Cardiac Myocyte Model Parameter Sensitivity Analysis and Model Transformation Using a Genetic Algorithm

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ABSTRACT
Cardiac arrhythmia is the disruption of the normal electrical rhythm of the heart and is a leading cause of mortality around the world. To study arrhythmogenesis, mathematical models of cardiac myocytes and tissues have been effectively employed to investigate cardiac electrodynamics. However, among individual myocytes, there is phenotypic variability that is dependent on factors such as source location in the heart, genetic variation, and even different experimental protocols. Thus, established cardiac myocyte models constrained by experimental data are often untuned to new phenomena under investigation. In this study, we show direct links to parameter changes and differing electrical phenotypes. First, we present results exploring model sensitivity to physiological parameters underpinning electrical activity. Second, we outline a genetic algorithm based approach for tuning model parameters to fit cardiac myocyte behavior. Third, we use a genetic algorithm to transform one model type to another, relating simulation to experimental data. This model transformation demonstrates the potential of genetic algorithms to extend the utility of cardiac myocyte models by comparing different functional regions in the heart.

Categories and Subject Descriptors
J.3 [**Computer Applications**]: Life and Medical Sciences—*biology and genetics*

General Terms
Algorithms, Design, Experimentation, Measurement, Performance, Reliability, Theory, Verification

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1. INTRODUCTION
The interplay of ion channels, pumps, transporters, and ion concentrations leads to cardiac electrical activity that induces contraction and the distribution of blood. Dysfunction of any component of the cardiac electrical system can increase the chance for cardiac arrhythmia, and thus sudden cardiac death. Annual mortality counts due to cardiac arrhythmia are estimated at 4-5 million globally [1].

Cardiac myocytes from different individuals and even within the same organism exhibit variable electrical behavior [2]. A key way in which cardiac myocytes differ is in the exact values of the maximum ionic conductances, which dictate maximum flow of ions through the cell membrane. This variance leads to different action potential (AP) morphology, such as different action potential duration (APD), when pacing at the same basic cycle length (BCL). The maximum conductance values themselves are affected by a number of factors, which include ion channel density, geometry of the cell membrane, genetic variation leading to structural differences, and regulation of the ion channels.

For our first aim, to see the impact of each maximum conductance value, we varied the conductances individually. However, to see the impact of multiple parameters together, there is a combinatorial explosion when considering a parameter sweep over tens of possible parameters with multiple values. For our second aim, we used a genetic algorithm (GA) to navigate through a large parameter space, where parameters are considered simultaneously as the GA progresses. To solve optimization problems, GAs use computational correlates of evolutionary processes: selection, crossover, and mutation. In this study, the genotype is an array of conductance values for an individual. The phenotype is the electrical behavior, and we use an objective function targeting the arrythmogenic behavior of alternans across multiple pacing frequencies.

Alternans of cardiac repolarization is a putative precursor to some lethal arrhythmias [3]. At the cellular level, alternans involves a beat-to-beat oscillation of the APD. Using pacing frequencies rapid enough to induce alternans, we construct an objective function containing alternans behavior. Rapid pacing induces alternans since ion channels are less likely to have recovered in subsequent beats. For our third aim, to study relations of different areas in the heart, we apply a GA to determine whether one myocyte type can be transformed into another, despite initial differences in AP morphology.

