Compositionality Results for Cardiac Cell Dynamics

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ABSTRACT

By appealing to the small-gain theorem of one of the authors (Girard), we show that the 13-variable sodium-channel component of the IMW cardiac-cell model (Iyer-Mazhari-Winslow) can be replaced by an approximately bisimilar, 2-variable HH-type (Hodgkin-Huxley) abstraction. We show that this substitution of (approximately) equals for equals is safe in the sense that the approximation error between sodium-channel models does not get amplified by the feedback-loop context in which it is placed. To prove this feedback-compositionality result, we exhibit quadratic-polynomial, exponentially decaying bisimulation functions between the IMW and HH-type sodium channels, and also for the IMW-based context in which these sodium-channel models are placed. These functions allow us to quantify the overall error introduced by the sodium-channel abstraction and subsequent substitution in the IMW model. To automate the computation of the bisimulation functions, we employ the SOSTOOLS optimization toolbox. Our experimental results validate our analytical findings. To the best of our knowledge, this is the first application of δ-bisimilar, feedback-assisting, compositional reasoning in biological systems.

1. INTRODUCTION

Technological advances in data acquisition and data processing have revolutionized the way we understand biological processes. From the molecular level to the organ level, new mechanisms underlying such processes are uncovered on a regular basis, and then formalized mathematically. If concentrations e.g. of ions, molecules, and proteins play an important role, the models of choice are systems of partial or ordinary differential equations (PDEs/ODEs).

This ever-increasing knowledge about biological processes is reflected in the ever-increasing complexity of the corresponding PDEs. The ionic processes underlying the transmembrane action potentials (APs) exhibited by excitable cells (e.g. neurons and cardiac myocytes) are no exception. In the case of myocytes, PDE models have evolved from 4 state variables in the Noble model [16] to 67 state variables in the Iyer-Mazhari-Winslow (IMW) model [11], pushing simulation efforts, not to mention formal analysis, up against the tractability boundary. The original benchmark for neurons was the 4-variable ODE model of Hodgkin and Huxley [9].

Two techniques have proved to be particularly useful in extending the reach of formal analysis: abstraction and decomposition. Abstraction reduces the size of the system under investigation by neglecting details irrelevant to the properties of interest. Decomposition, as the name suggests, decomposes the system into smaller pieces, which are then analyzed on their own. Together, these two techniques permit compositional reasoning: if $A_1$ abstracts $I_1$ and $A_2$ abstracts $I_2$, then their composition $A_1 || A_2$ abstracts $I_1 || I_2$.

Compositional reasoning has proved to be especially useful in the non-numerical setting, with simulation and bisimulation among the most widely used abstraction techniques. Intuitively, simulation is a game requiring that each move of $I$ from state $x_1$, with observation $o_1$, to a state $x_2$, with observation $o_2$, can be matched by a move of $A$ from state $y_1$, with observation $o_1$, to a state $y_2$, with observation $o_2$. Both $I$ and $A$ start in their initial states, and iteratively continue from the successor states. Bisimulation is the symmetric form of this game. Simulation and bisimulation have the very salient property of supporting compositional reasoning in the sense discussed above.

In the numerical setting, the notions of simulation and bisimulation were extended in two ways. First, the moves of the game are assumed to take some (equal) amount of time. Second, identical observations are replaced with the more robust notions of $\delta$-simulation and $\delta$-bisimulation, where $\delta$ is the maximum distance (error) between observations. In a previous paper [15], we used this concept to show that the 13-variable ODE model of the IMW sodium channel (IMW-SC) is $\delta$-bisimilar (for a very small $\delta$) to a 2-variable ODE-channel model of Hodgkin-Huxley type (HH-SC). Our proof was by construction: we showed that it is possible to identify the parameters of the HH-SC model such that the observations of the two systems are always less than $\delta$ apart.
Unfortunately, \( \delta \)-bisimulation does not automatically support compositional reasoning. When parallel composition feeds the outputs of subsystem \( A_1 \) to the inputs of subsystem \( A_2 \) (and vice versa), the error of \( A_1 \) with respect to \( I_1 \) can get amplified by \( A_2 \), which may lead to an even larger error of \( A_2 \) with respect to \( I_2 \), which is then again amplified by \( A_1 \) and so on. For example, in the context of the IMW model, let IMW with its sodium channel removed be denoted by IMW-RT (the “rest” of the IMW model). Then, replacing IMW-SC within IMW-SC \( \parallel \) IMW-RT with its \( \delta \)-bisimilar channel HH-SC may lead to widely divergent behavior by HH-SC \( \parallel \) IMW-RT with respect to IMW-SC \( \parallel \) IMW-RT in terms of their APs, even for a very small \( \delta \). Careful examination of the problem reveals that this is due to the HH-SC channel not properly closing as the AP reaches the conclusion of its upstroke phase.

To find the proper conditions under which the \( \delta \)-bisimulation abstraction HH-SC of IMW-SC behaves properly with respect to its feedback composition with IMW-RT, we enlist the support of bisimulation functions \([8]\). The value of a bisimulation function (BF) is required to cover (be greater than) the (observation) distance between all pairs of states of a system (say IMW-SC or IMW-RT), or of the states of one system (say HH-SC) and the states of another system (say IMW-SC). See Fig. 8 for a 3D rendering of the BFs relevant to this paper. Once such a cover is found, one can restrict it to the initial states of the system(s) and their successors. Similar to Lyapunov functions, one can search for BFs from among the square polynomials over pairs of states of the system. A very popular tool for automating this search is SOSTOOLS, which we use in this paper.

