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**Article**

**A Novel Computational Model of Porcine Heart Failure Ventricular Myocytes and Tissue**

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SIGNIFICANCE Pigs share many cardiac features with humans, especially during heart failure, however, few computational models have been created to help guide experiments. Physiologically accurate computational models can view levels of detail inaccessible by experimentation, and can provide insights into how certain drugs can cause or mitigate arrhythmogenesis

**ABSTRACT** Ischemic heart failure (HF) is a major cause of death worldwide. However, the consequences of electrophysiological (EP) remodeling that occurs post-ischemia remain poorly understood. Porcine experimental models have been developed to study HF, as pig and human hearts share many similarities, but computational models that can complement and accelerate experimental findings in pig are lacking. In this study, we created physiologically detailed models of porcine ventricular myocytes (PVMs) and tissue to investigate how the interplay between HF-induced electrical and structural heterogeneities initiates and maintains arrhythmias. We created three porcine models of action potentials (AP) and Ca2+ dynamics; (1) the healthy heart, (2) the infarct border and (3) remote zones of post-myocardial infarction HF. The Soltis-Saucerman rabbit ventricular myocyte model, devoid of transient outward (Ito) and with addition of small conductance Ca2+ dependent (ISK) K+ currents, provided the basis for the new models. Model parameters of ionic currents were fit to PVM data experimentally obtained with self AP-clamp sequential dissection. We applied global parameter optimization to recreate experimentally observed phenotypes. The models were then validated using experimental characteristics of the AP and Ca2+ transients at multiple pacing rates. Tissue simulations were performed to study wave propagation dynamics in the infarct border zone incorporating both electrical and structural heterogeneities. Our PVM models for healthy and HF cells can accurately reproduce measured porcine EP data, validated by the rate dependence of AP and Ca2+ dynamics. In tissue simulations, reduced coupling promoted initiation of arrhythmogenic AP waves in the infarct border zone. Arrhythmogenic wave break was observed when cell-to-cell coupling was reduced and/or cells were less excitable. Thus, we identified a vulnerable window for both initiation and propagation of arrhythmogenic AP waves near the infarct zone in HF. Our physiologically accurate porcine models provide a novel and much needed computational framework to study the arrhythmogenic mechanisms of ischemic HF at both the cellular and tissue levels.

# INTRODUCTION

Heart disease is the leading cause of death in the United States with nearly 800,000 Americans suffering a myocardial infarction (MI) annually [ref].

Once an MI occurs post heart failure (HF), an individual is more prone to arrythmias and sudden cardiac death. This is due to the structural and functional remodeling of the heart cells of the post-MI heart [ref]. Understanding the root causes and ion channel architecture of diseased hearts is an indispensable asset in the pursuit of treatment. The recent study by Hegyi et al. investigated exactly such a question and was able to determine the specific ion channels that are altered in a diseased post-MI heart using a minipig model [1].

Pigs have gained importance as an animal model for human cardiovascular research, as they share many similarities with the human heart, especially in regard to their response to heart failure. For example, pigs have similar limited collateralization responses to humans during acute episodes of ischemia, compared to canine models which have an extensive pre-existing network of collateral pathways for blood to flow around an occlusion [2]. Additionally, porcine hearts are more prone to arrhythmogenesis with reperfusion injury in a similar manner to humans as opposed to canine models [2].

Hegyi et al. investigated the cellular electrophysiology of a minipig 5 months post-MI. Compared to a healthy cell (control), the action potentials (APs) of the cells bordering (HF-Border) and remotely located from (HF-Remote) the region of infarction were altered. The HF-Border cells exhibited shortened action potential durations (APDs), while the HF-Remote cells exhibited prolonged APDs.

This difference in the overall AP of each cell type can be attributed to many factors, such as different ion channel expression levels,

Ions play a pivotal role in the excitation-contraction coupling of cardiac myocytes; K+ efflux, and Na+ influx being the main ions of the excitation response and Ca2+ dynamics allowing for the contractile response. In the past, the main method of analyzing ion channel dynamics was the patch clamp, which only measures single ion channel activity for a single cell. Thanks to the AP-clamp Sequential Dissection used in Hegyi et al, multiple ion channels for a single cell can be measured simultaneously, increasing efficiency and physiologic accuracy. Three different cell types were measured; a control cardiac myocyte with no MI present, a cardiac myocyte in an area remote of the MI, and a cardiac myocyte bordering the MI. They found ….

