Consequences of Spatial Organization of Cellular Connections on Action Potential Propagation

Elizabeth Doman

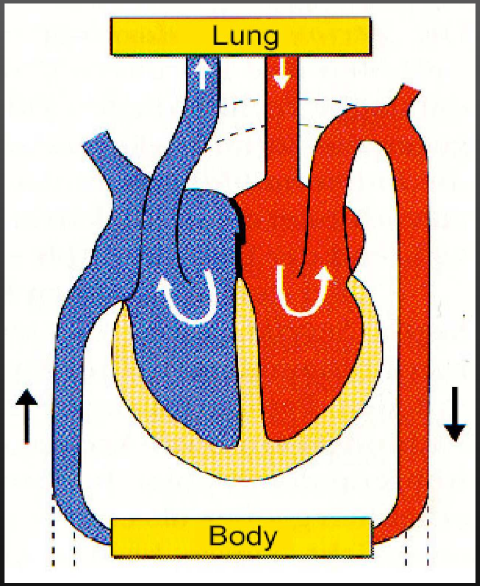
advisor: James P. Keener

Mathematical Biology

University of Utah

Background: the heart is a pump

- transports blood to and from the body and lungs
- two components, right and left, each consisting of atrium and ventricle



⋆ blood travels...

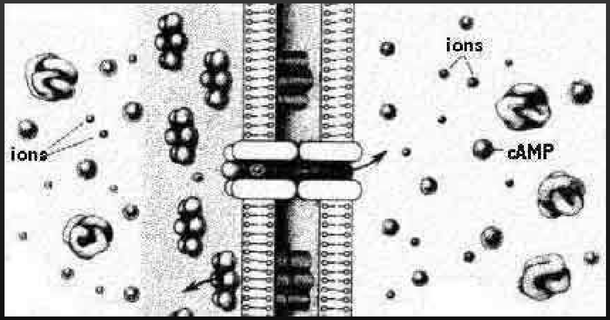
- into the right atrium...
- pumped, by the right ventricle, out of the heart, to the lungs
- into the left artrium...
- pumped, by the left ventricle, out of the heart, to the body

Background: the conduction system

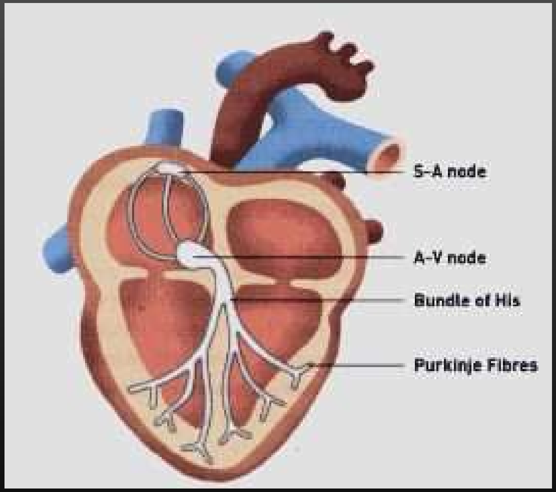
- cells in the ventricular myocardium are excitable and contractile
  - ⋆ allowing the spread of action potential over the cell membrane
  - ⋆ triggers an internal cascade of events, causing the cell to contract

- the action potential is able to jump from one cell to the next

  ⋆ via gap junction channels, located in the intercalated disks

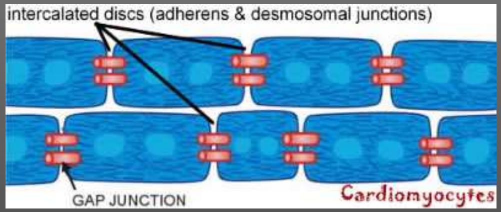


- spread of excitation $\Rightarrow$ muscle contraction

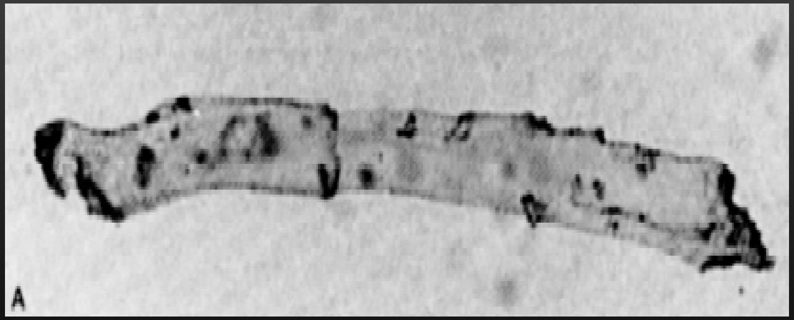


Motivation: organization of cellular connections

- the usual picture $\longrightarrow$
  ...end-to-end coupling



- but, we actually see intercalated disks all over the cell membrane!!!



