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Model-order reduction of ion channel dynamics using approximate bisimulation

Md. Ariful Islam[a], Abhishek Murthy[a,*], Ezio Bartocci[b], Elizabeth M. Cherry[e], Flavio H. Fenton[c], James Glimm[d], Scott A. Smolka[a], Radu Grosu[b]

[a] *Department of Computer Science, Stony Brook University, United States*
[b] *Department of Computer Engineering, Vienna University of Technology, Austria*
[c] *School of Physics, Georgia Institute of Technology, United States*
[d] *Department of Applied Mathematics and Statistics, Stony Brook University, United States*
[e] *School of Mathematical Sciences, Rochester Institute of Technology, United States*

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ABSTRACT

We show that in the context of the Iyer et al. (IMW) 67-variable cardiac myocycte model, it is possible to replace the detailed 13-state probabilistic subsystem of the sodium channel dynamics with a much simpler Hodgkin-Huxley (HH)-like two-state abstraction, while only incurring a bounded approximation error. We then extend our technique to the 10-state subsystem of the fast-recovering calcium-independent potassium channel. The basis of our results is the construction of an approximate bisimulation between the HH-type abstraction and the corresponding detailed ion channel model, both of which are input-controlled (voltage in this case) CTMCs.

The construction of the appropriate approximate bisimulation, as well as the overall result regarding the behavior of this modified IMW model, involves: (1) Identification of the voltage-dependent parameters of the m and h gates in the HH-type models via a two-step fitting process, carried out over more than 20,000 representative observational traces of the detailed sodium and potassium ion channel models. (2) Proving that the distance between observations of the detailed models and their respective abstraction is bounded. (3) Exploring the sensitivity of the overall IMW model to the HH-type approximations. Our extensive simulation results experimentally validate our findings, for varying IMW-type input stimuli.

1. Introduction

The emergence of high-throughput data acquisition techniques has changed cell biology from a purely wet lab-based science to also an engineering and information science. The identification of a mathematical model from cellular experimental data, and the use of this model to predict and control the cell's behavior, are nowadays indispensable tools in cell biology's arsenal [22,4].

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[*] Principal corresponding author.
E-mail addresses: mdaislam@cs.stonybrook.edu (Md. Ariful Islam), amurthy@cs.sunysb.edu (A. Murthy).
URLs: http://www.cs.sunysb.edu/~amurthy (A. Murthy), http://www.eziobartocci.com/ (E. Bartocci), http://www.rit.edu/cos/elizabeth-cherry (E.M. Cherry), https://www.physics.gatech.edu/user/flavio-fenton (F.H. Fenton), http://www.ams.sunysb.edu/~glimm/ (J. Glimm), http://www.cs.sunysb.edu/~sas/ (S.A. Smolka), http://ti.tuwien.ac.at/rts/people/grosu/ (R. Grosu).

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Improved data acquisition has led to the creation of increasingly sophisticated partial Differential Equation Model (DEMs) for cardiac cells (myocytes). Their main purpose is to elucidate the biological laws governing the electric behavior of cardiac myocytes, i.e., their underlying ionic processes [5].

Inspired by the squid-neuron DEM [13] developed by Hodgkin–Huxley (HH), Luo and Rudy devised one of the first myocyte DEMs, for guinea pig ventricular cells [19]. Adapting this model to human myocytes led to the ten Tusscher–Noble^2-Panfilov DEM [24], which has 17 state variables and 44 parameters. Based on updated experimental data, Iyer, Mazhari and Winslow (IMW) subsequently developed a DEM comprising of 67 state variables and 94 parameters [15]. This DEM reflects a highly detailed physiological view the electrochemical behavior of human myocytes.

From 17 to 67 variables, all such DEMs capture myocytic behavior at a particular level of abstraction, and hence all of them play an important role in the modeling hierarchy. It is essential, however, to maintain focus on the purpose of a particular DEM; that is, of the particular cellular and ionic processes whose behavior the DEM is intended to capture. Disregarding this purpose may lead to the use of unnecessarily complex DEMs, which may render not only analysis, but also simulation, intractable.

