Electrical Coupling of Cardiac Cells via Junctional K^+

RTG
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in Mathematical Biology

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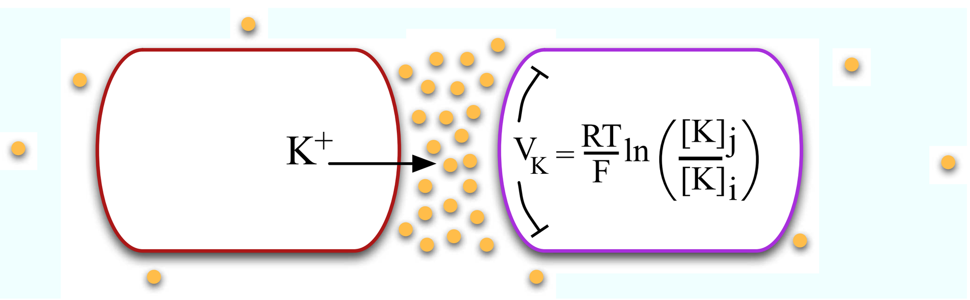
Background

- Cardiac cells are electrically coupled through gap junction channels.
- Before the discovery of gap junctions, Sperelakis proposed at least two mechanisms for ephaptic coupling of cardiac cells, [4].
  - ★ Negative junctional potentials (Electric Field Effect)
  - ★ Potassium accumulation in the junctional cleft space
- Previously, we used a simplified two cell model to characterize the dynamics of coupling through negative junctional cleft potentials, [1].
- Mori and Peskin have a detailed model in which they see both types of ephaptic coupling, [3]. They observed "reflection" of action potentials.
- Here, we use a simple model to study the dynamics of potassium coupling.

The Idea

- During an action potential, K^+ rushes into the junctional cleft space.
- Because the cleft is so narrow, K^+ concentration increases drastically.
- This raises the K^+ equilibrium potential across the junctional membranes.
  - ★ maybe enough to excite the neighboring cell?



Nondimensionalized Model

- Two isopotential cells, with membrane potentials ϕ_1 and ϕ_2, are coupled through c, the concentration of potassium in the junctional cleft space.

$$\frac{d}{d\tau}\phi_1 = -i_{ion}(\phi_1) - \alpha i_K(\phi_1, c)$$
$$\frac{d}{d\tau}\phi_2 = -i_{ion}(\phi_2) - \alpha i_K(\phi_2, c)$$
$$\epsilon\frac{d}{d\tau}c = i_K(\phi_1, c) + i_K(\phi_2, c) - \delta(c-1)$$

- We use Mitchell-Schaeffer membrane dynamics, [2], rewritten to look more like a cardiac ionic model,

$$i_{ion}(\phi) = i_{Na}(\phi) + i_K(\phi) = g_{Na}hm^2(\phi-1) + g_K\phi$$

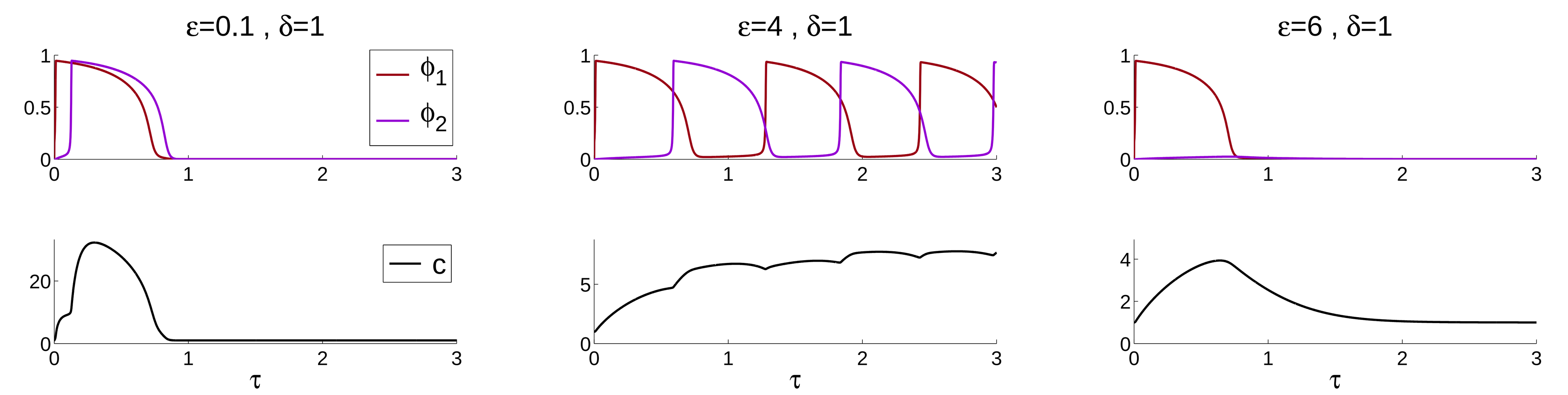
- The potassium current across the junctional membranes is given by,

