Cardiac Modeling of Steady-State Transients in the Ventricular Myocyte Model

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Notations

AP	*Action Potential*
$[Ca]_i$	*Intracellular calcium concentration*
$[Na]_i$	*Intracellular sodium concentration*
$[K]_i$	*Intracellular potassium concentration*
I_app	*Current injection*
t_app	*Current duration*
$\bar{I}_{NaK}$	*Maximum Na/K pump current*
K_{mNai}	*Km constant of Na/K pump for* Na^+
K_{mKo}	*Km constant of Na/K pump for* K^+
hill	*Hill coefficient for the Na/K pump*
I_{to}	*Transient outward K current*
I_{kr}	*Rapidly-activating K channel current*
I_{ks}	*Slowly-activiating K channel current*
I_{ki}	*Time-independent K current*
I_{CaK}	*L-type Calcium-activated K current*
I_{kp}	*Plateau K current*

Abstract

Investigating the process of ventricular myocyte excitation contraction coupling via computational modeling offers insight on the complex interactions involved in cardiac electrophysiology. By understanding the regulation and coordination of these processes, researchers can identify specific heart conditions. This is evident in Romero's discussion on ionic current properties that were found to modulate main cellular biomarkers associated with arrhythmic risk (Romero et al., 2011). Overall, it is necessary to incorporate modern experimental methods to further understand the mechanisms behind cardiac electrophysiology and explore future treatments.

The Shannon et al. model is composed of a series of differential equations which describe the ionic and electrical homeostasis in the ventricular myocyte (Shannon et al., 2004). The model incorporates a wide range of parameters that are consistent with laboratory data, and an investigator can utilize these sets to simulate a variety of controlled experiments. However, while the model is a powerful tool in producing outputs that accurately reflect experimental data, Shannon et al. states that the most important aspect of the model is to highlight areas where our knowledge of physiological processes is incomplete. This project focused on expanding the existing model to account for change in intracellular potassium during the excitation of the myocyte. We searched for a new steady-state of AP, $[Ca]_i$, $[Na]_i$, and $[K]_i$ by utilizing parameter sweeps and methods of optimization. While a steady-state of $[K]_i$ proved to be problematic throughout the project, new sets of data quantitatively described new ionic steady-state as well as the limitations of the Shannon et al. coupling model.

Objective

The Shannon et al. model was used to solve differential equations and to calculate the change of AP and intercellular ions over the time of the simulation. For this project, the transients of interest were AP, $[Ca]_i$, $[Na]_i$, $[K]_i$. The changes in concentration of these intracellular ions were attributed to the movement of the ions through specific channels and the following the cascade of interactions across the cellular membrane. Action potential was measured by calculating the change in voltage, which was influenced by the total ionic current and current injection in the myocyte. At a certain time in the simulation, each transient achieves a steady-state equilibrium. Steady-state describes the behavior of a specific transient when it continues to operate in the same repetitive stimulation over time; this state does not change unless the cellular environment is altered (Shannon et al. 2004). The model was stimulated at 1Hz for 2000 seconds, and the resulting ion transients are displayed in Figure 1. Whereas AP, $[Ca]_i$, and $[Na]_i$ transients are observed to plateau at a certain time in the 2000 second interval, $[K]_i$ remains constant.

