Recovery dynamics of the Fenton-Karma membrane model and their implications for modeling pharmacologically-induced atrial fibrillation

Matt Gonzales
Department of Bioengineering
University of California, San Diego
La Jolla, CA 92093
mjgonzales@ucsd.edu

Abstract

I used Continuity, a tool for finite element analysis, to model isotropic propagation of electrical activity based on the monodomain equation. I was able to induce action potential duration (APD) alternans, an important potential precursor to atrial fibrillation, and found that modulating several variables to mimic isoproterenol administration increased the slope of the restitution curve at low coupling intervals (25-75 ms). Meanwhile, mimicking the administration of ibutilide (by blocking the slow outward current in lieu of a potassium channel) actually increased the restitution slope, showing a limitation of this reductionist model. More work must be done in parameter optimization in order to deconvolve apparent restitution effects that are actually due to changes in the baseline action potential.

1 Introduction

1.1 Atrial Fibrillation

Atrial fibrillation (AF) is an electrical abnormality of the heart characterized by disorganized electrical activity lacking a predictable spatial or temporal pattern. Without pharmacological or surgical intervention, atrial fibrillation can lead to complications such as congestive heart failure or death from stroke[1].

Tissue anisotropy, cellular dynamics, and gross structural anatomy are all thought to play a role in the initiation and maintenance of AF [2]. One phenomenon that is suggested to precede ventricular fibrillation is action potential duration (APD) alternans, or the repeated oscillation of APD between two values over several beats. In concert with other factors, APD alternans is thought to cause wavebreak/wave collision, re-entry, and ventricular fibrillation [3]. It has been postulated that APD alternans may precede AF as well as ventricular fibrillation.

In vivo, AF can be induced in susceptible individuals through the use of pacing protocols, in which a clinician rapidly and repeatedly applies small currents without giving the heart a chance to recover; the susceptibility may be enhanced or suppressed with pharmacologic agents. These pacing protocols are not very dangerous in the atria, and are clinically indicated at the time of surgical ablation because they can uncover loci of electrical abnormality.

When an excitable medium is stimulated just after recovering from a previous stimulus, the medium may excite but exhibit properties that differ from fully "rested" medium. The properties of a medium exhibiting graded behavior after extrastimuli are known as "restitution properties" [4]. At the cellular level, restitution properties mainly are a consequence of the gradual time recovery of voltage-sensitive ion channels, and longer-term memory effects are often attributed to accumulation or depletion of cellular calcium levels over many excitations.

1.2 The Fenton-Karma cellular model

Fenton and Karma created a three state-variable model as a reductionist model representing the more physiologically-based models [5]. The three currents in their model were termed the "slow inward", "slow outward", and "fast inward" currents. The fast inward current principally represents the fast Na^+ channels responsible for the fast AP upstroke. The slow outward current principally represents K^+ efflux causing cellular repolarization. The slow inward current principally represents Ca^{2+}, and serves to maintain the APD for longer than it would in the presence of only the slow outward current. The three state variables are the membrane potential and two gating variables.

The Fenton-Karma has the potential to give rise to APD alternans in a manner that resembles the actual physiological basis of APD alternans. The net conductance of the slow inward current depends not only on voltage, but has a memory effect due to the complex voltage dependence of its rate constants. This, in concert with the sharp voltage dependence of its gating variable, lead it to a quite binary behavior and can be thought of as either "on" or "off" with some intermediate behavior. In practice, if the previous stimulation was too recent, then there is insufficient time for the slow-inward parameters to "recover". In this case, there will not be an appreciable amount of slow-inward current, so the APD will be short. In the next stimulus, there will have been ample time for the channel to recover, so the longer APD will be observed again. Thus, the model can recreate alternans in a way that preserves the physiological basis of this phenomenon in a loose way.

1.3 Restitution properties

The effects of previous stimulations or firings on the subsequent AP and conduction velocity (CV) are loosely referred to as restitution properties. In the Fenton-Karma model above, the alternation between two APDs is a manifestation of restitution properties in the Fenton-Karma model: the slow recovery of the slow inward current is such that short coupling intervals can cause a significantly different AP morphology.

