

# Consequences of Spatial Organization of Cellular Connections on Action Potential Propagation

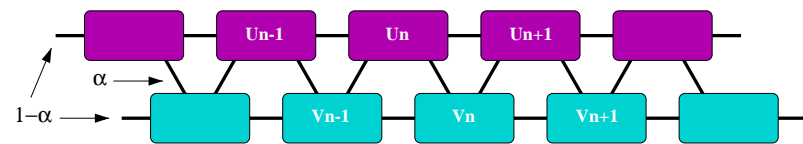
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## Motivation

- Cells in the ventricular myocardium are excitable, enabling the propagation of action potentials. This causes the cells to contract, which is how the heart pumps blood.
  - On the cellular level, propagation from one cell to another is not smooth, but rather jumpy with an average time delay of  $\sim 80\mu$  seconds [1].
  - Tissue architecture on the cellular level plays an important role in producing the reliable smooth wave fronts which are observed on the macroscopic level.
- \* The spatial organization of gap junctional connections is one characteristic of the tissue architecture. In particular, ventricular myocardial cells are each coupled to  $\sim 11.3 \pm 2.2$  neighboring cells via gap junction channels [4]. Therefore, wave fronts of excitation have many opportunities to propagate through connections in all directions.

**Questions:** How does the spatial organization of cellular connections via gap junction channels affect propagation on the macroscopic level? In particular, what are the benefits of being coupled to  $\sim 11$  other cells? Does this spatial organization make propagation failure less likely?

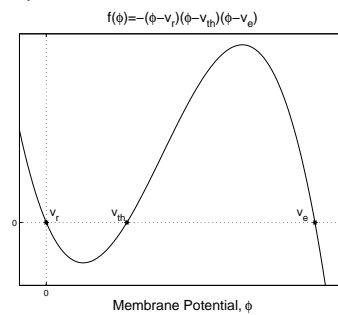
## Model



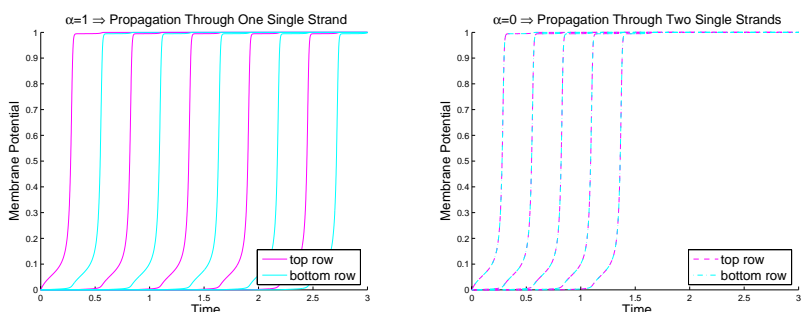
$$\frac{du_n}{dt} = c_g(1-\alpha)(u_{n+1} - 2u_n + u_{n-1}) + c_g\alpha(v_n - 2u_n + v_{n-1}) + f(u_n)$$

$$\frac{dv_n}{dt} = c_g(1-\alpha)(u_{n+1} - 2v_n + u_n) + c_g\alpha(v_{n+1} - 2v_n + v_{n-1}) + f(v_n)$$

$u_n$  = membrane potential of the  $n^{th}$  cell in the top row  
 $v_n$  = membrane potential of the  $n^{th}$  cell in the bottom row  
 $\alpha$  = the fraction of gap junctions making diagonal connections  
 $c_g$  = coupling term quantifying the strength of the connections  
 $f$  = generic dynamics for an excitable cell with no recovery



## Behavior

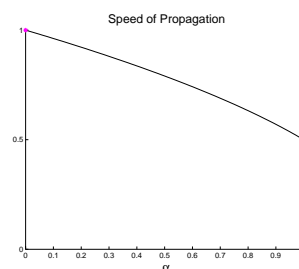


- \*  $\alpha = 1$  implies twice the cells, taking twice the time to cover the same distance as  $\alpha = 0$

## Continuous Approximation

- Let  $\Delta x$  be length of a cell
- Identify  $u_n(t) = U(n\Delta x, t)$  and  $v_n(t) = U((n + \frac{1}{2})\Delta x, t)$
- Assuming that  $U(x, t)$  is a smooth function, we Taylor expand about  $x$  to get,
 
$$\frac{\partial U}{\partial t} = c_g(1 - \frac{3}{4}\alpha)\Delta x^2 \frac{\partial^2 U}{\partial x^2} + f(U) \quad (\text{The Bistable Equation [2]})$$
- If  $\int_{v_r}^{v_e} f(U) > 0$  and  $v_{th} < \frac{1}{2}$ , then there is a unique traveling wave solution  $U(\xi)$ , with  $U(-\infty) = v_e$  and  $U(\infty) = v_r$ .
- The speed of the traveling wave is  $c = \sqrt{2}(\frac{1}{2} - v_{th})\sqrt{c_g(1 - \frac{3}{4}\alpha)\Delta x^2} \propto \sqrt{1 - \frac{3}{4}\alpha}$

