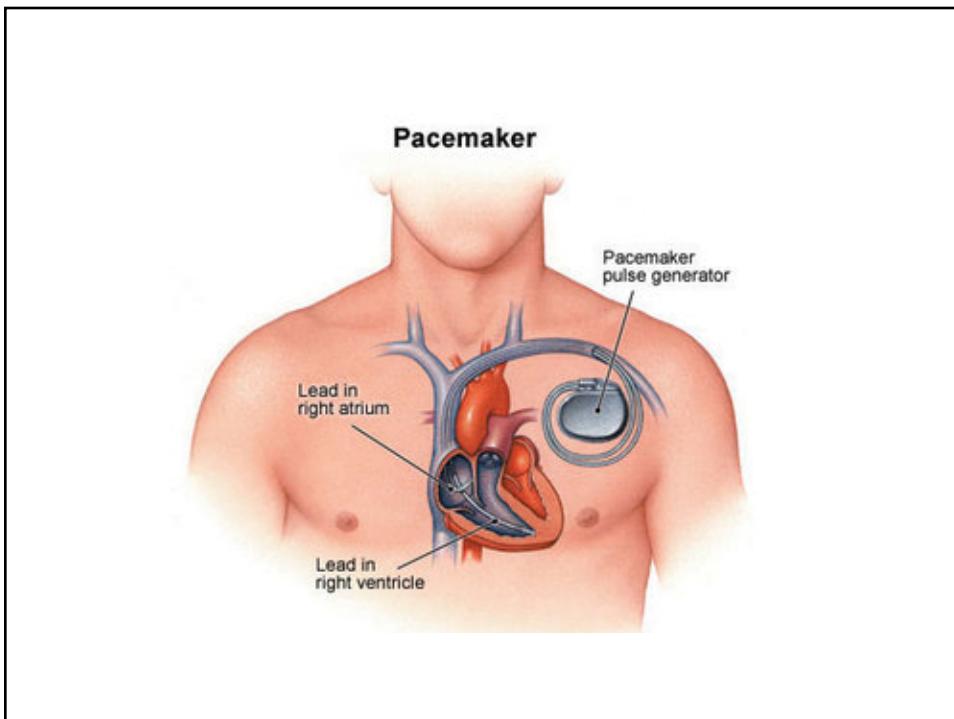


Introduction to Electrical Stimulation

2019/02/07

What you can expect to learn today

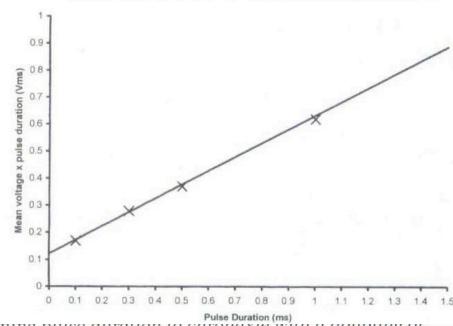
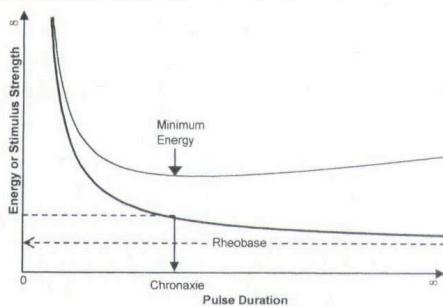
- The relationship between stimulus strength and duration
- How current, charge, and energy relate to stimulation thresholds
- How the stimulation threshold is modeled and what changes it.
- Considerations when applying currents and voltages to volume conductors
- *Uniform electric field stimulation*



The Strength-Duration Curve and Its Importance in Pacing Efficiency: A Study of 325 Pacing Leads in 229 Patients

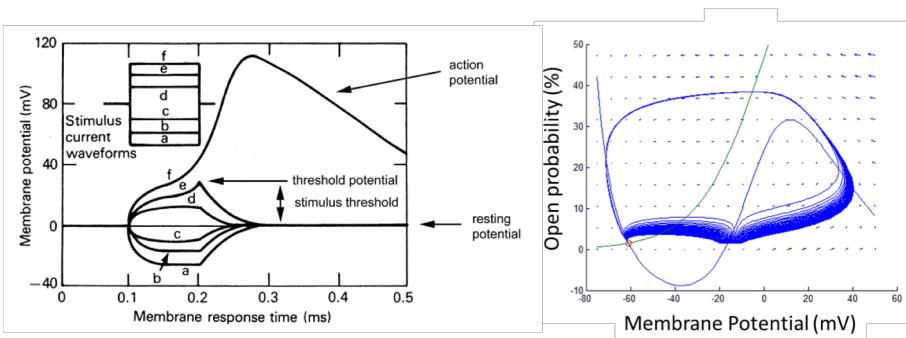
STEPHEN COATES and BARNABY THWAITES

From the Department of Cardiology, Wansbeck General Hospital, Ashington, Northumberland, the United Kingdom

