Dynamics of the Electric Field Mechanism

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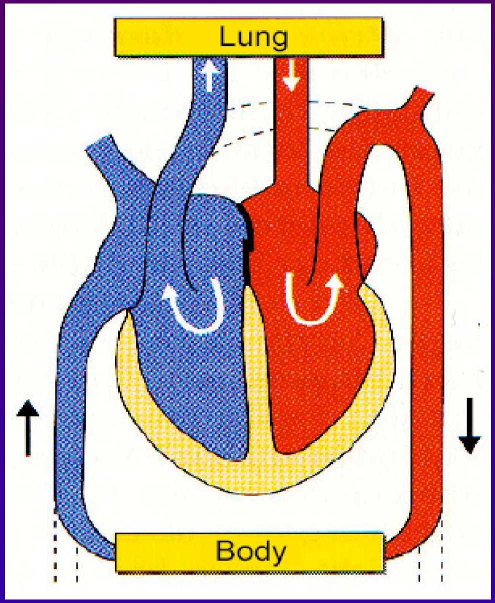
the heart...

- transports blood to and from the body and lungs
- right and left component...
  - each consisting of atrium and ventricle



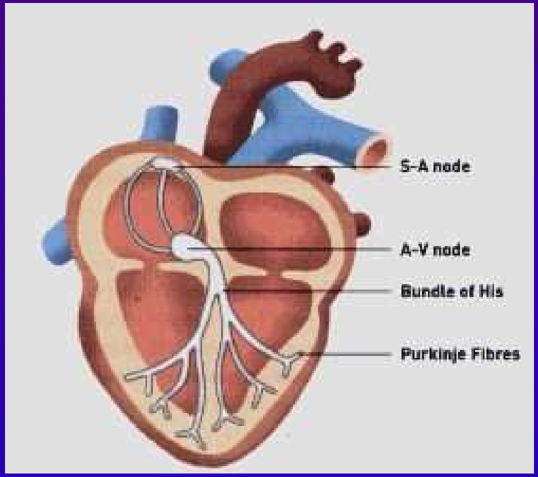
- blood travels...
  - into the right atrium...
  - pumped by the right ventricle, out of the heart, to the lungs
  - into the left artrium...
  - pumped, by the left ventricle, out of the heart, to the body

propagation...

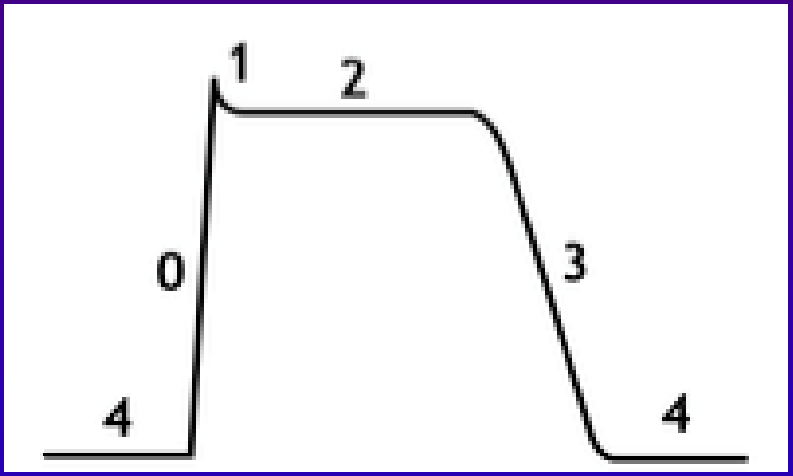
★ myocardial cells are excitable and contractile

- transmembrane potential can undergo an action potential
  - ⋆ ions (Na^{+}, K^{+}, Ca^{2+}) move across the cell membrane
  - ⋆ many models of single cell action potentials
- intracellular Ca^{2+} dynamics cause the cell to contract ← Nessy
- action potentials jump from cell to cell ⇒ propagation of excitation

