Computational
Mathematical and Informatics Challenges to
Translating Cardiovascular Models to Clinical Care

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What I Will Talk About
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• Biophysical modeling of the cardiac myocyte
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• Structural imaging and modeling of cardiac anatomy and its variations
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• Electrophysiological modeling of cardiac tissue and heart
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- Structural imaging and modeling of cardiac anatomy and its variations
- Electrophysiological modeling of cardiac tissue and heart
- Along the way, comments and questions relating to personalization of models
Biophysical Modeling of the Cardiac Myocyte
Tipping the Balance

-40 pA difference of inward Ca$^{2+}$ current

Work towards more accurate modeling of membrane currents, transporters, and their regulation.
Ionic Currents: From HH to Markov Models

**HH Equations**

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

\[ \dot{m}(t) = [1 - m(t)] \cdot \alpha_m [v(t)] - m(t) \cdot \beta_m [v(t)] \]

\[ \dot{h}(t) = [1 - h(t)] \cdot \alpha_h [v(t)] - h(t) \cdot \beta_h [v(t)] \]

**Equivalent Continuous Time Markov Chain**

```
\begin{array}{c}
[ m_0 h_1 ] \xleftrightarrow{\frac{3\alpha_m}{\beta_m}} [ m_1 h_1 ] \xleftrightarrow{\frac{2\alpha_m}{2\beta_m}} [ m_2 h_1 ] \xleftrightarrow{\frac{\alpha_m}{3\beta_m}} [ m_3 h_1 ] \\
[ m_0 h_0 ] \xleftrightarrow{\frac{3\alpha_m}{\beta_m}} [ m_1 h_0 ] \xleftrightarrow{\frac{2\alpha_m}{2\beta_m}} [ m_2 h_0 ] \xleftrightarrow{\frac{\alpha_m}{3\beta_m}} [ m_3 h_0 ] \\
\end{array}
```

Closed Non-Inactivated States

Open State

Non-Conducting Inactivated States

Independent Gating of Sub-Units

activation/inactivation processes independent

Experiments show independence doesn’t hold
**Time Varying Membrane Potential**

\[
\frac{dv(t)}{dt} = -\frac{1}{C_m} \left[ \sum_{i \in \text{ion currents}} I^i_{\text{ion}}(t) + \sum_{j \in \text{transporters}} I^j_{\text{tr}}(t) \right]
\]

- \(i\) indexes voltage-gated currents
- \(j\) indexes membrane transporter currents (algebraic functions)
- \(C_m\) is membrane capacitance
- \(v(t)\) is membrane potential

**Voltage-Gated Membrane Currents**

\[
I^i_{\text{ion}}(t) = G^i P^i_O(t) \left( v(t) - \frac{RT}{zF} \ln \left( \frac{c^i_{\text{ext}}(t)}{c^i_{\text{int}}(t)} \right) \right)
\]

- \(G^i\) is total conductance for current \(i\)
- \(P^i_O(t)\) is open state occupancy probability at time \(t\) for membrane current \(i\)
- \(v(t)\) is membrane potential at time \(t\)
- \(c^i_{\text{ext}}(t)\) and \(c^i_{\text{int}}(t)\) are external and internal concentrations of the ion to which conductance \(i\) is permeable

**State Occupancy Probabilities**

\[
\frac{dP^i_n(t)}{dt} = \sum_m \left[ P^i_m(t) K^i_{mn} - P^i_n K_{nm} \right]
\]

- \(n\) indexes states of current \(i\), \(m\) indexes states connected to state \(n\)

**Membrane Transporter Currents**

\[
I^j_{\text{tr}}(t)
\]

- \(j\) indexes transporter currents

**Time-Varying Concentrations**

\[
\frac{dC^k_j(t)}{dt} = -\frac{I^k_{\text{Total}}(t)}{zF V^{eff}_j}
\]

- Time rate of change of concentration of ion \(k\) in compartment \(j\)
- \(I^k_{\text{Total}}(t)\) is total current for ion \(k\)
- \(V^{eff}_j\) is volume of compartment \(j\)
Ca\textsuperscript{2+} Signaling is Intimately Involved in Cellular Arrhythmias

L-Type Ca\textsuperscript{2+} Channels (LCCs)

Ryanodine-Sensitive Ca\textsuperscript{2+} Release Channels (RyRs)

15 nm
Ca$^{2+}$ Signaling is Intimately Involved in Cellular Arrhythmias

Voltage-Dependent Activation (VDI)

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Extracellular

Cytosol

Sarcolemma

JSR Membrane

JSR Lumen

Diad

15 nm
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Ca-Induced Ca-Release (CICR)

Extracellular  \(\longleftrightarrow\) Cytosol  \(\longleftrightarrow\) JSR Lumen

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JSR Membrane

Ca$^{2+}$-$\text{Dependent Inactivation (CDI)}$

15 nm
Ca$^{2+}$ Signaling is Intimately Involved in Cellular Arrhythmias

Ca-Induced Ca-Release (CICR)

- **VDI** is slow and weak
- **CDI** is strong and fast
- LCCs and RyRs are so tightly coupled they gate as a single “macro-channel”
Many Different Properties of Ca$^{2+}$ Signaling Linked With EADs

**“Indirect”**

| Ca$^{2+}$ extrusion by serca pump |
| Recovery from CDI |
| Re-activation of LCCs |