With real experimental data, one could construct a scatter-plot of APD or CV versus the preceding coupling interval. Of course, if the dynamical system behaved as described above, this plot would look like a Heaviside function. In systems with a more gradual transition between "on" and "off" states, the change would be more gradual. In fact, recorded patient data does shows such a graded response (i.e. a longer APD) to progressively delayed extrastimuli.

Absolutely central to the idea of this work is the stabilization and destabilization properties of the **APD and CV restitution curves**. An APD restitution plot is best viewed as a scatter plot of two successive APDs, where, with a relatively tightly coupled extrastimulus. If a curve fit to the scatter points has a slope less than 1 at some point, a perturbation of the system's APD away from some reference value will tend to stabilize back to some reference value. If the slope is greater than 1, then a system will unstably oscillate away from the reference APD towards two limiting APD values.

In a dynamical system, the unstable oscillation of the APD away from some reference value is the result of the coupled behavior of membrane potential with at least one other dynamical variable causing unstable oscillation. In a dynamical system of two variables, one could envision this behavior from a system with two imaginary eigenvalues with positive real parts, where some other parameters in the system cause it to reach a limit rather than diverging. Physiologically, there may, for example, be a diverging oscillation of ion channel availability until repolarization is completely relegated to some other channel. A

representative example of the restitution curve is given below.

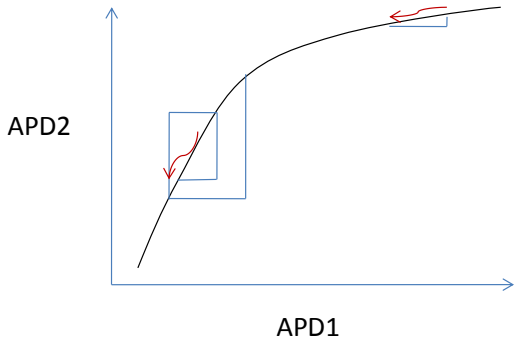

Figure 1: Behaviors on the steep (short coupling interval) and flat (longer coupling interval) portions of the restitution curve. On the left, a perturbation of a dynamical system from some condition leads to progressive drift of at least one dynamical state variable between two regions. On the right, a perturbation of the system away from a different dynamical system state results in stabilization: the dynamical system tends to revert to its original steady-state behavior.

1.4 Aims

I wish to investigate whether APD alternans is observed when extrastimuli are applied to the Fenton-Karma model If alternans is observed, I will characterize the effects of varying parameters of the Fenton-Karma model on the shape of the restitution curves. Investigation of the CV restitution curve will require propagation on a spatial domain.

2 Methods

I use Continuity, a finite element modeler, to construct a Hermite surface, ideally from patient-specific CT data but starting with generic test surfaces. The Hermite patches are C_0 and C_1 continuous and are fit by a least-squares algorithm that has an additional penalty term for excessive curvatures.

Continuity estimates a polynomial solution to the monodomain equation based on a Collocation-Galerkin method [6]. The monodomain equation is a reaction-diffusion type partial differential equation (PDE) based on the cable equation.

$$\nabla \cdot (\sigma \nabla V) = \chi (C_m \frac{dV}{dt} + I_{ion})$$

Where σ is a bulk conductivity tensor representing some composite of intracellular and extracellular conductivities, χ is the surface-to-volume ratio, and I_{ion} is specified by some specific cellular model, which in this case is Fenton-Karma. The conductivity tensor to be used is diagonal with entries 0.02 mS/ unit length. The spatial domain has 9 x 5 rectangular elements each with dimension 0.5 x 0.4 units, where the units of length are arbitrary and need not be specified.

Conduction velocities were estimated by measuring the distance between two nodes and definition their activation time by a 0.13 dimensionless voltage threshold. Restitution curves were plotted in Matlab.