⋆ conduction system ⋆



⋆ cardiac action potential ⋆



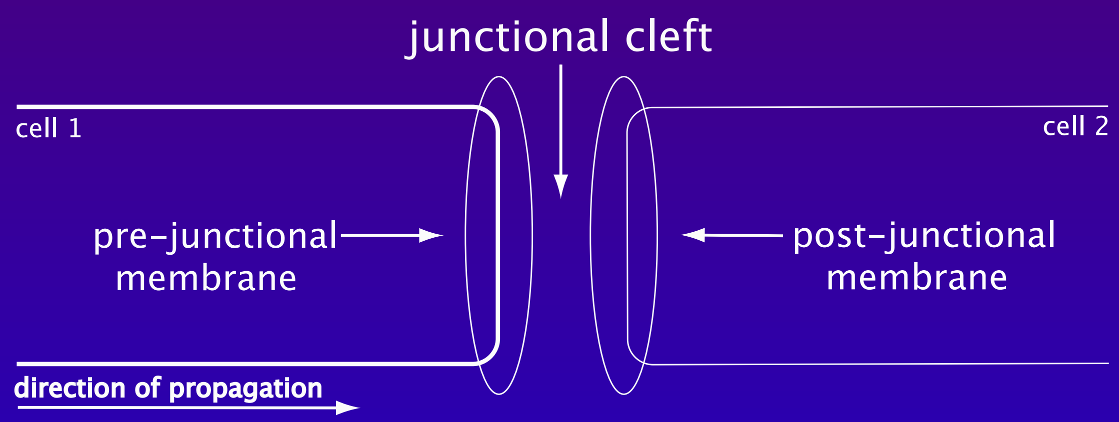
propagation...

- gap junction channels are the primary mechanism
  - they allow for the intracellular spread of current
  - propagation fails under conditions of gap junctional uncoupling
- is there a second mechanism to modulate propagation?
- Sperelakis, 1959
  - proposed an electric field interaction between cells
  - recent experimental findings...
    - ★ high density of Na^+ Chs in cell junctions
    - ★ propagation in Cx43 deficient mouse hearts

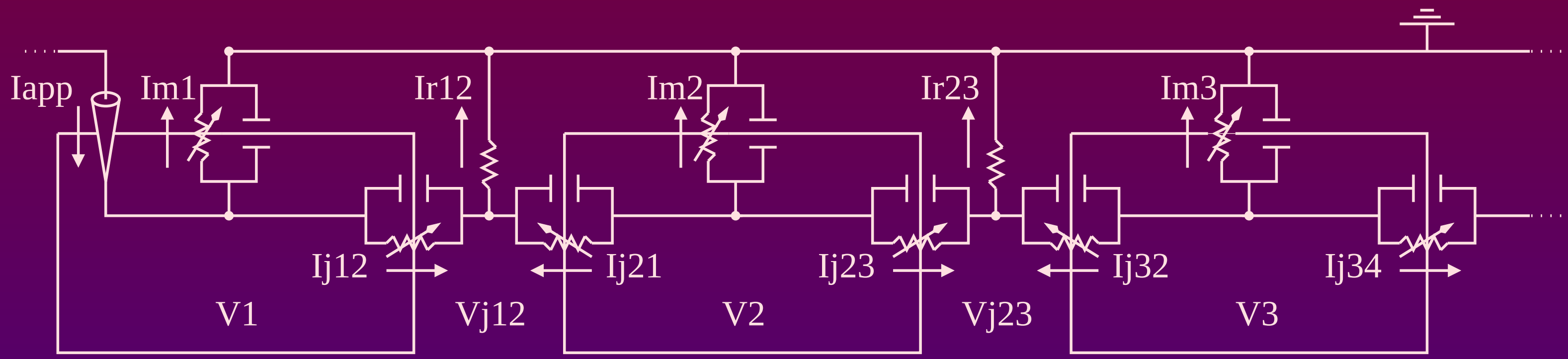
    ... the electric field mechanism might exist

Electric Field Mechanism...