Inspired by the notion of input-to-state stability, the approach of \([7]\) requires that BFs are exponentially decaying, and that the distance between inputs is bounded. The former condition, which corresponds to exponential stability, is stronger than asymptotic stability, but it has a very desirable compositional property: the BF of the composed system (for example, the one for HH-SC \( \parallel \) IMW-RT versus IMW-SC \( \parallel \) IMW-RT) is a linear combination of the BFs of its components (for example HH-SC versus IMW-SC and IMW-RT versus IMW-RT). The coefficients of the linear combination quantify the precision of the BF so obtained, and of its associated bisimulation relation.

Applying the compositional reasoning technique described above to the three components HH-SC, IMW-SC, and IMW-RT proved to be beyond the computational power of SOSTOOLS. IMW-RT has 54 variables; consequently, a BF over all pairs of states of IMW-RT has 108 variables, and has to be computed in a compositional fashion itself. We show how to do this by considering an IMW-RT consisting of only its one-variable membrane (IMW-ME) \([11]\). For IMW-ME paired with itself, as well as for IMW-SC versus HH-SC, SOSTOOLS is able to successfully compute the required BFs.

The other channels, pumps and exchangers of the IMW model can be treated in a similar manner, which is reserved for the full version of the paper. Fig. 1 provides an overview of our approach, which is geared toward incrementally reducing the complexity of cardiac-cell models through the use of \( \delta \)-bisimilarity-based abstraction and BF-based compositional reasoning. To the best of our knowledge, this is the first application of \( \delta \)-bisimilar, feedback-assisting, compositional reasoning in biological systems.
The rest of the paper is organized as follows. Section 2 provides relevant background information on the HH-SC and IMW-SC models, and on BFs. Section 3 describes our computation of BFs using SOSTOOLS. Section 4 contains our experimental results. Section 5 considers related work, while Section 6 offers our concluding remarks. A two-page, poster-style abstract of a preliminary version of this work appeared in [14].

2. BACKGROUND
Cardiac myocytes belong to the class of excitable cells, which also includes neurons and skeletal muscle cells. Such cells have the following, characteristic excitability property: Any above-threshold excitation (external of from neighboring cells), is amplified to an essentially the same pulse (transmembrane potential) known as the Action Potential (AP).

The transmembrane potential of the cell is determined by the differences in the concentrations of sodium (Na), potassium (K), and calcium (Ca) ions present in the extracellular and intracellular mediums. The resulting gradients of concentrations lead to the flow of ions across the membrane that can be measured as an ionic current for each type of flow. The ion flow is facilitated by ion channels present in the membrane of the cells. Ion channels are proteins that exhibit conformational changes on varying the transmembrane voltage, and are selectively permeable to either Na, K, or Ca ions. Some of the conformations allow ion flow, whereas others inhibit the respective current. The rate of change of voltage resulting from the ion flows is a function of the various ionic currents at any point in time.

Detailed cardiac cell models, such as the Iyer-Mazhari-Winslow (IMW) model [11], capture the voltage-dependent behavior of the various ion channels responsible for the movement of Na, K, and Ca ions. Each type of channel contributes a subsystem to the whole model that is responsible for the corresponding ionic current. The ion-channel subsystems are connected to the voltage subsystem, representing the membrane, using feedback. We present a Canonical Cell Model (CCM) that reflects the feedback composition used in the IMW model, and will be the subject of our compositionality results.

We define dynamical systems using the 6-tuple \((X, X^0, H, f, O, g)\), where \(X\) denotes the state space, \(X^0 \subseteq X\) denotes the set of initial conditions, \(H\) denotes the input space, \(f : X \times H \rightarrow X\) denotes the vector field defining the dynamics, \(O\) denotes the set of outputs and \(g : X \rightarrow O\) maps a state to its output. We begin by defining the IMW sodium-channel subsystem.

**Definition 1.** The sodium channel model \(\Sigma_I\) is given by \((X, X^0, V, f_I, O, g_I)\). A state \(x \in X \subseteq \mathbb{R}_+^{13}\) is the occupancy probability distribution over the 13 states of the voltage-controlled Continuous Time Markov Chain (CTMC) shown in Fig. 2 in the following order of the state labels: \([C_0, C_1, C_2, C_3, C_4, O_1, O_2, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, I]\). The dynamics \(f_I\) is given by

\[
f_I : x = A_I(V) x
\]

where \(V \in \mathbb{R}\), the transmembrane voltage, is the input to the system and \(A_I(V)\) is the \(13 \times 13\) voltage-controlled rate matrix. The off-diagonal entry \(A_I(i, j), i \neq j\), is the transition rate from state \(x_i\) to state \(x_j\). For example, \(A_I(5, 6) = \delta(V)\), the transition rate from \(O_1\) to \(C_4\). The diagonal entry \(A_I(i, i)\) is the sum of all the outgoing rates from state \(x_i\). The transition rates are exponential functions of \(V\), and can be found in Table 1 of [15].

The set of outputs \(O \subseteq \mathbb{R}_{\geq 0}\) contains the conductance values for the states. Given a state \(x\), \(g_I(x) \triangleq x_0 + x_2\) maps it to its conductance given by the sum of the occupancy probabilities of the states labeled \(O_1\) and \(O_2\). We use \(O_H\) to denote the output when the state can be inferred from the context.

The system has a single initial condition \(x_0 \in X^0\), which is defined in Table 4 of [11].

In [15], we presented a two-step curve-fitting procedure for identifying \(\Sigma_H\), a two-state abstract model that can (approximately) match the output of \(\Sigma_I\) and is based on the Hodgkin-Huxley (HH) model for neurons [9]. We define the HH-type model next.