3 Results

3.1 Cellular model comparisons

We first wished to characterize the appropriateness of the Fenton-Karma model compared to a comprehensive model like the Maleckar-Giles-Trayanova model [7] in investigating the

effects of isoproterenol and ibutilide. The effects of isoproterenol and ibutilide are best approximated by increasing the conductance of the L-type Ca^{2+} channel and decreasing the conductance of the delayed-rectifier K^+ channel (although ibutilide is known to have effects at certain fast Na^+ channels as well). Whereas these channels are described explicitly in the Maleckar-Giles-Trayanova model, the effects can be approximated by increasing the conductance of the slow inward current, and decreasing the conductance of the slow outward current, respectively. Gong et al. showed, *in silico*, that a 50% increase In L-Type Ca^{2+} channel could cause alternans in the Courtemanche atrial model. They also increased I_{K1} 200%, which Courtemanche says is within the normal physiological range [8]. A comparison between Fenton-Karma and Maleckar-Giles-Trayanova models is shown below for one stimulus.

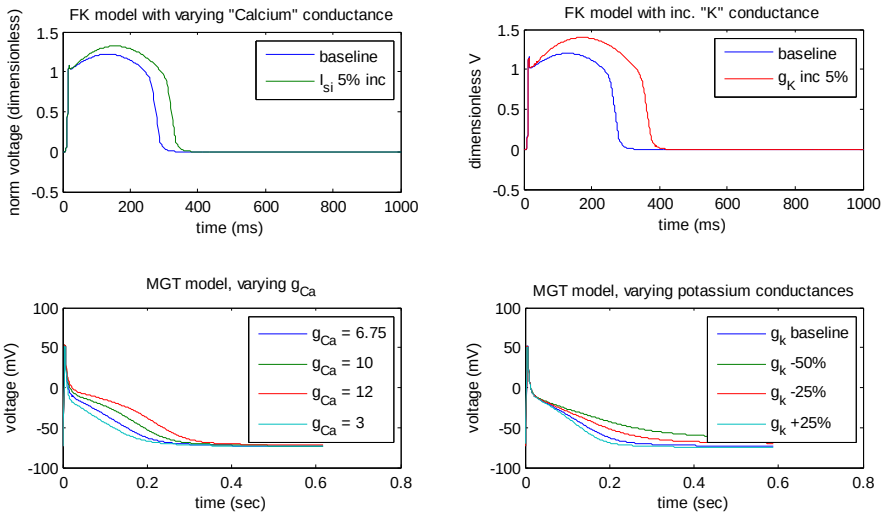

Figure 2: Behaviors of the FK and MGT cellular models. For baseline stimulus, a 5% increase in "slow inward" conductance in the FK model increased APD about 15%, whereas the MGT model required conductance increases on the order of 50% in order to effect such an increase in APD (left panels). The FK model appreciably shortened APD with "slow outward" conductance reduction around 5%. In contrast, the MGT model shortened APD only with much larger conductance reduction (lower right).

We observe that the FK model can lengthen and shorten an APD based on conductance changes that mimic the effect of isoproterenol and ibutilide, but it is unknown if the expected restitution properties can be recreated in this model. Namely, the slope of a restitution curve should be **increased** from baseline after administration of isoproterenol (Increased g_{Ca}) and **decreased** from baseline after administration of ibutilide (decreased g_K).

3.2 Induction of APD alternans

I tested to see if a periodic stimulus could elicit APD alternans, an important phenomenon that can precede wavebreak and fibrillation. An example of a simulation displaying APD alternans is below.

