

### The Onset of Fibrillation following a Heart Attack

J. P. Keener

Mathematics Department

University of Utah



#### Some Statistics:

- Cardiovascular disease is the number 1 killer in America (about 10<sup>6</sup> deaths per year).
- At least 250,000 people per year die from a heart attack before reaching a hospital.



#### Some Statistics:

- Cardiovascular disease is the number 1 killer in America (about 10<sup>6</sup> deaths per year).
- At least 250,000 people per year die from a heart attack before reaching a hospital.

#### Fundamental Questions:

- What are the mechanisms underlying the initiation of fibrillation following a heart attack?
- Why do only some heart attacks result in fibrillation?
- What can be done to prevent a heart attack from initiating fibrillation?



## Conduction system of the heart



- Electrical signal originates in the SA node.
- The signal propagates across the atria, through the AV node, and throughout the ventricles.
- The muscle cells contract in unison, and then relax awaiting the next signal.



## What is a heart attack?



- A coronary occlusion leads to loss of blood flow to some region of the heart.
- Ischemia develops.
- Fibrillation may or may not occur.



### Surface View of Fibrillation



The Real Thing

<u>Movie</u>



### Modeling Cardiac Electrical Activity





## Modeling Cardiac Electrical Activity



Transmembrane potential  $\phi$  is regulated by transmembrane ionic currents and capacitive currents:

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



### **Examples**

Examples include:

- Beeler-Reuter model
- Luo-Rudy model(s)
- Winslow-Jafri, Noble, etc.
- <u>Two Variable Models</u>(FHN, Morris-Lecar, Puschino, Mitchell-Schaeffer-Karma, etc.)

$$I_{ion} = g_{Na} m_{\infty}(\phi) h(\phi - \phi_{Na}) + g_k(\phi - \phi_K)$$
$$\tau_h(\phi) \frac{dh}{dt} = h_{\infty}(\phi) - h$$

Imagine the Possibilities Mathematical Biology University of Utah

# Suggested Mechanisms for Initiation of Reentrant Activity

Fundamental question: How is a dynamical system moved from one state (the normal heartbeat) to another (reentry)?



Fundamental question: How is a dynamical system moved from one state (the normal heartbeat) to another (reentry)?

 Anatomical - One way block on a closed 1D loop. (movie)





Fundamental question: How is a dynamical system moved from one state (the normal heartbeat) to another (reentry)?

 Anatomical - One way block on a closed 1D loop. (<u>movie</u>)



Vulnerable Period - Winfree (S1-S2) mechanism (<u>1D</u>) (<u>2D</u>)



Fundamental question: How is a dynamical system moved from one state (the normal heartbeat) to another (reentry)?

 Anatomical - One way block on a closed 1D loop. (movie)



- Vulnerable Period Winfree (S1-S2) mechanism (<u>1D</u>) (<u>2D</u>)
- Early After Depolarizations during Vulnerable Period.



Fundamental question: How is a dynamical system moved from one state (the normal heartbeat) to another (reentry)?

 Anatomical - One way block on a closed 1D loop. (movie)



- Vulnerable Period Winfree (S1-S2) mechanism (<u>1D</u>) (<u>2D</u>)
- Early After Depolarizations during Vulnerable Period.
- Dispersion (i.e. spatial inhomogeneity) of Refractoriness (Moe, et al.).



Fundamental question: How is a dynamical system moved from one state (the normal heartbeat) to another (reentry)?

 Anatomical - One way block on a closed 1D loop. (<u>movie</u>)



- Vulnerable Period Winfree (S1-S2) mechanism (<u>1D</u>) (<u>2D</u>)
- Early After Depolarizations during Vulnerable Period.
- Dispersion (i.e. spatial inhomogeneity) of Refractoriness (Moe, et al.).

Unfortunately, none of these has much explanatory power for fibrillation onset following heart attacks.



Fibrillation following a heart attack is the result of

- A border zone arrhythmia (autonomous pacing)
- that evokes a breakup instability.

Important questions:

- What is a border zone arrhythmia?
- What is a breakup instability?
- Is a border zone arrhythmia capable of evoking a breakup instability?



## **Border Zone Arrhythmias**

Following coronary occlusion:

- Extracellular Potassium increases,
- The resting potential of affected cells increases,
- A current, called current of injury, is created,



• which may stimulate action potentials.