**Definition 2.** The HH-type abstraction \(\Sigma_H\) is given by \((Y, Y^0, V, f_H, O, g_H)\). Its state \(y \in Y \subseteq \mathbb{R}_+^2\) measures the degrees of activation, denoted by \(m\), and inactivation of the channel, denoted by \(h\); see Fig. 2. Component \(y_1\) corresponds to \(m\) and \(y_2\) corresponds to \(h\). The dynamics \(f_H\) is given by

\[
f_H : y = A_H(V) y + B_H(V)
\]

where \(A_H = \begin{bmatrix} -(\alpha_m(V) + \beta_m(V)) & 0 \\ 0 & -(\alpha_h(V) + \beta_h(V)) \end{bmatrix}\) and

\(B_H = \begin{bmatrix} \alpha_m(V) \\ \alpha_h(V) \end{bmatrix}\) where \(V \in V \subseteq \mathbb{R}\), the transmembrane voltage, is the input. The rates \(\alpha_i(V)\) and \(\beta_i(V), i \in \{m, h\}\), are given in Eqs. (7)-(10) of Section 3 of [15], and were identified during the two-step curve-fitting process.

The set of outputs \(O \subseteq \mathbb{R}_{\geq 0}\) contains the conductance values for the states. Given a state \(y\), \(g_H(y) \triangleq y_1 y_2\) maps it to its conductance, which corresponds to \(m^h\). We use \(O_H\) to denote the output when the state can be inferred from the context.

The system has a single initial condition \(y_0 = [0.0026, 0.95]^T\), which was obtained after model identification. Details can be found in the discussion of procedure “Parameter Estimation from Finite Traces (PEFT)” in Section 3 of [15].

We now define the voltage subsystem, which represents the membrane and acts as the context for the various ion-channel subsystems in the CCMs (defined below).

**Definition 3.** The voltage subsystem, denoted by \(\Sigma_C\), is a capacitor-like model given by \((V, V^0, O, f_C, V, g_C)\). The state \(V \in V \subseteq \mathbb{R}\), denotes the voltage. The dynamics of \(V\) is given by

\[
f_C : V = -G_{Na}(V - V_{Na}) O
\]

where \(G_{Na} = 5\) and \(V_{Na} = 30\) mV are the parameters of the model, and \(O \in O \subseteq \mathbb{R}_{\geq 0}\), the conductance of the sodium channel, is the input. The system outputs its state i.e. for \(V \in V\), \(g_C(V) = V\). The initial condition \(V_0 = -30\) mV.

As per Eq. (3), \(V_{Na}\) represents the equilibrium for a fixed-
conductance input. Thus, $V$ takes values in $[-30, 30]$.

The feedback-composition of two dynamical systems is obtained by feeding the output of the first system as the input to the second system and vice versa. Next, we define the composite CCMs $\Sigma_{CI}$ and $\Sigma_{CH}$ using feedback composition.

**Definition 4.** Systems $\Sigma_{CI}$ and $\Sigma_{CH}$ (see Fig. 3) are obtained by performing feedback-composition on the voltage subsystem $\Sigma_C$ with ion-channel subsystems $\Sigma_I$ and $\Sigma_H$, respectively. The state spaces, initial conditions, dynamics and outputs are inherited from the subsystems, as explained below. Both $\Sigma_{CI}$ and $\Sigma_{CH}$ are autonomous systems and do not receive any external inputs.

A state of $\Sigma_{CI}$ is given by $[x, V_I]^T$, where $x$ denotes a state of $\Sigma_I$ and $V_I$ denotes a state of $\Sigma_C$. The subscript $I$ in $V_I$ is used to denote the copy of $\Sigma_C$ composed with $\Sigma_I$. The system dynamics are given by Eqs. (1) and (3). The output is given by $[g_I(x), V_I]^T$. The initial condition is the pair of the initial conditions of $\Sigma_I$ and $\Sigma_C$.

A state of $\Sigma_{CH}$ is given by $[y, V_H]^T$, where $y$ denotes a state of $\Sigma_H$ and $V_H$ denotes a state of $\Sigma_C$. The subscript $H$ in $V_H$ is used to denote the copy of $\Sigma_C$ composed with $\Sigma_H$. The system dynamics are given by Eqs. (2) and (3). The output is given by $[g_H(y), V_H]^T$. The initial condition is the pair of the initial conditions of $\Sigma_H$ and $\Sigma_C$.

The remainder of the paper focuses on proving the approximate equivalence of $\Sigma_{CI}$ and $\Sigma_{CH}$ based on i) the approximate bisimulation between subsystems $\Sigma_I$ and $\Sigma_H$, and ii) the ability of the context $\Sigma_C$ to tolerate small deviations in the input conductances. These ideas are formalized using bisimulation functions [7], i.e., contractive metrics characterizing the joint input-to-output stability of two systems. The following definition of bisimulation functions is adapted from [7] and uses $\| \cdot \|$ to denote the squared L2 norm.

**Definition 5.** Let $\Sigma_i = (X_i, \lambda_i, \mathcal{U}, f_i, \mathcal{Y}, g_i)$, $i = 1, 2$, be two dynamical systems such that $X_1 \subseteq \mathbb{R}^n$, $U \subseteq \mathbb{R}^m$ and $X_2 \subseteq \mathbb{R}^p$, $V \subseteq \mathbb{R}^q$. Let $V_1$, $V_2$ be the outputs of $\Sigma_1$ and $\Sigma_2$, respectively. Then $\Sigma_1$ is bisimilar to $\Sigma_2$, denoted $\Sigma_1 \sim \Sigma_2$, if there exist functions $\lambda : X_1 \times X_2 \rightarrow \mathbb{R}^+$ such that

$$\| g_1(x_1) - g_2(x_2) \| \leq S(x_1, x_2), \quad (4)$$

$$\exists \lambda > 0, \gamma \geq 0 : \frac{\partial S}{\partial x_1} f_1(x_1, u_1) + \frac{\partial S}{\partial x_2} f_2(x_2, u_2) \leq -\gamma S(x_1, x_2) + \| u_1 - u_2 \| \quad (5)$$

Next, we present a modified version of Theorem 1 of [7], which captures the joint input-to-output stability of 2 systems.