- the idea...
  - the juctional cleft is very narrow $\sim 35 - 250$ Å
  - high radial resistance to the movement of ions
  - high radial resistance to the flow of current
  - drastic changes in ionic cleft concentrations
  - possibility of a separate electric field in the cleft
  - consider the cleft as a separate domain



Electric Field Mechanism...



- non-junctional membrane current:

$$I_{m_n} = A_m \left(C_m \frac{d}{dt} V_n + I_{ion}(V_n) \right)$$

- junctional membrane current:

$$I_{j_{n,n+1}} = A_j \left(C_j \frac{d}{dt}(V_n - V_{j_{n,n+1}}) + \tilde{I}_{ion}(V_n - V_{j_{n,n+1}}) \right)$$

- radial cleft current:

$$I_{r_{n,n+1}} = \frac{1}{r_{jc}} V_{j_{n,n+1}}$$

Electric Field Mechanism...

- balancing the currents at the nodes...
  - cell 1:

$$(1+\alpha\epsilon)\frac{d}{dt}V_1 - \alpha\epsilon\frac{d}{dt}V_{j12} =$$
$$-\frac{1}{C_m}\left(I_{ion}(V_1) + \alpha\tilde{I}_{ion}(V_1 - V_{j12})\right) + \frac{I_{app}}{C_m A}$$

  - junction 1-2:

$$\alpha\epsilon\frac{d}{dt}V_1 - 2\alpha\epsilon\frac{d}{dt}V_{j12} + \alpha\epsilon\frac{d}{dt}V_2 =$$
$$-\frac{1}{C_m}\left(\alpha\tilde{I}_{ion}(V_1 - V_{j12}) + \alpha\tilde{I}_{ion}(V_2 - V_{j12})\right) + sV_{j12}$$

  - cell 2:

$$-\alpha\epsilon\frac{d}{dt}V_{j12} + (1+2\alpha\epsilon)\frac{d}{dt}V_2 - \alpha\epsilon\frac{d}{dt}V_{j23} =$$
$$-\frac{1}{C_m}\left(\alpha\tilde{I}_{ion}(V_2 - V_{j12}) + I_{ion}(V_2) + \alpha\tilde{I}_{ion}(V_2 - V_{j23})\right)$$

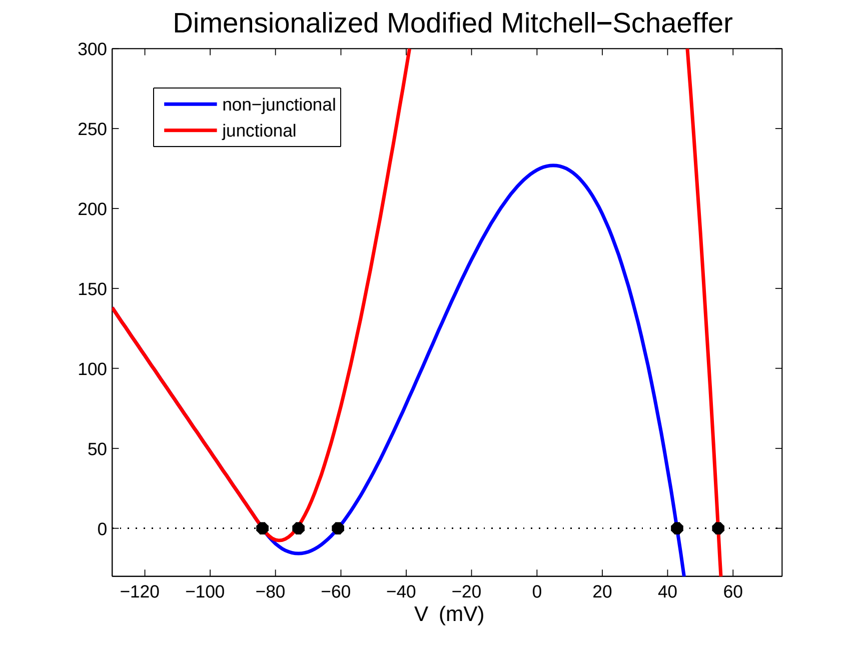
  - etc... a system of coupled ODEs
- important parameters...
  - surface area ratio: $\alpha = A_j/A_m$
  - capacitance ratio: $\epsilon = C_j/C_m$
  - junctional cleft conductance: $s = 1/A_m C_m r_{jc}$

Electric Field Mechanism...