(Hoyt et al. 89)

- each ventricular myocyte is coupled to $\sim$ 11 others (Saffitz et al. 97)
- excitation can travel in many directions
- propagation from cell to cell is saltatory with a delay on the order of μ seconds

Questions:

$\star$ However, propagation on the tissue level appears as a reliable wave front...

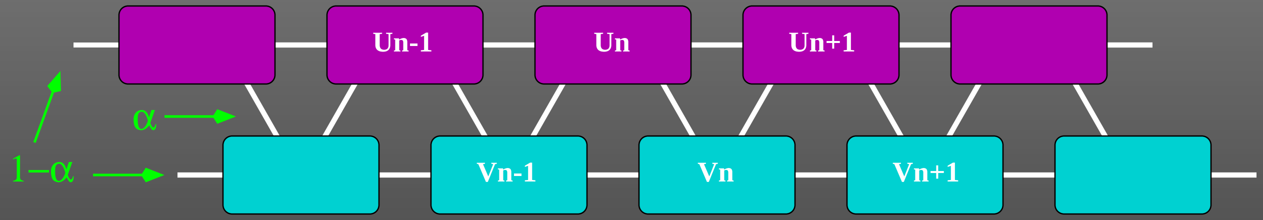
$\star$ Somehow, the saltatory cell-to-cell propagation is averaged to appear smooth

- How does the spatial organization of intercalated disks affect propagation on the macroscopic level?
- In particular, what are the benefits of being coupled to ~ 11 other cells?
- Does this spatial organization make propagation failure less likely?

$\longrightarrow$ this model is a first attempt to examine some of these questions...

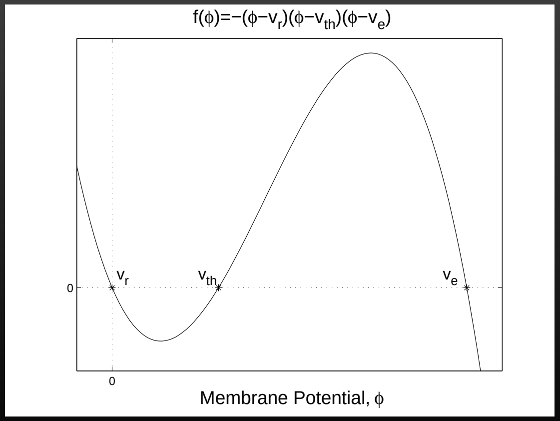
Model:

$\alpha =$ the fraction of diagonal connections



$u_n =$ membrane potential of the n^{th} cell in the top row
$v_n =$ membrane potential of the n^{th} cell in the bottom row

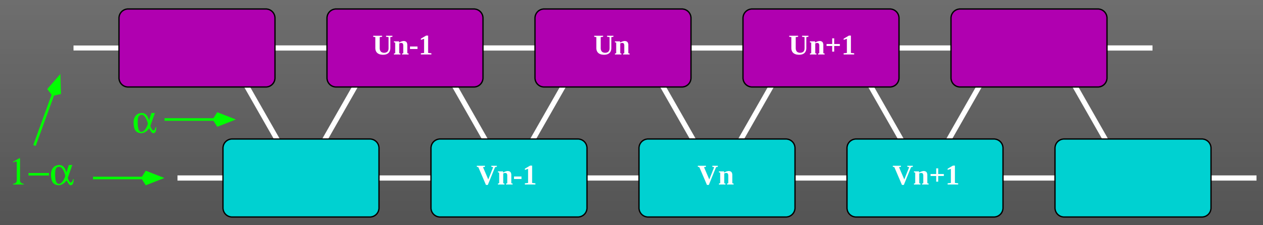
$$\frac{d}{dt}u_n = f(u_n)$$
$$\frac{d}{dt}v_n = f(v_n)$$