**Theorem 1.** Let $S$ be a BF, with parameters $\lambda$ and $\gamma$, between dynamical systems $\Sigma_i$, $i = 1, 2$, and let $x_1(t)$ and $x_2(t)$ be two trajectories of the systems. For all $t \geq 0,$

$$\| g_1(x_1(t)) - g_2(x_2(t)) \| \leq S(x_1(t), x_2(t))$$

$$\leq e^{-\lambda t} S(x_1(0), x_2(0)) + \gamma \| u_1 - u_2 \|$$
where \( \| \mathbf{u}_1 - \mathbf{u}_2 \|_\infty \leq sup_{t \geq 0} \| \mathbf{u}_1(t) - \mathbf{u}_2(t) \| \) denotes the maximum difference in the input signals being fed to the two systems.

**Proof.** See the supplementary document [10].

When subsystems are connected using feedback, their respective BFs can be composed subject to a small gain condition. We formalize this idea by stating a theorem based on Theorem 2 of [7].

**Theorem 2.** Let \( \Sigma = (\mathcal{X}_0, \mathcal{X}, \mathcal{U}, \mathcal{F}, \mathcal{O}, \mathcal{G}), i = 1, 2, A, B, \) be dynamical systems such that \( \mathcal{U}_1 = \mathcal{O}_A, \mathcal{U}_2 = \mathcal{O}_B \) and \( \mathcal{U}_2 = \mathcal{O}_B \). Let \( S_{12} \), parameterized by \( \lambda_{12} \) and \( \gamma_{12} \), be a BF between \( \Sigma_1 \) and \( \Sigma_2 \). Let \( S_{AB} \), parameterized by \( \lambda_{AB} \) and \( \gamma_{AB} \), be a BF between \( \Sigma_A \) and \( \Sigma_B \).

Let \( \Sigma_{A1} \) and \( \Sigma_{B2} \) be composite systems representing feedback-composition\(^3\) of \( \Sigma_A \) with \( \Sigma_1 \) and \( \Sigma_B \) with \( \Sigma_2 \), respectively. If the small gain condition (SGC) \( \frac{\lambda_{AB} \gamma_{12}}{\lambda_{12} \gamma_{AB}} < 1 \) is met, then a BF \( S \) can be constructed between \( \Sigma_{A1} \) and \( \Sigma_{B2} \) by composing \( S_{AB} \) and \( S_{12} \) as

\[
S(\mathbf{x}_{A1}, \mathbf{x}_{B2}) = \alpha_1 S_{AB}(\mathbf{x}_A, \mathbf{x}_B) + \alpha_2 S_{12}(\mathbf{x}_1, \mathbf{x}_2)
\]

where \( \mathbf{x}_A = [\mathbf{x}_A, \mathbf{x}_1]^T \) and \( \mathbf{x}_B = [\mathbf{x}_B, \mathbf{x}_2]^T \) and the constants \( \alpha_1 \) and \( \alpha_2 \) are as follows.

\[
\begin{align*}
\text{if } & \lambda_{AB} \leq \gamma_{12} \\
\alpha_1 = 1 & \text{ and } \alpha_2 = 2
\end{align*}
\]

\[
\begin{align*}
\text{if } & \lambda_{12} < \gamma_{AB} \leq \gamma_{12} \\
\alpha_1 = 1 & \text{ and } \alpha_2 = 1
\end{align*}
\]

**Proof.** See the supplementary document [10].

### 3. Computing Sum-of-Squares BFs

In this section, we show how to formulate the BFs \( S_{IH} \) and \( S_C \) as sum-of-squares (SoS) polynomials, thereby enabling us to automate their computation using SOSTOOLS [17]; the MATLAB-based SoS optimization toolbox. \( S_{IH} \) is a BF between \( \Sigma_I \) and \( \Sigma_H \), with parameters \( \lambda_{IH} \) and \( \gamma_{IH} \), while \( S_C \) is a BF between \( \Sigma_C \) and itself, with parameters \( \lambda_C \) and \( \gamma_C \). Values for these parameters must be determined such that Eq. (5) is satisfied. If the parameters satisfy the SGC of Theorem 2, then \( S_{IH} \) and \( S_C \) can be composed to obtain a BF between \( \Sigma_{CI} \) and \( \Sigma_{CH} \).

**I. Rewriting the system definitions**

The rate matrix \( A_I(V) \) of \( \Sigma_I \) has a zero eigenvalue for all \( V \in [-30, 30] \), the values that the input can take when \( \Sigma_I \) is composed with \( \Sigma_C \). The system dynamics were rewritten to make the new rate matrix Hurwitz, which is the necessary and sufficient condition for exponential stability. As the system is a voltage-controlled CTMC, one of the variables is always redundant; i.e., the occupancy probability of one state can be expressed as 1 - (sum of all other occupancy probabilities).

Using this fact, we removed the redundant state occupancy probability corresponding to state \( I \) of Fig. 2. The resulting dynamics are affine: \( \mathbf{x}' = A_I(V) \mathbf{x}' + B_I(V) \), where the state vector \( \mathbf{x}' \) now contains the first 12 probabilities from \( x \). The \( 12 \times 12 \) matrix \( A_I(V) \) and the \( 12 \times 1 \) affine term \( B_I(V) \) can be found in [10]. For a fixed voltage input \( V = v \), the equilibrium of the resulting linear system was shifted to the origin by solving \( A_I(v) \mathbf{x}' = -B_I(V) \).