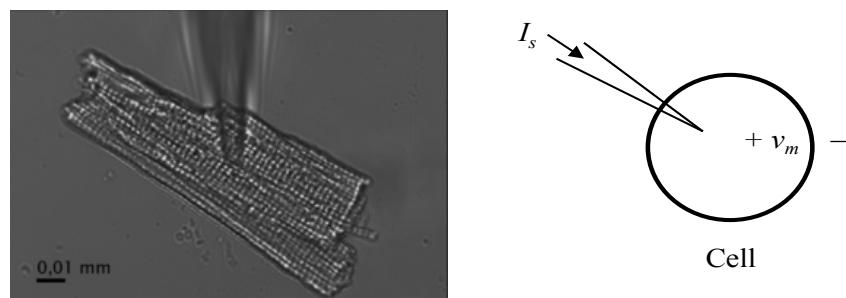


maxes longevity. Battery drain is reduced by programming pulse duration to chronaxie with a doubling of voltage threshold at this point to achieve a safety margin. Further study of chronaxie drift with time is required. (PACE 2000; 23:1273-1277)

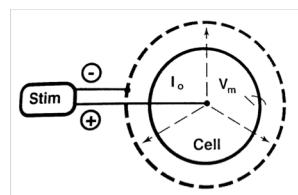
Simple threshold behavior



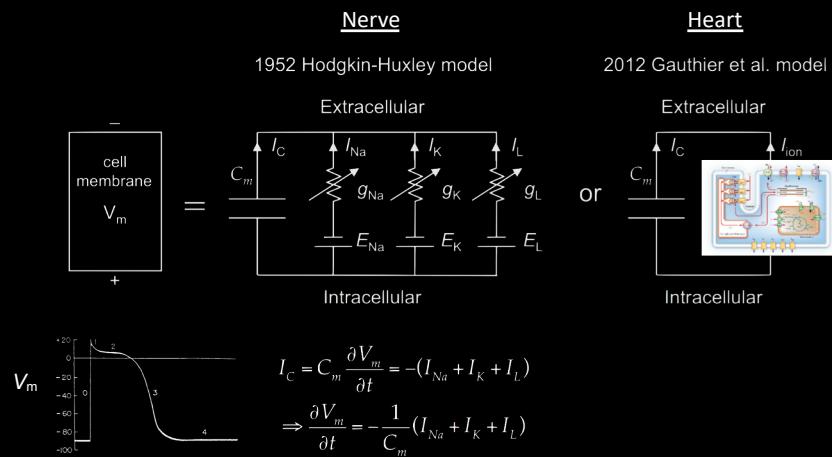
Insights from single cells



The isopotential assumption



Ionic Currents Give Rise to the Action Potential

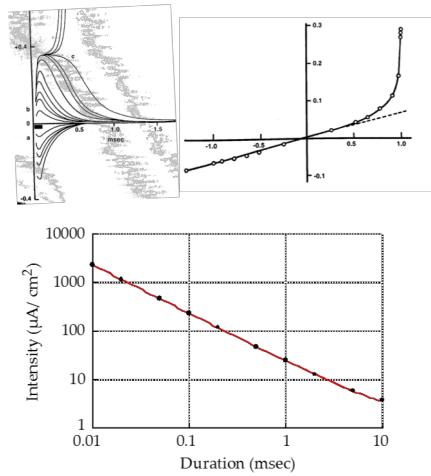


How are current, charge, and energy related?

- **Current** density through the electrode determines the electric field, which drives changes in transmembrane potential. It would be desirable to limit this parameter to minimize possible injury effects to the tissue.
- **Charge** is related to the storage capacity of the battery (usually expressed in Amp-hours, Ah), and it would be desirable to minimize this parameter to extend the number of shocks possible.
- **Energy** (in J) is often used to characterize the strength of pulses applied during defibrillation and is a function of pulse voltage and tissue resistance. The pain of defibrillation shocks is also related to the energy delivered. The capacity of batteries is sometimes expressed as energy density, either in J/kg or J/cm³. It is usually desirable to minimize this parameter to minimize possible injury effects to the tissue and to reduce pain.

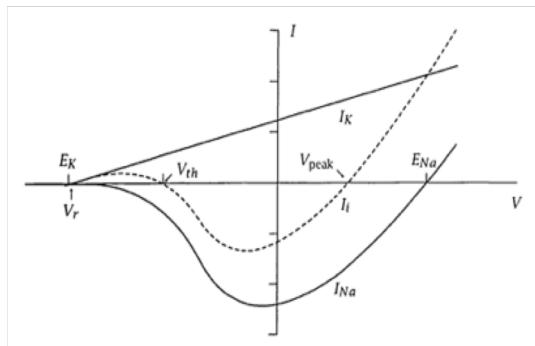
Predictive value?

- We assumed the simple RC dynamics were valid up to a static “threshold” value
- A fixed threshold doesn’t account for “accommodation.”
- We assumed an intracellular stimulus electrode. In general stimulation is accomplished with an extracellular electrode.