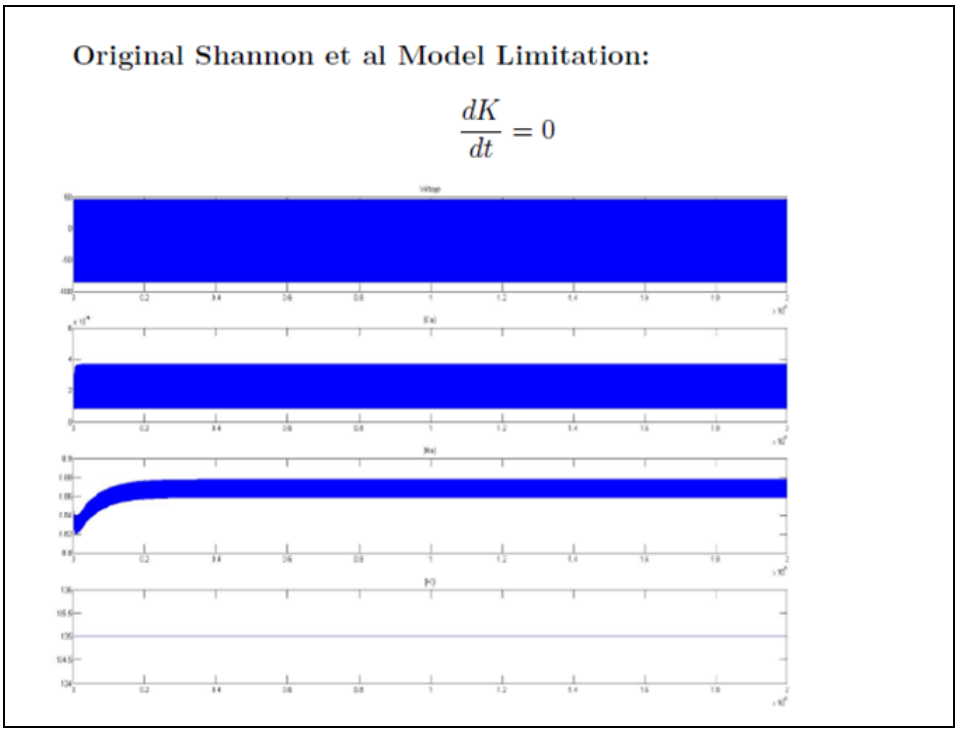

Figure 1: *Calculated AP, Ca^{2+}, Na^{+}, and K^{+} cytosolic transients (top to bottom) from 0-2000 seconds in response to a 1Hz stimulation.*

Although the change in intracellular potassium concentration is influenced by the regulation and movement of $[K]_i$ through seven different potassium channels, the Shannon et al. model assumes no change in $[K]_i$ throughout the simulation. Considering this limitation, the actual transients of AP, $[Ca]_i$, and $[Na]_i$ are also inaccurately predicted. My project focused on improving the coupling model and its limitations, as the model was revised to account for the change in intracellular potassium concentration. The expanded model was run at the same simulation time and conditions, and new steady-states were found for AP and $[Ca]_i$ (Figure 2). However, the $[Na]_i$ and $[K]_i$ transients remained problematic; under the same condition neither transient demonstrated stable behavior.

To further investigate the stability of $[Na]_i$ and $[K]_i$ transients, my project focused on stimulating the model with different values of applied current. Through the parametric modeling toolkit Nimrod I was able to conduct multiple parameter sweeps on the injected current and its duration in the cell. After analyzing applied current and its effect on AP and intracellular ion concentration, I applied optimization methods to search for steady-state of $[K]_i$ by exploring the parameter spaces of the Na/K pump current. Lastly, I tested combinations of the applied current and the Na/K pump to determine if a set of parameters could optimize the model to achieve a steady-state.