Mathematical modeling is a useful tool to demonstrate our understanding of physiological processes. Of course, mathematical models are limited to the availability of experimental evidence for the phenomenon that they are describing. Mathematical models cannot by themselves discover new truths about the world, and will always

In this study, the Soltis and Saucerman mathematical model of rapid pacing of rabbit ventricular myocytes [3] was adapted to match the results of Hegyi et al. Using multivariable linear regression techniques [4], we have developed three physiologically detailed mathematical models that recapitulates the three cell types (Control, HF-Remote, HF-Border) present in Hegyi et al.

# METHODS

In order to create the model of the pig ventricular myocyte, we began with a detailed mathematical model of a rabbit ventricular myocyte and modified many ionic conductances and Ca2+ cycling parameters to recreate the experimentally observed phenotypes (details in the Appendix). All simulations were evaluated after steady state was reached.

# RESULTS

**Figure 1:** *Porcine ventricular myocyte diagram. Our model includes the CaMKII and PKA signaling pathways as modeled by Soltis and Saucerman 2010. There are three compartments for Ca2+ to enter: the dyadic junction, subsarcolemmal, and cytosolic spaces, all of which can activate CaMKII. The ion channels shown are the key players in the ionic remodeling of the control, remote-HF, and border-HF cell types, with the exception of ICFTR which was not measured experimentally.*

***Figure 2:*** *Optimized simulated action potential (AP) traces overlaying experimental AP traces for the (A) control cell (B) remote-HF cell, and (C) border-HF cell paced at 1 Hz. Black lines represent deterministic AP simulations, red lines are for an individual experimental AP trace. There are approximately one-thousand experimental traces per cell type.*

The ultimate goal of creating this model was to recreate AP dynamics of each cell type at a corresponding pacing frequency. Each of the three experimental cell types (control, remote-HF, and border-HF) have distinct AP phenotypes due to electrophysiological remodeling post myocardial injury. However, even for cells of the same type there is significant variation in ion channel expression and AP dynamics. On average, the remote-HF cells had the longest AP, the control cells had the second longest AP, and the border-HF cells had the shortest AP. Using the optimization protocol outlined in the methods, we were able to recreate this relationship in our simulated cell types. The action potential durations at 95% repolarization (APD95) of each optimized simulated cell type was 216 ms, 269 ms, and 199 ms, compared with an experimental mean plus or minus SEM of 244.2±7.4 ms, 284±11.8 ms, and 209±5.1 ms and a range of 179.8-337.3 ms, 184.3-471.7 ms, and 158.7-267.9 ms for the control, remote-HF, and border-HF cells respectively paced at 1 Hz.

***Figure 3:*** *Overall AP, inward current, and outward current*

The overall shape of an AP is determined by the balance of total inward and outward ionic current at that moment in time. The inward current is mainly carried by the L-type Ca2+ current (ICaL), the fast Na+ current (INa), the late Na+ current (INaL), and INCX currents, while the outward currents are mainly carried by the IClCa, IKr, IKs, ISK or (IK(Ca)), and IK1 currents. This figure was recreated based on the main findings of Hegyi et al. 2018, namely the lengthening of the Remote-HF AP, the shortening of the Border-HF AP, and the ionic remodeling of the two different heart failure cells during heart failure compared with the control cell.

***Figure 4:*** *Inward and outward peak currents of the model and experimental data*

The secondary goal of the model was to match the peak inward current density of the experimental data. The principle way we did this was to change the maximum conductance of individual ion channels (g̅X, where X is an ionic current e.g. INaL, IKr etc.). Ideally, our model would have all the currents exactly matching

Notable deviations from the experimental peak current density include the L type Ca2+ channel (ICaL) and the Ca2+- dependent chloride channel (IClCa). This discrepancy is mainly due to our current understanding of Ca2+ dynamics in the cell.