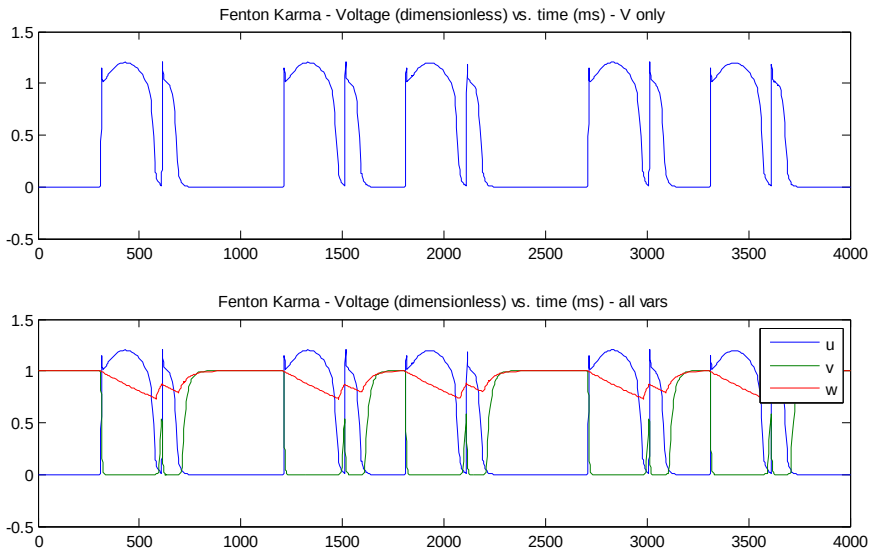

Figure 2: Alternans in the Fenton-Karma model with a stimulation period of 300 ms. The slow inward gating variable (red) is not allowed sufficient time to recover, disabling it from contributing to the elongation of the action potential.

The more gradual descent into oscillatory behavior was not observed in this system except in a very narrow window of circumstances. Below is a plot of "spiraling" into alternans that is described in the introduction.

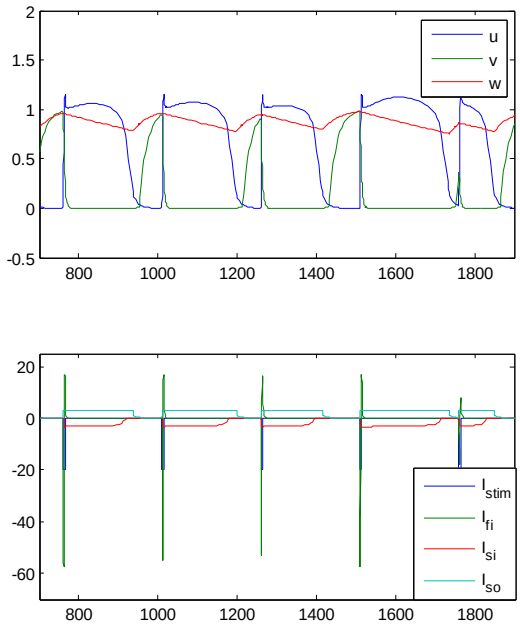

Figure 3: FK model shows gradual evolution into alternans with a periodic stimulus of 250 ms. The dynamic recovery variables "v" and "w" oscillate increasingly with every beat, both contributing to unstable drift of the APD (top). On the bottom are currents corresponding to each beat.

This narrow range of conditions under which gradual drift into alternans occurs does not fit

the classical description of alternans above, and may be at least in part attributable to the lack of spatial propagation term present in the simulations.

3.3 Restitution curves with parameter variance

Fenton and Karma state that the constant variable τ_w^-, which is the decay constant for the "fast inward" current, is responsible for the shape of the APD restitution curve behavior, and the two τ_v^- constants (each controlling "slow inward" effect at voltages separated by a Heaviside function) control the shape of the CV restitution curve. Both "v" and "w" have an influence on restitution properties; "v" since it directly controls the slow inward current, and "w" since its current, the fast inward current, "recruits" the slow inward current during the upstroke of the AP through its magnitude's effect on the membrane potential.

Several parameters were perturbed to investigate the potential influence of pro-arrhythmic and anti-arrhythmic drugs on the restitution curve using a periodic pacing protocol with various coupling intervals. The recovery variable τ_w^- was increased and decreased by 5% to verify Fenton and Karma's assertion. The conductances of the slow outward and slow inward current were increased and decreased 5%. The results are presented as coupling interval vs. subsequent APD, and as slope of the restitution curve using the "gradient' function in Matlab.

