From model to device and back

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Congratulations Dr. Jiang!
Last year’s PI meeting
What do we want in a model for device testing?

• Ability to reproduce interesting phenomena
  – For example, ventricular tachycardia

• Simulate said phenomena “reasonably fast”
  – Real-time: when connected to real device
  – or faster: when connected to software

• Formal properties
  – Opens the way to formal verification
What about validation?

• **Validation**: guarantee the model produces does not produce too many physiologically invalid behaviors
  – e.g. EGM morphology consistent with the simulated condition

• **Verification**: guarantee the model’s behavior is a correct solution of its equations
  – E.g. solve PDE correctly
  – Avoid solver-dependent phenomena
What about validation?

• Can be a deal-breaker
• UCLA cardiac modeling group: 6 months of model development, 18 months of validation.
Multiple models

Device-in-the-loop

in vitro

Heart-in-the-loop

in silico
WHY CARE?
ICD Shocks
Bad detection

Sample results on incidence of inappropriate therapy:

1. 40% to 60% of delivered therapy episodes were inappropriate (n = 2000 patients) [RIGHT, 2011]

2. Up to 40% of patients are affected by inappropriate therapy when followed long-term [Kolb et al., JACC 2014]

3. 33.6% of 190 patients received inappropriate therapy, mostly due to VT/SVT detection errors [Jodko et al., Cardiology 2009]
WHAT ARE WE MODELING?
Right atrium

Right ventricle
What are we modeling?

The generation and propagation of electrical activity in cardiac muscle
What are we modeling?

The generation and propagation of electrical activity in cardiac muscle
Model the heart and ICD algorithms
THE CARDIAC MUSCLE MODEL

[Abbas et al., ARCH 2016]
Connection to device software

*in vitro*

*Device-in-the-loop*

*Heart-in-the-loop*

*in silico*
Connection to device software

Kuk’s talk

Device-in-the-loop

Heart-in-the-loop

in vitro

in silico
Excitable tissue
Excitable tissue

Voltage in a given cell is function of the voltages in neighboring cells.
Action Potential

- Quiescent
- Upstroke
- Notch
- Plateau
- Absolute Refractory (ERP)
- Relative Refractory (RRP)

$mV$
$V_m$
$V_{max}$
$V_{th}$
$V_{min}$
$V_{min}$
Model of Action Potential in myocyte

\[ \dot{V}(i, j) = a(i, j)TV \]
\[ i = 1 \]

Quiescent

\[ V(i, j) > V_{th}? \]
\[ V(i, j) \leq V_{min}? \]
\[ APD_n \leftarrow f(DI_{n-1}) \]

Upstroke

\[ V(i, j) = d \ (d > 0) \]
\[ i = 1 \]

Notch

\[ V(i, j) = -g \ (g > 0) \]
\[ i = 1 \]

ERP

\[ V(i, j) = -b \ (b > 0) \]
\[ i = 1 \]

Plateau

\[ t > PD? \]
\[ V(i, j) = 0 \]
\[ i = 1 \]

RRP

\[ V(i, j) = a(i, j)TV \]
\[ i = 1 \]

Upstroke 2

\[ V(i, j) = d_2 \ (d_2 < d) \]
\[ i = 1 \]

\[ V(i, j) \geq V_{th,2}? \]
\[ APD_n \leftarrow f(DI_{n-1}) \]

\[ V(i, j) \geq V_{max,2}? \]
Excitable tissue: quiescent mode

\[ V_{ij}(t) = \frac{1}{R_{h}(i,j)} [V_{i,j-1}(t) + V_{i,j+1}(t) - 2V_{i,j}(t)] \]
\[ + \frac{1}{R_{v}(i,j)} [V_{i-1,j}(t) + V_{i+1,j}(t) - 2V_{i,j}(t)] \]

\[ x_{ij} = (V_{ij}, t_{ij}) \in \mathbb{R}^{2} \] : voltage and local timer.

Voltage in a given cell is function of the voltages in neighboring cells.