- single cell membrane dynamics: Mitchell-Schaeffer
  - a generic cardiac ionic model with two currents
  - we care about excitation only $\Rightarrow$ ignore recovery

$$I_{ion}(V) = G_{Na} m^2(V)(V - V_{Na}) + G_K(V - V_K)$$

$$\tilde{I}_{ion}(V) = \beta G_{Na} m^2(V)(V - V_{Na}) + G_K(V - V_K)$$



Electric Field Mechanism...

- numerical simulation...

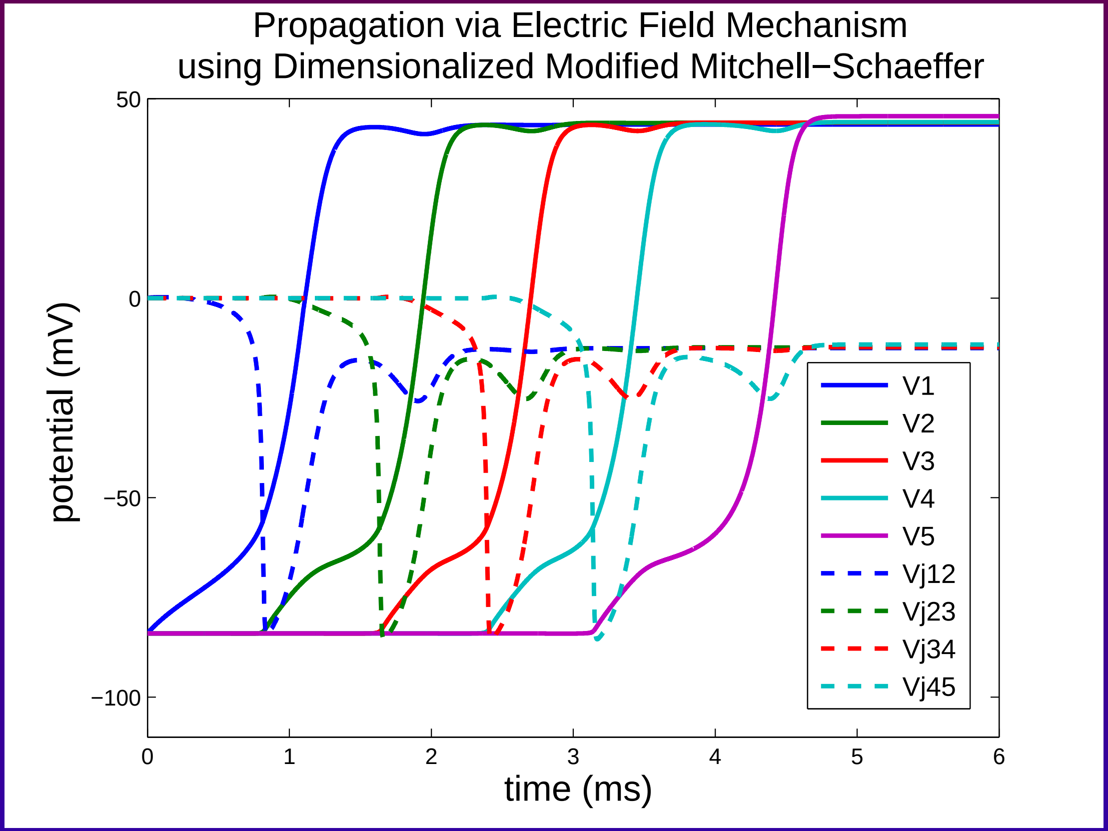
▶ parameters:

$$\alpha = 1/20$$

$$\epsilon = 1/10$$

$$\beta = 6$$

$$s = 1.3$$



analysis?

