Compositionality Results for Cardiac Cell Dynamics

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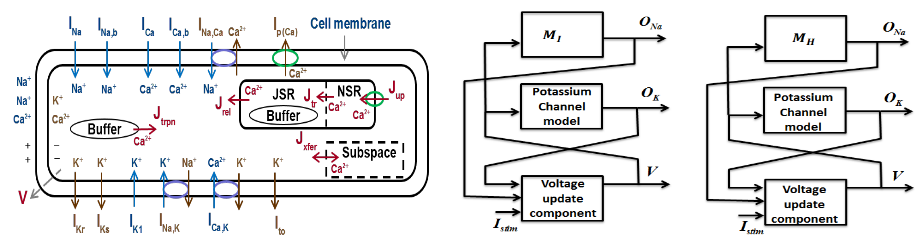
Abstract. We show that the 13-state sodium channel component of the Iyer et al. cardiac cell model can be replaced with a previously identified δ-bisimilar 2-state Hodgkin Huxley-type abstraction by appealing to a small gain theorem. To prove this feedback compositionality result, we construct quadratic-polynomial exponentially decaying bisimulation functions between the two sodium channel models and also for the rest of a simplified version of the Iyer et al. model using the SOSTOOLS toolbox. Our experimental results validate the analytical ones. To the best of our knowledge, this is the first application of δ-bisimilar, feedback-assisting, compositional reasoning in biological systems.

The Iyer et al. model (IMW) [3] is a physiologically detailed cardiac myocyte (ventricular) model that can be used to to simulate the change in a cell's transmembrane potential in response to an external electrical stimulus, also known as the *Action Potential (AP)*. In this work, we ask *"assuming that the AP is the only observable, can we replace the sodium current component, M_I, of IMW with an equivalent model-order reduced Hodgkin Huxley (HH)-type model M_H?"* The HH model [2], uses two variables m and h to model a squid neuron's transmembrane sodium current. In [4], we proposed an algorithm to identify M_H that is δ-bisimilar (equivalent) to the 13-state voltage-controlled M_I.



(a) (b)

Fig. 1. (a)The IMW model, showing various currents. (b)The sodium channel components M_I (detailed) and M_H (abstract) composed with the potassium and voltage components forming the rest of a simplified version (IMW') of the IMW model.

Compositionality of the equivalent sodium channels with the rest of the simplified IMW model (IMW-RT') can be established using Bisimulation Functions (BFs) and a small gain theorem based on them.

Definition 1. *Consider two dynamical systems Σ_i, as per [1], but with $g_i : \mathcal{X}_i \to \mathcal{Y}_i$, being the output functions that map a state to $\mathbf{y}_i \in \mathcal{Y}_i \subseteq \mathbb{R}^p$. Let $R_\delta = \{(\mathbf{x}_1, \mathbf{x}_2) | \parallel g_1(\mathbf{x}_1) - g_2(\mathbf{x}_2) \parallel \leq \delta\}$.A smooth function $S : R_\delta \to \mathbb{R}_0^+$ is a **δ-Restricted BF (δ-RBF) over** Σ_1 **and** Σ_2 if:*

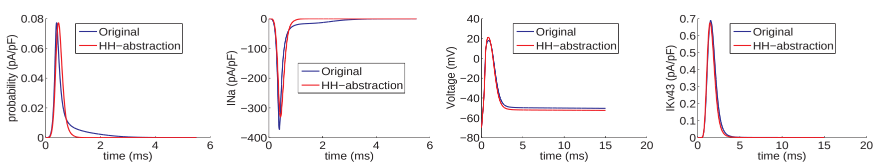
$$\parallel g_1(\mathbf{x}_1) - g_2(\mathbf{x}_2) \parallel \quad \leq S(\mathbf{x}_1, \mathbf{x}_2) \tag{1}$$

and there exists $\lambda > 0$, $\gamma \geq 0$ such that $\forall \mathbf{u}_1 \in \mathcal{U}_1, \mathbf{u}_2 \in \mathcal{U}_2$,

$$\frac{\partial S}{\partial \mathbf{x}_1} f_1(\mathbf{x}_1, \mathbf{u}_1) + \frac{\partial S}{\partial \mathbf{x}_2} f_2(\mathbf{x}_2, \mathbf{u}_2) \leq -\lambda S(\mathbf{x}_1, \mathbf{x}_2) + \gamma \parallel \mathbf{u}_1 - \mathbf{u}_2 \parallel \tag{2}$$

Theorem 1. *Let Σ_1, Σ_2 and Σ_3 be three dynamical systems. Let Σ_{13} and Σ_{23} be interconnections (as defined in [1]) of Σ_3 with Σ_1 and Σ_2 respectively. Let S_{12} be a δ-RBF between Σ_1 and Σ_2 and S_3 be δ-RBF for Σ_3. We denote by λ_{12} and γ_{12} (λ_3 and γ_3 respectively) the constants such that Eq. (2) holds. If $\frac{\gamma_{12}\gamma_3}{\lambda_{12}\lambda_3} < 1$, then there exists a BF S between Σ_{13} and Σ_{23} of the form $S(\mathbf{x}_{13}, \mathbf{x}_{23}) = \alpha_1 S_{12}(\mathbf{x}_1, \mathbf{x}_2) + \alpha_2 S_3(\mathbf{x}_3, \mathbf{x}_3')$ where, $\mathbf{x}_{13} = [\mathbf{x}_1, \mathbf{x}_3]$, and $\mathbf{x}_{23} = [\mathbf{x}_2, \mathbf{x}_3']$ The real constants α_1 and α_2 can be chosen as in Eq.4 of [1] by replacing $\lambda_1 = \lambda_{12}$, $\gamma_1 = \gamma_{12}$, $\lambda_2 = \lambda_3$ and $\gamma_2 = \lambda_3$.*

The two BFs, 1) between M_I and M_H and 2) for IMW-RT' were identified in the SOSTOOLS toolbox [5] by adding the following constraint along with the ones that define a BF: $S(\mathbf{x}, \mathbf{x}') - \parallel g_1(\mathbf{x}) - g_2(\mathbf{x}') \parallel \leq \delta$. The parameter λ was fixed to either 10^{-4} and 10^{-5} for the two BFs and γ was found to be 10^{-6}, which resulted in the small-gain condition being satisfied. Fig. 2 shows experimental evidence of the model equivalence on replacing M_I by M_H.



(a) Na channel conductance. (b) I_{Na} current. (c) APs. (d) I_{Kv43} current.

Fig. 2. IMW' was stimulated using -100 pA/pF stimulus with M_I and then M_H. The resulting mean L1 errors were O_{Na} : 9.15×10^{-4}, I_{Na}: $3.8pA/pF$, I_{Kv43}: $0.0078pA/pF$, V: $2.29mV$.

References

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