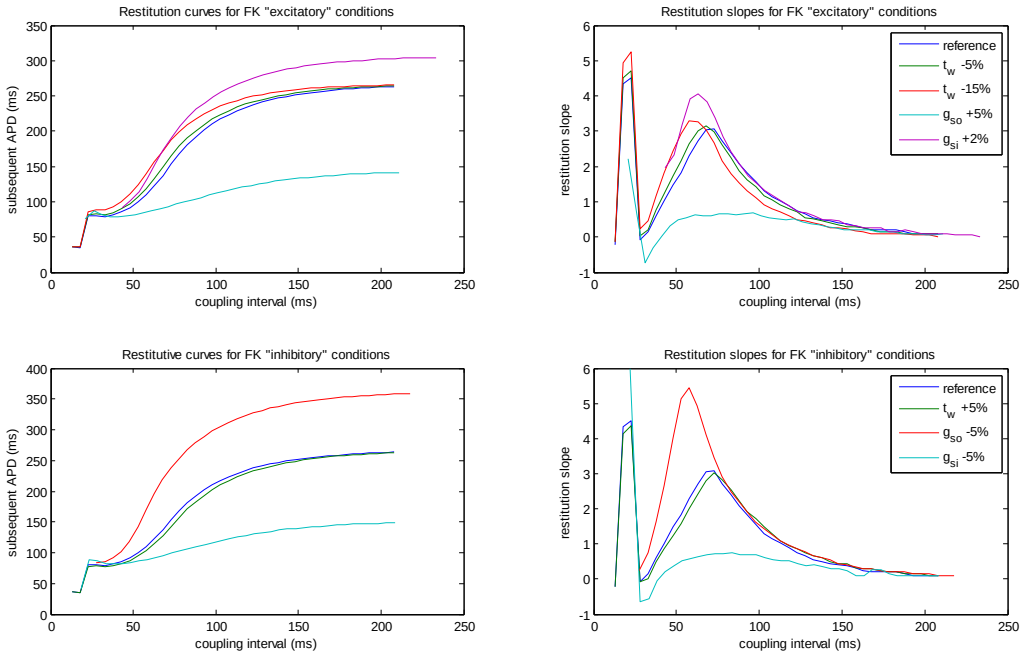

Figure 4: Effect of varying model parameters on restitution curves (left) and slopes of these curves (right). The behavior of the systems at very low coupling interval demonstrates an artefact of dynamical system behavior that is entirely dictated by "fast inward" current, and can be considered outside the area of interest. All systems approach zero restitution slope as coupling intervals become large, and regions where restitution slope is greater than 1 are nominally considered a danger for alternans.

This figure displays that for the nominally excitatory conditions (top panels), the restitution slope is actually slightly higher than or equal to the reference curve (blue) for larger coupling intervals, while at increasingly shortened coupling intervals, the trend reverses itself, and the restitution slopes are greater than the reference curve. The exception to this trend is the increase in conductance of the slow outward current, that has a restitution slope below 1 for all coupling intervals. This is a result of the fact that with a short enough AP, the dynamical variable "w" does not decay during the AP as it normally does, so its recovery

is unneeded, even at short coupling interval, if only two beats are considered as in this simulation.

In the bottom panels, the trend for nominally "inhibitory" parameter variations tends to be the opposite of the excitatory. Slowing the recovery of variable "w" slightly increases the slope at larger coupling intervals and slightly decreases the slope at smaller coupling intervals, a surprising result. Decreasing the conductance of the slow outward current by 5% shows little change relative to reference parameters, then a huge increase in slope for coupling intervals < 75 ms. Decreasing the slow inward current conductance predictably shortened the AP significantly such that the restitution slope was flattened below 1 for all coupling intervals.

3.4 Propagation with the monodomain equation

Using Continuity to create spatial propagation with finite element analysis, CV restitution curves were generated for baseline system parameters, and for variance of the τ_{v2}^{-}, which, according to Fenton and Karma, controls the CV restitution curve. Figure 5 below shows a typical result for spatial propagation.

