

Propagation of Cardiac Action Potentials: How does it *Really* work?

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Introduction

- A major cause of death is due to heart failure, for example, due to a heart attack and development of a fatal arrhythmia. The direct cause of fatal cardiac arrhythmias is still not completely known, however, in many cases the cause can be traced to a failure of the cardiac action potential to propagate correctly.

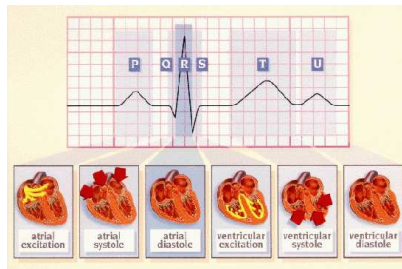
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- Remarkably, the propagation of action potentials is still not completely understood in spite of many years of investigation.

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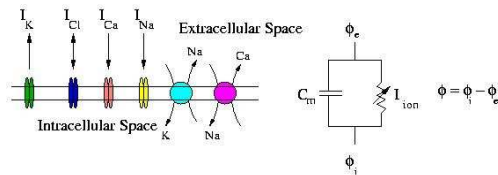
- A major cause of death is due to heart failure, for example, due to a heart attack and development of a fatal arrhythmia. The direct cause of fatal cardiac arrhythmias is still not completely known, however, in many cases the cause can be traced to a failure of the cardiac action potential to propagate correctly.
- Remarkably, the propagation of action potentials is still not completely understood in spite of many years of investigation.
- The purpose of this talk is to describe some of the unresolved issues and the attempt to use mathematical models to understand these issues.

Conduction system of the heart



- Electrical signal (an action potential) originates in the SA node.
- The signal propagates across the atria (2D sheet), through the AV node, along Purkinje fibers (1D cables), and throughout the ventricles (3D tissue).

Modeling Membrane Electrical Activity



- Membrane separates **extracellular** and **intracellular** space with potentials ϕ_e and ϕ_i , and **transmembrane potential** $\phi = \phi_i - \phi_e$.
- Transmembrane potential ϕ is regulated by transmembrane ionic currents and capacitive currents:

$$C_m \frac{d\phi}{dt} + I_{ion}(\phi, w) = I_{in} \quad \text{where} \quad \frac{dw}{dt} = g(\phi, w), \quad w \in R^n$$

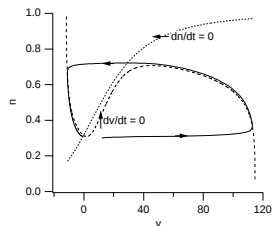
Examples Include

- Neuron - **Hodgkin-Huxley model**
- Purkinje fiber - Noble
- Cardiac cells - **Beeler-Reuter**, **Luo-Rudy**, Winslow-Jafri, Bers
- Two Variable Models - **reduced HH**, FitzHugh-Nagumo, Mitchell-Schaeffer, Morris-Lecar, etc.)

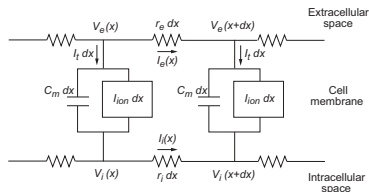
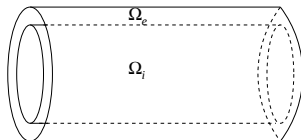
$$C \frac{d\phi}{dt} = \bar{g}_{Na} m_{\infty}^3(\phi)(N - n)(\phi - \phi_{Na}) + \bar{g}_K n^4(\phi - \phi_K) + \bar{g}_I(\phi - \phi_L),$$

$$\tau_n(\phi) \frac{dn}{dt} = n_{\infty}(\phi) - n.$$

Threshold Behavior, Refractoriness
Alternans
Wenckebach Patterns



Spatially Extended Excitable Media - Axons and Fibers



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- These potentials drive currents,

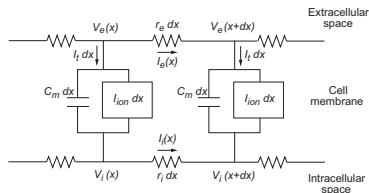
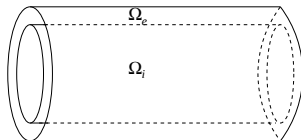
$$I_i = -\frac{1}{r_i} \frac{d\phi_i}{dx}, \quad I_e = -\frac{1}{r_e} \frac{d\phi_e}{dx}.$$

where r_e and r_i are **resistances per unit length**.