$$i_K(\phi, c) = g_K(\phi - \nu ln(\beta c))$$

- Nondimensional parameters,
  - α = the junctional to non-junctional surface area ratio
  - ★ δ = potassium leak rate from cleft space to extracellular space
  - ★ ϵ = proportional to the width of the cleft (cells are cylindrical)

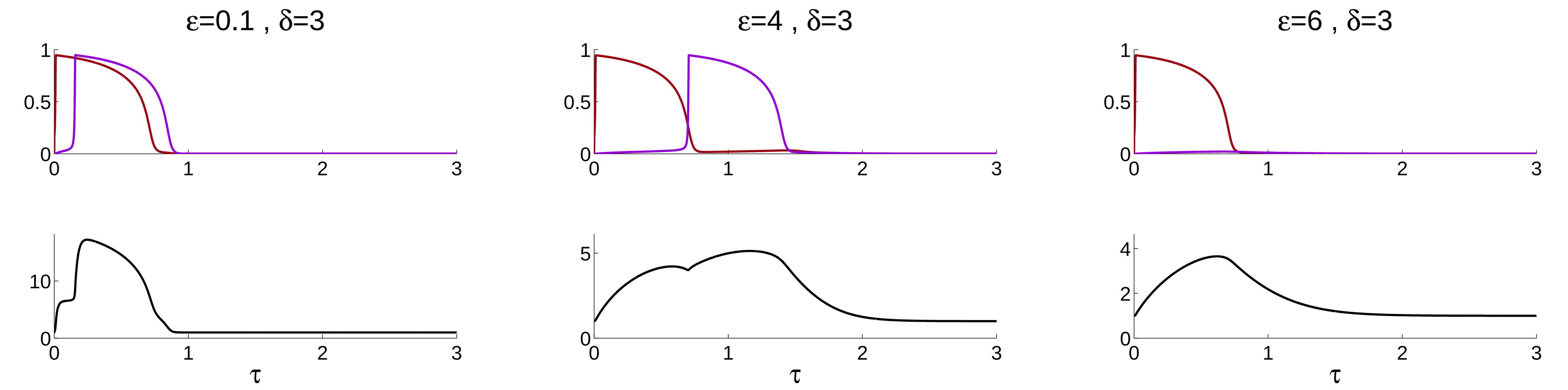
Numerical Solutions

- For small δ ...



★ $\epsilon \to 0 \Rightarrow$ cells are well-coupled ★ oscillatory transition phase ★ $\epsilon \to \infty \Rightarrow$ cells are uncoupled

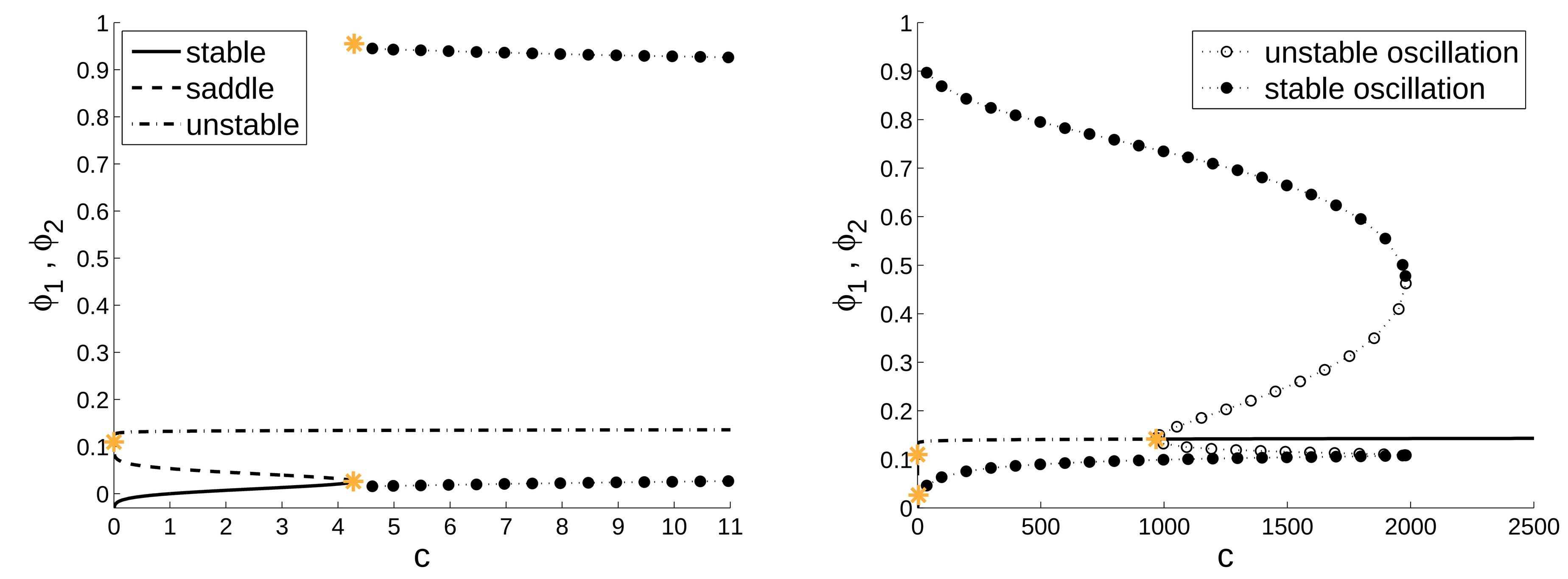
- For larger δ ...