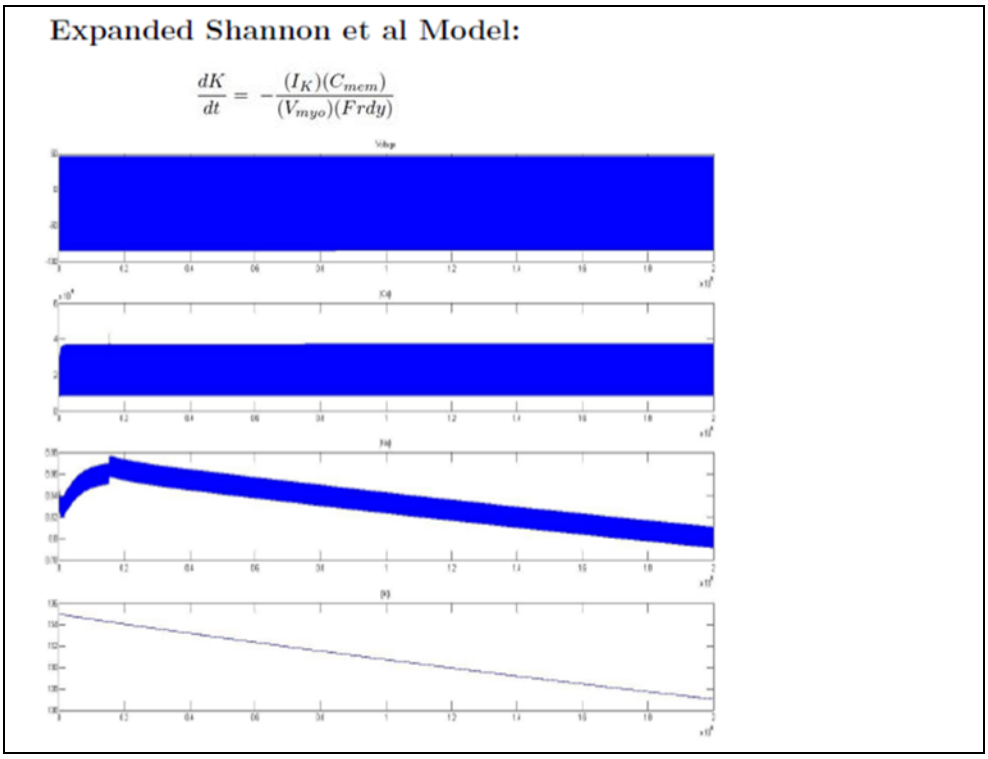

Figure 2: *Calculated AP, Ca2+, Na+, and K+ cytosolic transients (top to bottom) accounting for change in intracellular potassium from 0-2000 seconds in response to a 1Hz stimulation.*

Methods

The Shannon et al. model was expressed in MATLAB. The original model was adjusted to account for change in potassium current, and it was simulated at a frequency of 1 Hz and 2000 seconds. All scripts that accompanied model analysis were also written in MATLAB. The Shannon et al. model was then integrated with the parametric modeling toolkit Nimrod.

Parametric modeling is a powerful tool for the analysis of computational models and systems. By conducting a parameter sweep, a scientist can perform multiple computational experiments simultaneously and generate large amounts of data. The Shannon et al. model was integrated with Nimrod/G to investigate the effects of steady-state in different parameter spaces. Nimrod/G offered several advantages: 1) It utilized distributed computing middleware across different resources to execute large scale parameter sweeps 2) Its scheduling services provided the researcher with the flexibility and convenience of accessing experiments on a local network. Specifically, Nimrod/G was used to test the response of AP and intracellular transients to a applied current in the cell. A range of values related the physiological current was incorporated in the parameter sweep, and the large amount of jobs generated was handled through MATLAB and then analyzed.

Concerning the experiments with Na/K pump, Nimrod/G could not be used to test all possible parameters—this was due to the large area of parameter spaces in the Na/K pump. To

minimize the large amount of jobs produced in the parametric sweeps, Nimrod/O was incorporated after. Nimrod/O possesses all the parametric modeling capabilities of Nimrod/G; however, its main functionality is in its utilization of various optimization algorithms to optimize model output. The objective of the Na/K pump experiments was finding a steady-state $[K]_i$ transient; therefore the proposed objective function to minimize was the last 200 seconds of the simulation, where the model would be assumed to have been in a steady-state. As the optimization experiments continued to develop, starting points—parameter sets that produced stable transient behavior—drove the optimization algorithms. Simplex optimization methods were used to evaluate the effect of Na/K pump and its interaction with varying current.