- continuous approximation? traveling wave solutions?
  - not yet...
- can we characterize propagation failure?
  - what are the important parameters?
    - $\epsilon \longrightarrow$ capacitance ratio
    - $s \longrightarrow$ junctional resistance
    - $\beta \longrightarrow$ junctional sodium conductance
  - what are the underlying dynamics?

... notice: cleft potentials appear to be *fast* variables

dynamics...

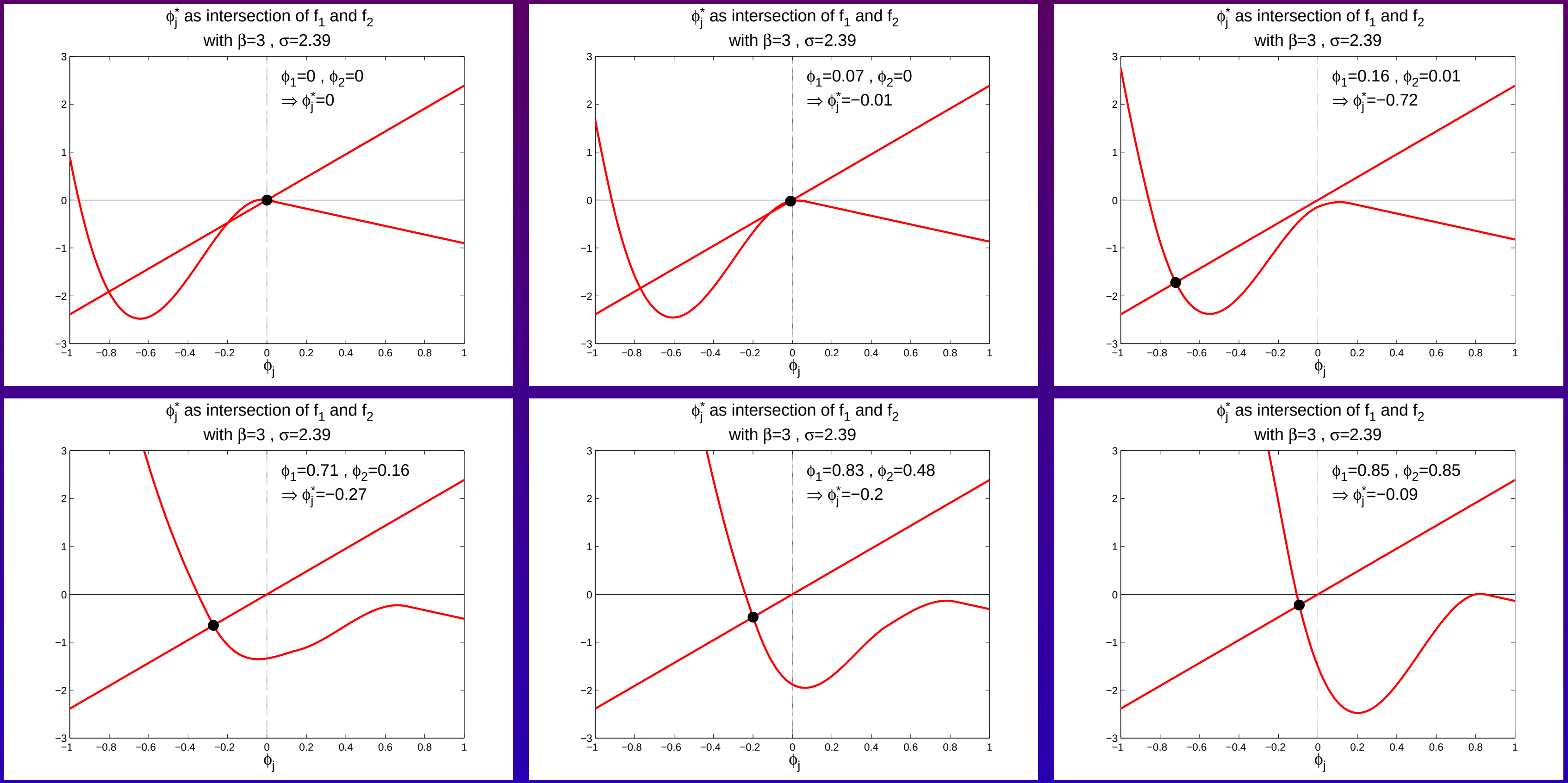
- nondimensionalize...
  - $V_n \to \phi_n$ and $t \to \tau$, such that $0 < \phi_n < 1$ and $0 < \tau < 1$
- two cell system...
  - $\frac{d}{d\tau}\phi_1 + \alpha\epsilon\frac{d}{d\tau}(\phi_1 - \phi_j) = -i_{ion}(\phi_1) - \alpha\tilde{i}_{ion}(\phi_1 - \phi_j) + i_{app}$
  - $\alpha\epsilon\frac{d}{d\tau}(\phi_1 - \phi_j) + \alpha\epsilon\frac{d}{d\tau}(\phi_2 - \phi_j) = -\alpha\tilde{i}_{ion}(\phi_1 - \phi_j) - \alpha\tilde{i}_{ion}(\phi_2 - \phi_j) + \sigma\phi_j$
  - $\frac{d}{d\tau}\phi_2 + \alpha\epsilon\frac{d}{d\tau}(\phi_2 - \phi_j) = -i_{ion}(\phi_2) - \alpha\tilde{i}_{ion}(\phi_2 - \phi_j)$
- notice: the variable $\alpha\epsilon$ is very small $\sim 10^{-2}$
- quasi-steady state approximation:
  - letting $\alpha\epsilon \to 0$, we assume the junctional potentials are in qss
  - not the same as taking $\frac{d}{d\tau}(\phi_1 - \phi_j) = 0$ and $\frac{d}{d\tau}(\phi_2 - \phi_j) = 0$
  - rather... ϕ_j is changing while restricted to some manifold

