The Onset of Fibrillation following a Heart Attack

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Basic Problem

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

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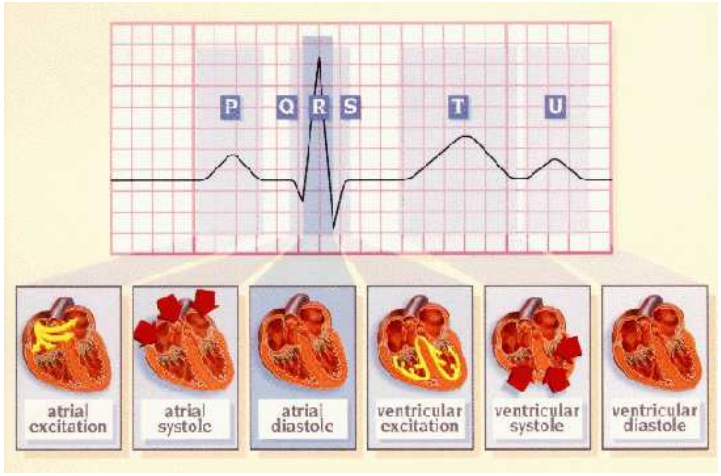
Fundamental Questions:

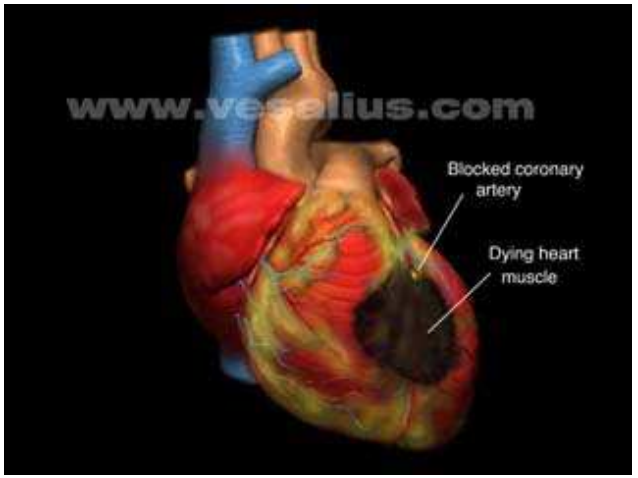
- What are the mechanisms underlying the initiation of fibrillation following a heart attack?
- Why do only some heart attacks result in fibrillation?
- What can be done to prevent a heart attack from initiating fibrillation?

Conduction system of the heart



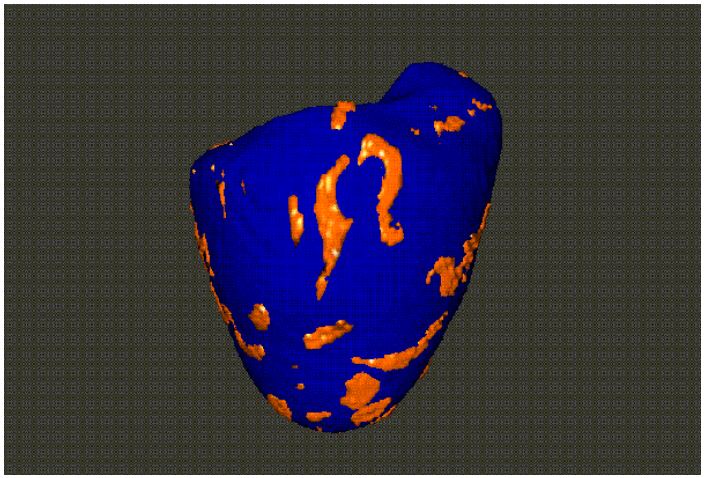
- Electrical signal originates in the SA node.
- The signal propagates across the atria, through the AV node, and throughout the ventricles.
- The muscle cells contract in unison, and then relax awaiting the next signal.

What is a heart attack?