- *Total current* $i_T = I_e + I_i$ is conserved,

$$i_T = -\frac{1}{r_i} \frac{d\phi_i}{dx} - \frac{1}{r_e} \frac{d\phi_e}{dx}.$$

The Cable Equation



Transmembrane current is balanced

$$C_m \frac{\partial \phi}{\partial t} + I_{ion} = I_t = -\frac{\partial I_i}{\partial x} = \frac{\partial I_e}{\partial x}.$$

Combining everything gives

$$C_m \frac{\partial \phi}{\partial t} = \frac{\partial}{\partial x} \left(\frac{1}{r_i + r_e} \frac{\partial \phi}{\partial x} \right) - I_{ion}$$

This equation is referred to as the **cable equation**.

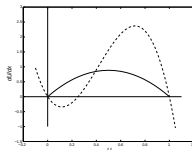
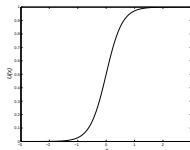
Action Potential Upstroke - Fronts

For *all* ion models, the upstroke (leading edge or front) is governed to a good approximation by the **bistable equation**

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} + f(u)$$

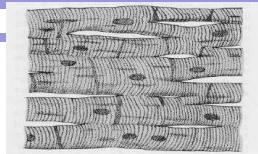
with $f(0) = f(a) = f(1) = 0$, $0 < a < 1$.

- There is a unique traveling wave solution $u = U(x - ct)$,
- The solution is stable up to phase shifts,
- The speed scales as $c = c_0 \sqrt{D}$,
- U is a homoclinic trajectory of $U'' + c_0 U' + f(U) = 0$



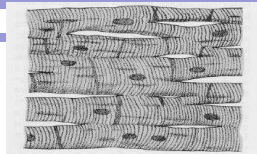
Modelling Cardiac Tissue

The Bidomain Model:



Modelling Cardiac Tissue

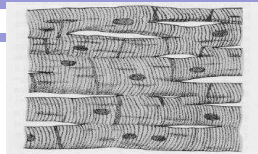
The Bidomain Model:



- At each point of the cardiac domain there are two mingled regions, the **extracellular** and the **intracellular** domains with potentials ϕ_e and ϕ_i , and **transmembrane potential** $\phi = \phi_i - \phi_e$.

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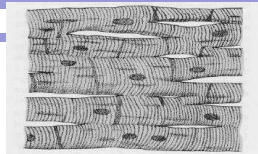
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- These potentials drive currents, $i_e = -\sigma_e \nabla \phi_e$, $i_i = -\sigma_i \nabla \phi_i$, where σ_e and σ_i are **conductivity tensors**.

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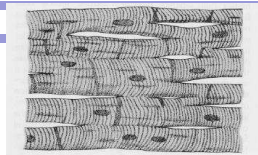


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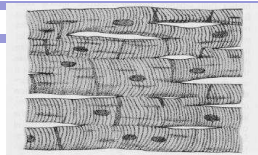
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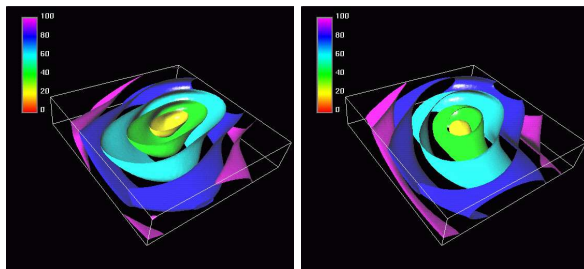
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$$\chi \left(C_m \frac{\partial \phi}{\partial t} + I_{ion} \right) = \nabla \cdot (\sigma_i \nabla \phi_i)$$

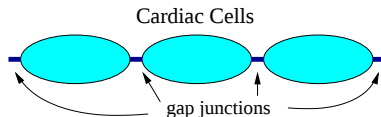
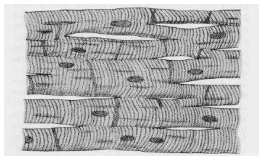
Comments



- The bidomain model is derived using homogenization theory; σ_i and σ_e are *effective* conductivities and the equations are spatially homogeneous.
- Plane wave velocities scale like $\sqrt{\frac{\sigma_i \sigma_e}{\sigma_i + \sigma_e}}$
- So far, no one can explain the 3:1 conduction anisotropy ratio, compared to 6:1 cell size.

