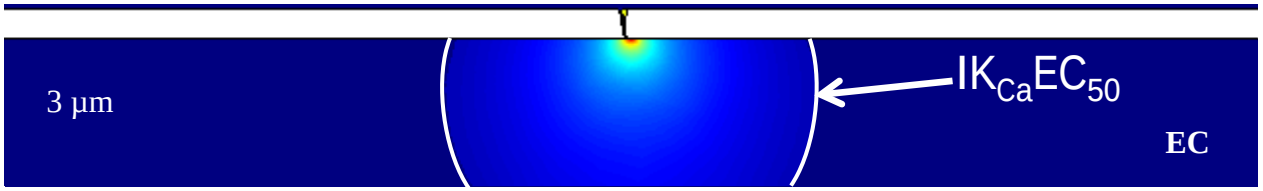
TRPV4 SPARKLET ACTIVITY



- µM peak Ca^{2+} concentrations locally
- Activation of IK_{Ca} channels 6 µm away



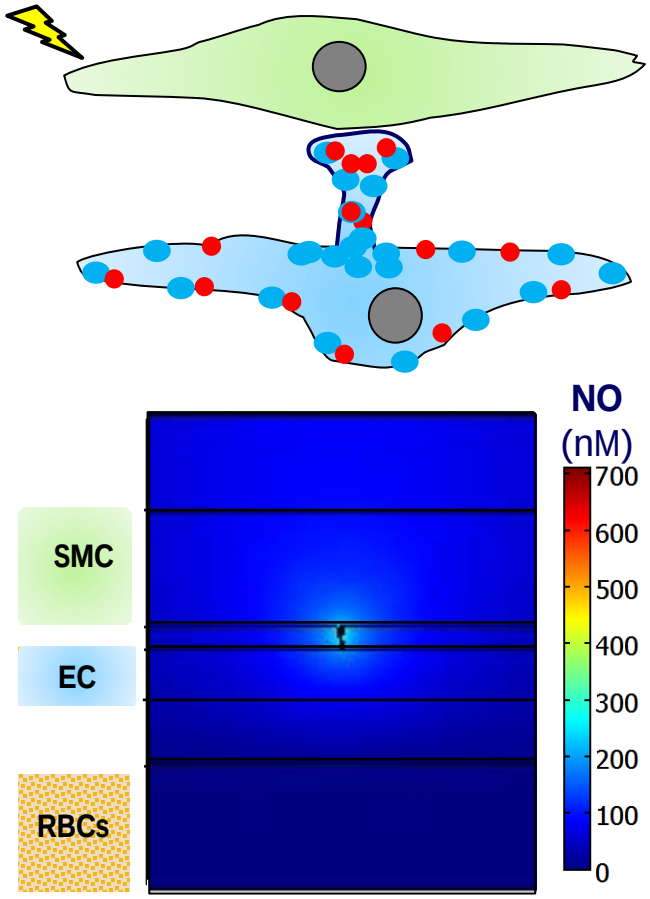


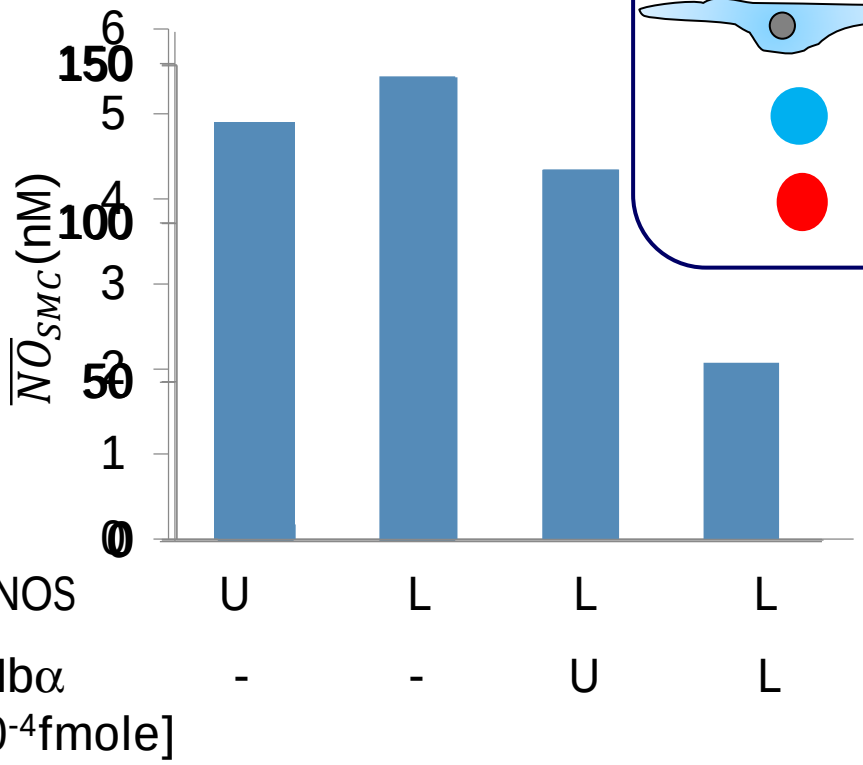


RELAXATION OF VESSEL TONE

RESULTS

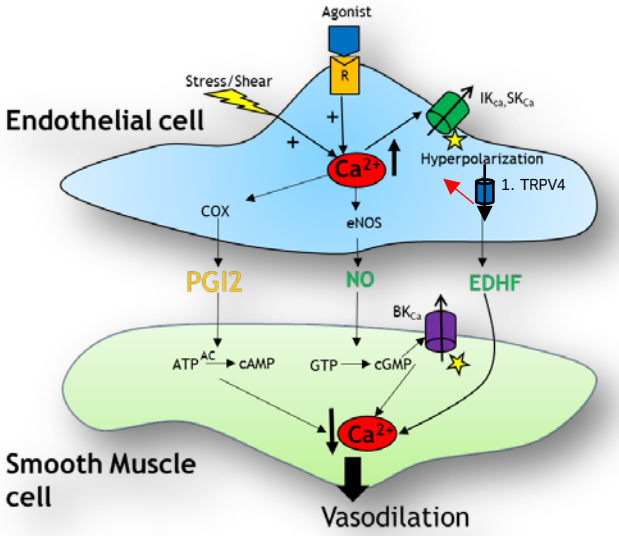
NO DIFFUSION DURING SMC STIMULATION





SUMMARY

- The developed models serves as a tool for assisting investigations on the regulation of vascular tone in health and disease, and development of rationale therapeutic strategies for disease like hypertension.
- Allows quantification and better understanding of Ca^{2+} dynamics regulation.
- Activation of single TRPV4 channel can result in few mM peak Ca^{2+} concentrations locally which may result in 8-10 mV hyperpolarization of SMC and vessel relaxation.'
- Localization of eNOS in the vicinity of MP may result in NO mediated feedback during SMC stimulation (i.e. PE, NE)
- Modulation of NO biovailability by Hbα is enhanced by the colocalization in the MP
- RBC perfusion will decrease the ability of Hbα to modulate NO levels and μM levels of EC Hbα are required for a significant modulation of SMC NO availability



REFRENCES

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4. **Tsoukias NM. et al.** A theoretical model of nitric oxide transport in arterioles: frequency- vs.amplitude-dependent control of cGMP formation. Am J Physiol Heart Circ Physiol 286: H1043–H1056, 2004.
5. **Tran CH. et al**. Endothelial Ca^{2+} wavelets and the induction of myoendothelial feedback. Am J Physiol Cell Physiol 302: C1226-1242, 2012.

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THANK YOU