Results

The experiments run on Nimrod/G testing variations of the applied current produced a wide range of results—while some AP and $[Ca]_i$ transients were in experimental agreement with the original model, none of the jobs produced stable $[Na]_i$ and $[K]_i$ state. The first experiment evaluated I_app, as its initial value of 9.5 varied from the range of 9 to 20. The generated data indicated that steady-state behavior for AP and $[Ca]_i$ could be stabilized in agreement with the original model. However, the model response in [Na]i and [K]i indicated negative results. Although [Na]i transients did not reach equilibrium, the $[Na]_i$ transients that were close to being stabilized behaved contrary to those of the original model—instead of a upstroke in ion concentration followed by the plateau, $[Na]_i$ decreased negatively before slowing down to approach a close steady-state. This behavior was especially consistent with I_app values that were greater than approximately 17 (Figure 3). Furthermore, the [K]i transient proved to be the most problematic of ions. None of the transients produce a steady-state [K]i—rather the [K]i concentration continued to decrease (Figure 4). This potassium change was consistent throughout all the tested stimulations of I_app.

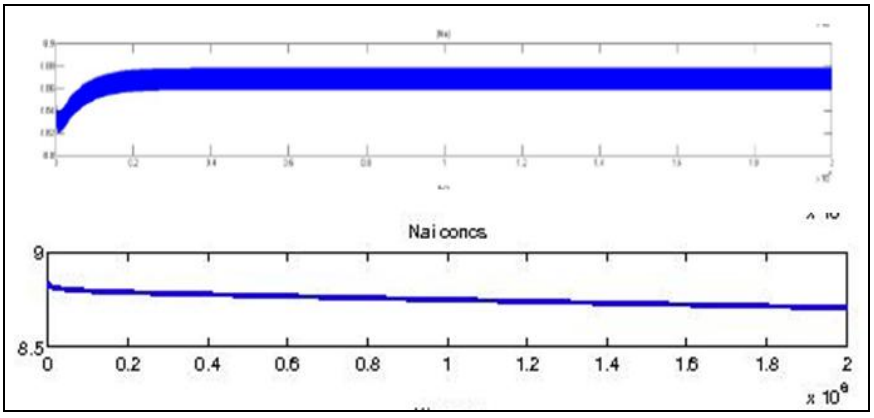

Figure 3*: The original $[Na]_i$ transient (top) compared to the new $[Na]_i$ transient (bottom) at I_app = 17.7. This transient was the closest to stabilized potassium.*

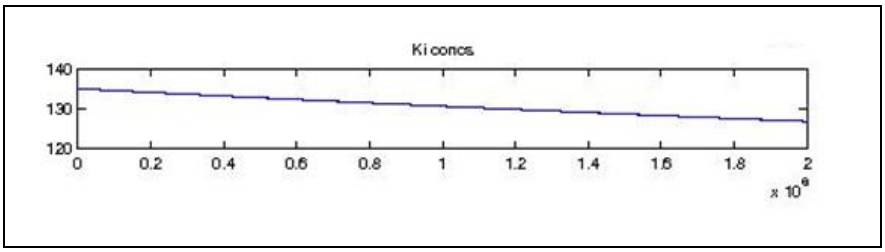

Figure 4: *The [K]i transient at I_app = 10.0. All of the transients from I_app of 9.0 to 20.0 produced [K]i that could not reach a steady-state.*

The next step in testing the applied current was to combine duration (t_app) with injection (I_app). After analyzing the negative results for [Na]i and [K]i it was predicted that changing the duration of the applied current would not help the model output with achieving steady-state. An experiment was run varying combinations of t_app at the default value 5 from a range of 5 to 20. Nimrod/G conducted the parameter sweep with the previous values of I_app with the new spaces of t_app. The response of the model agreed with the hypothesis after the first experiment; changing the duration of the current injection could not stabilize the $[Na]_i$ or $[K]_i$ currents. The transients behaved in a similar manner to the output of the first experiment—$[Na]_i$ transients decreased close to a stable behavior and $[K]_i$ continued to decrease at a fast rate past the end of the simulation.

After testing the parameter sets of the applied current and observing its effect on the transients, we investigated the set of parameters in the Na/K. The following parameters were evaluated with the specified ranges: $\bar{I}_{NaK}$ (.1-10 A/F), K_{mNai} (1-20 mM), K_{mKo} (.1-10 mM), hill (.1 -10). Because of the large number of combinations produced with this set of parameters (values of one parameter set incremented by .1 each run), Nimrod/O was used to revise the experimental design. By using Nimrod/O, we adjusted the tool to specifically search all the parameter spaces to minimize the change in $[K]_i$. Because $[K]_i$ was the most problematic steady-state, the experiment designated spaces where the change in $[K]_i$ would be minimized near the end of the simulation, potentially indicating an equilibrium.