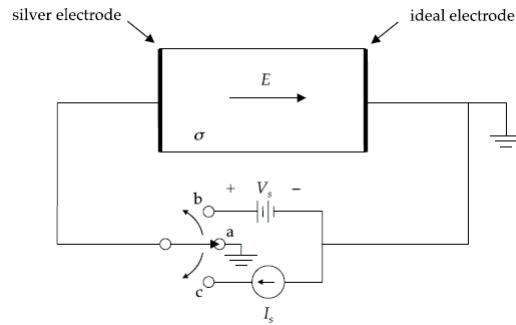


Revisiting the idea of a static threshold

- How does membrane nonlinearity alter the threshold – let’s revisit SBE I

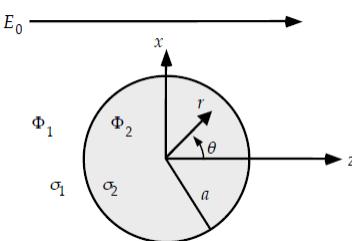


Applying voltages and currents in a volume conductor



How do we account for extracellular application of stimulation?

- Assume we apply a field, E_0 to a spherical cell lying in a volume conductor.
- Potentials must satisfy Laplace's equation.
- What boundary conditions can we use to solve for the potentials inside and outside the sphere?



$$\nabla^2 \Phi = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \Phi}{\partial r} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left(\sin \theta \frac{\partial \Phi}{\partial \theta} \right) + \frac{1}{r^2 \sin^2 \theta} \frac{\partial^2 \Phi}{\partial \phi^2} = 0.$$

$$\Phi_a = -E_0 r \cos \theta$$

$$\Phi_1 = Ar \cos \theta + \left(\frac{B}{r} \right)^2 \cos \theta$$

$$\Phi_2 = Cr \cos \theta + \left(\frac{D}{r} \right)^2 \cos \theta$$

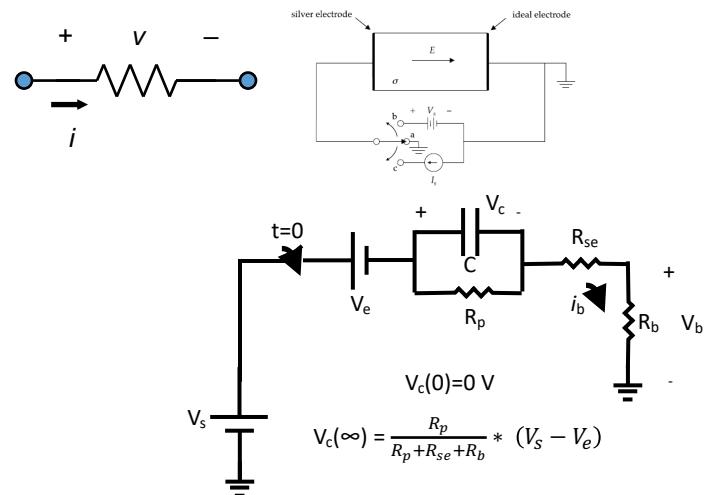
Electrical Stimulation II

2019/02/12

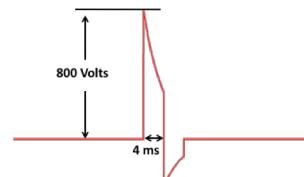
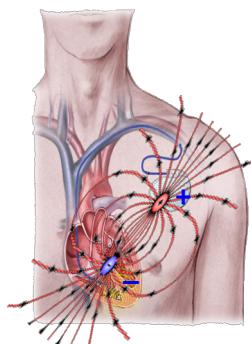
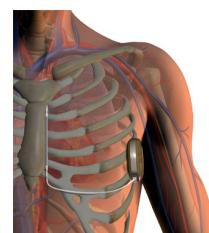
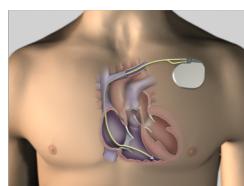
What you can expect to learn today

- Circuit questions / Hodgkin Huxley questions
- How an electric field distributes around cells
- Uniform electric field stimulation of a spherical cell
- Cable equations for 1-D fiber stimulation
- *Activating function*