\( \Sigma_H \) has a nonlinear output function of degree 4, which would require \( S_H \) to be an 8th-order polynomial. Higher-order polynomials lead to possibly intractable instances of SoS optimization due to the relatively higher number of decision variables that are used to define the BF. To resolve this issue, the 2-state system was converted to an equivalent 8-state stochastic model that has a linear output function. In [13], the author shows that \( \Sigma_H \) is the exact invariant manifold of the 8-state voltage-controlled CTMC shown in Fig. 2.

The output of \( \Sigma_H \), \( m'h \), is interpreted as follows. It stands for the probability of three activation (m-type) and one inactivation (h-type) gate to be open. As they are all independent, we get the net probability of the event as \( m'h \). This event corresponds to the occupancy probability of the state labeled \( O \), which is the output of the 8-state model.

Similarly, the occupancy probability of each of the other 7 states corresponds to a certain number of m-type (maximum 3) and the h-type (maximum 1) gates being open. For example, the state labeled \( C_1 \) corresponds to one m-type and the h-type gates being open, resulting in a net probability of \( mh \). Similarly, the state labeled \( C_1I \) corresponds to one m-type gate being open and the h-type gate being closed, resulting in a net probability of \( m(1-h) \).

The 8-state stochastic version has dynamics of the form \( \dot{y} = A_H(V) \), where \( y \in \mathbb{R}^8 \) is the vector representing the occupancy probability distribution among the eight states in the order: \( [C_0, C_1, C_2, O, C_0I, C_1I, C_2I, C_0H] \). \( A_H(V) \) is an \( 8 \times 8 \) matrix similar to \( A_I(V) \) in Definition 1. The linear system was converted to its affine form to remove the zero eigenvalue, as was done for \( \Sigma_I \): \( \dot{y}' = A_H(V) y' + B_H(V) \), by eliminating the state labeled \( C_0I \). The new state vector \( y' \) denotes the occupancy probabilities of the first 7 states from \( y \). The \( 7 \times 7 \) rate matrix \( A_H \) and the \( 7 \times 1 \) affine term \( B_H \) can be found [10]. The output of this system is \( y_4' \), corresponding to the occupancy probability of the state labeled \( O \).

For a fixed voltage input \( V = v \), the equilibrium of the resulting linear system was shifted to the origin by solving \( A_H(V)y' = -B_H(V) \). Similarly the equilibrium of \( \Sigma_C \), for a fixed conductance input, was shifted to the origin using an offset of \( V_{Na} \).

**II. SoS Optimization**

A multivariate polynomial \( p(x_1, x_2, \ldots, x_n) = p(x) \) is an SoS polynomial if there exist polynomials \( f_1(x), \ldots, f_m(x) \) such that \( p(x) = \sum_{i=1}^m f_i^2(x) \). We denote the set of all SoS polynomials by \( \mathcal{S} \). An instance of SoS optimization involves finding an \( s \in \mathcal{S} \) such that a linear objective function, whose decision variables are the coefficients of \( s \), is optimized. The constraints of the problem are linear in the decision variables. A formal definition of an SoS optimization instance can be found in the SOSTOOLS user guide (p. 7).

We constructed two instances of SoS optimization: \( P_H \) and \( P_C \), to compute \( S_{IH}(\mathbf{x}'(t), \mathbf{y}') \) and \( S_C(V_t, V_H) \) respectively.
The two problems were solved using SOSTOOLS, which internally calls the semidefinite programming solver *sedumi*. We next explain the construction of $P_{IH}$ and $P_C$.

### III. Choosing the form of the SoS BFs

Defining an instance of SoS optimization starts with declaring the form of the desired polynomial. We chose ellipsoidal forms, for the BFs using the toolbox `sossosvar`.

Defining an instance of SoS optimization starts with declaring using the polynomial variable toolbox (`pvar`). The coefficients of the BFs, which form the decision variables of the SoS optimization problems, are contained in the positive semidefinite matrices $Q_{IH}$ $(19 \times 19)$ and $Q_{C} (2 \times 2)$.

Eq. (4), the first constraint defining a BF, was implemented as:

$$ P_{IH} : S_{IH} - ((\mathbf{x}' + \mathbf{y}') - (\mathbf{y}'))^2 \in \mathbb{S} $$

$$ P_C : S_C - (V_I - V_H)^2 \in \mathbb{S} $$

### IV. Input-space quantization

Eq. (5), the second constraint defining a BF, must be satisfied for all the pairs of states and inputs. The optimizer searches over the state space to optimize $Q_{IH}$ and $Q_{C}$, but does not search over the input space. We therefore sampled pairs of inputs to the two subsystems: $\Sigma_I$ and $\Sigma_H$ for $P_{IH}$, and the two copies of $\Sigma_C$ for $P_C$. Eq. (5) was thus implemented as follows:

$$ P_{IH} : \begin{bmatrix} \frac{\partial S_{IH}}{\partial x} (A'_I(v_I, \mathbf{x}')) + \frac{\partial S_{IH}}{\partial y} (A'_H(v_I, \mathbf{y}')) \\ -\lambda_{IH}S_{IH}(\mathbf{x}', \mathbf{y}') + \gamma_{IH}|v_I - v_H| \end{bmatrix} \in \mathbb{S} $$

$$ P_C : \begin{bmatrix} \frac{\partial S_C}{\partial V_I} (-G_{N_a}o_{V_I}) + \frac{\partial S_C}{\partial V_H} (-G_{N_a}o_{V_H}) \\ -\lambda_{C}S_C(V_I, V_H) + \gamma_{C}|o_I - o_J| \end{bmatrix} \in \mathbb{S} $$

For $P_{IH}$, the input pairs are $(v_I, v_H) \in \mathcal{V} \times \mathcal{V}$, where $\mathcal{V} = \{-60, -30, 0, 20, 30\}$. For $P_C$, the input pairs are $(o_I, o_J) \in \mathcal{O} \times \mathcal{O}$, where $\mathcal{O} = \{0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1\}$.