The results from the optimization experiments produced steady-state AP, $[Ca]_i$, and $[Na]_i$ transients along with $[K]_i$ behavior that appeared to approach stability near the last 500 seconds of model simulation. Of the jobs generated, there were AP, $[Ca]_i$, and $[Na]_i$ steady-states that appeared to be in agreement with those of the original model; however, it was observed that $[Ca]_i$ took longer to reach a steady-state while $[Na]_i$ deviated from ideal steady-state behavior (Figure 5).

Similar to the first experiment testing current injection, this optimization experiment could not find any interval where $[K]_i$ reached a steady-state. However, it was observed that some of the $[K]_i$ transients that were produced appeared to slow in change during the last 500 seconds of the experiment, potentially approaching stable behavior. To further investigate the stability of the $[K]_i$ transient, we extended the time of the model simulation from 2000 seconds to

3000 seconds and evaluated the model output by optimizing the same parameter spaces. The resulting transients also did not produce a steady-state $[K]_i$ transient despite extending the time of the simulation by 50%; instead, the observed transients at the end of the extended simulation shared the same behavior as those of 2000 second simulation (Figure 6).

We continued to investigate the same parameter spaces. By extracting the relevant sets of parameters from the best simulations— containing a steady-state AP, $[Ca]_i$, $[Na]_i$, and an almost stable $[K]_i$— a new optimization experiment was created to verify whether $[K]_i$ could be achieved in this parameter space. Each extracted set of parameters was integrated into the optimization experiment as a starting point. There were 38 starting points that drove optimization algorithms on Nimrod/O. The results matched those of the previous experiments; all steady-state transients could be identified aside from $[K]_i$.

To conclude all of the tests with the applied current and the Na/K pump, the final procedure of the project was to combine both of their parameters to test whether a steady-state [K]i could be found. The applied current parameters I_app (9-20) and t_app (5-20) were combined with the parameters I_{NaK} (.1-10 A/F), K_{mNai} (1-20 mM), K_{mKo} (.1-10 mM), hill (.1 - 10). The results of the experiment produced transients with stable AP, $[Ca]_i$, and $[Na]_i$ consistent with the steady-states of the Na/K experiment. The $[K]_i$ transient remained problematic and we finished our experiment concluding that although we could find steady-state AP, $[Ca]_i$, $[Na]_i$ for the expanded model ,we could not find a steady-state $[K]_i$ by assessing the parameters of the applied current and the Na/K pump.