quasi-steady state approximation...

- letting $\alpha\epsilon \longrightarrow 0$,
  - $\frac{d}{d\tau}\phi_1 = -i_{ion}(\phi_1) - \alpha\tilde{i}_{ion}(\phi_1 - \phi_j) + i_{app}$
  - $\frac{d}{d\tau}\phi_2 = -i_{ion}(\phi_2) - \alpha\tilde{i}_{ion}(\phi_2 - \phi_j)$
- ϕ_j changes while restricted to some manifold,
  - $\alpha\tilde{i}_{ion}(\phi_1 - \phi_j) + \alpha\tilde{i}_{ion}(\phi_2 - \phi_j) = \sigma\phi_j$
- remember, $\tilde{i}_{ion}(\phi)$ is a cubic
- the quasi-steady state, ϕ_j^*, depends on ϕ_1 and ϕ_2
- let's characterize this quasi-steady state ϕ_j^*

dynamics...

- the quasi-steady state, ϕ_j^*, will be intersections of ...
  - $f_1(\phi_j) = \sigma\phi_j$
  - $f_2(\phi_j) = \alpha\tilde{i}_{ion}(\phi_1 - \phi_j) + \alpha\tilde{i}_{ion}(\phi_2 - \phi_j)$



conclusions...

- conditions for successful propagation...
  - ▶ ϵ must be small enough
    - ⋆ quasi-steady state approximation must be valid
    - $\Rightarrow$ junctional membranes must have little or no capacitance
  - ▶ σ must be small enough
    - ⋆ the slope of the line must not be too steep
    - $\Rightarrow$ radial cleft resistance must be high
  - ▶ β must be large enough
    - ⋆ the amplitude of the cubic must be large enough
    - $\Rightarrow$ the junctional membranes must be highly excitable
- otherwise... propagation will fail