The heart, cardiac action potentials, and arrhythmias ... and how we model them

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Cardiac action potentials vary by region
Cardiac action potentials

- Upstroke of ventricular AP is Na$^+$ mediated.
- At the peak, Ca$^{2+}$ channels open, causing an inward current that prolongs AP (plateau).
- Ca$^{2+}$ influx triggers additional Ca$^{2+}$ release from the sarcoplasmic reticulum.
- Cytoplasmic Ca$^{2+}$ produces muscle contraction.
- Cardiac cells have many different types of K$^+$ channels.
What is “computational modeling”?

\[ \frac{dV}{dt} = \sum \frac{I_i}{C_m} \]

\[ I_i = g_i \cdot (V - E_i) \]

\[ g_i = f(V,t) \]

CVM model of the canine ventricular myocyte
~13 state variables and ~60 parameters
courtesy of R. Gilmour
What is “computational modeling”?

\[ \frac{dV}{dt} = f(\sum I_i) \]

\[ I_i = g_i (V - E_i) \]

\[ g_i = f(V, t) \]

\[ I_{Na} = \bar{G}_{Na} m^3 h j (V - E_{Na}) \]

\[ \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m \]

\[ \frac{dh}{dt} = \alpha_h (1 - h) - \beta_h \]

\[ \frac{dj}{dt} = \alpha_j (1 - j) - \beta_j \]

\[ E_{Na} = \frac{RT}{F} \ln \left( \frac{[Na^+]_o}{[Na^+]_i} \right) \]

\[ \alpha_m = 0.32 \frac{V + 47.13}{1 - e^{-1(V + 47.13)}} \]

\[ \beta_m = 0.08 e^{\frac{V}{11}} \]

\[ \alpha_h = 0.135 e^{-6.8} \]

\[ \beta_h = \frac{7.5}{1 + e^{-1(V + 11)}} \]

\[ \alpha_j = 0.175 e^{-23} \]

\[ \beta_j = \frac{0.3}{1 + e^{-1(V + 32)}} \]
Cardiac ionic models

- Surge in development of models of cardiac myocyte EP over the last 5-10 years.

- 37 models included on Cell ML website through 2004

- ~1/3 in most recent 3 years.

- Multiple models for same species/region.
Why use computational modeling for cardiac electrophysiology?

- Rodent cardiac myocytes have fundamentally different channel expression levels (especially repolarizing currents). Therefore, transgenic models are not always appropriate.

- Modeling allows one to monitor each component simultaneously – not possible in experiments.

- Dynamics can be observed at resolutions that are unattainable experimentally or clinically.

- It is often cheaper and easier to do so
Cardiac electrical activity: from one cell to many
Gap junctions behave according to Ohm’s law

\[ I = \frac{V}{R} \]

CELL 1

CELL 2
Normal and pathological electrocardiograms (ECG)

An ECG recording of a normal heart rhythm at rest.

An ECG recording of an arrhythmia.

Ventricular Fibrillation
The cause of ventricular arrhythmias

- The majority of ventricular arrhythmias are a direct result of the deterioration of heart tissue resulting from a myocardial infarction (commonly known as a heart attack).

- Arrhythmias are electrical events. Infarctions are mechanical/fluid events.

F. Netter, 1978
How can scar tissue cause arrhythmias?

Ventricular tachycardia is usually characterized by reentrant waves of excitation.

Wave propagating in presence of dense scar

Wave propagating in presence of scar with viable, but damaged, tissue within scar
How can scar tissue cause arrhythmias?

Wave propagates around, but not into, scar

Wave propagates around, and into, scar
How can scar tissue cause arrhythmias?

Wave propagates through scar slowly because the tissue is poorly coupled.
How can scar tissue cause arrhythmias?
How can scar tissue cause arrhythmias?

Waves from either side of the scar merge and propagate beyond scar.

Waves from either side of the scar merge and propagate back into scar (excitable waves propagate into any tissue that is viable and non-refractory).
How can scar tissue cause arrhythmias?

The two intra-scar waves, flowing in opposite directions, annihilate one another. No reentrant rhythm occurs.
How can scar tissue cause arrhythmias?

Now let’s examine what can happen when an *ectopic beat* occurs at the “wrong place and wrong time”.

How can scar tissue cause arrhythmias?

Because the slow conduction zone can also lengthen refractory period, the ectopic wave can block by running into the tail of the preceding wave.
How can scar tissue cause arrhythmias?
How can scar tissue cause arrhythmias?
How can scar tissue cause arrhythmias?

By the time the ectopic wave reaches the top of the scar, the slow pathway has recovered, and the wave can reenter the scar. A reentrant rhythm ensues.
How can scar tissue cause arrhythmias?
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The electrophysiology study
EP study – an effort in signal processing and pattern recognition

• Catheters inserted via venous circulation are used to pace and record from localized areas.