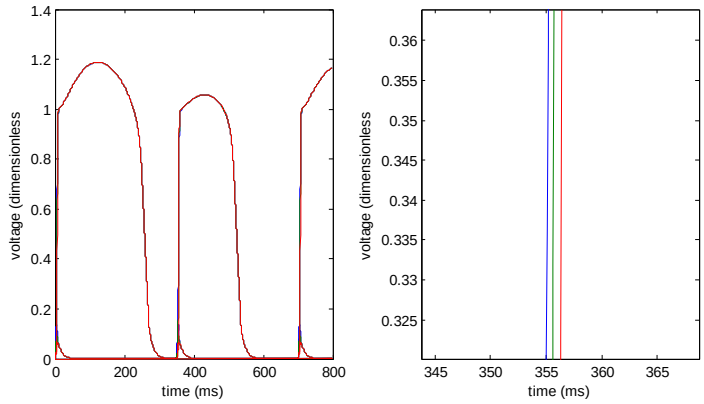

Figure 5: Baseline CV properties. At stimulus periodicity 350 ms and baseline FK parameters, the beginning of alternans is observed. Examining the action potential upstroke on the right (enalarged on the second AP upstroke from the left figure) implies different activation times which can be used to calculate a nominal conduction velocity.

Using several different coupling intervals, a curve was generated of conduction velocity vs. coupling interval for baseline parameters (see below).

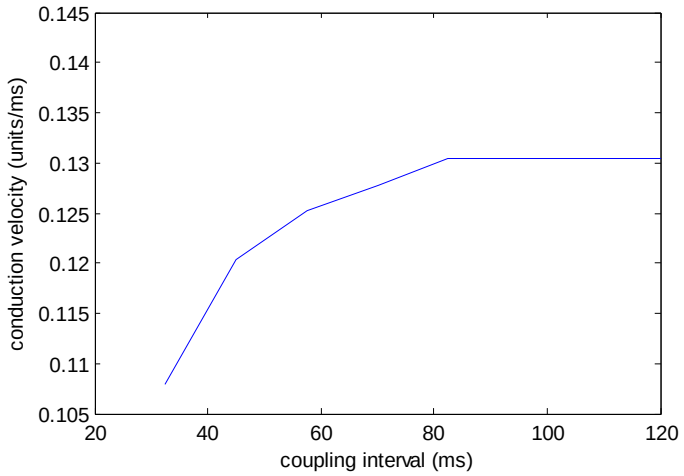

Figure 6: CV restitution curve. For baseline FK parameters, the model predictably shows a reduced nominal conduction velocity for reduced coupling intervals due to the decreased recovery of "v", the fast inward gating variable. At relatively low coupling intervals (compared to the APD restitution curves), the slow inward gating variable appears to be completely recovered (CV reaches a limit of about 0.13 length units/ms).

4 Discussion

Alternans was successively recreated in the Fenton-Karma model, both in a model lacking any spatial element, and in a model on a spatial domain. Executing multiple simulations enabled reconstruction of restitution curves. Changing parameters such as recovery time constants and channel conductances had an effect on the restitution curves and slopes. It was noted that due to the change of AP from some parameters, the restitution slope vs. coupling interval may be a slightly more accurate depiction of the stability of the system, and was presented in concert with the standard restitution slopes.

Concretely, the interventions considered to be "excitatory" (lowering the slow inward recovery constant, and increasing the conductance of the slow outward and slow inward currents) was supposed to model the administration of isoproterenol, and showed mixed behavior. Lowering the inward recovery constant and increasing the conductance of the slow inward current slightly increased the restitution slope for large coupling intervals > 75 ms (Figure 4) but moderately raised the restitution slope for coupling intervals from 25-75 ms. The increase in conductance was supposed to be to simulate the opposite effect of ibutilide (i.e. increase rather than decrease availability of slow outward current) but the short action potentials intrinsically kept the restitution slope high because long baseline action potential is required to cause the slow inward gating variable "w" to decay enough to cause restitution effects. Hence, a flat restitution slope was observed.