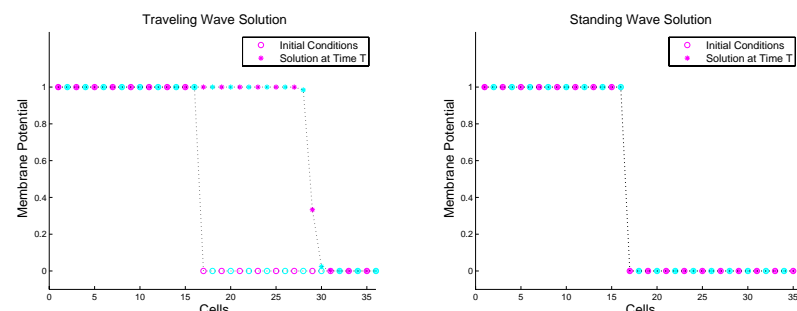
- \*  $\alpha = 1 \Rightarrow \text{speed} \propto 1$
- \*  $\alpha = 0 \Rightarrow \text{speed} \propto 1/2$



**Notice:** Propagation will fail only if  $c_g = 0$

## Discrete System

**Question:** If a region of cells is excited, will excitation propagate through the tissue?



- traveling wave solution  $\Rightarrow$  propagation
- standing wave solution  $\Rightarrow$  propagation failure
- For the single strand cases,  $\alpha = 0$  and  $\alpha = 1$ , with cubic  $f(\phi)$ , where  $v_r = 0$ ,  $v_e = 1$ , and  $0 < v_{th} < \frac{1}{2}$  it can be shown [3] that propagation will fail for  $c_g \leq c_g^*$  where,

$$\frac{v_{th}^2}{4} < c_g^* < \frac{2v_{th}^2 - v_{th} + 2 - 2(v_{th} + 1)\sqrt{v_{th}^2 - 3v_{th} + 1}}{25}$$

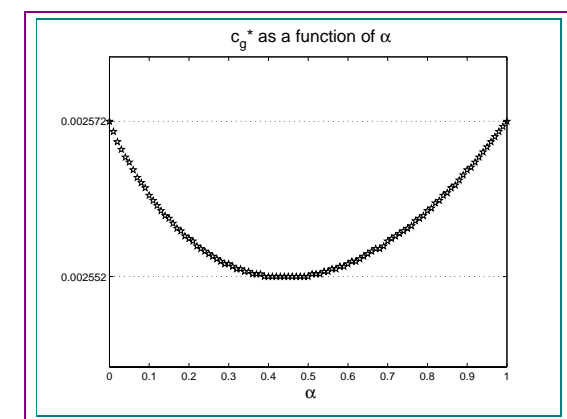
- \* for  $v_{th} = 0.1 \Rightarrow 0.00250 < c_g^* < 0.00265$

**Notice:** Propagation will fail for  $c_g \leq c_g^*$  where  $c_g^* > 0$

## Question

- Recall:** The parameter  $\alpha$  reflects the spatial organization of cellular connections.
- Note:** For each  $\alpha$ , there exists a  $c_g^*$  such that  $c_g \leq c_g^*$  implies propagation failure.
- \* Is there some  $0 < \alpha < 1$  for which propagation failure is the least likely?
- \* How does  $c_g^*$  depend on  $\alpha$ ?

## Results



- $\rightarrow c_g^*$  is the same for  $\alpha = 1$  and  $\alpha = 0$ .
- $\rightarrow$  It is beneficial to have some connections in each direction.
- $\rightarrow$  There is not symmetry about  $\alpha = \frac{1}{2}$ ?

## Future Work

- What are the effects of more complicated lattice structures?
  - \* more connections, different patterns?
  - \* perhaps some type of random organization?
- What happens to propagation when certain cells are systematically "knocked out"?
  - \* a different way to induce propagation failure?
- Propagation in the lateral direction?
  - \* maybe even a three dimensional model?
- What are the implications of using a bidomain rather than a monodomain model?
  - \* how about using different membrane dynamics,  $f(\phi)$ ?
- Take a closer look at the mechanisms of propagation from one cell to another?
  - \* propagation in the absence of gap junction channels?
  - \* electric field effect?
  - \* spatial localization of ion channels?

## References

- [1] Fast V.G. Kleber A.G. Microscopic conduction in cultured strands of neonatal rat heart cells measured with voltage sensitive dyes. *Circulation Research*, 73:914-925, 1993.
- [2] Keener J.P. Sneyd J. *Mathematical Physiology*, chapter 9. Springer-Verlag New York, Inc., 1998.
- [3] Keener J.P. Propagation and its failure in coupled systems of discrete excitable cells. *SIAM J. Appl. Math.*, 47(3):556-572, June 1987.
- [4] Saffitz J.E. Green K.G. Schuessler R.B. Structural determinants of slow conduction in the canine sinus node. *J. Cardiovascular Electrophysiology*, 8:738-744, 1997.