• Pacing allows the physician to take control of the heart and probe its function, including:
  • Induction of arrhythmia via timed stimuli to confirm risk;
  • *Entrainment mapping* and *pace mapping* – techniques that employ pattern matching to determine when an electrode has been properly positioned to within an arrhythmia circuit;
  • *CARTO* mapping – GPS-like mapping system;
  • *Endocardial Solutions* – multielectrode basket catheter.
One treatment: ablation

Radiofrequency energy destroys tissue by resistive heating that creates a non-viable lesion.

Tissue that shouldn’t conduct, sometime does  

Ablation is a cure !!!
Ablation – engineering advances

- **Cryoablation** - reversibly test the effectiveness of an ablation site with moderately cold temperature; more extreme temperature makes lesion permanent.

- **Ultrasound** and **microwave** - which have better depth penetration than radiofrequency ablation.

- **Diode lasers** - can deliver controlled low energy through a variety of fiber configurations (such as loops) to achieve thin, continuous lesions in and around defined anatomical structures such as valve orifices.
Implantable cardioverter defibrillator (ICD)
Implantable Cardioverter Defibrillator (ICD)

Antitachycardia pacing therapy

Defibrillation therapy

Endocardial leads are positioned inside your heart through a vein.
• ICDs don’t always work.
• ICD shocks can be painful.
• High-power shocks drain batteries quickly.

• The more “turbulent” a system becomes, the more difficult it is to alter that system’s dynamics.
• Can we detect the progression to arrhythmia onset and disrupt it?
• Can we improve the efficacy of low-power therapy (i.e., antitachycardia pacing)?
ICDs – engineering advances

• Size reduction; longevity increase.

• Arrhythmia detection improvement – reduction in false shocks, reducing pain and chronic anxiety.

• Indication expansion – e.g., biventricular pacing for heart failure.

• Incorporation of understanding of arrhythmia nonlinear dynamics into termination algorithms:
  • The more “turbulent” a system becomes, the more difficult it is to alter that system’s dynamics.
  • Can we detect the progression to arrhythmia onset and disrupt it?
  • Can we come up with better pacing algorithms?
How can modeling help us understand cardiac arrhythmias?
0-dimensional cardiac simulation (i.e., single cell)

Can be used to investigate rate-dependence of repolarization

“restitution”
Restitution hypothesis of alternans

**Incomplete recovery of $I_K$, $I_{Ca}$**

**Incomplete cycling of $Ca^{2+}$**
Alternans control

Basic concept: control alternans by applying (small) electrical stimuli at well-timed intervals

\[ BCL_{n+1} = \begin{cases} 
BCL^* & \text{for } \Delta BCL_{n+1} > 0, \\
BCL^* + \Delta BCL_{n+1} & \text{for } \Delta BCL_{n+1} \leq 0,
\end{cases} \]

with

\[ \Delta BCL_{n+1} = \frac{\gamma}{2} (APD_{n+1} - APD_n), \]

Ionic model:
Small pieces of ventricular tissue:
Purkinje fiber experiments (length ~2 cm)

Small amplitude alternans: control everywhere

Larger amplitude concordant alternans: control at stimulus end plus some

Discordant alternans: control at stimulus end, concordant alternans
One-dimensional virtual cardiac fiber
Dynamical spatial heterogeneity

CV restitution

Incomplete recovery of $I_{Na}$

Propagation of two closely-timed waves down a cable
Alternans in space

Graphs showing APD and DI at different positions x=0 and x=a.

- APD graph at x=0 and x=a.
- DI graph at x=0 and x=a.
Why alternans is problematic:
Discordant APD alternans to conduction block

modified from R. Gilmour
Alternans control in spatially extended systems

Purkinje fiber model:

Control off

Alternans suppressed everywhere

Control on

Alternans suppressed at stimulus end

Alternans suppressed everywhere
Two-dimensional virtual cardiac tissue
Reentry and tachyarrhythmias
Conduction block can induce reentry
Ionic heterogeneity and alternans

2D sheet

fiber

Anisotropy

$I_{to}$, $I_{Ks}$

Ionic heterogeneity


w/o ionic heterogeneity: effect of SB is minimal

with ionic heterogeneity: presence of SB causes qualitative change in the dynamics
Three-dimensional virtual cardiac tissue
Whole organ computational modeling – 3D atria

3D model is built from 2.5-million sets of single-cell kinetic equations, and realistic human atrial geometry.

In addition to anatomical structures such as valves, the model incorporates heterogeneity in conduction characteristics (diffusion coefficient).
PV ectopic focus initiation of AF

Discordant alternans produces a gradient of refractoriness, which causes conduction block and reentry.

50 mV

200 ms

in inferior view; isthmus region in green
Take-home message

Cardiac modeling is fun and worthwhile