Cardiovascular Dynamics *in-silico*

Pharmacological Targeting of Long QT 3 Syndrome: Proof of Concept for an *in-silico* Drug Development Platform

Jonathan D. Moreno  
MD/PhD Candidate  
Colleen Clancy Laboratory  
Institute for Computational Biomedicine  
Weill Cornell Medical College

Outline

- Biophysics | Clinical Medicine | Cardiovascular Pharmacology | Mathematics | Engineering | HPC
- Ion-channel mutations (long QT)  
  - Biophysics, genotype, phenotype and clinical characteristics
- Current treatment strategies
- *In-silico* predictive modeling and computational biomedicine  
  - Formulation of Markov models of drug-receptor interactions  
  - Channel | cell | cable | tissue | 3D heart  
    - Numerical techniques  
    - High performance computing
Ion-channel mutations and their arrhythmogenicity

- **Channelopathy**: Mutations in genes that encode ion channels can lead to abnormal channel function leading to perturbation of the AP to cause arrhythmias. Specific Na⁺ channel mutations:
  - Gain of function during AP plateau (LQT)
  - Overall loss of channel function (Brugada, ICCD, SSS)

- Hereditary Long QT (LQT) syndrome
  - Prolongation of QT interval on ECG can lead to life-threatening arrhythmias and sudden cardiac death
  - **LQT3**: Usually bradycardic; occurring during sleep or relaxation

The Long QT (3) Syndrome

- Heterogeneous group of mutations in cardiac sodium channel α subunit
  - Genetically distinct, clinical presentation similar with subtle differences
  - Overlapping syndromes with clinical characteristics coexisting in a single patient

- ΔKPQ identified in 1995
  - Transient failure of inactivation → persistent \( I_{Na} \)
- D1790G: C terminal mutation, LQT3 clinical phenotype, possible distinct mechanism of action
Na⁺ Channel Macromolecular Complex

Spectrum of Mutations in SCN5A
The Excitatory Cycle of an Ion Channel

- Open
- Closed
- Inactivated
- Recovery
- Transient failure of inactivation

ΔKPQ increases arrhythmogenic triggers
Hodgkin Huxley Formulation

- HH formulation computes conductance for each current as a function of the P(O) of a series of hypothetical gates
  - Conductance is f(t, V) via gates
  - 1st order transitions from C → O and O → C that are independent of the other gates
  - Ions can only pass through the open state of the gate
- Based on experimental data, Na⁺ activation can be modeled by 3 identical activation gates (m³)
- Inactivation shortly after activation (h)
- LRd also includes slow inactivation gate (j)

\[ I_{Na} = G_{Na} * m^3 * h * j \times (V - E_{Na}) \]

Markov-based Models

**Motivation**

- Need for models with explicit representation of single ion-channel states
- HH models are limited in their ability to describe specific aspects of single channel behavior
  - Inactivation of the Na⁺ channel greater when in state O
- Assumption of independent gating (m³hj) fails
- MM can represent the dependence of a given transition on the occupancy of different states of the channel
  - Assume that transitions between channel states depend on the present conformation of the channel, but not on previous behavior
Formulating the model

• Wild Type: Use as many states as necessary to recapitulate the kinetics of channels
• Experimental data:
  - $k_{on}, k_{off}$ rates
  - pKa – for drug partitioning
  - Steady State Availability
  - Tonic Block - $k_{closed}$
  - Use Dependent Block - $k_{open}$
  - Frequency dependence of UDB
  - Recovery from UDB

• Models adhere to 2nd law of thermodynamics (microscopic reversibility)
• Start playing!
ΔKPQ Channel with Bursting States

Runge Kutta Formulation

Forward Euler
- Error O(h²)

Fourth Order Runge Kutta
- Error O(h⁴)

\[\frac{dy}{dt} = f(t,y)\]

\[k_1 = h \cdot f(t_n, y_n)\]

\[k_2 = h \cdot f\left(t_n + \frac{h}{2}, y_n + \frac{k_1}{2}\right)\]

\[k_3 = h \cdot f\left(t_n + \frac{h}{2}, y_n + \frac{k_2}{2}\right)\]

\[k_4 = h \cdot f\left(t_n + h, y_n + k_3\right)\]

\[y_{n+1} = y_n + \frac{k_1}{6} + \frac{k_2}{3} + \frac{k_3}{3} + \frac{k_4}{6} + \text{Error}\]
The failure of antiarrhythmics

- Sudden Cardiac Death is the #1 cause of death in the US, CVD in general will be global cause of death by 2020
- CAST, CAST II trials:
  - an incomplete understanding and inability to predict interaction of intrinsically complex drug pharmacology with complexity of cardiac tissue
    - Drug receptor dynamics
    - Anatomical and electrical heterogeneity
    - Mutant channel interactions
- Off target effects of noncardiovascular therapeutics
  - 40% of all new pharmaceuticals affect repolarization process
  - Vast majority of drugs pulled off market (Vioxx)
  - Side effects may occur <1% of patient population
    - Predict vulnerable populations?
    - Discard compounds earlier in the product development pipeline?
  - 50:1 failure to success rate

“All you have to do is to decrease our attrition rate from around 98% to 96% and you would make us twice as successful.”
Cardiovascular Dynamics *in-silico*

- Single channel $\rightarrow$ single cell $\rightarrow$ 1D fiber $\rightarrow$ 2,3D tissues
  - *Spatiotemporal trends that emerge in higher dimensions that allow for propagation of arrhythmia are missed at smaller spatial scales*

- Develop a computational framework for an *in-silico* drug screen of cardiovascular medications
  - Predictive simulations of pharmacodynamics in an engineered virtual cardiac tissue
  - Identification of key parameters for drug-receptor dynamics

Model “wish list”

- Transport phenomena: Diffusion
- Kinetics of drug receptor interactions
- Macroscopic wave propagation
- Scalability: 0D $\rightarrow$ 3D
- Optimize with high performance computing
  - Numerical optimizations
  - Parallel computations
  - GPGPU
Sodium Channel Block Subclassification

• Class IA (e.g., quinidine)
  – Moderate Na⁺ channel blockade
  – ↑ ERP
• Class IB (e.g., lidocaine)
  – Weak Na⁺ channel blockade
  – ↓ ERP
• Class IC (e.g., flecainide)
  – Strong Na⁺ channel blockade
  – ⇒ ERP

Flecainide – Class 1C antiarrhythmic
  – pKa ~ 9.3
  – 99% charged at physiologic pH

Lidocaine – Class 1B antiarrhythmic
  – pKa ~ 7.6
  – 50% charged at physiologic pH
**pH Dependent Partitioning**

1. **Partitioning**

\[ \text{H}^+ + [D] \leftrightarrow [DH^+] \]

3. **Hydrophobic pathway**

6. **Neutral drug**

4. **Repartitioning**

2. **Flux**

\[ \text{H}^+ + [D] \leftrightarrow [DH^+] \]

5. **Charged drug**

Clancy, CE.

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**Channel | Cell | Cable | Tissue | 3D Heart**

- Troponin
- Calmodulin
- Sarcoplasmic Reticulum
- JSR
- NSR
- Leak
- Rel
- Na,b
- Ca
- NaCa
- K\(_{\text{Ca}}\)
- p(Ca)
- Ca(T)
- Ca,b
- Up
- Ks
- K1
- Kp
- Kr
- NaK
- K\(_{\text{ATP}}\)
- ins(Ca)

Institute for Computational Biomedicine | Weill Cornell Medical College of Cornell University