Math 6790: Case Studies in Computational Engineering and Science

Mathematical Modeling of Cardiac Electro-Mechanics: From Protein to Whole Organ

Cellular Electrophysiology II
Overview

- Recapitulation Electrophysiology I

- Cellular Electrophysiology II
  - Ordinary Differential Equations
  - Numerical Techniques
  - Myocyte Models
  - Channel Models

- Summary
Ordinary Differential Equations (ODEs)

ODEs of n-th order can be reduced to set of 1st order ODEs

2nd order ODE
\[ \frac{\partial^2 u}{\partial x^2} + q(x) \frac{\partial u}{\partial x} = r(x) \]

System of 1st order ODEs
\[ \frac{\partial u}{\partial x} = z(x) \]
\[ \frac{\partial z}{\partial x} = r(x) - q(x)z(x) \]
1st Order ODE for Describing Transmembrane Voltage

\[ I_m = I_i + C_m \frac{d}{dt} V_m \]

- \(I_i\): Injected current [A]
- \(I_m\): Current through membrane [A]
- \(C_m\): Membrane capacitor [F]
- \(V_m\): Membrane voltage [V]
Numerical Solution of ODEs

**Procedure**

Discretization: \[ \frac{\partial u}{\partial x} \Rightarrow \frac{\Delta u}{\Delta x} \]

Choose appropriate step length \( \Delta x \): Distance between \( x_n \) and \( x_{n+1} \)

Determining factor for numerical error

**Numerical Methods**

- Euler Method
- Runge-Kutta Method 2. Order
- Runge-Kutta Method 4. Order
- Richardson-Extrapolation, Bulirsch-Stoer Method
- Predictor-Corrector Methods
- …
Euler Method

\[ \frac{\partial u}{\partial x} = f(x,u) \]

Finite Difference Approximation

\[ \frac{u_{n+1} - u_n}{x_{n+1} - x_n} = f(x_n,u_n) \]

Rewriting

\[ u_{n+1} = u_n + hf(x_n,u_n) \]
Euler Method: Example

$$\frac{dV_m}{dt} = I_{stim}(t) - \frac{1}{C_m} I_{ion}(t,V_m)$$

Finite Difference Approximation

$$\frac{V_{n+1} - V_n}{t_{n+1} - t_n} = I_{stim}(t_n) - \frac{1}{C_m} I_{ion}(t_n,V_n)$$

Rewrite

$$V_{n+1} = V_n + \Delta t \left( I_{stim}(t_n) - \frac{1}{C_m} I_{ion}(t_n,V_n) \right)$$
Runge-Kutta Method 2nd Order

\[ \frac{\partial u}{\partial x} = f(x,u) \]

\[ k_1 = hf(x,u_n) \]
\[ k_2 = hf\left(x_n + \frac{1}{2}h, u_n + \frac{1}{2}k_1\right) \]

\[ u_{n+1} = u_n + k_2 \]
Runge-Kutta Method 2nd Order: Example

\[ \frac{dV_m}{dt} = I_{\text{stim}}(t) - \frac{1}{C_m} I_{\text{ion}}(t, V_m) \]

\[ k_1 = \Delta t \left( I_{\text{stim}}(t_n) - \frac{1}{C_m} I_{\text{ion}}(t_n, V_n) \right) \]

\[ k_2 = \Delta t \left( I_{\text{stim}}(t_n + \frac{h}{2}) - \frac{1}{C_m} I_{\text{ion}}(t_n + \frac{h}{2}, V_n + \frac{k_1}{2}) \right) \]

\[ V_{n+1} = V_n + k_2 \]
Runge-Kutta Method 4th Order

\[ \frac{\partial u}{\partial x} = f(x,u) \]

Discretization

\[ k_1 = hf(x,u_n) \quad k_2 = hf\left(x_n + \frac{1}{2}h,u_n + \frac{1}{2}k_1\right) \]
\[ k_3 = hf\left(x_n + \frac{1}{2}h,u_n + \frac{1}{2}k_2\right) \quad k_4 = hf\left(x_n + h,u_n + k_3\right) \]