The "inhibitory" interventions were supposed to mimic Ibutilide by increasing the "w" recovery variable time constant, and decreasing the conductances of the slow inward and slow outward channels. A five percent increase in the time constant for the slow inward current did not appreciable change the restitution slope; it appeared to be slightly greater than the baseline slope for larger coupling intervals (>75 ms) and slightly smaller for shorter coupling intervals (25-75 ms), a behavior opposite of that discussed above for the five percent decrease. Raising the conductance of the slow inward channel changed the restitution slope dramatically, as evidenced in Figure 4. With increased conductance of slow outward channel, the restitution slope dropped, as was the case with the decrease in conductance of the same channel. The source of this behavior was much more straightforward; a decrease in slow outward current allows the slow inward current to repolarize the AP much faster, keeping the AP relatively small at all coupling intervals.

There remains much work to be explored on this project. Firstly, many of the interventions

change the APD. Since the true meaning of the baseline time constants is specific to some baseline APD, any parameter intervention that changes the APD, rescales the contribution of each parameter to some behavior such as restitution slope. Hence, it is not immediately clear how much parameters which change a fully-recovered APD truly contribute to the development of alternans, and how much a steep restitution slope is simply due to a larger reference APD. A future study may track the tendency of gating variables to oscillate increasingly, and claim this is a more physiological correlate of alternans development than the restitution slope, but the coupling interval over which this behavior was observed for the FK model was so narrow that it would not have been a useful strategy. Another strategy would be to attempt to rescale all of the parameters for a single intervention that modifies the APD, but such a reparameterization would be non-linear and complicated.

CV restitution was observed, but its behavior was only assessed for baseline FK parameters. A future study should vary parameters such as the $\tau_{v,2}^{-}$ and examine the behavior of such parameter changes on the CV restitution slope. Another important addition would be to examine the contribution of anisotropy of the conductivity tensor to changes in CV restitution.

In sum, the modulation of the time constants for the gating variables "w" and "v" is sufficient to change the restitution slopes in the way that Fenton and Karma describe, both with and without propagation in space. Attempting to perturb physiological parameters and examine the effects of these changes on the restitution slope is inconclusive because these interventions change the reference APD. In order to get more meaningful results, the model parameters must be non-linearly rescaled for any change that affects the APD, or a different model will have to be used that directly correlates to the physiological changes being modeled.

Acknowledgments

Thanks to Jazmin Aguado-Sierra for her help with Continuity, Wouter-Jan Rappel for conversations about the Fenton-Karma model, and Chris MacDonald, Doug Roubino, and Professor Cauwenberghs for their feedback.

References

[1] Chugh, S.S, Blackshear, J.L., & Gersh B.J. (2001) Epidemoiology and natural history of atiral fibrillation: clinical implications. *Journal of American College of Cardiology* **37**:371-378

[2] Weiss, J.N, Karma A., & Qu Z. (2006) From Pulsus to Pulseless: the Saga of Cardiac Alternans (Review). *Circulation Research* **98**:1244

[3] Walker, M.L., & Rosebaum, D.S. (2005) Cellular alternans as mechanism of cardiac arrhythmogenesis. *Heart Rhythm* **2**:1383-1386

[4] Franz, M.R., Swerdlow, C.D., & Schaefer, J. (1988) Cycle length Dependence of human action potential duration in vivo. Effects of single extrastimuli, sudden sustained rate acceleration and deceleration, and different steady-state freqeuncies. *Journal of Clinical Investigation* **82**:972-979

[5] Fenton, F., & Karma, A. (1998) Vortex dynamics in three-dimensional continuous myocardium with fiber rotation: Filament Instability and fibrillation. *Chaos* (8)**1**:20-47

[6] Rogers, J., & McCulloch, A. (1994) A Collocation-Galerkin Finite Element Model of Cardiac Action Potential Propagation. *IEEE Transactions on Biomedical Engineering* (41)**8**:743-757

[7] Maleckar, M.M, Greestein, J.L., & Trayanova, N.A. (2009) K^+ current changes account for the rate dependence of the action potential in the human atrial myocyte. *American Journal of Physiology - Heart and Circulatory Physiology* **297**:1398-1410

[8] Courtemanche, M., Ramirez, R.J., & Nattel, S. (1998) *American Journal of Physiology - Heart and Circulatory Physiology* **275**:301-321