The Physics of the Heart

Sima Setayeshgar

Department of Physics
Indiana University
Stripes, Spots and Scrolls
DYNAMICS OF CARDIAC ARRHYTHMIAS
The Heart as a Physical System

- Sudden cardiac failure is the leading cause of death in industrialized nations.

**1000 deaths/day in North America**

- Growing experimental evidence that self-sustained patterns of electrical activity in cardiac tissue are related to fatal arrhythmias.

- Goal is to use analytical and numerical tools to study the dynamics of reentrant waves in the heart on physiologically realistic domains.

And ...

- The heart is an interesting arena for applying the ideas of pattern formation.
The heart is an electrically activated mechanical pump

Electrical Activity → Mechanical Function

Seconds

Sinus Node (0.0)
Atria (0.09)
AV Node (0.03)
Purkinje Fibers (0.19)
Ventricles (0.22)

Action Potential
-15 mV
-85 mV
200 ms

From Textbook of Medical Physiology, by Guyton and Hall
Electric potential propagation in a biological cable

Cable Equation:
Hodgkin and Rushton (1946),
Rall (1957,...)

\[ \tau_m \frac{\partial V}{\partial t} + R_m I_{ion} = \lambda_m^2 \frac{\partial^2 V}{\partial x^2} \]

Adapted from Mathematical Physiology, by Keener & Sneyd (1998).

Axial current : \( I_a = I_i + I_e \)

Transmembrane current : \( I_t = I_{ionic} + I_{capacitive} + I_{applied} \)

Transmembrane potential : \( V = V_i - V_e \)

Physical properties : \( C_m, R_m, r_i, r_e, p, d \)

- Kirchoff’s law: \( I_i(x + dx) - I_i(x) = I_e(x) - I_e(x + dx) = -I_t dx \)
- Conservation of charge: \( \partial I_a / \partial x = 0 \)
- Ohmic axial currents: \( V_{i,e}(x + dx) - V_{i,e}(x) = -I_{i,e}(x)r_{i,e}dx \)
Ionic currents in the cardiac cell

Ionic Currents \((I_{Na+}(V), I_{K+}(V), I_{Ca++}(V), \ldots)\): \(I_{ion} \neq V/R_{ion} \)!!

- Electrophysiologically realistic models:
  - **Hodgkin-Huxley (1952):** Squid giant axon

- Reduced models:
  - FitzHugh-Nagumo (1960), ...

The heart is a three-dimensional anisotropic medium

Tissue structure:

- 3d conduction pathway with uniaxial anisotropy

- Propagation speeds:
  \[ c_\parallel = 0.5 \text{ m/s}, \]
  \[ c_\perp = 0.17 \text{ m/s} \]

From Textbook of Medical Physiology, by Guyton and Hall

Excitability and Nonlinear Traveling Waves

(a) Propagating band

\[ \Omega_+ : \text{Excited} \]
\[ \Omega_- : \text{Rest} \]

- speed \( c = c(v) \)
- \( c(v_{\text{front}}) = -c(v_{\text{back}}) \)

Click for movie.

(b) Spiral wave

- \( c(v) \) varies continuously through zero:
  \( c(v_{\text{front}}) > 0 \) and \( c(v_{\text{back}}) < 0 \)

- Existence of pivot point:
  \( c(v^*) = 0 \)

Click for movie.

Experimental Evidence of Spiral Waves


- Time spacing between frames $\sim 5$ ms
- Image size $\sim 5$ cm

Click for movie.
**Big Picture**

What are the basic mechanisms of the onset of fibrillation? How can we control them?

**Tachycardia:**

![Tachycardia Image]

**Fibrillation:**

![Fibrillation Image]

Courtesy of Sasha Panfilov, University of Utrecht

[Click for animation.]
Postgenomic Systems Biology/Physiology ... 

...allows linking genetic information to cellular phenotypes that lead to cardiac arrhythmias

Calculating the heart’s function from first principles ...