We use the dynamics of the system, with the origin shifted to the equilibrium corresponding to the input pair $(v_I, v_H)$. Note that each input pair contributes one constraint to the corresponding problem. Thus, Eq. (5) was implemented as 25 constraints in $P_{IH}$ and 100 constraints in $P_C$.

The input-space-sampling-based approach to computing BFs can be justified as follows. As per Theorem 1, the BF $S_{IH}$ bounds the difference in the outputs of $\Sigma_I$ and $\Sigma_H$ when the maximum difference in the voltage (input) signals is $||V_I - V_H||_\infty$. Voltage signals $V_I(t)$ and $V_H(t)$ can be approximated by quantizing them using the set $\mathcal{V}$. At any point in time, the voltage signals would be rounded off to the nearest member of $\mathcal{V}$. The error in the outputs due to the quantization error in the inputs can be bound using sensitivity analysis. Then, the bound on the output difference given by $S_{IH}$ would have to take into account the output error resulting from the quantization.

A similar analysis can be performed for $S_C$, where the conductance signals would now be quantized using $\mathcal{O}$. Providing revised bounds that reflect input-space quantization is part of our future work.

### V. Handling the parameters

Eqs. (8) and (9) were implemented in SOSTOOLS with fixed values for parameters $\lambda_{IH}$, $\gamma_{IH}$ of $P_{IH}$, and for $\lambda_C$, $\gamma_C$ of $P_C$.

<table>
<thead>
<tr>
<th>Problem</th>
<th>BF</th>
<th>$\lambda$</th>
<th>$\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{IH}$</td>
<td>$S_{IH}$</td>
<td>$\lambda_{IH} = 0.1$</td>
<td>$\gamma_{IH} = 0.001$</td>
</tr>
<tr>
<td>$P_C$</td>
<td>$S_C$</td>
<td>$\lambda_C = 0.04$</td>
<td>$\gamma_C = 0.0001$</td>
</tr>
</tbody>
</table>

**Table 1: Parameter values used for the BFs.**

To obtain a BF that provides tight bounds on the output difference, we implemented an objective function that minimizes the BF at the initial states of the two subsystems:

$$ P_{IH} : \text{Minimize } S_{IH}(\mathbf{x}'(0), \mathbf{y}'(0)) $$

$$ P_C : \text{Minimize } S_C(-30, -30) $$

where $\mathbf{x}'(0)$ and $\mathbf{y}'(0)$ represent the initial conditions of $\Sigma_I$ and $\Sigma_H$ as per Definitions 1 and 2, respectively.

$P_{IH}$ and $P_C$ were respectively solved for $S_{IH}$ and $S_C$ in SOSTOOLS. Additionally, SOSTOOLS also outputs feasratio, pinf, dinf and numerr that reflect the accuracy of the solutions. Both $P_{IH}$ and $P_C$ were solved by error-free executions with feasratio = 1 and pinf = dinf = numerr = 0, resulting in reliable and accurate BFs.

The computed value of $S_{IH}$, defined by the $19 \times 19$ matrix $Q_{IH}$, can be found in the supplementary document [10]. $S_C$, the BF between $\Sigma_C$ and itself, was computed as:

$$ S_C(V_I, V_H) = 1.27V_I^2 - 1.4599V_I V_H + 1.27V_H^2 $$

### VII. Composing $S_{IH}$ and $S_C$

The parameters of $S_{IH}$ and $S_C$, given in Table 1, satisfy the SGC of Theorem 2, as $\frac{\gamma_{IH}}{\gamma_{IH} + \gamma_C} = 0.0001 < 1$. Applying Theorem 2, we linearly composed $S_{IH}$ and $S_C$ to obtain $S = \alpha_1 S_{IH} + \alpha_2 S_C$, where $\alpha_1 = \alpha_2 = 1$. $S$ is a BF between the composite systems $\Sigma_{CI}$ and $\Sigma_{CH}$. Using Theorem 2, the parameter $\lambda$ of $S$ can be calculated as

$$ \lambda = \min \left( \frac{\alpha_1 \lambda_{IH} - \alpha_2 \gamma_C}{\alpha_1}, \frac{\alpha_2 \lambda_C - \alpha_1 \gamma_{IH}}{\alpha_2} \right) = 0.009. $$

### 4. RESULTS
In this section, we experimentally validate BFs $S_{1H}$, $S_C$ and $S$, which were obtained as described in Section 3. As per Theorem 1, BFs decay along a pair of trajectories of the two systems under consideration. To this end, we simulated $\Sigma_I$ and $\Sigma_H$ (for $S_{1H}$), $\Sigma_C$ (for $S_C$), and $\Sigma_{CI}$ and $\Sigma_{CH}$ (for $S$) using different inputs and initial conditions, and evaluated the BFs along the resulting trajectories.

Empirical validation of the BFs is first provided by plotting them in 2D along the time axis. As the time proceeds in the same manner in both systems, the corresponding BF is plotted for the pair of states occurring at the same time along the trajectories of the systems. The difference in outputs observed for the pair of states is also plotted in the same graph. The resulting plots show that the BFs bound the output difference and decay in time along the pairs of trajectories, as per Theorem 1.

We also provide 3D plots, where the $x$- and $y$-axes measure time and the BF, along with the output differences, is plotted on the $z$-axis. This form of plotting allows us to indirectly depict that the BF upper bounds the difference in the outputs for all possible pairs of states. These plots also show that the BF decays along pairs of trajectories, even when there is a delay between the systems.