***Figure 5:*** *Simulated ionic current overlayed experimental ionic current traces*

Once the model was optimized, we then compared the simulation with individual experimental ionic densities in order to ensure that our model was within observed ranges. Since every cell has a unique action potential duration, all ionic current traces were normalized to their own AP in order for meaningful comparisons.

Again notable deviations from the experimental curves are the ICaL channel in all three cell types and the IClCa channel in the control cell, which have much larger current densities than the experimental results suggest.

Matching the experimental ICaL current densities result in a cell that is extremely Ca2+ deprived, delaying the Ca2+ transient and depleting the SR Ca2+ stores.

The experimental ICaL current has unexpected behavior that our model does not account for, namely the delay in the peak ICaL current density. This phenomenon can be attributed to a negative feedback loop resulting from the Ca2+ dependent inhibition (CDI). Historically, many experimental studies utilize chelators to measure a cell’s action potential, deviating from the true physiology (include references). As our model was formulated using these studies, it was outside the scope of our investigation to recreate the Ca2+ cycling.

**Figure 6:** Rate dependency

All multivariable regressions optimizations were performed at 1 Hz. The parameters were then hand tuned to further increase or decrease the APD at the following pacing frequencies: 0.2 Hz, 0.5 Hz, 1 Hz, 2 Hz, 3 Hz, 4 Hz, and 5 Hz.

For the control cell, compared to the 1 Hz multivariable regression optimization, the gK1 was decreased, the gNaK was increased, and the ko,RYR (the forward rate constant for RyR opening) was increased. Although gNaK was not measured in Hegyi et al., it was used as a “free” parameter to increase or decrease the APD to match experimental observations when the other ion channels were already at their target current density. In this case, when gNaK is increased, the APD is also increased due to …. INSERT HERE TODO. The increased ko for the RyRs essentially sensitizes them to Ca2+, and was done so in order to match the early experimental Ca2+ transient peak observed.

In our model, we encountered APD alternans at 170, 180, and 160 ms for the control, remote, and border cells respectively (not shown). The experimental cells did not experience alternans for the PCLs they were tested at (200 ms – 5000 ms), and our model was tuned to reflect that.

For the remote cell, gCaL, gKs, gSK, gCl(Ca), and ko,RYR were increased while gK1 was decreased.

**Figure 7:** Ca2+ cycling and transient

Due to the lack of direct Ca2+ experimental evidence, our model sought to remain within physiologically observed [Ca2+] for the Ca2+ transient (0-0.1 mM during diastole and 0.2-1 mM during systole). All three cell types have similar peak Ca2+ transient times, with the border cell peaking first (tpeak = 67 ms) and the control cell peaking last (tpeak = 69.3 ms). The control cell had the largest Ca2+ transient peak, at 0.62 mM, the remote cell had the second largest at 0.55 mM, and the border cell had the smallest at 0.3 mM. The decay times for each of the cell types also slightly differed.

The junctional Ca2+ compartment (JNX) is also shown,

**Figure 8:** Early after-depolarization (EAD) analysis

The three cell types were subjected to varying maximum conductance of their optimized values of gCa, gKr, and a combination

**Figure 9:** 2D tissue simulations of the 3 cell types

# DISCUSSION

There is not yet a sufficiently precise way to directly convert fluorescence data to concentration values for Ca2+ related experiments. For this reason, while the experiments from Hegyi et al. 2018 provided Ca2+ transient information, we were unable to use our model for them

# CONCLUSION

# AUTHOR CONTRIBUTIONS

Author1 designed the research. Author2 carried out all simulations, analyzed the data. Author1 and Author2 wrote the article.

# ACKNOWLEDGMENTS

We thank…

# REFERENCES

# SUPPLEMENTARY MATERIAL

Single cell physiologically detailed model

In the present study, we began with the Soltis-Saucerman model [1] of a Rabbit Ventricular Myocyte, which in turn was based off the Shannon model [2] and the Mahajan model [3]. This model incorporates different mathematical descriptions of various ion channels, and the membrane potential of a cell is given by:

Where is the membrane potential, is the total transmembrane current density, is the applied stimulus current, and is the membrane capacitance.