... requires data-driven modeling over orders of magnitude in space and time scales!

Ion channel: $10 \text{ nm} \sim 1 \text{ channel/} \mu \text{m}^2$

Cardiac cell: $150 \mu \text{m} \times 15 \mu \text{m} \times 15 \mu \text{m}$
  - 500 to 30,000 channels per cell depending upon cell type

Heart: $10 \text{ cm}$
  - $4 \times 10^9$ cells
  - $2 \times 10^{14}$ channels

**Ratio of spatial scales:** $10^8$

Channels change in $1 - 10 \text{ ns}$, fibrillation time scale $\sim 10 \text{ s}$

**Ratio of temporal scales:** $10^9$
The Problem of Scales: Numerical Approaches

Fibrillation occurs on the scale of the entire heart!

Divide each cardiac cell into 10 segments:
- $4 \times 10^{10}$ segments/heart

50 currents/variables per segment:
- $2 \times 10^{12}$ variables/heart

5 $\mu s$/timestep:
- $2 \times 10^6$ timesteps/$10 s$ of fibrillation

1 year on a TFLOPS workstation!
Ongoing Research

Approaches:
- Use combination of analytical and computational tools
- Use combination of idealized and realistic modeling

Topics:
- Electrophysiology
- Electro-mechanical coupling
- Solid and fluid mechanics

What is my group doing:

Paradigm: Breakdown of single spiral to disordered state resulting from various mechanisms of spiral instability.

- Questions: Role of passive versus active properties of heart tissue as a conducting medium on the generation of electrical wave instabilities
- Members: Jianfeng Lv (G), Xianfeng Song (G), Le Mai Nguyen (UG)
A snapshot of what we do ... 

with Prof. Andrew Bernoff, Harvey Mudd College
Rotating anisotropy

Diffusion constants:

\[ D_{\parallel} > D_{\perp 1} \sim D_{\perp 2} \]

Natural coordinate system defined by fiber direction:

\[
\begin{pmatrix}
\tilde{x} \\
\tilde{y} \\
\tilde{z}
\end{pmatrix}
= \begin{pmatrix}
1 & 0 & 0 \\
0 & \alpha & 0 \\
0 & 0 & 1
\end{pmatrix}
\begin{pmatrix}
\cos \Theta(z) & \sin \Theta(z) & 0 \\
-\sin \Theta(z) & \cos \Theta(z) & 0 \\
0 & 0 & 1
\end{pmatrix}
\begin{pmatrix}
x \\
y \\
z
\end{pmatrix}
\]

\(S\): rescaling, according to 2d anisotropy \(\alpha \equiv (D_{\perp 1}/D_{||})^{1/2}\)

\(R\): rotation, according to fiber direction \(\Theta(z)\)
Governing Equations

Governing equations in new coordinates:

\[ \ddot{\vec{u}} = \vec{f}(\vec{u}) + D_{\parallel} \cdot \Delta_2 \vec{u} + D_{\perp} \cdot \vec{u}_{zz} \]

\[ + D_{\perp} \cdot \left\{ \Theta'^2 \left[ \frac{\partial^2}{\partial \theta^2} + (\alpha^2 - 1) x^2 \frac{\partial^2}{\partial y^2} + \left( \frac{1}{\alpha^2} - 1 \right) y^2 \frac{\partial^2}{\partial x^2} \right] \vec{u} 
- 2 \Theta' \left[ \frac{\partial}{\partial \theta} + (\alpha - 1) x \frac{\partial}{\partial y} - \left( \frac{1}{\alpha} - 1 \right) y \frac{\partial}{\partial x} \right] \frac{\partial \vec{u}}{\partial z} 
- \Theta'' \left[ \frac{\partial}{\partial \theta} + (\alpha - 1) x \frac{\partial}{\partial y} - \left( \frac{1}{\alpha} - 1 \right) y \frac{\partial}{\partial x} \right] \vec{u} \right\} , \]

Only depends on fiber rotation rate, \( \Theta' \) (no explicit dependence on \( \Theta(z) \)).