Applying voltages and currents in a volume conductor

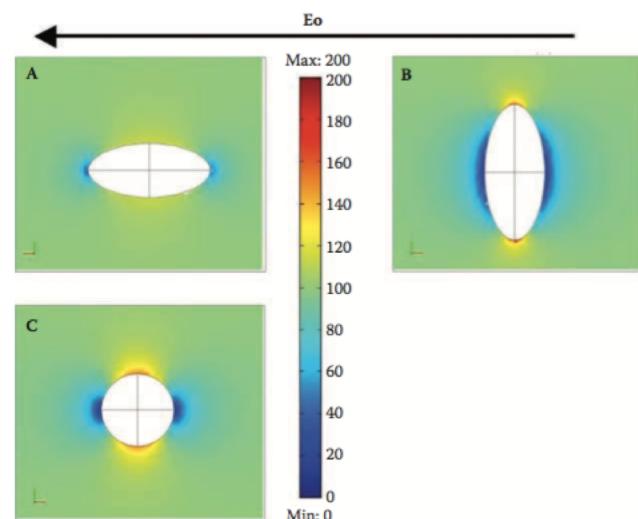


Implantable Cardioverter Defibrillator

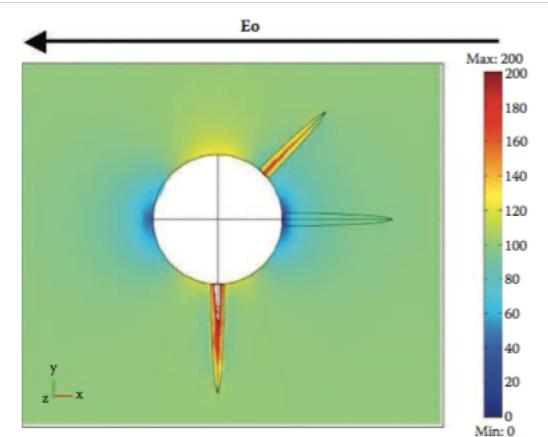


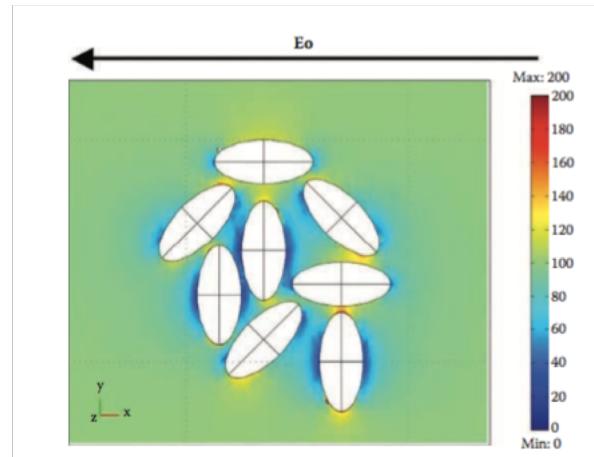
Back to single cells

- How will the electric field distribute around cells?



What about less round shapes?



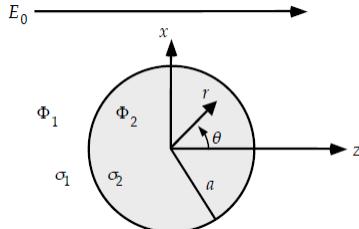


If we apply an electric field E_0

- What is the potential at a given point in space?
- What are the units of E_0 ?
- Since $\mathbf{J}=\sigma\mathbf{E}$ we can envision an applied field as the flow of current.
- How can we express the potential at a point in terms of a radius and an angle?

How do we account for extracellular application of stimulation?

- Assume we apply a field, E_0 to a spherical cell lying in a volume conductor.
- Potentials must satisfy Laplace's equation.
- What boundary conditions can we use to solve for the potentials inside and outside the sphere?



$$\nabla^2 \Phi = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \Phi}{\partial r} \right) + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left(\sin \theta \frac{\partial \Phi}{\partial \theta} \right) + \frac{1}{r^2 \sin^2 \theta} \frac{\partial^2 \Phi}{\partial \phi^2} = 0.$$

$$\Phi_a = -E_0 r \cos \theta$$

$$\Phi_1 = Ar \cos \theta + \left(\frac{B}{r} \right)^2 \cos \theta$$

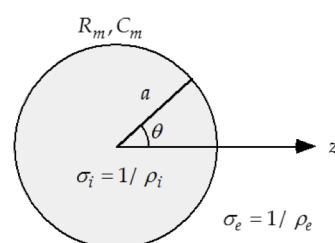
$$\Phi_2 = Cr \cos \theta + \left(\frac{D}{r} \right)^2 \cos \theta$$

Now consider a spherical cell's response

$$-\sigma_i a \cos \theta = \frac{\sigma_e 2b \cos \theta}{R^3} + \sigma_e E_a \cos \theta.$$

$$\begin{aligned} & \frac{\Phi_i(R) - \Phi_e(R)}{R_m} + C_m \frac{d}{dt} [\Phi_i(R) - \Phi_e(R)] \\ &= -\sigma_i a \cos \theta. \end{aligned}$$