Fig. 4 shows $S_{1H}$ plotted along three pairs of trajectories of $\Sigma_I$ and $\Sigma_H$. Each pair of trajectories was generated by supplying a pair of constant voltage signals ($V_1(t), V_2(t)$) as inputs to $\Sigma_I$ and $\Sigma_H$, respectively. The two subsystems were initialized as per Defs 1 and 2, and simulated using MATLAB’s ODE45 solver. $S_{1H}$ was then evaluated along the resulting pair of trajectories after shifting the origin to the equilibrium defined by ($V_1(t), V_2(t)$). Fig. 4(a) plots, in blue, the output difference along two trajectories that receive the same input of -30mV. The BF $S_{1H}$ along the trajectories is plotted in red and shows the decaying behavior predicted by Theorem 1. Fig. 4(b) plots the output difference along two trajectories with the maximum possible difference in inputs: $V_1(t) = -30mV$ and $V_2(t) = 30mV$. This results in a relatively large output difference observed from the two subsystems. $S_{1H}$ is shown to upper bound this difference and decay along the pair of trajectories. Fig. 4(c) inverts the inputs with $V_1(t) = 30mV$ and $V_2(t) = -30mV$.

$S_C$ characterizes the ability of $\Sigma_C$ to tolerate small changes in the input conductance signals. In the composite systems $\Sigma_{CI}$ and $\Sigma_{CH}$, these signals are provided by subsystems $\Sigma_I$ and $\Sigma_H$, and thus vary slightly due to the fitting errors incurred by the abstraction process of [15].

In Figs. 5(a)-(c), $S_C$ is plotted along three pairs of trajectories of $\Sigma_C$. Each pair of trajectories was generated by supplying constant conductance (input) signals, $(O_1(t), O_2(t))$. $\Sigma_C$ was initialized at -30mV and simulated using the Euler method. $S_C$ was evaluated along the resulting trajectories after shifting the origin to the equilibrium, 30mV ($V_{Na}$). Fig. 5(a) shows the case when both $O_1(t)$ and $O_2(t)$ were 0.01, resulting in equal voltage traces with an output difference of 0. We have not scaled the systems nor the BFs; thus the scale of Fig. 5 is very different from that of Fig. 4. We can see that even when the input conductances vary by a factor of 8, in Fig. 5(c), $S_C$ bounds the output difference and decays along the trajectories.

The CCMs $\Sigma_{CI}$ and $\Sigma_{CH}$ are autonomous dynamical systems and do not receive any external inputs. To visualize the composite BF $S$, we simulated $\Sigma_{CI}$ and $\Sigma_{CH}$ using the Euler method. Fig. 7 plots the trajectories obtained from these simulations. The matching conductance traces of Fig. 7(a) and the voltage traces of Fig. 7(b) empirically validate that the composed models are approximately equivalent as predicted by Theorem 2. The BF $S$ along this pair of trajectories is plotted in Fig. 6(a). The value of $S$ is dominated by the value of $S_C$, as it bounds the squared difference of voltages and is much larger than $S_{1H}$, which bounds differences in probabilities. This is reasonable as voltage is the primary entity of interest when analyzing excitable cells. One could scale subsystem $\Sigma_C$ such that its output lies in $[0,1]$ and is thus comparable to the outputs of $\Sigma_I$ and $\Sigma_H$.

To test extreme cases, we simulated $\Sigma_{CI}$ and $\Sigma_{CH}$ by initializing $\Sigma_C$ at different values. Fig. 6(b) shows OD plotted along pairs of trajectories where $\Sigma_C$ in $\Sigma_{CI}$ starts at $V_2(0) = -30mV$ and in $\Sigma_{CH}$ at $V_2(0) = 30mV$. Fig. 6(c) plots the other extreme, where the copy of $\Sigma_C$ in $\Sigma_{CI}$ starts at 30mV and the copy in $\Sigma_{CH}$ is initialized to -30mV. $S$ bounds the OD in all these cases and decays along the trajectories.

![Figure 7: Simulations of $\Sigma_{CI}$ and $\Sigma_{CH}$: when the $\Sigma_I$ subsystem is replaced by the $\Sigma_H$ abstraction, feedback composition tends to accumulate error incurred by the abstract model. BF $S$ proves that these errors remain bounded, due to the approximate equivalence of $\Sigma_I$ and $\Sigma_H$, established by BF $S_{1H}$, and the ability of context $\Sigma_C$ to tolerate deviations in the conductance inputs, established by BF $S_C$. The mean L1 errors: $O_{Na} : 9 \times 10^{-3}$, $V$ : 1.42mV.](image-url)
$V_H(t) = 30 \text{ mV}$. The two models were simulated using $ODE45$ starting from the nominal initial conditions specified in Definitions 1 and 2 until steady state was reached. Let $T$ denote the time steps $[t_1, t_2, \ldots, t_n]$ of the two discrete-time simulations, and $O_I(t)$ and $O_H(t)$ denote the resulting conductance (output) time series, with their origins shifted to the respective equilibria. Fig. 8(a) plots in red the squared output difference $(O_I(t_i) - O_H(t_j))^2$ for all $(t_i, t_j) \in T \times T$. $S_{IH}$ is plotted at the pair of states $(x'(t_i), t'(t_j))$ obtained in the simulation for all $(t_i, t_j) \in T \times T$. The 3D view of $S_{IH}$ shows that the BF provides an upper bound for the output difference at all pairs of states of the two systems. It also shows that $S_{IH}$ decays along the trajectories even when the two systems have a delay between them.

Fig. 8(b) was obtained by simulating $\Sigma_C$ with two constant conductance signals of 0.1 and 0.01. The resulting voltage output signals differ significantly due to a 10-fold difference in the input signals. Fig. 8(c), on the other hand, was obtained by simulating $\Sigma_{CI}$ and $\Sigma_{CH}$ using different initial conditions. In both the cases, the respective BFs $S_C$ and $S$ bound the output difference and decay along the trajectories (even when the two systems have a delay between them).