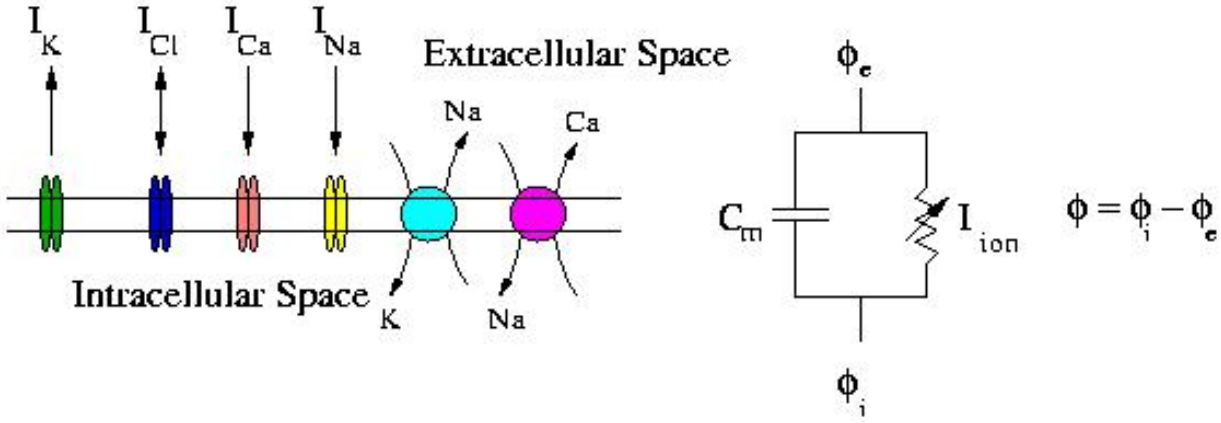
- A coronary occlusion leads to loss of blood flow to some region of the heart.
- Ischemia develops.
- Fibrillation may or may not occur.

Surface View of Fibrillation



Movie

Modeling Cardiac Electrical Activity



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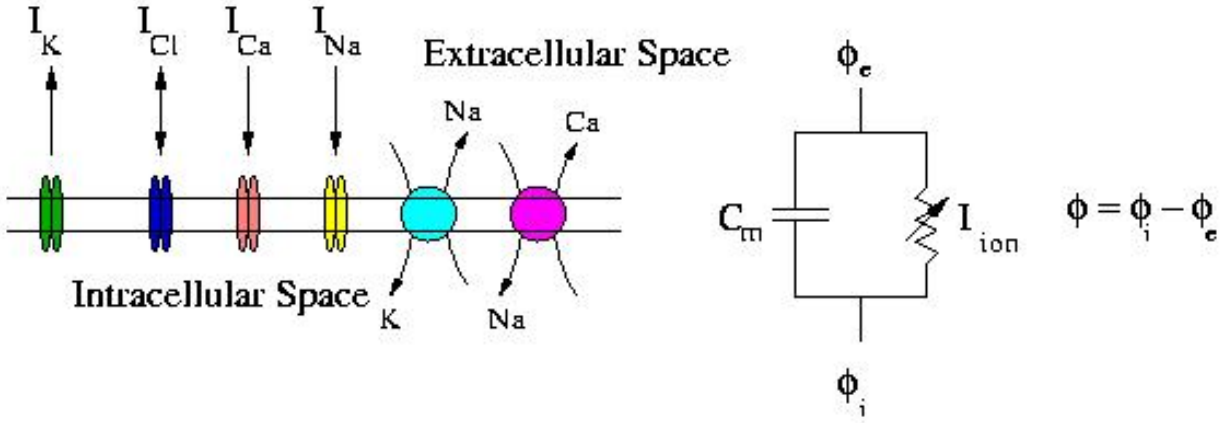

Transmembrane potential ϕ is regulated by transmembrane ionic currents and capacitive currents:

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

Examples

Examples include:

- Beeler-Reuter model (complicated bad model)
- Luo-Rudy model(s) (more complicated, bad models)
- Winslow-Jafri, Noble, etc. (even more complicated, bad models)
- Two Variable Models(FHN, Morris-Lecar, Puschino, Mitchell-Schaeffer-Karma, etc. - highly simplified bad models)