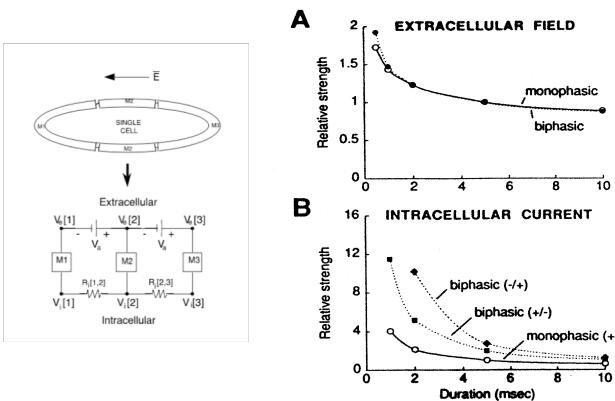
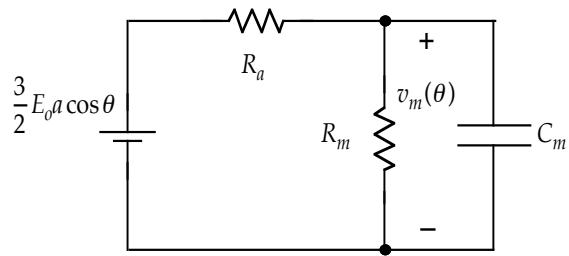
$$\begin{aligned} v_m &= \frac{3\sigma_i \sigma_e R_m E_o a \cos \theta}{a\sigma_i + 2a\sigma_e + 2\sigma_i \sigma_e R_m} (1 - e^{-t/\tau'}) \\ &= \frac{R_m}{R_m + R_a} \left(\frac{3}{2} E_o a \cos \theta \right) (1 - e^{-t/\tau'}) \end{aligned}$$

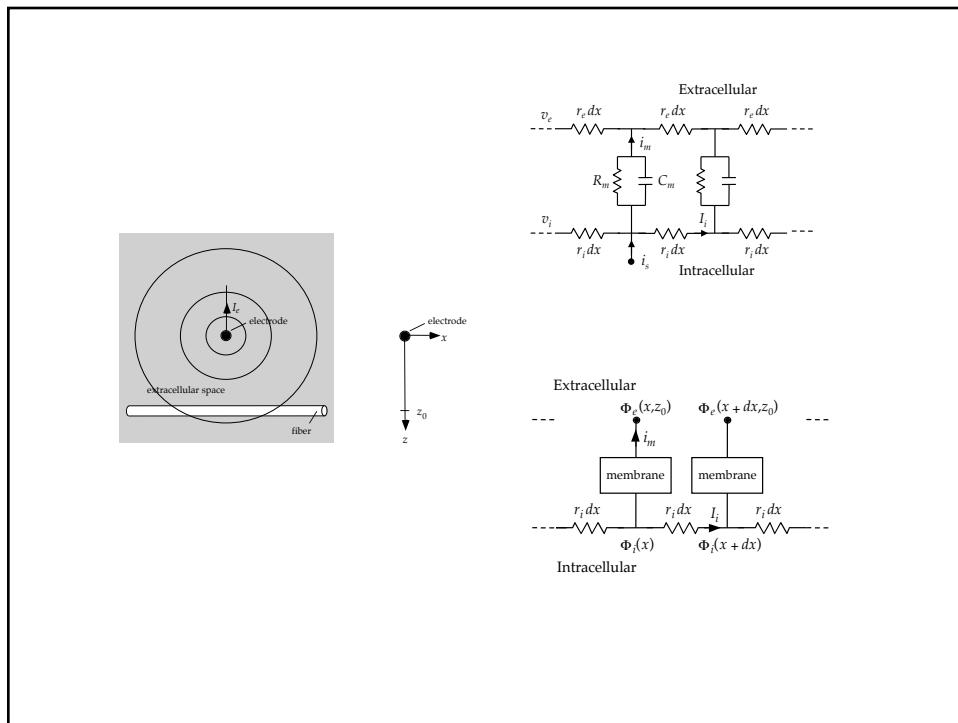


$$\frac{1}{\tau'} = \frac{1}{R_m C_m} + \frac{2\sigma_i \sigma_e}{a C_m (\sigma_i + 2\sigma_e)}$$

$$= \frac{1}{R_m C_m} + \frac{1}{R_a C_m}$$

$$R_a = a(\rho_i + 0.5\rho_e)$$





Electrical Stimulation III

2019/02/14

What you can expect to learn today

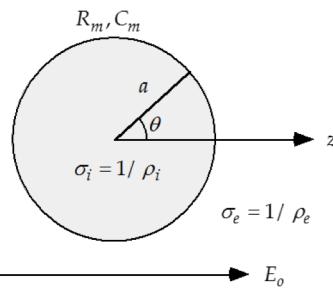
- Review of electric field and induced V_m around cells
- More on the activating function
 - Revisiting derivation
- Steady state and step response of a fiber
- Review of assumptions made for each stimulation type
- Back to physiology -- Implications for therapy (defibrillation, pacing, CCM)

Now consider a spherical cell's response

$$-\sigma_i a \cos \theta = \frac{\sigma_e 2b \cos \theta}{R^3} + \sigma_e E_o \cos \theta.$$

$$\begin{aligned} \frac{\Phi_i(R) - \Phi_e(R)}{R_m} + C_m \frac{d}{dt} [\Phi_i(R) - \Phi_e(R)] \\ = -\sigma_i a \cos \theta. \end{aligned}$$

$$\begin{aligned} v_m &= \frac{3\sigma_i \sigma_e R_m E_o a \cos \theta}{a\sigma_i + 2a\sigma_e + 2\sigma_i \sigma_e R_m} (1 - e^{-t/\tau'}) \\ &= \frac{R_m}{R_m + R_a} \left(\frac{3}{2} E_o a \cos \theta \right) (1 - e^{-t/\tau'}) \end{aligned}$$

