Sensitivity analysis of a smooth muscle cell electrophysiological model.

Sanjay R. Kharche^{1,2}, Galina Yu. Mironova³, Daniel Goldman², Christopher W. McIntyre¹, and Donald G. Welsh³.

¹ Lawson Health Research Institute, London, Canada. N6A 5W9.

² Department of Medical Biophysics, Western University, London, Canada. N6A 5C1.

³ Robarts Research Institute, Western University, London, Canada. N6A 5C1.
Sanjay.Kharche@lhsc.on.ca

Abstract. Cardiac smooth muscle cell mathematical models are increasingly being used in clinical decision making and drug testing. The cell models also have the potential to assist interpretation and extending of our multi-scale experimental findings. Components of the models interact with each other to regulate model behavior in a non-linear manner. To permit meaningful deployment of the models, it is therefore a necessity to understand the regulatory significance of model components' parameters on the model's behavior. In this study, the regulation of mean intra-cellular calcium and mean membrane potential (model behavior) by underlying model parameters (regulators) in a smooth muscle cell mathematical model was quantified using two sensitivity analysis methods. It was found that extracellular electrolytes and gating kinetics are prime model behavior regulators. A representative case relevant to widespread hypertension focusing on the L-type channel's parameters is presented. This sensitivity analysis will guide our future data driven modelling efforts.

Keywords: Smooth muscle cell, mathematical model, coronary vasculature, sensitivity analysis.

1 Introduction.

Electrically active building blocks of blood vessels called smooth muscle cells (SMCs) effect vascular tone [1, 2] in arteries, including those in cardiac walls (coronary arteries). We think that debilitating conditions such as hypertension and renal failure alter L-type calcium ion channel (I_{CaL}) function and promote accumulation of intracellular calcium ($[Ca^{2+}]_i$) in SMCs [3]. In accordance with experimental protocols, SMC model behavior is characterized by $[Ca^{2+}]_i$ and membrane potential, V_m . An understanding of how I_{CaL} parameters regulate SMC mathematical model behavior will guide our future experimental-modelling investigations.

In multiple SMC modelling studies, the regulation of model behavior by either maximal transport rates and conductances [4, 5] or biochemical availability [6] has previously been demonstrated. However, it can be appreciated that other modelling parameters also play a vital role in model behavior (see **Fig. 1**). We have previously observed

that the inherently coupled nature of mathematical model components (e.g. ion channel gating and intracellular $[Ca^{2+}]_i$ processes) necessitates the inclusion of all model parameters in meaningful sensitivity analysis [7]. *In silico* studies should take into account multiple modelling parameters in light of experimental findings where $[Ca^{2+}]_i$ increase has been attributed to both an augmented ion channel expression density [8] as well as altered ion channel gating pathways independently of conductance alterations [9].

Fig. 1. Bifurcation diagram illustrating regulation of $[Ca^{2+}]_i$ dynamics by extracellular potassium, $[K^+]_o$. For low concentrations of $[K^+]_o$ (less than 21 mM), the SMC model generated a steady state $[Ca^{2+}]_i$. For larger values of $[K^+]_o$ (21 mM to 78 mM), $[Ca^{2+}]_i$ oscillations were observed.

In this preliminary work, an established smooth muscle cell model [4] was used to rank the regulatory impact of all parameters in a SMC model [4] on its mean intracellular $[Ca^{2+}]_i$ and mean membrane potential, V_m . To do so, two sensitivity analysis methods [7, 10] were adopted. As a case of interest, findings focused on I_{CaL} and related parameters are presented.

2 Methods.

The smooth muscle cell, SMC, model [4] adopted in this work is a system of 27 coupled ordinary differential equations. The model computer program was obtained from CellML repository [11] and programmed into our robust ordinary differential equations solver based on an advanced external library [12]. The model has 48 parameters that consist of all conductance values, maximum transport fluxes, steady state gating parameters, time constant scaling factors, extracellular electrolyte concentrations, and the capacitance. Parameters' descriptions, acronyms, and their control values relevant to this work are provided in **Table 1**. Model behavior was defined as mean values of $[Ca^{2+}]_i$ and membrane potential, V_m .

To permit sensitivity analysis, a control model population of 10^4 instances was constructed. To generate the population, 48 modelling parameter were each sampled simultaneously from Gaussian distributions using a non-repetitive Mersenne Twister ran-

dom number generator [13], with sampling constrained using Latin Hypercube Sampling [14]. The mean values in each parameter's Gaussian distribution was obtained from the original model [4], while a coefficient of variation of 1.5 was adopted. The adopted coefficient of variation provided a large ($\pm 100\%$) range sampling for each parameter. A model instance in the population was defined by one sampling, and was used in the model to generate mean $[Ca^{2+}]_i$ and V_m . Each model instance required 9.5 s to generate 100 seconds of simulated activity on one Linux processor. The population of 10^4 models was generated using 128 processors within four hours using open source GNU tools. In addition to the control population, a second population where cell capacitance was reduced to 15 pF was also generated. The model parameters and model outputs were stored and further processed using two sensitivity analysis methods.

Table 1. Relevant model parameters.