The cell’s dimensions were the same as in Shannon et al. 2004.

* Put this in the appendix, physical constant table TODO

*Na+ Channels*

The total Na+ ion current dynamics are comprised of both the fast activating voltage dependent Na+ current (INa), and the late Na+ current (INa,L). The total Na+ ionic current is also carried by the two exchanger currents, namely the inward component of the Na+-Ca2+ exchanger (INCX) and the outward component of Na+-K+ exchanger (INaK). There is also a background inward Na+ (INa,BK). The formulations of these channels are the same as in Shannon et al. 2004.

*Ca2+ Channels*

Our model incorporates a 7-state Markov model of the L-type Ca2+ channels (Ca2+) as formulated by Mahajan et al. 2008. Additionally, our model has 3 spaces for Ca2+ diffusion: junctional (CaJNX), subsarcolemmal (CaSSL), and cytosolic (Cai). Most ion channels

L-Type Ca2+ Channel

Ca2+ Release (RyRs)

JSR

*K+ Channels*

The delayed rectifier K+ current, comprised of the rapid rectifier (IKr), slow rectifier (IKs), and the inward rectifier K+ current (IK1) were the same as in Shannon et al. 2004.

We added an updated formulation of ISK, the small conductance Ca2+ sensitive K+ current, as in Kennedy et al. 2017 [4].

Where is the channel conductance, is the gating variable, is the membrane voltage, and is the potassium Nernst potential. We also compartmentalized this ion channel into the junctional, and subsarcolemmal spaces, as indicated by Shannon et al. 2004 and Terentyev et al. 2013 [5].

The transient outward K+ current, Ito is the main early repolarizing current in rabbits, canines, and humans, responsible for the early “notch” of the AP after the upstroke phase. However, Ito is not appreciably detectable in the porcine ventricular myocyte, and thus it was removed [6, 7]. Instead, ICl(Ca), the Ca2+ sensitive Chloride channel, is the dominant early repolarizing current.

*Cl – Channels*

The Cl– current was carried by the cystic fibrosis transmembrane conductance regulator current (ICFTR) as in Soltis and Saucerman model, and the Ca2+ sensitive Cl– current (ICl(Ca)) as in the Shannon model.

In our model, as ICl(Ca) is the main current responsible for early repolarization and the “notch” phase, we increased the sensitivity of this channel to [Ca2+] by 10 times (Kd(ClCa) = 0.01 mM from 0.1 mM).

In order to convert the rabbit model into a pig model, we changed the starting ion concentrations of the model to match the experiment and changed the conductance’s of each ion channel to better match the experimental current traces.

|  |  |  |
| --- | --- | --- |
| Ion Name | [Ion]experiment (mM) | New [Ion]model (mM) |
| [Na+]o | 149 | 149 |
| [Ca2+]o | 1.2 | 1.8 |
| [K+]o | 4 | 5.4 |
| [K+]i | 155 | 135 |
| [Cl-]o | 132.4 | 132.4 |
| [Cl-]i | 30 | 30 |
| [Mg2+]i | 0.567 | 0.567 |

In order to maintain similar IK1 dynamics and the resting membrane potential, the [K+] concentrations had to be adjusted.

TODO Provide justification for ion concentrations. I.e. I wanted to maintain the Nernst potential of K+ to roughly match the resting membrane potential of the experimental results. Note: The membrane potential is well established to be defined by the GHK equation. TODO: Do a “quick” analysis of an optimized AP Clamp compared with a current clamp.

Single cell optimization protocol

In order to change the ion conductance’s, we used Fminsearch, the derivative free optimization protocol available through MatLab.