⋆ each cell has generic excitable membrane dynamics (like Fitzhugh/Nagumo or HH fast/slow subsystem, with no recovery)

Model:

$\alpha =$ the fraction of diagonal connections



$u_n =$ membrane potential of the n^{th} cell in the top row

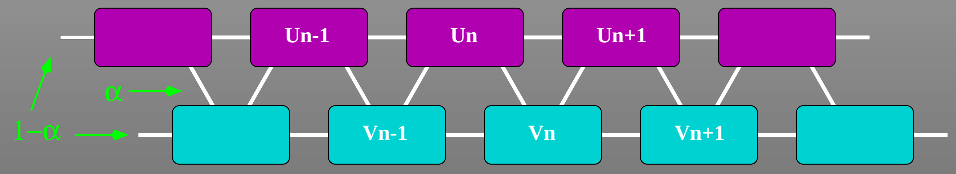
$v_n =$ membrane potential of the n^{th} cell in the bottom row

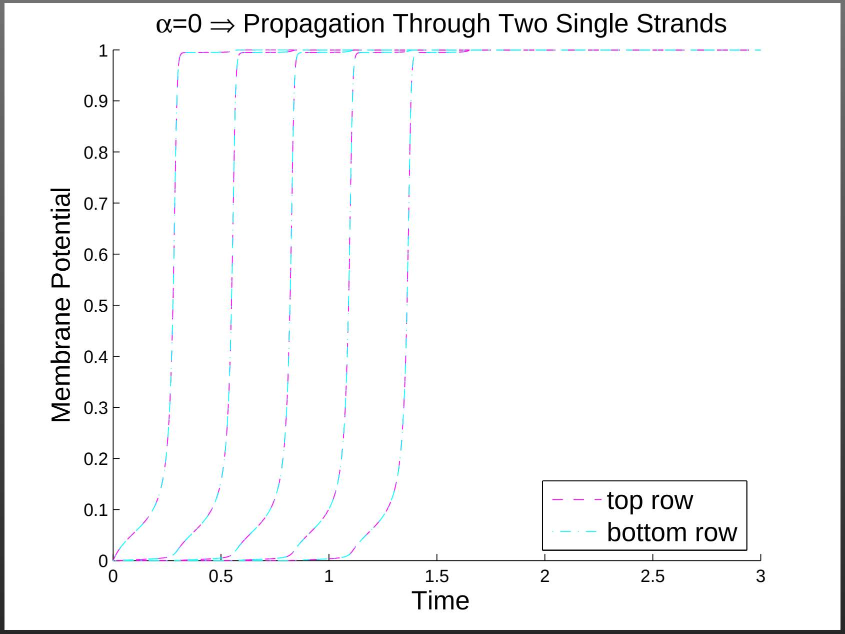
$c_g =$ coupling term, $(capacitance \cdot resistance)^{-1} \sim 1/time$

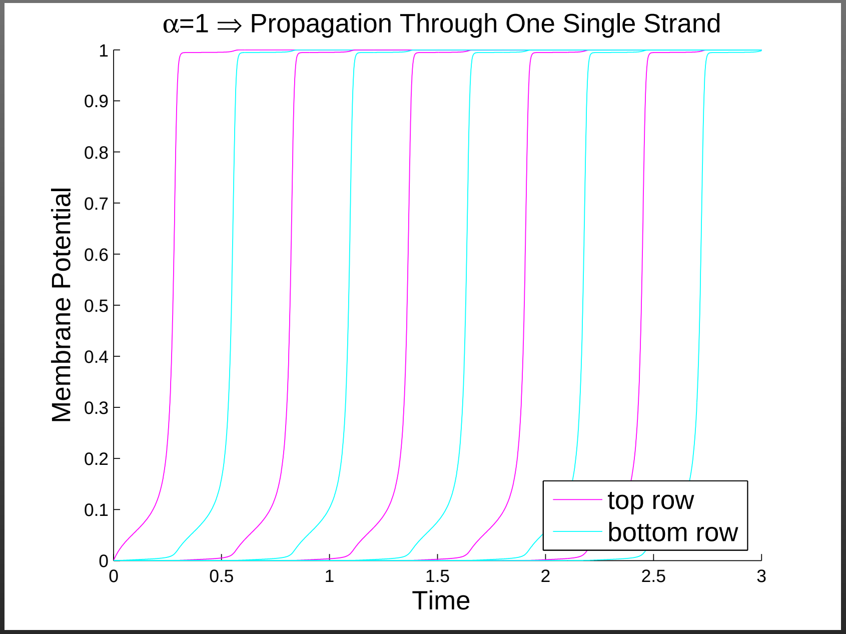
$$\frac{d}{dt}u_n = f(u_n) + (1-\alpha)c_g(u_{n+1} - 2u_n + u_{n-1}) + \alpha c_g(v_n - 2u_n + v_{n-1})$$