Parameter.	Description.	Control value.
Extracellular electrolytes and capacitance.		
$[Ca^{2+}]_o$	Calcium.	2 mM.
$[Na^+]_o$	Sodium.	140 mM.
$[K^+]_o$	Potassium.	5 mM.
$[Cl^-]_o$	Chlorine.	129 mM.
C_m	Cell capacitance.	25 pF.
Membrane current conductance values.		
P	L-type calcium channel conductance.	1.88×10^{-5} cm/s.
g_K	Delayed rectifier potassium channel conductance.	1.35 nS.
Intra-cellular calcium release/uptake.		
I_{SERCA}	Maximum $[Ca^{2+}]_i$ uptake by sarcoplasmic reticulum (SR).	6.68 pA.
K_{leak}	SR $[Ca^{2+}]_i$ leak parameter.	1.07×10^{-7} (unitless).
L-type calcium channel gating.		
τ_a	Time constant of activation.	Seconds. (fast).
τ_i	Time constant of inactivation.	Seconds (slow).
$V_{1/2,a}$	Half voltage of steady state activation.	0 mV.
$V_{1/2,i}$	Half voltage of steady state inactivation.	-42 mV.
k_a	Slope of steady state activation.	8.3 mV.
k_i	Slope of steady state inactivation.	9.1 mV.

Sensitivity analysis which ranked parameters according to their impact on model behavior was performed using partial rank correlation coefficients (PRCC) [10] as well as mutual information [7]. Briefly, PRCC performs partial correlation on rank transformed data. The data's rank transformation is used to construct PRCC, and is distinct from sensitivity analysis generated parameter ranking. PRCC assumes a linear underlying statistical model (regression) as well as monotonicity to provide the strength of

the linear relationship between a given pair of parameter and model behaviour (output) [10, 15], which are $[Ca^{2+}]_i$ or V_m in the present study. The range of PRCC is from -1 to +1 by its mathematical definition. Information theoretic motivated mutual information index [16, 17] provides a measure of the amount of mutual dependence of a given parameter on a chosen model output. Normalization of the mutual information index provides a normalized mutual information index (NMII), which permits comparison across parameters and populations. The NMII ranges between 0 and +1 when mutual information is computed in bits.

Whereas the sensitivity analysis considered all model parameters (48 in total), **Table 1** provides the 15 parameters whose sensitivities are presented in this study.

3 Results.

As illustrated in **Fig. 2**, the maximal intracellular calcium ($[Ca^{2+}]_i$) PRCC values belong to extracellular calcium, cell capacitance, and I_{CaL} activation gate parameter, k_a . The I_{CaL} gating parameters, $V_{1/2,a}$ and $V_{1/2,i}$, have larger numerical values of $[Ca^{2+}]_i$ PRCC, in comparison to the conductances, P and g_K . $[Ca^{2+}]_i$ transport rates, represented by I_{SERCA} and K_{leak} , have a low intracellular PRCC ranking.

The maximal membrane potential (V_m) PRCC values belong to extracellular chloride, sodium, as well as cell capacitance. The I_{CaL} gating parameters, τ_a and τ_i , are ranked higher than the I_{CaL} conductance by the PRCC sensitivity analysis. The $[Ca^{2+}]_i$ transport processes were seen to have minimal ranking. The PRCC ranking of the potassium conductance, g_K , is higher for membrane potential as compared to intra-cellular calcium. Reduction of capacitance altered the numerical values of PRCCs, but rankings were largely unaffected.

Fig 2. PRCCs for intracellular calcium ($[Ca^{2+}]_i$, top two panels) and membrane potential (V_m , bottom two panels) each under control and reduced capacitance (C_m reduced) conditions. Symbols are described in **Table 1**.

Normalized mutual information indices (NMIs) (**Fig. 3**) show that model behavior (i.e. both $[Ca^{2+}]_i$ and V_m) depend maximally on extracellular sodium, potassium, I_{CaL} inactivation gating parameters (τ_i and $V_{1/2,i}$), and capacitance. NMIs ranked all I_{CaL} gating parameters higher than ion channel conductances. Among intracellular calcium transport rates, the uptake process (I_{SERCA}) was consistently ranked higher than the leak process, regulated by parameter K_{leak} . Similar to PRCC, reduction of capacitance altered NMII numerically, but rankings were largely unaffected.

Fig. 3. NMII for intracellular calcium ($[Ca^{2+}]_i$, top two panels) and membrane potential (V_m , bottom two panels) under control and reduced capacitance (C_m reduced) conditions. Symbols are described in **Table 1**.

4 Conclusions and Discussion.

Both sensitivity analysis measures, PRCC as well as NMII, suggest that the prime regulators of model $[Ca^{2+}]_i$ are electrolytes and cell capacitance rather than calcium induced calcium release processes, which is in line with experimental protocols that use external biochemical and biophysical stimulation to study $[Ca^{2+}]_i$ dynamics [1, 18]. In addition, both analyses demonstrated that ion channel gating processes supersede conductance in their impacts on $[Ca^{2+}]_i$ and V_m , which is also aligned with experimental findings related to I_{CaL} alterations under hypertension [9]. The SMC model used in this study [4], similar to several cardiac models [19-21], rely upon a membrane I_{CaL} calcium induced sarcoplasmic calcium release mechanism to represent $[Ca^{2+}]_i$ dynamics. The higher impact of I_{CaL} in comparison to intracellular calcium transporter processes was reflected by both, PRCC and NMII.

PRCC and NMII provide very different insights regarding model properties. The partial regression based coefficients (PRCC) provide a quantitative manner in which model parameters can be estimated in relation to experimental data using appropriate methods [22]. It can be appreciated that PRCC based parameter estimation is likely to be in the vicinity of the baseline model, after which new PRCC values are required. On the other hand, mutual information provides a quantitative index providing co-dependence information. The measurement of model behaviour is likely to provide information regarding the highly ranked parameters. As such, disease conditions are known to affect model parameters, and the two methods used in this preliminary work offer a reliable approach to guide our modelling efforts.

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