5. RELATED WORK

In response to the increasing complexity of biological models, model reduction and abstraction have become active areas of research in computational biology. In [4, 6], the authors propose the idea of towers of abstraction, consisting of a hierarchy of models that capture biological details at varying scales of space and complexity. Compositionality is a vital aspect of constructing such a hierarchy, as pointed out in [5].

Approximate bisimulation equivalence of a detailed model to an abstract model supports such compositional reasoning. In [1], the authors use bisimulation to constrain the $U$-projections of deterministic systems of algebraic differential equations of biochemical networks. The projected automaton is $U$-bisimilar to the original system and thus satisfies the same temporal logic formulae. Compositionality of the models-of-interest is not investigated.

In other related work, a number of efforts, including [3, 18, 2], have been devoted to developing process algebras that are capable of describing biological systems (e.g., interactions among bacteria and bacteriophage viruses) via special biologically motivated operators. Bisimulation in these calculi are typically congruences, thereby allowing compositional reasoning through substitution of equal for equals. These approaches typically do not consider continuous system dynamics and feedback through composition.

6. CONCLUSIONS
Figure 6: \( S \) and \( O_D \) along pairs of trajectories of \( \Sigma_{CI} \) and \( \Sigma_{CH} \). Subfig. (a) plots \( S \) and \( O_D \) along trajectories shown in Fig. 7. Subfigs. (b) and (c) plot \( O_D \) and \( S \) along trajectories where \( \Sigma_{C} \) is initialized at different voltages. Value of \( O_D \) is dominated by difference of outputs of the two copies of \( \Sigma_{C} \), which is in mV. Similarly, value of \( S \) is dominated by \( S_C \), which bounds differences in voltages as opposed to \( S_{IH} \), which bounds differences in probabilities.

Figure 8: 3D visualization of BF’s (in blue): \( S_{IH} \) in subfig. (a), \( S_{C} \) in subfig. (b) and \( S \) in subfig. (c) are plotted for pairs of states obtained at time points \((t_{i}, t_{j}) \in T \times T\), where \( T = \{t_1, t_2, \ldots\} \) are the time steps of discrete-time simulations of the corresponding pairs of systems. The BF’s upper bound the squared output differences (ODs), plotted in red for all pairs of states, and decay along the trajectories even when there is delay between the two systems. The captions of subfigs. (a)-(b) specify the input signals used for simulation and the caption of subfig. (c) provides the initial conditions used for \( S_{C} \) while simulating \( \Sigma_{CI} \) and \( \Sigma_{CH} \).

We used the small-gain theorem of [7] to show that the 13-variable sodium-channel component of the IMW cardiac cell model can be safely replaced with the \( \delta \)-bisimilar, 2-variable HH-abstraction we developed in [15]. This substitution of (approximately) equals for equals is “safe” in the sense that, despite the feedback nature of the composition of the sodium-channel component and the rest of the IMW model, the approximation error remains bounded in this context. Our experimental results, which include the SOSTOOLS-based derivation of the appropriate bisimulation functions and their 2-d and 3-d renderings, validate our analytical findings.

When factoring out the sodium-channel component from the IMW model, we are left with a 54-variable subsystem (IMW-RT) comprising a multitude of (non-sodium) ionic currents, including potassium and calcium. Applying the compositional reasoning technique discussed above in this context proved to be beyond the computational power of SOSTOOLS. Consequently, we limited our current investigation to an IMW-RT consisting of only its one-variable membrane (IMW-ME) [11]. The other channels, pumps and exchangers of IMW can be treated in a similar manner, which is reserved for future work.

Motivated by the challenges we encountered in using SOSTOOLS to find a tightly fitted, exponentially stable cover for the observation distance between all pairs of states of a system (or a pair of systems), we plan to investigate how to limit the domain of BF’s to states of interest: typically those states very close to each other (in terms of their observation distance), and which remain close to each other as time progresses. Such states are \( \delta \)-bisimilar to each other, for \( \delta \) sufficiently small. In such cases, we can show that the compositionality result of Theorem 2 still holds, as do the coefficients of the linear combination of the component BF’s.

One approach to computing a BF restricted to \( \delta \)-bisimilar states is to add the constraint \( \{x_1, x_2\} \parallel g_{1}(x_1) - g_{2}(x_2) \leq \delta \) to the BF optimization problem, where, recall, \( g_{1}, g_{2} \) are the respective system output functions. Unfortunately, SOSTOOLS reported that the resulting optimization problem is infeasible. The authors of [12] present an alternative approach to computing BF’s restricted to subsets of the state.
space based on finding two functions $g'_1$, $g'_2$ such that the constraint $\{ (x_1, x_2) | g'_1(x_1) \geq 0 \land g'_2(x_2) \geq 0 \}$ represents the subspace in question. Unfortunately, their approach is not immediately applicable to our problem, as there is no apparent way to decompose the $\delta$-bisimilarity constraint into one based on $g'_1$ and $g'_2$.

The BFs computed by SOSTOOLS can be scaled by applying an exponential scaling function to them. For a BF $S$, the scaled version $S'$ would be of the form $S' = S \exp(-CS)$, where $C > 0$. The problem is to find a $C$ such that $S'$ also satisfies both conditions of a BF (Def. 5). Note that scaling can be applied recursively to $S$. Fig. 9 illustrates the first- and second-order effects of scaling on $S_{1H}$. For this figure, we chose $C$ as 15 and 42 for first level and second level scaling, respectively. Future work will include formalizing this notion of scaled BFs.

![Figure 9: Scaling function applied recursively to $S_{1H}$. The BF cover of the observational difference is tightened after each level of scaling. All the curves use the same pair of trajectories of $\Sigma_I$ and $\Sigma_H$ corresponding to input pair (-30,30)mV.](image)

### 7. REFERENCES