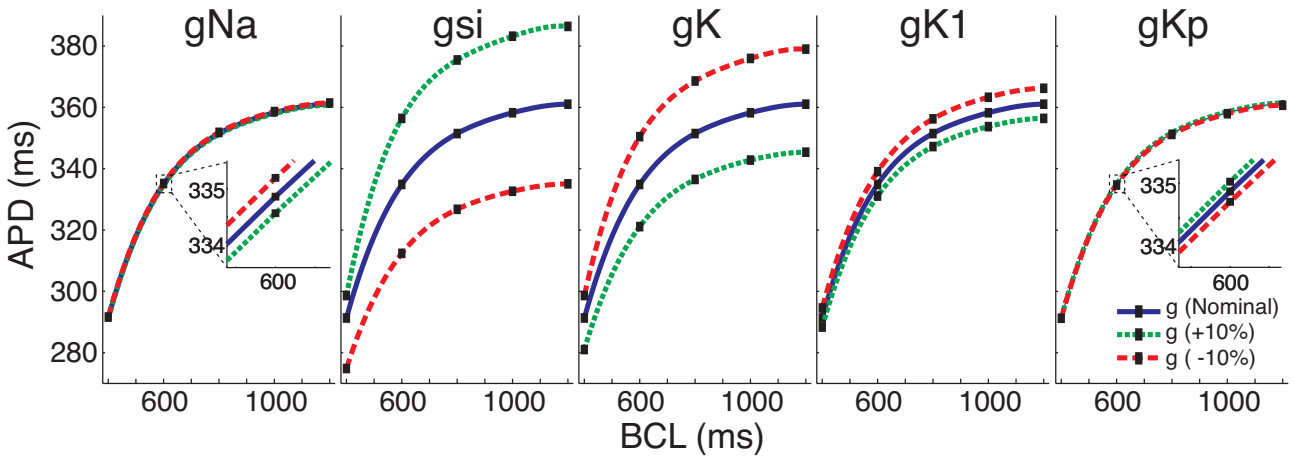

Figure 1. LR1 restitution profiles with maximum conductance values varied separately. Restitution profiles with a 10% increase and 10% decrease from the nominal conductance value are denoted in green and red respectively. BCL began at 1200 ms and was decremented by 200 ms to 400 ms. APD was denoted by 90% repolarization.

2. METHODS

This study uses a combined computational and experimental approach. The computational component focuses on determining model sensitivity to physiological parameters and then using a GA to match arrhythmogenic behavior. The experimental component provides a target phenotype that tests the ability of a GA to transform one cell type to another. This further increases model utility by elucidating how changes in underlying ion channel maximum conductance values can lead to different functions in cardiac tissue.

2.1 Cell Models

The Luo Rudy (LR1) ventricular cell model [4], which was originally derived from the Beeler Reuter (BR) model [5], was selected for this modeling study because it reliably reproduces key features of experimental AP morphology. In addition, the system dynamics converge to steady state in a few beats, while subsequent models, such as the Luo Rudy dynamic (LRd) model [6], can take more than tens of beats to reach steady state. For the cell transformation aim, we used the Nygren atrial myocyte model [7]. Both the LR1 and Nygren models use Hodgkin Huxley type formulations for the ionic currents [8], where the cell is modeled as a circuit with parallel branches for each ion channel type.

The original nominal maximum conductance values and descriptions for the LR1 and Nygren models are in [4] and [6], respectively. For the sensitivity analysis on the LR1 model, nominal values were shifted +/- 10% and restitution curves were plotted at steady state for each BCL, decrementing from 1200 to 400 ms by 200 ms. For a cell, the restitution curve shows recovery to resting membrane voltage at differing BCLs.

2.2 Genetic Algorithm

As models become increasingly complex, it becomes ever more critical to understand parameters' individual and coupled impact. Genetic algorithms traverse large portions of parameter space by using computational correlates of evolutionary processes. In this study an individual is a model instantiation, with the genotype as the array of maximum ionic conductances, and phenotype as the membrane potential. Competitive pressure was introduced by using tournament selection without replacement, with a tournament size of 2. Crossover probability of 0.9 and was done by simulated binary crossover with a genewise swap probability of 0.5 and polynomial order of 10. Mutation probability was set at 0.1 and done by polynomial method with order of 20 [9].

For the GA optimization, the objective function was pairs of action potentials from three pacing frequencies near the alternans onset frequency for the LR1 cardiac myocyte model. Thus, there are a total of six action potentials in the objective function, seen as the nominal phenotype in both Figure 2A and 2B. Pacing near alternans onset was used to distinguish between individuals, as different genotypes lead to alternans resistance or susceptibility. The Genetic Algorithms Toolbox [9] from the University of Illinois Genetic Algorithms Laboratory was used for GA implementation, with a +/- 50% parameter variation range for each conductance parameter in the original nominal model. For the cell transformation aim a large +/- 2000% parameter range was allowed due to the different cell types. Equation 1 shows the form of the objective function.

$$E = \sqrt{\sum_{t=t_0}^{t_{max}} \left(V_{Nominal}(t) - V_{Individual}(t) \right)^2} \quad (1)$$

For the LR1 model, 20 individuals over 20 generations were sufficient for phenotype matching while for the Nygren model 40 individuals over 60 generations were required. More individuals and generations were required for the Nygren model GA runs since the Nygren model is comparatively more complex than the LR1 model. Specifically, the Nygren model has more underlying parameters and detailed equations for intracellular ion handling which the LR1 model lacks.

There is a natural parallelism in GAs where each fitness computation is independent of others within a generation. For each run of the GA we used OpenMP to distribute each individual's phenotype and fitness calculation within a generation to different threads. Threads would join upon completion of a generation and then split again after selection, crossover, and mutation operations occurred. It is this parallelism that drew us to GAs, as a single individual evaluation is on the order of minutes.

