Simulation-guided Data Assimilation for Kinetics Modeling of Potassium Channel Isoforms in Mouse Cardiomyocytes

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Abstract

Electrical signaling initiates and controls the contraction of cardiac muscles. Voltage-gated ion channels (VGICs) are the functional unit of electrical activities in cardiomyocytes, so they have been important subjects of research in cardiac electrophysiology. Among major cardiac VGICs, K^+ channel (K_v) has a distinctive feature in that it has multiple isoforms. Each isoform produces a different but slightly overlapping component of the total K^+ current (I_{Ksum}). Despite the importance of studying each K_v isoform rigorously, only I_{Ksum} can be recorded during in-vitro experiments. Hence, we need a data assimilation method that combines mathematical models with experimental data, I_{Ksum}, to estimate individual K^+ currents. Exponential fitting is a traditional method to estimate the current functions of K_v isoforms from I_{Ksum} data based on the observation that K^+ currents have the shape of an exponential decay function. It has been proven that exponential fitting accurately describes I_{Ksum} with estimated K^+ currents. However, this classical method does not consider the kinetics of ion channels at the cellular level but only the shape of each I_{Ksum} recording. On the other hand, computer models of cardiac electrophysiology can simulate complex dynamics of electrical activities in the heart. This study proposes a data assimilation method based on simulation of K_v kinetics that combines in-vitro experimental results I_{Ksum} with in-silico models of K_v isoforms by calibrating the computer models. The proposed method differs from the exponential fitting in a way that it estimates the characteristics of current functions and underlying kinetics. In addition, the suggested approach assimilates I_{Ksum} recordings at cellular level rather than analyzing each recording independently. An accompanying graphical user interface (GUI) is developed to provide a user-friendly environment to test the proposed method for practitioners. We conducted a case study with our in-vitro experimental data that investigated the effect of reduced glycosylation on K_v.

Keywords: Cardiac electrophysiology models, data assimilation, model calibration, K_v isoforms, mouse cardiomyocytes

Introduction

Electrical signaling plays a vital role in the heart conduction system that controls electrical excitation propagation through the heart, which triggers and synchronizes the contraction of a myriad of cardiac muscle cells (Veeraraghavan, Gourdie, and Poelzing 2014). In turn, this electrical stimulation is responsible for the heart to pump blood throughout the body properly. Cardiac voltage-gated ion channels (VGICs) are membrane proteins in a cardiomyocyte that control specific ions to flow through the membrane (Bezanilla 2005). They are fundamental functional units of electrical activities in cardiomyocytes as the electrical excitation results from the orchestrated dynamics of different types of ionic currents controlled by the gating kinetics of VGICs as shown in Figure 1 (Nerbonne 2003; Grant 2009). This electrical simulations is called the action potentials (AP), which is the net change of membrane potential, and there are three major cardiac VIGCs contributing to the shape and length of the AP: Na^+ (Na_v), Ca^{2+} (Ca_v), and K^+ (K_v) channels. Na_v are responsible for AP initiation (depolarization phase), Ca_v are responsible for the prolonged depolarization

phase ("plateau'') particularly in larger species like human, while various isoforms of K_vs are collectively responsible for AP deactivation (repolarization phase).

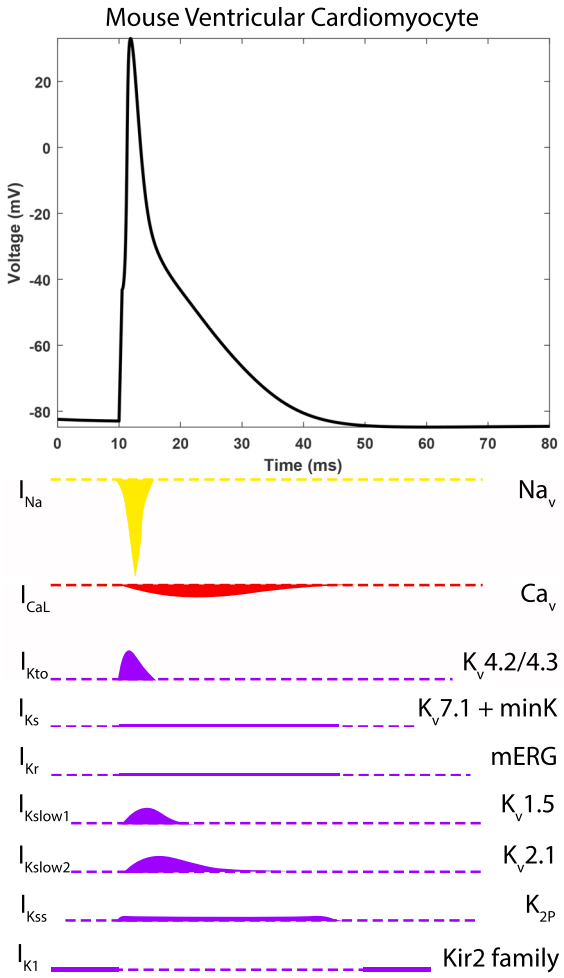

Figure 1: A schematic illustration of action potentials in mouse ventricular cardiomyocytes and underlying ionic currents of Na extsubscriptv, Ca extsubscriptv, and K extsubscriptv isoforms

