The Challenges of Spatial Scales in Modeling and Understanding Cardiac Fibrillation

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Theme

• The abrupt termination of the Cardiac Arrhythmia Suppression Trial (CAST) was the result of fatal drug effects that were not anticipated by model or experiment.
• There is a rapidly growing knowledge base on the structure and function of membrane ion channels.
• What is involved in providing a stronger numerical connection between the ion channel and the electrophysiology of the entire heart?
• Models of the electrical activity of the heart during cardiac fibrillation provide serve as a valuable example of just how hard this might be.
Will a particular antiarrhythmic drug alter either the fibrillation or defibrillation thresholds?

• Or… Why I use rabbit hearts as analog computers.
The **Ultimate Forward Problem**: How can we use knowledge of the protein sequence for voltage-gated ion channels to predict numerically the electrocardiogram during a long episode of fibrillation?
The characteristics of cardiac fibrillation are set by the spatial scale of the entire heart.
10 nanometers: Ion channels are in control
1 nanometer: Pore in a gated ion channel

10^4 meters

10^{-9} meters

The Ultimate Device
Two extremes: Models of cardiac activity

Einthoven triangle and the cardiac dipole moment
1 m, 10 sec

Channel kinetics from patch clamp
10 nm, 1-10 nsec
The problem of scales:
The characteristic lengths and times in biological systems span MANY orders of magnitude.

- An ion channel: 10 nm ~ 1 channel/mm$^2$
- Cardiac cell: 150 mm x 15 mm x 15 mm
  500 to 30,000 channels per cell depending upon cell type
- The heart: 10 cm
  4 x 10$^9$ cells
  2 x 10$^{14}$ channels
- The body: 1 m
- **Ratio of spatial scales:** $10^8$ in distance, $10^{24}$ in volume
- Channels change in 1 - 10 ns, fibrillation time scale ~10 s
- **Ratio of temporal scales:** $10^9$ in time
The Ultimate Forward Problem:

- Assume gated ion-channel protein sequence: 1 nm
- Assume that you can compute
  - Protein structure: 1 – 10 nm
  - Protein kinetics: 1 ns – 100 ms
  - Channel response to antiarrhythmic drugs: 10 nm, 1 ns – 100 ms
  - Cellular, tissue and cardiac electrodynamics: 10 mm, 10 ms
  - Electrocardiogram: 1 m, 10 s
  - Fibrillation and defibrillation thresholds: 1 m, 10 s

- What will this involve?
Start with the DNA sequence for a potassium channel...

Courtesy of Dirk Schneiders
Assemble the proteins
And we solve the protein folding problem...
Insert the folded proteins into the membrane

Voltage-gated Na\textsuperscript{+} channel

Voltage-gated Ca\textsuperscript{++} channel

Voltage-gated K\textsuperscript{+} channel
Compute how the protein conformation depends upon voltage or ligand binding.
See which drugs block the channel
Compute the channel kinetics to determine the switching behavior

Courtesy of Dirk Schneiders
Compute the time-dependent channel conductance

Stochastically activate the channels
Describe the channel currents in terms of a Hodgkin-Huxley-like model such as Luo-Rudy I or II

**Current**
- sodium current
- L-type calcium current
- T-type calcium current
- Na-Ca exchange
  - $I_{T,01}$ (4-AP-sensitive)
  - $I_{T,02}$ (Ca-activated)
- $I_{K,p}$
- $I_{C,p}$ or $I_{K,p}$
- $I_{K,1}$ (inward rectifier)
- $I_{Na}$, $I_{Ca}$, $I_{p}$ (pacemaker current)

**Probable clone**
- H1, SCN5A*
- Na-Ca exchanger
- Kv4.3 (?1.2, 1.4, 1.5, 2.1, 4.2)*
- KvLQT1 + minK (IsK)
- HERG + MiRP1
- Kv1.5
- CFTR, TWIK (?others)
- Kir2.x
- Kir3.1/3.4; Kir6.x/SUR
- hCNG

*+sub-units 20
Sprinkle the channels and their currents onto a family of virtual cardiac cells
Divide each cell into a numerically stable subunit
Assemble the cells into small regions of cardiac tissue.
Include the three-dimensional cable properties of the anisotropic cardiac syncytium.
Assemble the regions into a whole heart
Compute 10 seconds of fibrillation …

Traces of experimental data

Courtesy of Debra Echt
The computer runs forever….

Look at the model

81 free parameters for each volume element in the model
The Problem of Scale: Numerical Models

- Divide each cardiac cell into 10 segments: $4 \times 10^{10}$ segments/heart
- At least 50 currents and other variables/segment $2 \times 10^{12}$ variables/heart
- $5 \mu s$/timestep: $2 \times 10^6$ timesteps/10s of fibrillation
- $4 \times 10^{18}$ equations to solve ... micromoles ....
- 46,000 years on a 25 MFLOP workstation
- 10 years on 1200 100 MFLOP workstations
- 1 year on a 1 TFLOP workstation
- At 100 bytes/segment, 4 Tbytes of memory or disk to store the model

Cherry, Greenside, Henriquez PRL 2/7/00: Whole-heart, minimal adaptive mesh LR1 estimated $10^{-5}$ real time with a 533 MHz DEC a; 70x increase with a 100-parallel computer.
Discussion

• Whole-heart cardiac models involve brute-force solution of partial differential equations, using either HH-type models (LR, etc), or eikonal equations

• At present, there are few if any numerical, theoretical, or analytic connections between the molecular description of the channel and either HH-type or eikonal models
Solutions to the *Ultimate Forward Problem*

- Develop efficient multiscale/mesoscale models to span the full range of space and time
  - Molecular dynamics vs. statistical mechanics vs. thermodynamics
  - Eikonal equations for the wave front properties
  - Direct physiological determination of eikonal equation parameters

- An isolated rabbit heart: **a self-assembling, multivariable, multistate, massively parallel, non-linear analog computer**
  - Solves $\sim 10^{17}$ equations/second at $30/hour$
  - Requires improved programming techniques
  - Requires improved readout of the answer
Characterizing the Cardiac State

What do you do with all the data?

• **Ontological failure**: “The phenomena you are interested in requires elements or laws outside of the set you have been given.”

• **Epistemological Failure**: “You have enough elements and the laws do apply, but you yourself cannot understand the explanation that they provide.”

D Bray, TIBS 22, pp 325-326 (1997)
Visualizing Fibrillation

$V_m$  Phase

Variance  Curl

Vm_Var_Phase_Curl.mp4
And the Third Dimension…

- Transmural waves can exist in 2-D (thin) or 3-D (thick)
- Intramural waves require ~1 cm wall thickness

Spiral vs Scroll Waves
Understanding Cardiac Dynamics

$V_m$ & $Ca^{++}$

vs.

Methoxyverapamil (D-600)

Vm_Ca.mp4
Questions