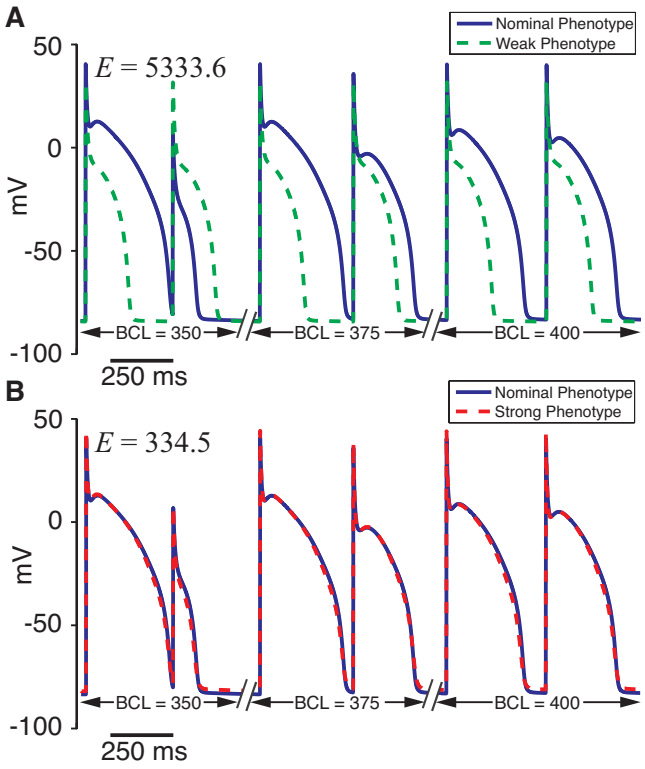

Figure 2. Comparison of phenotypes with objective nominal phenotype. (A) is a weak phenotype from the first generation and (B) is a strong phenotype from the last generation of a GA run (see Figure 3A). The hatch marks delineate the three pairs of action potentials from different BCL pacing.

2.3 Electrophysiology

Myocytes were isolated from the left ventricle of adult (400-600 gram) Hartley guinea pigs [10]. Whole cell voltage recordings were obtained using the ruptured patch clamp technique. Cells were bathed in Tyrode's solution, and all experiments were done at room temperature (~23 C). 2-4 Mohm pipettes were filled with solution containing the following (in mM): 113 KCl, 10 NaCl, 5.5 Dextrose, 5 K2ATP, 0.5 MgCl2, 11 KOH, and 10 HEPES (pH = 7.1). After formation of a gigaohm seal, suction was applied to the pipette interior to rupture the membrane patch. Membrane current and voltage was measured using an A-M systems Model 2400 patch clamp amplifier. After waiting 5 min for cell dialysis and current stabilization, APs were elicited with 1 ms square current pulses at 1.5 times threshold at a BCL of 500 ms until stable action potential were seen.

3. RESULTS

3.1 Sensitivity Analysis

As seen in Figure 1, the LR1 model is least sensitive to changes in gNa and gKp and most sensitive to changes in gsi. Changes in gK and gK1 produce an intermediate impact on the restitution curve when compared to changes in the other conductances. The low sensitivity of gNa on restitution is understandable as that parameter is typically associated with AP upstroke velocity as opposed to APD. The AP plateau is mediated in large part by calcium, which is represented by gsi.

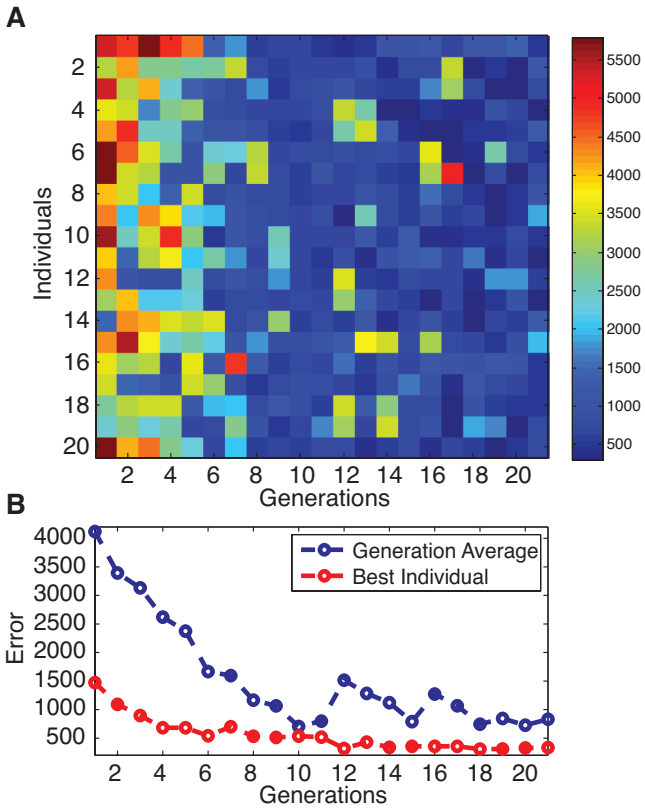

Figure 3. Genetic algorithm progression. (A) Original population of individuals evolving over specified generations. Colorbar denotes error value for individuals. (B) Generation average error best individual error.