Step

\[ u_{n+1} = u_n + \frac{k_1}{6} + \frac{k_2}{3} + \frac{k_3}{3} + \frac{k_4}{6} \]
Runge-Kutta Method 4th Order: Example

\[ k_4 \left\{ \frac{1}{2} k_3 \right\} \left\{ \frac{1}{2} k_2 \right\} \left\{ \frac{1}{2} k_1 \right\} \]

\[ u_{n+1} \]

\[ x_n \quad x_{n+1} \]

\[ \frac{h}{2} \quad \frac{h}{2} \]
Electrophysiological Models of Cells: Motivation

Description of Insights in Prediction of electrophysiological phenomena

Applications
• Diagnostics
  • Electro- und magneto-cardiography
  • Electro- und magneto-myography
  • Electro- und magneto-neurography
  ...

• Therapy
  • Parameterization and optimization of electrical nerve stimulators, defibrillators, and pace maker
    • electrode material, shape and position
    • signal
  • Development, evaluation and approval of pharmaceuticals
  • Education and teaching in cardiology, bioengineering, and pharmacology
  ...

CVRTI
Electrophysiology of Cardiac Myocytes: Basics

Depolarisation:
After reaching of threshold voltage:
short term increase of $g_{Na}^+$

Plateau phase:
Fast increase followed by slow decrease of $g_{Ca}^{2+}$
Fast decrease followed by slow increase of $g_{K}^+$

Repolarisation:
Return of $g_{Na}^+$, $g_{K}^+$ and $g_{Ca}^{2+}$ to resting values
Partly, $g_{K}^+$ increase leads to hyperpolarisation
Development of Electrophysiological Cell Models

Measuring system

- Space-, voltage- and patch-clamp
- Voltage sensitive dyes
- Channel blockers, e.g. TTX for Na channels
  ...

Measurement results

- Action voltage, membrane currents, conductivities, ion concentration, membrane capacitance
- length, volumes
  ...

Mathematical model

- Commonly, system of ODEs
  e.g. of Hodgkin-Huxley and Markov type
## Models of Cellular Electrophysiology

<table>
<thead>
<tr>
<th>Year</th>
<th>Model</th>
<th>Type</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>1952</td>
<td>Hodgkin-Huxley</td>
<td>axon membrane</td>
<td>giant squid</td>
</tr>
<tr>
<td></td>
<td>Noble</td>
<td>Purkinje fiber</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beeler-Reuter</td>
<td>ventricular myocyte</td>
<td>mammal</td>
</tr>
<tr>
<td></td>
<td>DiFrancesco-Noble</td>
<td>Purkinje fiber</td>
<td>mammal</td>
</tr>
<tr>
<td></td>
<td>Earm-Hilgemann-Noble</td>
<td>atrial myocyte</td>
<td>rabbit</td>
</tr>
<tr>
<td></td>
<td>Luo-Rudy</td>
<td>ventricular myocyte</td>
<td>guinea pig</td>
</tr>
<tr>
<td></td>
<td>Demir, Clark, Murphey, Giles</td>
<td>sinus node cell</td>
<td>mammal</td>
</tr>
<tr>
<td></td>
<td>Noble, Varghese, Kohl, Noble</td>
<td>ventricular myocyte</td>
<td>guinea pig</td>
</tr>
<tr>
<td></td>
<td>Priebe, Beuckelmann</td>
<td>ventricular myocyte</td>
<td>human</td>
</tr>
<tr>
<td></td>
<td>Winslow, Rice, Jafri, Marban, O’Rourke</td>
<td>ventricular myocyte</td>
<td>canine</td>
</tr>
<tr>
<td></td>
<td>Seemann, Sachse, Weiss, Dössel</td>
<td>ventricular myocyte</td>
<td>human</td>
</tr>
</tbody>
</table>

Models describe cells by set of ordinary differential equations. Equations are assigned to a whole cell and/or a small number of its compartments.
Beeler-Reuter Model 1977