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

Behavior:



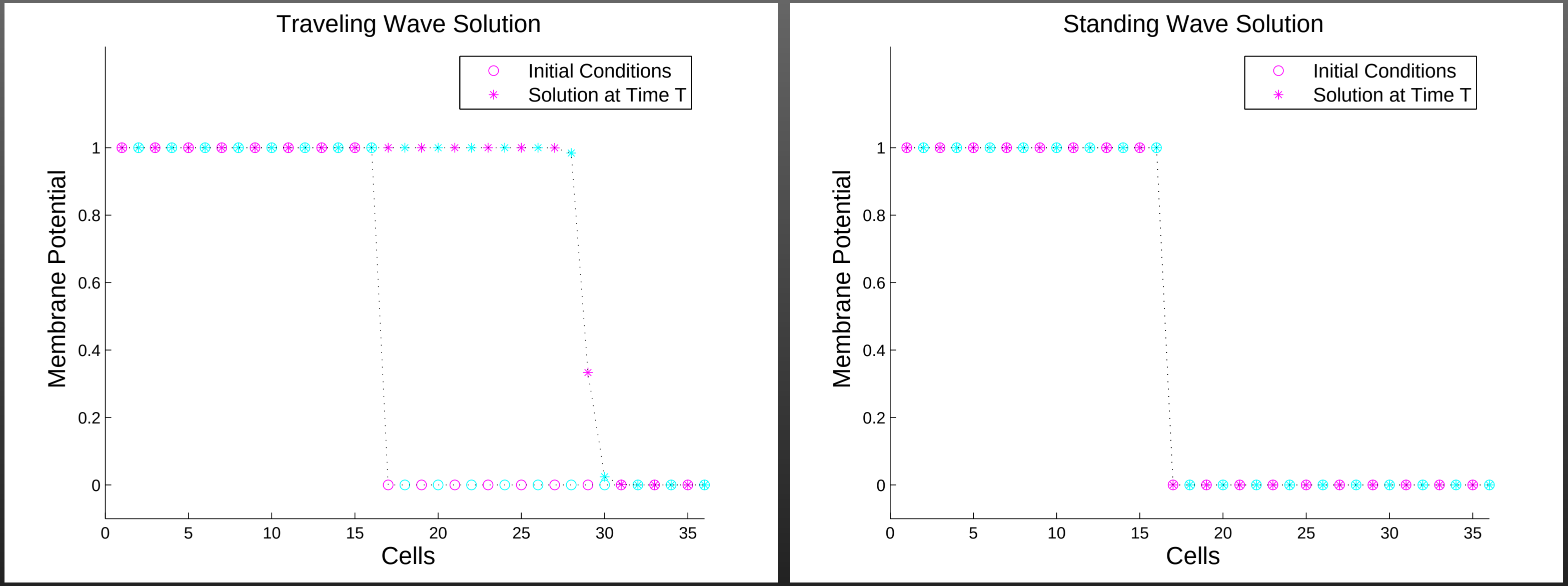




$\alpha = 1 \Rightarrow$ twice the cells $\Rightarrow$ twice the time
...to cover the same distance
...as compared to $\alpha = 0$

Propagation Failure:

- If a region of cells is excited, will excitation propagate through the tissue?