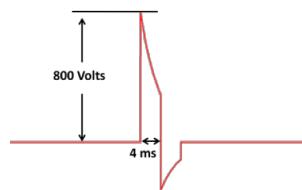
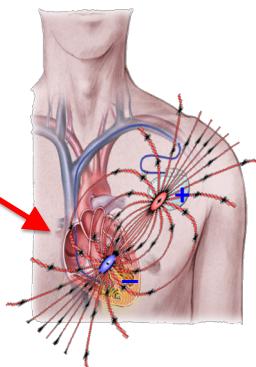


$$\begin{aligned} \frac{1}{\tau'} &= \frac{1}{R_m C_m} + \frac{2\sigma_i \sigma_e}{a C_m (\sigma_i + 2\sigma_e)} \\ &= \frac{1}{R_m C_m} + \frac{1}{R_a C_m} \end{aligned}$$

$$R_a = a(\rho_i + 0.5\rho_e)$$

How does defibrillation work?

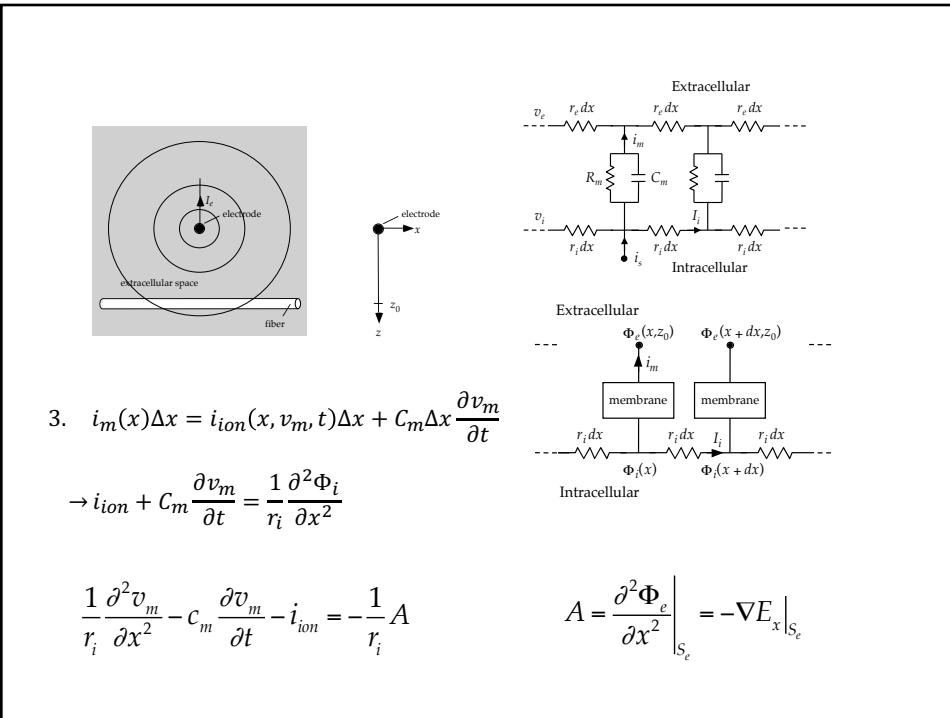
Happy Valentine's Day!



Several theories have been proposed

- “Incapacitation” effects on the myocardium – the tissue is temporarily stunned and cannot sustain fibrillation.
- Stimulation theory – direct stimulation of the myocardium terminates existing activity
- Critical Mass hypothesis – 75-95% of the heart needs to be directly stimulated to terminate fibrillation. Any remaining areas not stimulated will self-terminate
- Upper limit of vulnerability hypothesis – the shock terminates all wavefronts of fibrillation and produce a sufficient voltage gradient everywhere in the heart to not re-induce fibrillation
- Progressive depolarization – Progressively stronger shocks depolarize more refractory myocardium to progressively stop activity.
- Virtual electrode hypothesis – some areas of myocardium are excited and some are deexcited.

What about pacing? Should we pace with an anode or cathode?

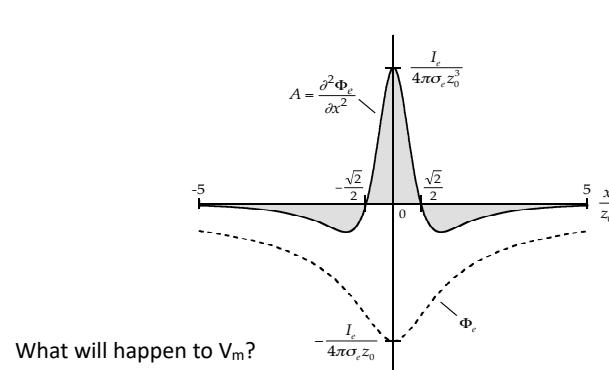


What does the activating function look like?