Electrophysiological model of mammalian ventricular myocyte membrane

Parameterization by measurement with clamp techniques

\[ \begin{align*}
I_{Na} & : \text{Inward current of sodium} \\
I_{Ca} & : \text{Inward current (primarily calcium)} \\
I_{K1} & : \text{Outward current of potassium} \\
I_{X1} & : \text{Outward current (primarily potassium)} \\
[Ca^{2+}]_i & \\
\end{align*} \]

\( V_m \)
Beeler-Reuter: Equations for Currents

\[ i_{X1} = X1 \cdot 0.8 \left( \frac{e^{0.04(V_m+77)}}{e^{0.04(V_m+35)}} - 1 \right) \]

\[ i_{Na} = \left( g_{Na} m^3 h j + g_{NaC} \right) (V_m - E_{Na}) \]

\[ i_{K1} = 0.35 \left( \frac{4e^{0.04(V_m+85)} - 1}{e^{0.08(V_m+53)} + e^{0.04(V_m+53)} + \frac{0.2(V_m+23)}{1-e^{-0.04(V_m+23)}}} \right) \]

\[ i_s = g_s d f (V_m - E_s) \]

\[ E_s = -82.3 - 13.0287 \ln \left[ Ca^{2+} \right] \]

\[ E_{Na} = 50 \text{ mV} \]

\[ i_{X1}, i_{Na}, i_{K1}, i_s: \text{Current densities } [\text{µA/cm}^2] \]
\[ V_m: \text{Transmembrane voltage } [\text{mV}] \]
\[ E_s, E_{Na}: i_s \text{ and sodium Nernst voltages } [\text{mV}] \]
\[ g_s: \text{Conductivity } [\text{mS/cm}^2] \]
\[ g_{Na}: \text{Conductivity of open Na channels } [\text{mS/cm}^2] \]
\[ g_{NaC}: \text{Conductivity of closed Na channels } [\text{mS/cm}^2] \]
\[ d, m, X1: \text{Activation state (described by ODE)} \]
\[ f, h, j: \text{Inactivation state (described by ODE)} \]
\[ \left[ Ca^{2+} \right]: \text{Concentration of intracellular calcium } [\text{mmol/cm}^3] \]
Beeler-Reuter: Equations for Currents and Concentrations

\[
\frac{dV_m}{dt} = -\frac{1}{C_m}\left(i_{K1} + i_{X1} + i_{Na} + i_{Ca} + i_{\text{external}}\right)
\]

\[
\frac{d[Ca^{2+}]}{dt}_i = -10^{-7}i_s + 0.07(10^{-7} - [Ca^{2+}]_i)
\]

\[
C_m = 1\frac{\mu F}{cm^2}: \text{Membrane capacitance per area}
\]

Results of simulations for stimulus frequency of 1 Hz
Luo-Rudy Model

Electrophysiological model of ventricular myocyte membrane from guinea pig

Parameterization by measurement with clamp techniques

• Phase I: 1991
• Phase II: 1994

Motivation

• Improved measurement techniques (e.g. single ion channel measurements)
• Deficits of Beeler-Reuter, e.g.
  • Fixed extracellular ion concentrations
  • Neglect of calcium transport and buffering in sarcoplasmic reticulum
  • Neglect of cell geometry
  ...

CVRTI

Case Studies in Computational Engineering and Science - Page 19
Luo-Rudy Model

Extracellular space

Sarcoplasmic reticulum

Myoplasm

Geometry
cylinder-shaped
length: 100 µm
radius: 11 µm

<table>
<thead>
<tr>
<th>Current</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca,b</td>
<td>I_{Ca,b}</td>
</tr>
<tr>
<td>Ca</td>
<td>I_{Ca}</td>
</tr>
<tr>
<td>Na-Ca</td>
<td>I_{NaCa}</td>
</tr>
<tr>
<td>p(Ca)</td>
<td>I_{p(Ca)}</td>
</tr>
<tr>
<td>Up</td>
<td>I_{Up}</td>
</tr>
<tr>
<td>leak</td>
<td>I_{leak}</td>
</tr>
<tr>
<td>rel</td>
<td>I_{rel}</td>
</tr>
<tr>
<td>ns(Ca)</td>
<td>I_{ns(Ca)}</td>
</tr>
<tr>
<td>Kp</td>
<td>I_{Kp}</td>
</tr>
<tr>
<td>K1</td>
<td>I_{K1}</td>
</tr>
<tr>
<td>K</td>
<td>I_{K}</td>
</tr>
<tr>
<td>Na-K</td>
<td>I_{NaK}</td>
</tr>
<tr>
<td>Na</td>
<td>I_{Na}</td>
</tr>
<tr>
<td>Na,b</td>
<td>I_{Na,b}</td>
</tr>
</tbody>
</table>
Mathematical description of ionic currents and concentrations, transmembrane voltage, and conductivities of guinea-pig ventricular myocytes