Simple Examples:

- Coupled Cells
- <u>1D Cable</u>







Action Potential Duration Restitution Curve  $APD_n + DI_n = BCL.$ 

where  $APD_n = A(DI_{n-1})$  is the restitution curve. It follows that

$$DI_n = BCL - A(DI_{n-1}),$$

**APD Map Animated** 



## The APD Instability

Stable Pulse on a Ring

Unstable Pulse on a Ring

Collapse of Unstable Pulse



## The APD Instability

Stable Pulse on a Ring

Unstable Pulse on a Ring

Collapse of Unstable Pulse



APD Instability in 2 Dimensions



## Key Observation:

The breakup instability does not require a spiral core to drive it.



Observations:

- The breakup always occurs at some distance from the center. Why?
- The frequency of the spiral is larger than can be achieved by pacing. Why?



## Key Observation:

The breakup instability does not require a spiral core to drive it.



Key Question:

• Can a periodic source or a constant stimulus evoke the breakup instability?



Can a periodic source or a constant stimulus evoke the breakup instability?

- Answer #1: **NO!** 
  - Reason #1: Periodic stimuli cannot excite tissue fast enough to evoke the breakup instability.
  - Reason #2: The APD for a stimulated action potential is too long.
  - Illustration: 1D Cable w/ Monophasic Forcing



Can a periodic source or a constant stimulus evoke the breakup instability?

- Answer #2: **YES!** 
  - Reason: If action potentials are shortened via hyperpolarization, then the breakup instability can be evoked.
  - Illustration: 1D Cable w/ Biphasic Forcing

Question: Is "Biphasic Forcing" possible?



- During ischemia, ATP levels in the cell decrease.
- K<sub>ATP</sub> channels (ATP activated potassium channels) have increased activity when ATP is depleted.
- Increased  $K_{ATP}$  activity shortens the APD of affected cells.
- Shortened action potentials in the border zone provide a source of "biphasic forcing".
- With shortened action potentials, a border zone arrhythmia can elicit the breakup instability.



### Consequences

#### **Results from Simulations:**

1D Border Zone Arrhythmia



### Consequences

#### **Results from Simulations:**

1D Border Zone Arrhythmia





### Consequences

#### **Results from Simulations:**

1D Border Zone Arrhythmia



2D Border Zone Arrhymia



- A possible mechanism for the initiation of fibrillation following a heart attack is:
  - A border zone region resulting from locally high extracellular potassium causes autonomous pacing,
  - A decrease in ATP activates K<sub>ATP</sub> channels locally which shortens action potentials,
  - Rapid pacing with shortened action potentials exposes the breakup instability,
  - resulting in VT and/or fibrillation onset.
- The mathematical observations:
  - This is a generic behavior (a bifurcation), requiring no external stimulus or special physical assumptions.



Does this bifurcation occur in more complicated ionic models?



- Does this bifurcation occur in more complicated ionic models?
- Does this bifurcation occur in real tissue?



- Does this bifurcation occur in more complicated ionic models?
- Does this bifurcation occur in real tissue?
- What is the mathematical structure of this bifurcation?



- Does this bifurcation occur in more complicated ionic models?
- Does this bifurcation occur in real tissue?
- What is the mathematical structure of this bifurcation?
- What are the controlling parameters and parameter ranges? (It took only ten minutes of fooling around with parameters to produce the last 1D figure.)



- Does this bifurcation occur in more complicated ionic models?
- Does this bifurcation occur in real tissue?
- What is the mathematical structure of this bifurcation?
- What are the controlling parameters and parameter ranges? (It took only ten minutes of fooling around with parameters to produce the last 1D figure.)
- Does this have anything to do with reperfusion arrhythmias?



#### Collaborators

- Sasha Panfilov, University of Utrecht
- Brad Peercy, Rice University
- Eric Cytrynbaum, UC Davis, University of British Columbia

#### Notes

- Funding provided by a grant from the NSF.
- This talk can be viewed at http://www.math.utah.edu/ keener/lectures/onset
- No Microsoft products were used or harmed during the production of this talk.

#### The End



### **Real Heart Tissue**



**Potential Reentry Circuit paths** 

#### Go Back.