What does the extracellular potential look like?

$$\Phi_e = \frac{-I_e}{4\pi\sigma_e r}$$

$$\Phi_e = \frac{-I_e d \cos(\theta)}{4\pi\sigma_e r^2}$$



At t=0 with the membrane at rest:

$$v_m = 0 \quad \frac{\partial^2 v_m}{\partial x^2} = 0$$

$$\text{So} \quad r_i \frac{\partial v_m}{\partial t} = \frac{1}{c_m} \times \frac{\partial^2 \Phi_e}{\partial x^2}$$

$$i_{ion} = \frac{v_m}{r_m} = 0$$

Revisit single cell

Where does the cell experience depolarization?

How does this relate to our forms of stimulation?

Spherical cell, current injection

- Assumed simplified spherical geometry
- Assumed the cell was isopotential
- Solved for the transmembrane potential response

Spherical cell, uniform field

- Assumed simplified spherical geometry
- Assumed a uniform applied field
- Considered the effect of the cell on the applied field
- Solved for the induced transmembrane potential

Fiber, non-uniform field

- Slightly more realistic situation where the field is non-uniform
- The activating function is not the solution for $V_m(t)$!
- Did not account for the impact of the fiber on current flow!

What about active responses?

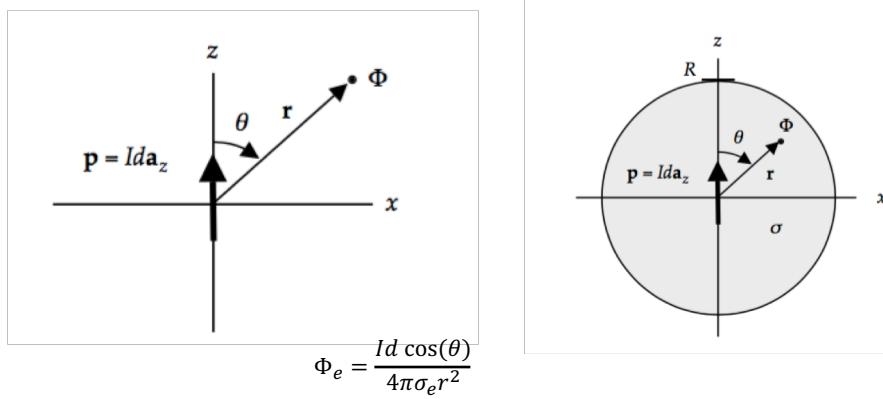
What about non-uniform media?

Limitations of the fiber analysis

- The activating function only gives the initial rate of change for V_m .
 - For passive membrane properties.
 - As stimulus duration increases this initial approximation is less valid.
- V_m will change over time both during and after the stimulus.
- V_m depends on the entire function of the applied field, not simply its initial values.
- V_m will depend on fiber properties (including the space constant).
- If the fiber is not infinite there will be boundary conditions that will change the solution to the cable equation and therefore the induced V_m .
- Assumed that distance from the fiber is much greater than the fiber radius.

What if the volume conductor is not homogenous?

$$\mathbf{A} = \mathbf{G}_i \cdot \nabla(\nabla\Phi_e) + (\nabla \cdot \mathbf{G}_i) \cdot \nabla\Phi_e$$

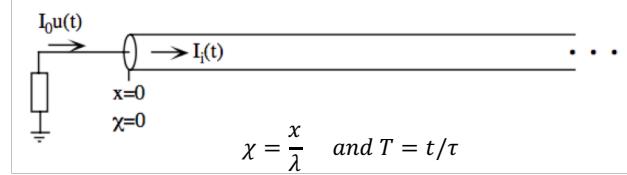


What happens over time? Space?

$$\frac{1}{r_i} \frac{\partial^2 v_m}{\partial x^2} - c_m \frac{\partial v_m}{\partial t} - i_{ion} = -\frac{1}{r_i} A \quad \text{If we assume linearity below threshold: } i_{ion} = \frac{v_m}{R_m}$$

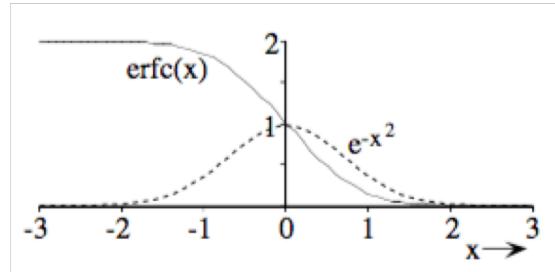
$$\lambda^2 \frac{\partial^2 v_m}{\partial x^2} - \tau \frac{\partial v_m}{\partial t} - v_m = -\lambda^2 A \quad \lambda = \sqrt{\frac{R_m}{r_i}} \quad \tau = R_m C_m$$