extracellular space

Myoplasma

Sarcoplasmic reticulum

Troponin

Geometry

cylinder-shaped
length: 74 µm
radius: 12 µm

Mechano-electrical feedback by stretch activated ion channels

Neural influence by transmitter activated ion channels etc.

pump

I_{Ca,stretch} I_{bCa} I_{Ca,L,Ca} I_{Ca,L,Ca,ds} I_{NaCa} I_{NaCa,ds} I_{NaK}

I_{Ca,stretch} I_{bCa} I_{Ca,L,Ca} I_{Ca,L,Ca,ds} I_{NaCa} I_{NaCa,ds} I_{NaK}

I_{Na} I_{p,Na} I_{b,Na} I_{Ca,L,Na} I_{Na,stretch} I_{K,stretch} I_{K} I_{K1} I_{Ca,L,K} I_{b,K} I_{K,ACh}

I_{Na} I_{p,Na} I_{b,Na} I_{Ca,L,Na} I_{Na,stretch} I_{K,stretch} I_{K} I_{K1} I_{Ca,L,K} I_{b,K} I_{K,ACh}
Results of simulations for stimulus frequency of 1 Hz
Prediction of Mechano-Electrical Feedback

Reduction of action potential duration (APD) by strain
Increase of resting voltage by strain
SL: sarcomere length
Prediction: Triggering of Action Potential by Strain

\[ t=1 \text{ s: Electrical stimulus} \]

\[ t=2 \text{ s: Strain for 5 ms} \]

Triggering of action potential for SL > 2.7 µm
Cellular Electrophysiology: Normal and Failing

Simulation of normal and failing human ventricular myocytes with modified Priebe-Beuckelmann model

Pathology: Hypertrophy

Significant changes of density of proteins relevant for calcium transport:

- sarcolemmal NaCa-exchanger $\uparrow$
- sarcoplasmic Ca-pump $\downarrow$

(Sachse, Seemann, Chaisaowong, and Weiss. JCE, 2003)
Electrophysiology of Mammalian Sinoatrial Node Cell

Autorhythmicity with a frequency of ~3 Hz
Markov Modeling of Ion Channels and Mutations

Markov models allow
- reconstruction of single channel behavior
- to be based upon thermodynamic principals
- assignment of physical meaning to rate constants

Example: State diagram of cardiac sodium channel model
O: Open, I: Inactivated, C: Closed


- Markov models consist of sets of ODEs
- Commonly, one Hodgkin-Huxley based channel description of an established cell model is substituted by an appropriate Markov model
- Recently, the usage of Markov models increased for generation of new models
Modeling of Calcium Channel Mutation

Channel Modeling

Differences of steady state inactivation between wild type (WT) and mutated channels

Numerical optimization

Prediction of course of transmembrane voltage in myocyte

Changes dependent on % of mutated channels

Significant increase of action potential duration (and intracellular calcium concentrations)

Integration in Myocyte Model
Modeling of Sodium Channel Mutation delF1617

Differences of inactivation at negative voltages

Differences of voltage dependence of sodium channel availability

Channel Modeling

Parameter study

Reduction of gating charge
Loss of voltage dependence of inactivation

Case Studies in Computational Engineering and Science - Page 29
Summary

• Recapitulation Electrophysiology I

• Cellular Electrophysiology II
  • Ordinary Differential Equations
  • Numerical Techniques
  • Myocyte Models
  • Channel Models