Using the concentrations listed above, we optimized each of the three cell types. A healthy cell (Control), a HF cell remotely located from the infarction zone (Remote), a HF cell bordering the infarction zone (Border).

|  |  |  |  |
| --- | --- | --- | --- |
| Target Experimental Values | | | |
| Ion (A/F) | Control | Remote - HF | Border - HF |
| ICaL | -2.02 ± 0.13 | -1.79 ± 0.09 | -1.40 ± 0.10 |
| INCX | -0.72 ± 0.12 | -0.77 ± 0.08 | -0.88 ± 0.14 |
| INaL | -0.33 ± 0.01 | -0.46 ± 0.03 | -0.43 ± 0.02 |
| IK1 | 2.64 ± 0.16 | 2.59 ± 0.10 | 2.01 ± 0.07 |
| IKr | 1.00 ± 0.04 | 0.88 ± 0.03 | 0.90 ± 0.04 |
| IKs | 0.23 ± 0.02 | 0.24 ± 0.03 | 0.23 ± 0.02 |
| IK(Ca) | 0.23 ± 0.04 | 0.48 ± 0.05 | 0.46 ± 0.02 |
| ICl(Ca) | 2.21 ± 0.10 | 2.75 ± 0.18 | 2.76 ± 0.12 |

Our cost function generally took the form of the following,

Where is the total error for a given cell, is the calculated error for a given parameter, is the “weight” associated with each parameter (chosen heuristically), n is the total number of biomarkers, is the experimental value for a given biomarker, is the experimental standard error of the mean, and is the model value.

The cost function was further split into the ionic and the action potential dynamics components.

The ionic components were comprised of the ion channels to be optimized, namely: ICaL, INCX, INaL, IK1, IKr, IKs, ISK, and ICl(Ca)

The action potential dynamics components were comprised of various action potential biomarkers, some with experimental data and others with standard physiological limits. The biomarkers are as follows: APD95, APD50, Vmax, Vmin, dV/dtmax, dV/dtmin CaTmax, CaTmin, CaDτ , CaDT,max, INa,max, CaSRmax, and CaSRmin.

Where APD95 is the APD at 95% repolarization, APD50 is 50% repolarization, Vmax is the peak voltage of the AP, Vmin is the minumu voltage, dV/dtmax is the maximum slope of the AP, is the minimum slope, CaTmax and CaTmin are the maximum and minimum cytostolic [Ca2+], ([Ca2+]i), CaDτ  is the exponential decay constant of the Ca2+ transient, CaDT,max is the time at which the peak of the Ca2+ transient occurred, INa,max is the maximum current density of the fast inward Na+ current, CaSRmax and CaSRmin are the maximum and minimum [Ca2+] of the SR

The optimization protocol was then allowed to change the following model parameters: GCa, GNCX, GNaL, GK1, GKr, GKs, GSK, GClCa, and koCa. Where Gx is the maximum conductance of the ionic current “x” and koCa is the forward rate constant for the RyR [Ca2+] sensitivity

Optimization philosophy

The goal of the optimization was to exactly match AP waveform dynamics and ion channel dynamics. In theory, if the ion channel currents match the experimental data precisely, the overall AP should also match, since the AP is comprised of these inward and outward currents. In practice, however, there are many more factors at play than our model captures, such as the true cytosolic Ca2+ transient as well as various signaling pathways like phosphorylation by CaMKII or PKA. Therefore, the overall shape of the AP was valued more highly than individual ion channels matching the experimental values.

For each cell, to ensure convergence, five separate, independent protocols were run simultaneously, until each reached an agreed upon set of parameters. For each iteration of the optimization, the cell was paced for two-hundred beats to ensure steady state values. Steady state was classified as beat to beat changes in cytosolic [Na+] of less than one percent. (TODO FIND REFERENCE FOR THIS)

Sensitivity Analysis

For each model, a sensitivity analysis of the parameters was performed t. The goal of a sensitivity analysis is to relate changes in the input parameters to certain output parameters. For example, an increase in INa will lead to increased Vmax (peak voltage) for the AP. We used the partial multivariable linear regression (PLS) protocol outlined by Sobie 2009 [8]. Briefly, we slightly varied the fourteen scaling parameters (array X in Sobie 2009) by multiplying them by fourteen random values obtained from a log normal distribution for five-hundred trials. The resulting effects on the outputs (array Y in Sobie 2009) were then recorded. Using the procedure outlined in Sobie 2009, we produced a resulting B matrix (Figure 9) containing linear regression coefficients. The values within the B matrix are between negative one and one, for absolute negative correlation and absolute positive correlation, respectively.