Consider the simpler case:



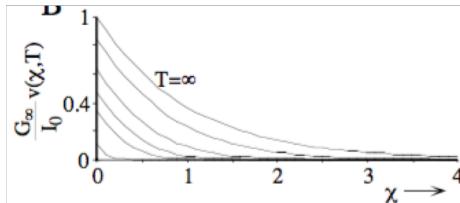
$$v(\chi, T) = \frac{I_0}{2 G_\infty} \left\{ e^{-\chi} \operatorname{erfc} \left[\frac{\chi}{2\sqrt{T}} - \sqrt{T} \right] - e^{\chi} \operatorname{erfc} \left[\frac{\chi}{2\sqrt{T}} + \sqrt{T} \right] \right\}$$

$$G_\infty = \frac{1}{R_\infty} = \sqrt{r_i R_m} = \frac{1}{r_i \lambda} \quad \text{Consider the loading effects...}$$



In space at different times:

- At $T=\infty$ the potentials fall off exponentially with the space constant

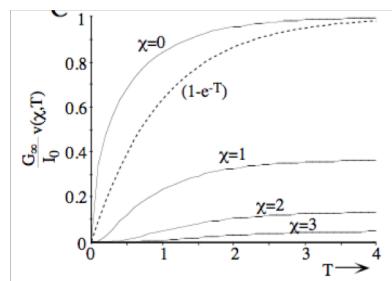


$$v(x, T \rightarrow \infty) = \frac{I_0}{G_\infty} e^{-x} = \frac{I_0}{G_\infty} e^{-x/\lambda}$$

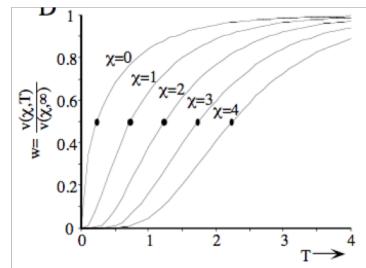
- The input conductance term can be clearly seen now.

In time at different points:

- At $X=0$ the response is very quick (faster than exponential)
- At further distances the response is delayed and smaller



Normalized to steady state:



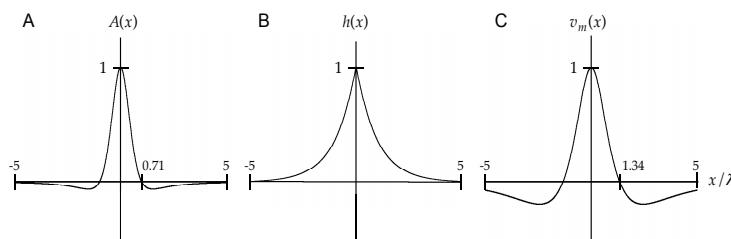
- Can now consider how fast electrotonic spread occurs.
- Plotting X versus 'half times'

$$\xrightarrow{\text{yields}} \text{speed} = 2 \frac{\lambda}{\tau_m} = \sqrt{\frac{2a}{R_m R_i C^2}}$$

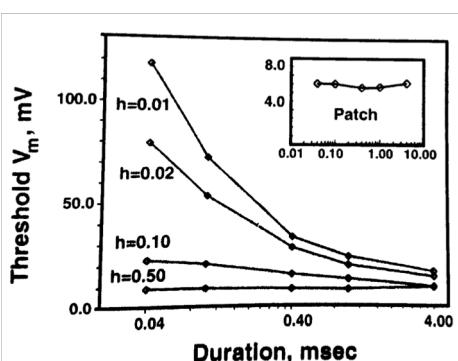
Bounded case

- This is not a true conduction velocity because this is not an active wave!
- But it does inform how fast the passive spread of current occurs.
- It depends on a (the fiber radius)
- A note on myelinated neurons: Myelin increases r_m which increases the space constant.
 - This increases the speed of passive conduction.

Now let's reconsider the activating function:



Revisiting thresholds: an active membrane



- “Patch” refers to the space clamped threshold (axially uniform V_m response)
- Point stimulation at different heights (h) above the fiber
- Why is the threshold higher at closer distances?

What do you think now? Are any of these more viable?

- “Incapacitation” effects on the myocardium – the tissue is temporarily stunned and cannot sustain fibrillation.
- Stimulation theory – direct stimulation of the myocardium terminates existing activity
- Critical Mass hypothesis – 75-95% of the heart needs to be directly stimulated to terminate fibrillation. Any remaining areas not stimulated will self-terminate
- Upper limit of vulnerability hypothesis – the shock terminates all wavefronts of fibrillation and produce a sufficient voltage gradient everywhere in the heart to not re-induce fibrillation
- Progressive depolarization – Progressively stronger shocks depolarize more refractory myocardium to progressively stop activity.
- Virtual electrode hypothesis – some areas of myocardium are excited and some are deexcited resulting in high post shock gradients in potential.

Should we pace with an anode or cathode?

We always pace with both!