★ $\epsilon \to 0 \Rightarrow$ cells are well-coupled ★ no oscillatory phase ★ $\epsilon \to \infty \Rightarrow$ cells are uncoupled

- Physiologically, oscillations correspond to "back propagation" of action potentials - Arrhythmogenic?
- Where do these oscillations come from? Let's think of c as a bifurcation parameter for ϕ_1 and ϕ_2 ...

Bifurcation Diagram



- The oscillations arise with a constant amplitude through a Saddle-Node Infinite PERiod bifurcation.
- There is a critical junctional potassium concentration, $c^* = 4.275$, above which the cells are coupled.
  - ★ For small δ, junctional potassium concentration can remain elevated, $c > c^* \Rightarrow$ oscillations
  - ★ For larger δ, junctional potassium equilibrates to extracellular levels, $c < c^* \Rightarrow$ no oscillations

Discussion/Questions

- What about stability of the oscillations?
  - ★ The dynamics of c depend on ϕ_1 and ϕ_2
  - ... some curve above which $dc/d\tau > 0$ and below which $dc/d\tau < 0$,

$$\phi_1 + \phi_2 = 2\nu ln(\beta c) + \frac{\delta}{g_K}(c-1)$$

- Why are the oscillations always out of phase?
  - ★ Notice that the curve depends on the sum of ϕ_1 and ϕ_2
- Can we find the critical curves in (ϵ, δ) space?

Gap Junctional-like Coupling

- In the limit that $\epsilon \to 0$, the cells are well-coupled.
  - ★ Let's take c to be in quasi-steady state,

$$g_K(\phi_1 - \nu ln(\beta c)) + g_K(\phi_2 - \nu ln(\beta c)) - \delta(c-1) = 0$$

  ... which we cannot solve explicitly for c.
  - ★ However, in the case that $\delta = 0$, we obtain

$$\frac{d}{d\tau}\phi_1 = -i_{ion}(\phi_1) + \frac{1}{2}\alpha g_K(\phi_2 - \phi_1)$$
$$\frac{d}{d\tau}\phi_2 = -i_{ion}(\phi_2) + \frac{1}{2}\alpha g_K(\phi_1 - \phi_2)$$

  - ★ Current is driven through gated potassium channels due to a difference in potential between the two cells... looks like gap junctional coupling!

Summary

- Using a simple two cell model, we investigate the dynamics of ephaptic coupling through junctional potassium accumulation.
- We find that ...
  - ★ If the cleft width is narrow, then the cells are well-coupled.
  - ★ If the leak rate is also small, then the coupling looks like gap junctional coupling, but via K^+ channels rather than gap junctions.
  - ★ For wider cleft widths, "back propagation" can occur.
    - What does this mean physiologically?
- There are still many unanswered questions...
  - ★ Are ϵ and δ really independent parameters?
    - Preliminary results suggest that δ is dependent on cleft width.

References

[1] E.D. Copene and J.P. Keener. Ephaptic coupling through junctional potentials. *Journal of Mathematical Biology*, to appear.

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[3] Y. Mori. Ph.D. Thesis, New York University, 2006.

[4] N. Sperelakis and K. McConnell. Electric field interactions between closely abutting excitable cells. *IEEE Engineering in Medicine and Biology*, pages 77–89, January/February 2002.