More Observations

Cardiac tissue is highly inhomogeneous, leading to the question of the validity of spatially homogeneous models.

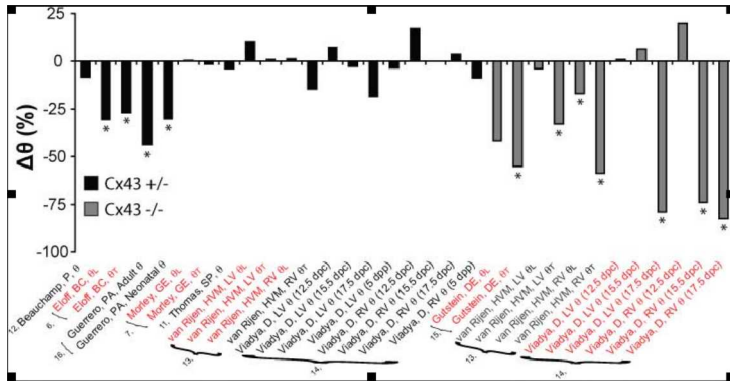


For example, reduced gap junctional coupling can lead to propagation failure. Suppose cells are isopotential

$$\frac{dv_n}{dt} = f(v_n) + d(v_{n-1} - 2v_n + v_{n+1})$$

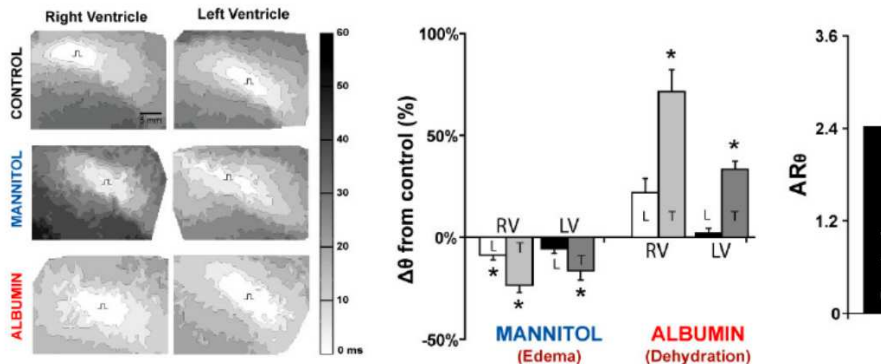
Discrete Cells

Some interesting data



Question: Why did exactly the same mutation lead to such different results in different laboratories?

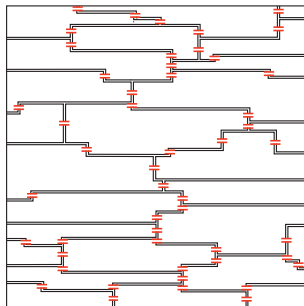
Some interesting data



Question: Why does the size of extracellular space lead to changes in conduction velocity and anisotropy ratio? Nothing in the bidomain model explains this.

Cardiac Structure

- Gap junctional coupling is only end-to-end. There is no side-to-side coupling.
- Extracellular space is highly inhomogeneous.
- Sodium Ion channels are *not* uniformly distributed on the cell membrane.

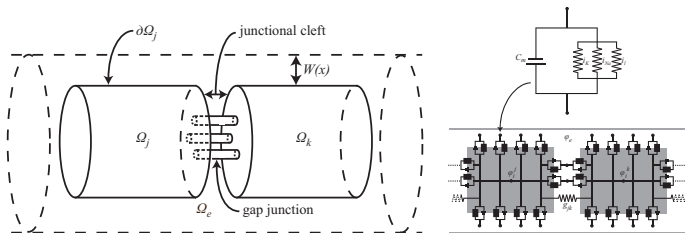


Could these be important (and not captured by the bidomain model)?