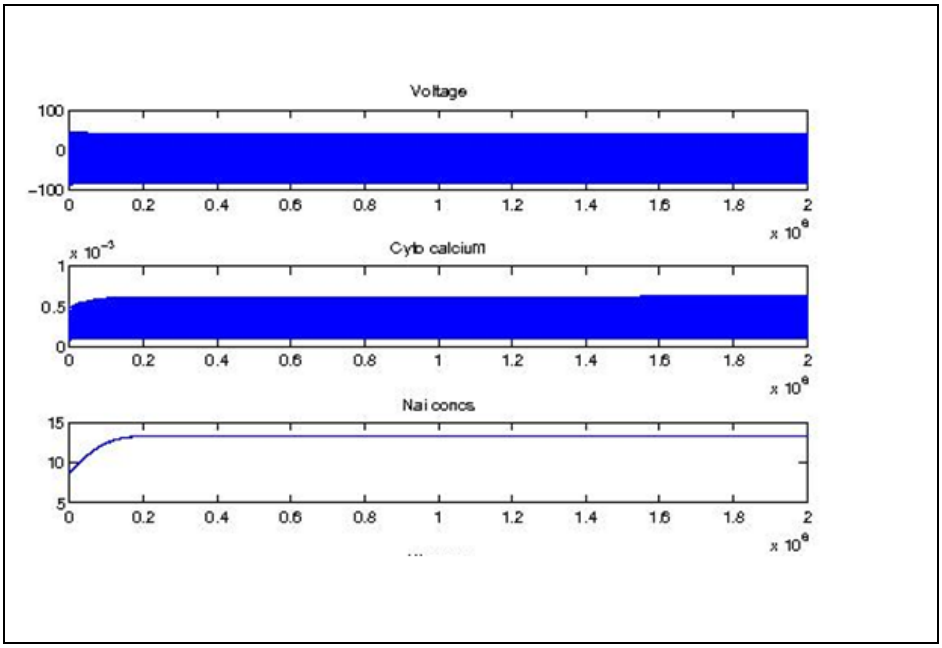

Figure 5: *The steady-state AP, [Ca]i, and [Na]i produced in the Na/K pump optimization experiment. For this set, K_{mKo} = 2 mM , K_{mNai} = 18 mM, hill = 10 , $\bar{I}_{NaK}$ = 10 A/F.*

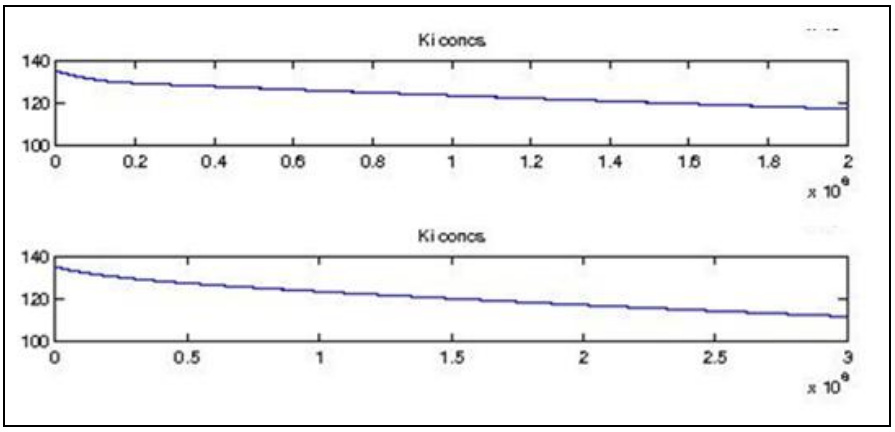

Figure 6: *One of the intracellular potassium transients at 2000 seconds (top) and 3000 seconds (bottom).*

Conclusion

Expanding the model to account for change in intracellular potassium proved to be a difficult task in finding stable ionic and AP states. Through optimization methods and parameter sweeps of the Na/K pump, we found new steady-states for AP, $[Ca]_i$, and $[Na]_i$ that are in agreement to the transients featured in the original model. However, through the process of experimentation we learned that a $[K]_i$ steady-state could never be produced with the targeted parameters. Despite the optimization algorithms targeting a stable $[K]_i$, the transients for the ion could only be optimized to change at a slow rate. The negative results for this project on applied current stimulation and the Na/K pump potentially indicate the shortcomings of the Shannon et al electron coupling model. The $[K]_i$ transient proved problematic once the change in intracellular potassium was incorporated to the original computational model, and if a steady-state of the transient existed then the experiments would have readily produced stable $[K]_i$. Although there are many untested ion channels and complexes that can influence the change in intracellular potassium, the results from these experiments suggest that it likely that $[K]_i$ cannot reach a steady-state.

The next step is to verify our conclusion that the model cannot produce a steady-state intracellular potassium transient. The Na/K pump is one of seven potassium currents that contribute to the change of $[K]_i$; therefore, future work is in assessing the parameters in the six remaining currents. The six remaining currents and ion channels are I_{to}, I_{kr}, I_{ks}, I_{ki}, I_{CaK}, and I_{kp}. The existing parameter sets for each current are currently in the process of evaluation, as we are exploring different optimization approaches to effectively search these spaces for steady-state $[K]_i$.

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