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

$$\tau_h(\phi) \frac{dh}{dt} = h_\infty(\phi) - h$$

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

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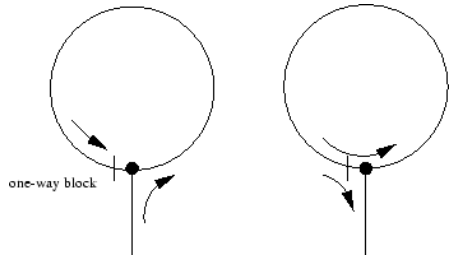

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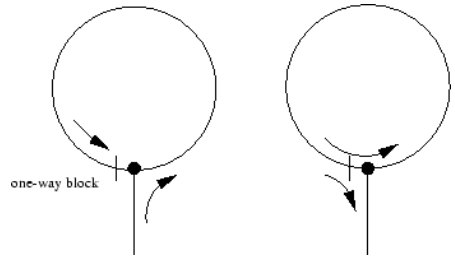

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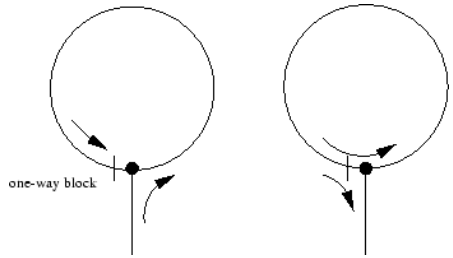

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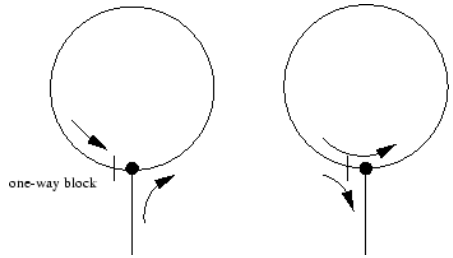

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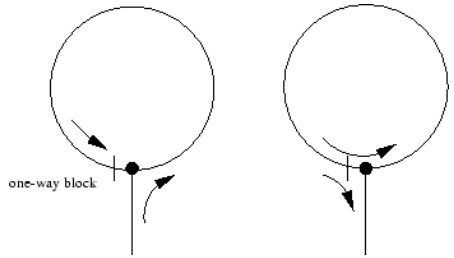

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Unfortunately, none of these has much explanatory power for fibrillation onset following heart attacks.

Hypothesis:

Fibrillation following a heart attack is the result of

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

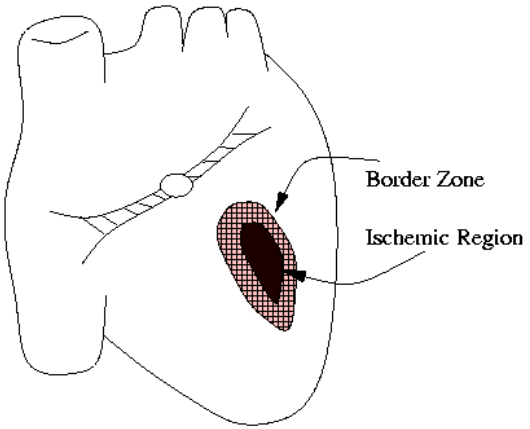
Important questions:

- 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:

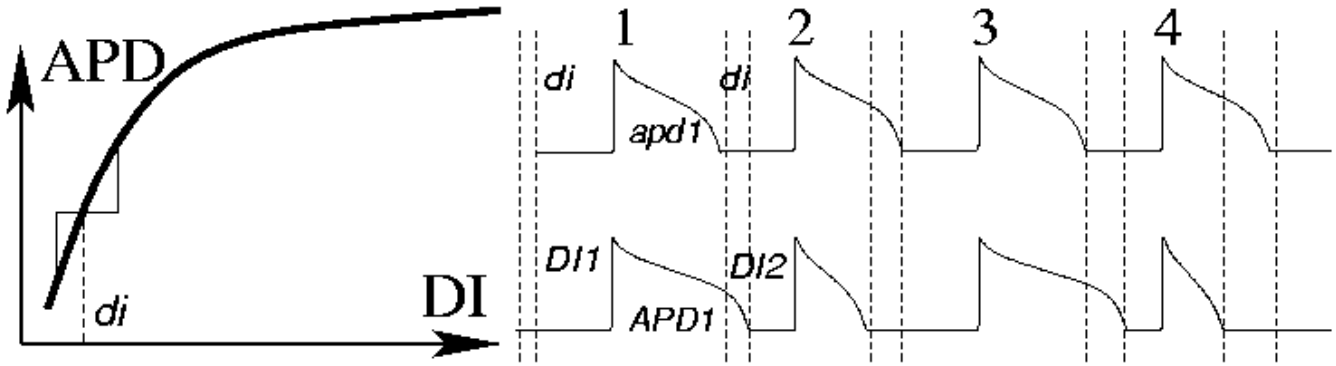
- Extracellular Potassium increases,
- The resting potential of affected cells increases,
- A current, called current of injury, is created,
- which may stimulate action potentials.



Simple Examples:

- Uncoupled Cells Coupled Cells
- 1D Cable

APD Alternans



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

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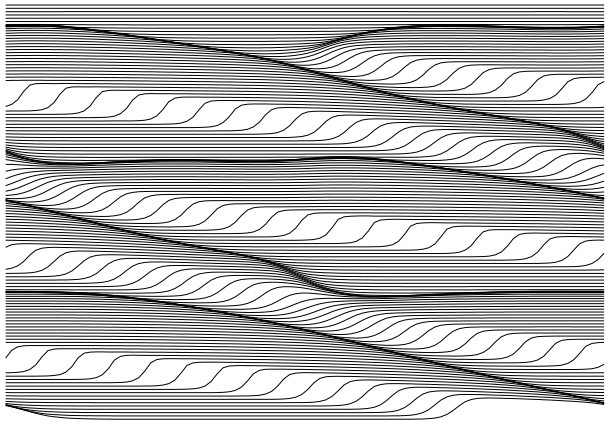

APD Instability in 2 Dimensions

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?

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- 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

Key Question:

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?

Important Facts:

- During ischemia, ATP levels in the cell decrease.
- K_{ATP} 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

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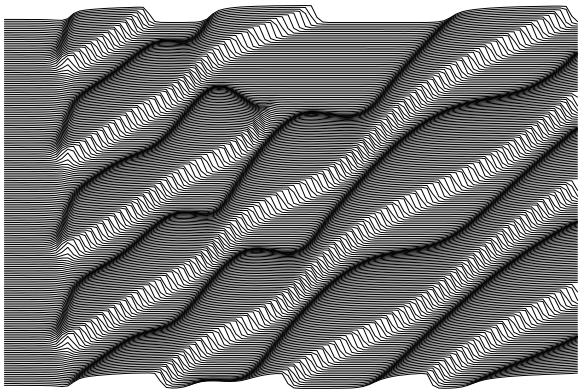

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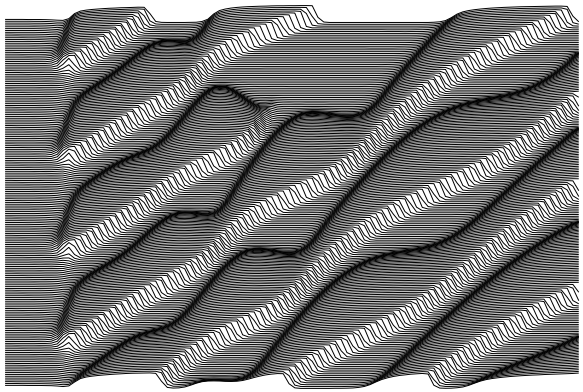

2D Border Zone Arrhymia

Conclusion:

- 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_{ATP} 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.

Many Remaining Questions

There are numerous unresolved questions:

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- Does this have anything to do with reperfusion arrhythmias?

Acknowledgments

Collaborators

- Sasha Panfilov, University of Utrecht
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- 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