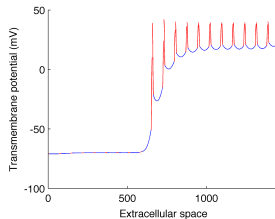
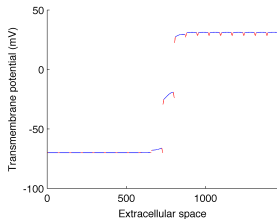
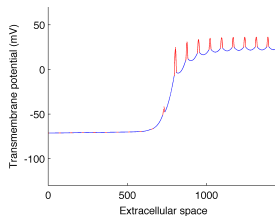
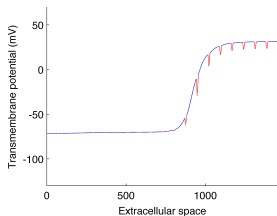
1-D Fiber Reexamined

As before, do a careful balance of currents, however,

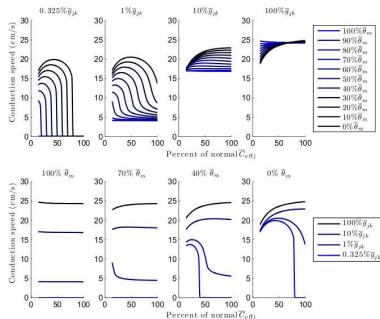
- Cells are discrete, isopotential, coupled by gap junctions.
- Extracellular space includes narrow junctional clefts; extracellular space is *not* isopotential
- Sodium channels are not uniformly distributed.



Some interesting results



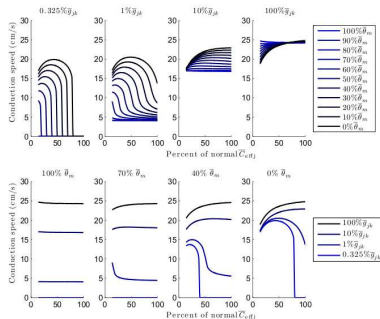
Surprise, Surprise (contrary to Cable Theory):



Because of ephaptic coupling

- Propagation velocity is less sensitive to changes in gap junctional coupling;

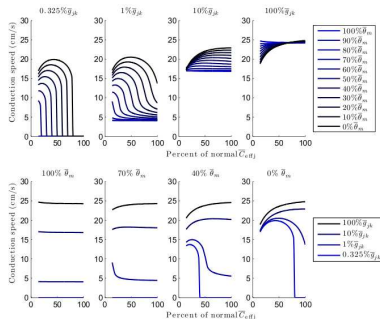
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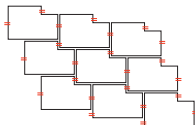
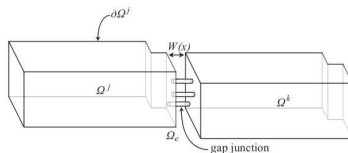
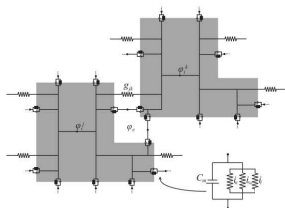


Because of ephaptic coupling

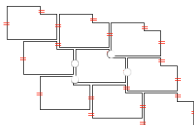
- Propagation velocity is less sensitive to changes in gap junctional coupling;
- The width of junctional space matters;
- The distribution of ion channels matters.

3-D Tissue Model

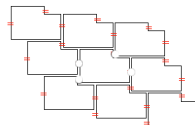
- Intracellular space (rather than extracellular space) is isopotential
- Extracellular space is comprised of thin 2-D sheets - not isopotential
- Gap junctional coupling is only end-to-end



Normal Propagation

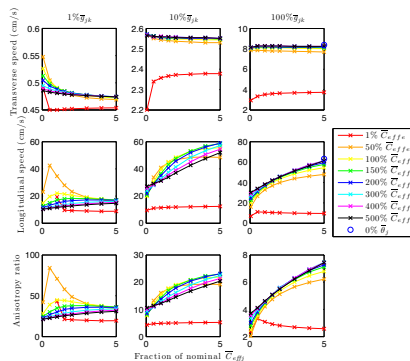


High C_e



Low C_e

Some interesting Observations



- Propagation in transverse direction is much faster than predicted by bidomain model, because of side-to-side ephaptic coupling.

Summary and Conclusion

- Propagation in cardiac tissue is much more complicated than cable theory or the bidomain model suggest;
- There is a substantial amount of ephaptic coupling, due to the spatially inhomogeneous extracellular potential, and the microdomain effects of junctional spaces;
- The mathematical understanding of these features is still incomplete. Homogenization completely fails to account for these effects.

Acknowledgements

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