Rate Dependency Optimization

*Experimental Frequency Optimization*

Once the single cell model was optimized at 1 Hz, we then paced the cell at 0.2, 0.5, 1, 2, 3, 4, and 5 Hz for two-hundred beats each to reach steady-state. We then manually altered the fourteen computer optimized parameters found at 1 Hz in order to obtain a global fit for the 0.2, 0.5, 2, 3, 4, and 5 Hz action potentials (Figure 5). The goal was to be within one standard deviation of the mean of experimental APDs at each pacing frequency. The sensitivity analysis of each cell type guided our hand tuning, trying to obtain the most effect on the APD while remaining as close as possible to the experimentally derived values.

As we tuned our parameters, we also sought to remove alternans at fast pacing as much as possible, as the experiments indicated this phenomenon did not occur.

|  |  |  |  |
| --- | --- | --- | --- |
| Final ion channel conductance multipliers | | | |
| Ion Conductance | Control | Remote | Border |
| gCa | 1.17 | 0.80 | 0.80 |
| gNa | 0.90 | 0.92 | 0.92 |
| gNaL | 2.39 | 4.00 | 4.00 |
| gK1 | 0.50 | 0.55 | 0.55 |
| gKr | 1.35 | 1.19 | 1.19 |
| gKs | 1.37 | 2.20 | 2.20 |
| gSK\* | 5.92 | 8.00 | 8.00 |
| gCl(Ca) | 1.15 | 1.00 | 1.00 |
| gNCX | 0.78 | 1.55 | 1.55 |
| gNaK | 1.20 | 1.00 | 1.00 |
| koCa | 5.00 | 5.00 | 5.00 |

Table: Multipliers of each parameter in the model. Values represent relative increase compared to the original Soltis-Saucerman model of a rabbit ventricular myocyte, e.g. a value of 2 means two times the original value. \*: this value was taken from Kennedy et al. 2017.

Bifurcation Diagram

Once the model was optimized at the seven different pacing frequencies, we then stimulated the cells from 100 ms to 300 ms pacing cycle length (PCL) every 10 ms, and again from 300 ms to 2000 ms every 50 ms for 200 beats each until steady state.

For these simulations, we created an APD vs PCL bifurcation diagram, an APD (n+1) vs the Diastolic Interval (DI) of the preceding beat (n), the systolic and diastolic [Ca2+]i (µM) vs PCL, and the [Na+]i,max vs PCL diagram (Figure 6).

S1S2 pacing

Extra stimulus (S1S2) pacing occurred with the final rate-dependency optimized model. After two-hundred beats paced at 1 Hz, the cell was stimulated with progressively shorter and shorter S1S2 coupling intervals (in 10 ms intervals), from 1000 ms down to 200 ms until loss of capture occurred.

EAD analysis

The cell models were paced at 5000 ms with varying multiples of the optimized gCa, gKr, and gKs values which are the conductance of ICaL, IKr and IKs respectively. GCa was multiplied by 1.0 to 4.0 by intervals of 0.075. GKr and GKs were multiplied by 1.0 to 0.05 by intervals of 0.025. The parameter space of GCa vs GKr (GKs unchanged) and GCa vs GKs (GKr unchanged), and GCa vs GKs (GKr 50%) were then explored with the Z-axis being the APD of each resulting action potential (Figure 8).

2D tissue spiral waves

Once the single cell models were completed, the model was integrated into an existing code framework for atrial tissue. All relevant parameters were changed to recreate the single cell optimized results exactly. The tissue geometry consisted of 600 x 600.

* TODO
  + Tissue Analysis (Stability)
  + Method for Spiral Wave
  + Reference (Daisuke’s Paper, EAD PNAS paper)
  + Ask Haibo, look at Haibo’s paper for the tissue
    - CVODE (adaptive time step, write out the abbreviation)
    - General explanation of this method
    - To explain how the tissue is solved
    - One or two sentences is fine

An online supplement to this article can be found by visiting BJ Online at [http://www.biophysj.org](http://www.biophysj.org/).

Manuscript submitted to Biophysical Journal **3**

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