For FitzHugh-Nagumo (FHN) kinetics:

\[ \vec{u} = \left( \begin{array}{c} V \\ v \end{array} \right) , \quad \vec{f} = \left( \begin{array}{c} -V^3 + 3V - v \\ \epsilon(V - \delta) \end{array} \right) , \quad D_{\parallel} = \left( \begin{array}{cc} D_{\parallel} & 0 \\ 0 & 0 \end{array} \right) , \quad \text{etc} \ldots \]
**Peskin Fiber Distribution Profile**

**Measured**


**Derived**


\[ \Theta(z) = \sin^{-1}\left(\frac{z}{rL}\right) \]

**\( r = \) cutoff parameter**

**\( 2L = \) thickness of ventricular wall**
Perturbation Analysis

Consider the limit of 'small rotating anisotropy':

- Non-dimensional small parameter:

\[ \epsilon^2 = \frac{D_{\perp 2}}{\omega_0 L^2} \frac{1}{r^2 - 1} \left( \frac{\gamma^2}{4} - 1 \right) \left( \frac{D_{\perp 2}}{\omega_0} \right)^{1/2} \]

: transverse diffusion length, \( \ell \)

\[ \frac{2L}{r} \]

: thickness of ventricular wall

\[ \gamma = \alpha + 1/\alpha \]

: 'anisotropy'

- Seek a solution in the form of:

\[ \vec{u} = \vec{U}_0(r, \theta - \omega_0 t + \Theta(z) + \phi(z, t)) + \epsilon^2 \vec{u}_2, \]

where \( \vec{U}_0(r, \theta - \omega_0 t) \) satisfies:

\[ \mathcal{O}(1) : \frac{\partial \vec{U}_0}{\partial t} = \vec{f}(\vec{U}_0) + D_\parallel \cdot \Delta_2 \vec{U}_0 \]

- Scaling assumptions:

\[ \vec{u}_2 \sim \mathcal{O}(1), \quad \phi_z \sim \mathcal{O}(\epsilon), \quad \phi_t \sim \mathcal{O}(\epsilon^2). \]
Validity of Perturbation Analysis?

What is the value of the small parameter for the human ventricle?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{\parallel}$</td>
<td>$1.0 \text{ cm}^2 \text{s}^{-1}$</td>
</tr>
<tr>
<td>$D_{\perp}$</td>
<td>$0.1 \text{ cm}^2 \text{s}^{-1}$</td>
</tr>
<tr>
<td>$\omega_0$</td>
<td>$12.6 \text{ s}^{-1}$</td>
</tr>
<tr>
<td>$\Delta \Theta$</td>
<td>$180^\circ$</td>
</tr>
<tr>
<td>$2L$</td>
<td>$1.0 \text{ cm}$</td>
</tr>
<tr>
<td>$r$</td>
<td>$1.5$</td>
</tr>
</tbody>
</table>

$\epsilon^2 \sim 0.45$
A > 0: Formation of large twist in boundary layer in bulk
A < 0: Expulsion of large twist from bulk to boundaries


Rotating anisotropy of medium generates scroll twist.
Filament buckling instability above twist threshold.

Buckled filament

Tip trajectory

Destabilizing (‘‘sproing instability’’) role of cardiac tissue structure as a conducting medium on dynamics of scroll waves depends on membrane ion kinetics.

Setayeshgar and Bernoff, preprint.
The heart is an important physiological system that is amenable to physical analysis.

From 1920’s: first clinical EKG machine (1920’s) …
To 2020’s: engineered heart on a scaffold??

Polymer Scaffold  Disordered Culture  Ordered Culture

from Ratner Group, University of Washington, Bioengineering