**“Direct”**

- Slowed VDI, reduced CDI (LCC mutation - Timothy Syndrome)
- Reduced JSR Ca$^{2+}$ load (serca down-regulation, RyR leak in HF)
- CaMKII phosphorylation of LCCs, (increased mode 2 gating), ischemia & HF
- CaMKII phosphorylation of Na channels, incomplete inactivation, late current
- ROS$_m$ $\Rightarrow$ H$_2$O$_2$ $\Rightarrow$ CaMKII
- PKA phosphorylation of LCCs, increased mode 2 gating

- Drug block of I$_K$’s
- Mutations
  - loss of function mutations I$_{K_s}$ (LQT1), I$_{K_r}$ (LQT2)
  - Incomplete inactivation of I$_{Na}$ (late Na current, LQT3)
Spontaneous RyR Openings, NCX Current, and Delayed Afterdepolarizations (DADS)

DADs Upon Increased JSR Ca\textsuperscript{2+} Load

Cardiovascular Physiology (Pappano & Wier)

RyR P\textsubscript{0} Increases with JSR Ca\textsuperscript{2+} Load

Spontaneous RyR Openings, NCX Current, and Delayed Afterdepolarizations (DADS)

The Metabolic Sink Hypothesis

Maack & Bohm (2011) JACC 58(1): 83
ROS-Induced ROS-Oscillations

Loss of $\psi_m$, Low ATP, Increased $P_o$ K$_{ATP}$ Channels, Conduction Block
Comments & Questions
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• How do these cellular arrhythmias trigger ventricular arrhythmias?
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• How do these cellular arrhythmias trigger ventricular arrhythmias?
  • multiple regions of partial EAD synchronization (Sato et al 2009 PNAS 106(9): 2983)
  • something simpler? - afterdepolarizations arising in electrically isolated tissue (Purkinje fibers, trabecular muscle fibers, viable cells within necrotic regions) propagate into ever larger tissue masses.
Anatomical Modeling of the Heart

Manual Dissections


Quantitative Histology & Fiber Mapping


Sheet Reconstruction


The Auckland Heart Finite Element Model

Microstructure

Diffusion Imaging

DTMRI & Fiber Inclination Angle


Transmural Inclination Angle Histologic & DTMRI Reconstruction


DTMRI-Based Anatomic Reconstruction and Cardiac Computational Anatomy


- 11 normal, 12 failing canine hearts
- 1 normal human heart
- All data available at www.bme.jhu.edu

DTMRI and Sheet Orientation


Average DTMRI $\varphi$: -45° and 117°
Experimental $\varphi$: Dokos et al 45° and 110°; Ashikaga et al 36° and 116°
Cardiac Atlasing Using the Large Deformation Diffeomorphic Metric Mapping Algorithm (LDDMM)
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Structural Analysis of the Failing Canine Heart Ex-Vivo

Relative Wall Thickness

Fiber Inclination Angle

Sheet Angle

Top: Normal canine voxel-by-voxel mean values on atlas
Middle: Failing canine voxel-by-voxel mean values on atlas
Bottom: Statistically significant differences (p=.01) between normal and failing populations

Between “Subject” Variability of Fiber Inclination Angle

- Fiber inclination angle (6 hearts) mapped onto atlas
- Sampled multiple corresponding anterior, lateral posterior regions
- Standard deviation about mean across hearts at corresponding locations < 7°

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• It is therefore unlikely that fiber structure can be measured in the beating heart. Measurements may represent residual fiber strain
• Low subject to subject variability of fiber structure may mean that diffeomorphic mapping of atlas fiber structure to individual hearts may be reasonable
High Resolution Heart Reconstruction

Langendorff-Perfused Heart
Ischemia, Hoechst & Mito-Red Labeling

Collect Optical Stack
Repeat in x-y plane
(Optical Cross Section)

Slice & Stack

Two-Photon Imaging &
Microtome Reconstruction

Image Processing &
Volume Reconstruction

High Resolution Heart Reconstruction
Long QT Syndrome 1 (LQT1)

- 34 known mutations of KCNQ1
- LQT1 ⇒ risk for sudden death

Study

- 633 LQT1 Subjects
- Functional characterization of each KCNQ1 mutant
- AP model ionic model based on genotype
- 1-D model of transmural conduction and ECG

Hoefen et al (2012) JAC 60: 2182
Image-Based Modeling for Surgical Ablation Therapy

Patient-Specific Design of Cardiac Ablation Therapy

MRI-Based Anatomical Models of 12 Patient Hearts

Simulations Reveal Optimal Ablation Site per Patient

What do simulations predict re burns outside the predicted/optimal ablation zone?
How can the physician be guided to the right location with error < 5 mm in a beating heart?
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Subject to Subject Transmural Molecular Heterogeneity

- 16 replicates
- Local protein controls
- 10% expression change
- 80% power

Transmural Protein Expression 4 Canines, LV Lateral Wall

SERCA2A ~ Δ30%, JSR Ca$^{2+}$ Δ 30%, APD$_{90}$ Δ 50 mSec

NCX1 ~ same

CX43 Δ ~ 40%, CV 60-70 cm/Sec (LV lateral), 45-70 cm/Sec (LV anterior)

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• Delivering real, working diagnostics/therapies is a very hard problem with long event horizon that includes FDA
  - Use animal models, where much more can be probed, to test ideas and approaches
Thanks to all who have contributed

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<tr>
<th>Myocyte Modeling</th>
<th>Genomics &amp; Proteomics</th>
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<tbody>
<tr>
<td>Saleet Jafri</td>
<td>Christina Yung</td>
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