3.2 Model Fit

With experimental data the actual genotype is not known, and so to test our GA approach we started with random LR1 model genotypes in search of the known nominal model. Figure 2 shows examples of a weak phenotype (Figure 2A) and a strong phenotype (Figure 2B) taken from individuals in the first and last generations of a LR1 GA run (Figure 3A), having high and low error, respectively. With our objective including alternans, a weak phenotype could have a different electrical abnormality or even normal activity. As the GA progressed, the best individual and average error of the population decreased (Figure 3B).

3.3 Cell Transformation

In [11], it was shown that an AP with different morphology could be transformed to another AP from the same species and same heart region. Here we show that with a GA, it is possible to do a fit across species and heart region. Figure 4 shows the phenotype transformation, and required genotype changes, to go from the human Nygren atrial cell model to that of matching experimental guinea pig ventricular data. The different heart chambers have different functions, with the atria responsible for pumping blood to the ventricles, and the ventricles responsible for pumping blood to the body. Considering these different roles, the fit in Figure 4A is not as close as in Figure 2B, likely due to irreconcilable differences in the model equations outside of conductances, perhaps showing species specific differences.

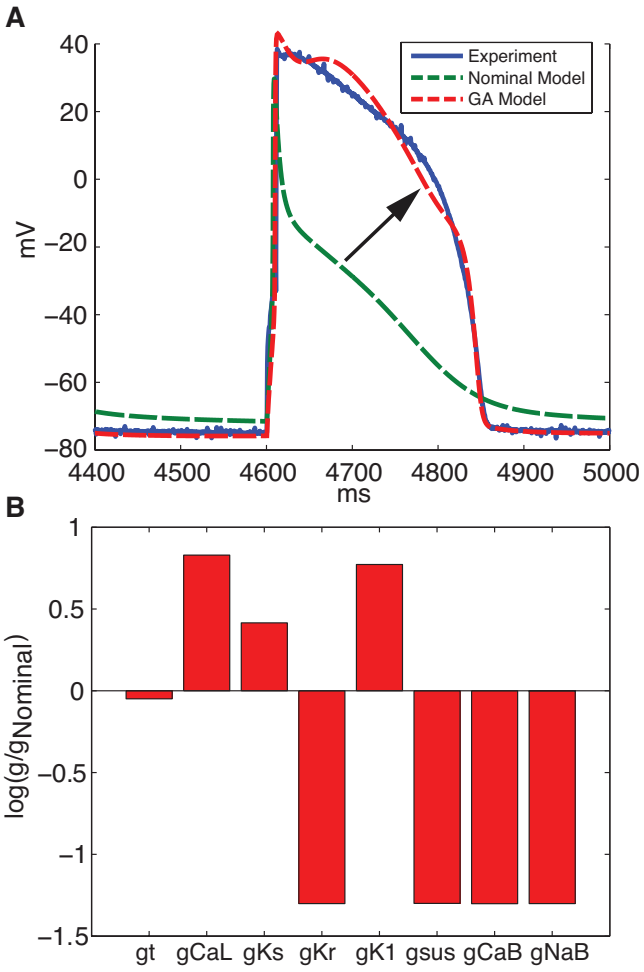

Figure 4. Transformation of atrial cell model to match ventricular cell experimental data. (A) Overlay of experimental, nominal, and GA transformed model. The arrow denotes the transformation of the Nygren model to that of one fitting experimental data from a different heart region. (B) Bar graph shows change of each Nygren atrial conductance parameter to fit phenotype of ventricular cell, relative to nominal values.

4. DISCUSSION

Every cell has a different genotype that needs to be in a physiological range for the cell to be viable and functional. An individual model instantiation's genotype is formalized as its maximum ionic conductance values. Single parameter perturbations in the sensitivity analysis led to different phenotypes, with different conductances having large or small effects on the restitution curve. Those model parameters that are denoted as model-sensitive can be prioritized for optimization, while those denoted as model-insensitive can be revisited in the model formulation. In addition, sensitivity to a parameter can have dosage implications in drug treatments, as some ion channels contribute little to the target of the treatment.

The multiple parameter perturbations conducted via the GA led to the successful fit of an objective with alternans, a precursor to some cardiac arrhythmia, as well as a fit for a model transformation. Cross-species cell transformations are important because different species offer different advantages and disadvantages for arrhythmia research. For example, guinea pigs are used as a model for human disease, but with mice there is a wealth of genetic techniques available. In this study, we show that a cross-species as well as cross-heart region transformation is possible using a GA. Taken together, the GA is a powerful tool for the study of cardiac electrophysiology.

5. ACKNOWLEDGMENTS

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