In contrast to Na_v and Ca_v, K_v have a distinctive feature that they have multiple isoforms. Each isoform produces different but slightly overlapping component of the total K^+ current (I_{Ksum}) and contributes to different portions of the AP repolarization. To be specific, as shown in Figure 1, there are various K_v isoforms and currents they produce: the transient outward K^+ current I_{Kto} ($K_v4.2$/$K_v4.3$) several components of delayed rectifier K^+ currents including I_{Ks} ($K_v7.1$ and minK), I_{Kr} (mERG), I_{Kslow1} ($K_v1.5$), and I_{Kslow2} ($K_v2.1$), non-inactivating steady-state K^+ current I_{Kss} (K_{2P}), and time independent K^+ current I_{K1} (Kir2 family) (Brouillette et al. 2004; Liu et al. 2011). Note that although there are two types of transient outward currents, I_{Ktof} and I_{Ktos}, only one of them is presented and referred to as I_{Kto} because I_{Ktof} is only found in ventricular apex myocytes, while I_{Ktos} is reported to appear only in the septum (Xu, Guo, and Nerbonne 1999). There are several K_v isoforms whose exact roles in shaping the cardiac AP are still subject of intensive research. Although it is highly desirable to study each unique K^+ current rigorously, only I_{Ksum} can be recorded during in-vitro experiments.

Hence, we need a data analysis tool to estimate individual K^+ currents from I_{Ksum}. Data assimilation is a scientific method that combines mathematical models and experimental data to calibrate the models; thereby, the in-silico models are compatible with the in-vitro observations. To be specific, for our case, a data assimilation method is required that couples mathematical models of K^+ models with experimental

data of I_{Ksum} using whole-cell patch-clamp recordings to estimate various K^+ currents. Exponential fitting is a traditional method based on the assumption that prominent K^+ currents from patch-clamp recordings such as I_{Kto}, I_{Kslow1}, and I_{Kslow2} have the shape of an exponential decay function $A_i e^{-t/\tau_i}$ as in Equation~**??**, where t is time variable, and A_i and τ_i are the shape parameters. I_{kss} is simplified as constant A_{Kss}. It has been proven that exponential fitting accurately describes I_{Ksum} with estimated K^+ currents and served as a standard method to analyze the sum of K^+ currents [Brunet et al. (2004); liu2011dissection]. However, the mathematical model of this classical method only characterizes the shape of the currents, not the kinetics of corresponding K_v isoforms. In addition, exponential fitting handles I_{Ksum} recordings from the same cell with different conditions independently, so it lacks systematic analyses at the cellular level.

$$I_{Ksum} = \sum_i A_i e^{-t/\tau_i} + A_{Kss},\ i \in I \subseteq \{\text{Kto, Kslow1, Kslow2}\} \tag{1}$$

On the other hand, computer models of cardiac electrophysiology can simulate complex dynamics of electrical activities at the cellular level that enable the quantitative understanding of biophysical functions such as gating kinetics of VGICs in the behavior of cardiomyocytes (Winslow et al. 2011). Therefore, this paper proposes a data assimilation method based on the computer models of K_v isoforms that facilitates kinetics modeling at the cellular level. K_v models are developed on biophysical principles of VGICs that are encoded in terms of mathematical equations. These equations have parameters that act like "knobs' ', allowing to control the behavior of the models. Tunning computer models to couple with experimental data requires trial-and-error investigations and domain knowledge in both the kinetics of cardiomyocytes and mathematics of computer models. Since modeling of cardiac electrophysiology is an interdisciplinary field that incorporates biology and engineering, calibration of computer models and interpretation of modeling results can be challenging for researchers in biology or medicine communities without engineering training. This hurdle hinders researchers in physiology from utilizing computer models to analyze their experimental data. A graphical user interface (GUI) is provided in which researchers can easily calibrate K_v models to their data and visualize the modeling results. A new model calibration method will allow researchers to utilize computer models to analyze complex potassium dynamics in cardiomyocytes without engineering background. A GUI will provide an interactive environment to use the calibration method and analyze the results easily with visualizations.

Material and Methods

Results

Conclusions

References

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