If the only entity of interest is the myocyte's transmembrane voltage, co-authors Cherry and Fenton have experimentally shown that a Minimal Model (MM) consisting of only 4 variables and 27 parameters can accurately capture voltage propagation properties in 1D, 2D, and 3D networks of myocytes [3]. The MM has allowed us to obtain dramatic simulation speedups [1], and to use its linear hybridization as the basis for formal symbolic analysis [12].

Since new technological advances are expected to lead to further insights into myocytic behavior, it is likely that the IMW model will be further refined by adding new variables. As in model checking and controller synthesis, one would therefore like to compute the smallest approximation that is observationally equivalent to the state-of-the-art DEM with respect to the property of interest, modulo some bounded approximation error. This, however, is not easily accomplished, as it implies the automatic approximation of very large nonlinear DEMs.

A first step toward the desired automation is to identify a set of approximation techniques that allow one to systematically remove unobservable variables from say, a detailed model such as IMW to end up with the MM, if the only observable variable is the voltage. This is one of the goals of the project entitled Computational Modeling and Analysis of Complex Systems [23]. A byproduct of this work is to establish a long-missing formal relation among the existing myocyte DEMs, that facilitates the transfer of properties established at one layer of abstraction to the other layers. Building such *towers of abstraction* is becoming increasingly prevalent in systems biology [16,6].

In this paper, we focus on model-order reduction and abstraction of ion channel dynamics. The main question posed in this paper is the following: *Assuming that the conductance of the ion channel is the only observable, is the behavior of an HH-type channel equivalent to the behavior of the IMW channel, modulo a well-defined approximation error?* Specifically, we answer this question in the affirmative for the sodium and the calcium-independent potassium channels. Rather than dealing with behavioral equivalence explicitly, we ask if it is possible to construct an approximate bisimulation [7,9,8,10] between the HH and IMW channel models? This notion of equivalence is stronger than the conventional behavioral equivalence, which compares the observed behaviors (trajectories) of the two given systems.

The answer to the above-posed question is of broad interest, as it reduces to showing the existence of an approximate bisimulation between two continuous time Markov decision processes; that is, two input-controlled (voltage in this case) Continuous Time Markov Chain (CTMCs). We answer this question in the positive, by explicitly constructing such a bisimulation. See Fig. 1 for an overview of our approach.

The rest of the paper is organized as follows. Section 2 introduces the HH and the IMW DEMs and their sodium and potassium channel components. Section 3 presents our parameter identification technique and the resulting HH-type abstraction for the sodium and potassium channels. Section 4 presents empirical evidence of the equivalence of the detailed models and their abstractions. Section 5 proves the existence of an approximate bisimulation between the detailed ion channel models and their abstractions. Section 6 is dedicated to our conclusions and future directions.

2. Background

Cardiac myocytes belong to the class of excitable cells, which also includes neurons. Such cells respond to an external electrical stimulus in the form of an Action Potential (AP), the characteristic change of the transmembrane potential in time. A typical ventricular myocyte AP and its associated phases are shown in Fig. 2(Right). Either an external stimulus, or the diffusing charge from the neighboring cells can excite the myocyte, causing an AP to quickly depolarize the membrane from a negative resting potential of V_{res} mV to a maximum of V_{max} mV followed by gradual repolarization.

2.1. The IMW cardiac cell model

The IMW DEM, a physiologically detailed model, describes the ionic processes responsible for the generation of an AP in human ventricular myocytes:

$$-C\dot{V} = I_{Na} + I_{Nab} + I_{Ca} + I_{Cab} + I_{Kr} + I_{Ks} + I_{K1} + I_{to1} + I_{p(Ca)} + I_{NaCa} + I_{NaK} + I_{CaK} + I_{st}, \tag{1}$$

where V is the membrane potential, $\dot{V}$ is its first-order time derivative, C is the membrane's capacitance, and I_v are the ionic currents shown in Fig. 2(Left), except for I_{st}. This is the stimulus current, which could be either an external stimulus