- traveling wave solution $\Rightarrow$ propagation
- standing wave solution $\Rightarrow$ propagation failure

Propagation Failure: continuous approximation

- let Δx be length of a cell
- identify u$_n(t) = U(n\Delta x, t)$ and v$_n(t) = U((n+\frac{1}{2})\Delta x, t)$
- assume that $U(x,t)$ is a smooth function, and Taylor expand about x to get,

$$\frac{\partial}{\partial t}U = c_g(1-\tfrac{3}{4}\alpha)\Delta x^2 \frac{\partial^2}{\partial x^2}U + f(U) \qquad \text{(The Bistable Equation)}$$

  - 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 $c = \sqrt{2}\left(\frac{1}{2} - v_{th}\right)\sqrt{c_g(1-\frac{3}{4}\alpha)\Delta x^2}$

    $\Rightarrow$ propagation will fail only if $c_g = 0$

- however...

Propagation Failure: discrete problem

- for the single strand cases, $\alpha = 0$ and $\alpha = 1$
  - with cubic membrane dynamics, $f(\phi)$,
  - where $v_r = 0$, $v_e = 1$, and $0 < v_{th} < \frac{1}{2}$
  - it is shown (Keener 87) that propagation will fail for all $c_g \leq c_g*$ where,

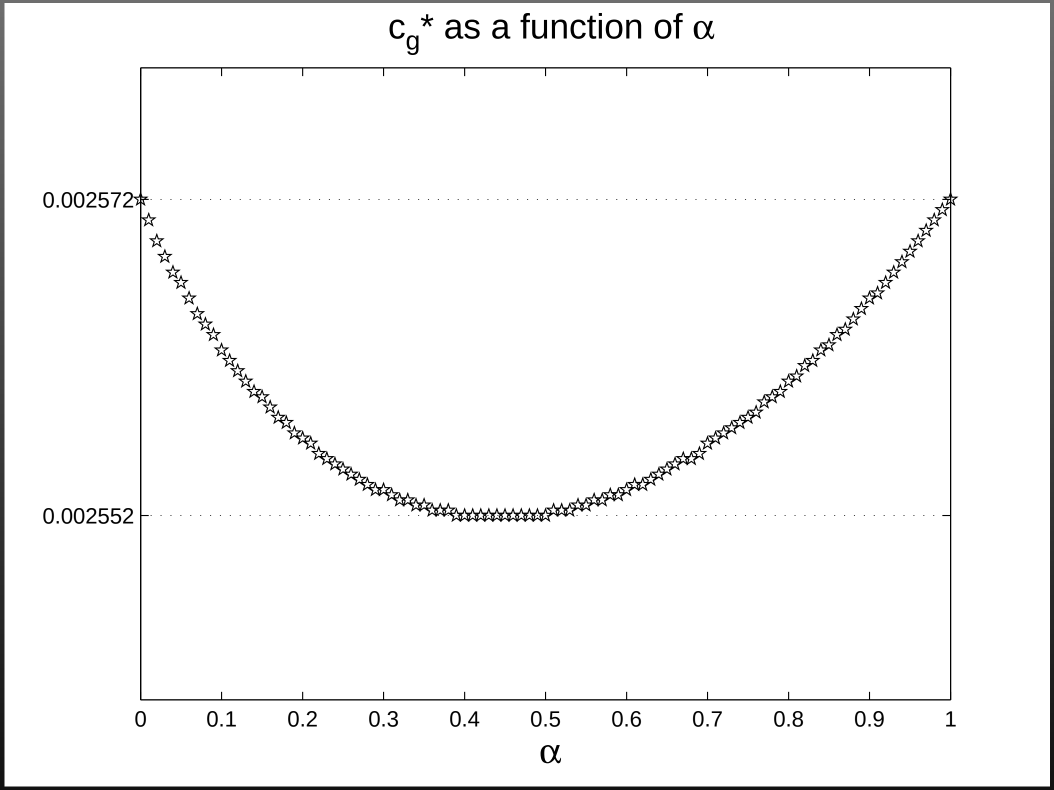
$$\frac{v_{th}^2}{4} < c_g* < \frac{2v_{th}^2 - v_{th} + 2 - 2(v_{th}+1)\sqrt{v_{th}^2 - 3v_{th} + 1}}{25}$$

$\Rightarrow$ propagation will fail for $c_g \leq c_g*$ where $c_g* > 0$

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

- QUESTION: How does c_g* change with α?

Results ???



- as expected...
  - $c_g *$ is the same for $\alpha = 1$ and $\alpha = 0$
  - it is beneficial to have some connections in each direction
- not good...
  - there is no α such that $c_g * < \frac{v_{th}^2}{4}$
  - it is not a result, but just a start...