Cell-specific horizontal and vertical resistances control contributions of neighbors.
Excitable tissue: scars

\[ V_{ij}(t) = \frac{1}{\infty} [V_{i,j-1}(t) + V_{i,j+1}(t) - 2V_{i,j}(t)] \]
+ \[ \frac{1}{\infty} [V_{i-1,j}(t) + V_{i+1,j}(t) - 2V_{i,j}(t)] \]
Excitable tissue

\[ V_{ij}(t) = \frac{1}{R_{h}(i,j)} [V_{i,j-1}(t) + V_{i,j+1}(t) - 2V_{i,j}(t)] \]
\[ + \frac{1}{R_{v}(i,j)} [V_{i-1,j}(t) + V_{i+1,j}(t) - 2V_{i,j}(t)] \]

\[ x_{ij} = (V_{ij}, t_{ij}) \in \mathbb{R}^2 \]: voltage and local timer.

\[ x = (V_{11}, t_{11}, ..., V_{NN}, t_{NN}) \in \mathbb{R}^{2N^2} \]
Model data

• For n-by-n grid,
  
  – 2n^2 state variables (voltage and local timer for each cell)

  – 18n^2 parameters
    • Threshold voltages
    • Resistances
    • etc
Model of Action Potential in myocyte

Quiescent

\[ \dot{V}(i, j) = a(i, j) \cdot V \]
\[ V(i, j) > V_{th}? \]
\[ V(i, j) \leq V_{min}? \]
\[ APD_n \leftarrow f(DI_{n-1}) \]

Upstroke

\[ \dot{V}(i, j) = d \quad (d > 0) \]
\[ V(i, j) > V_{max}? \]
\[ V(i, j) \leq V_{th} \]

Notch

\[ \dot{V}(i, j) = -g \quad (g > 0) \]
\[ V(i, j) < 0.9 \cdot V_{max}? \]
\[ t \leftarrow 0 \]

ERP

\[ V(i, j) = -b \quad (b > 0) \]
\[ t > PD? \]

Plateau

\[ \dot{V}(i, j) = 0 \]

Plateau

Relative Refractory (RRP)

\[ \dot{V}(i, j) = a(i, j) \cdot V \]
\[ V(i, j) \geq V_{th}\text{,2}? \]
\[ APD_n \leftarrow f(DI_{n-1}) \]

RRP

Upstroke 2

Absolute Refractory (ERP)

\[ V(i, j) \geq V_{max,2}? \]
\[ V(i, j) \geq V_{th}\text{,2}? \]
Simulated Action Potential

![Simulated Action Potential Diagram]
Action Potential propagation
Model of Action Potential in myocyte

Quiescent

\[ \dot{V}(i, j) = a(i, j) \]  
\[ \dot{V}(i, j) > V_{th} \]  
\[ i = 1 \]

Upstroke

\[ \dot{V}(i, j) = d (d > 0) \]  
\[ \dot{V}(i, j) > V_{max} \]  
\[ i = 1 \]

Notch

\[ \dot{V}(i, j) = -g, (g > 0) \]  
\[ i = 1 \]

ERP

\[ V(i, j) = -b, (b > 0) \]  
\[ i = 1 \]

Plateau

\[ \dot{V}(i, j) = 0 \]  
\[ t > PD \]

RRP

\[ \dot{V}(i, j) = a(i, j) \]  
\[ i = 1 \]

Upstroke 2

\[ \dot{V}(i, j) = d_2, (d_2 < d) \]  
\[ i = 1 \]
Simulated Action Potential

\[ \text{APD}_n, \text{DI}_n, \text{APD}_{n+1} \]
Restitution curve
Excitable Tissue
Coming soon

• C implementation + visualization from Stanley Bak
Connection to real device

David Corman last year: How soon will we see any of this research in practice?
Connection to real device

- **Device-in-the-loop**
- **Heart-in-the-loop**
- **in vitro**
- **in silico**

Marco’s talk tomorrow
Whole heart / tissue models

• Models based on Reaction-Diffusion equations [e.g. Trayanova 2015]
  – Computationally intensive – e.g. 45mins for one heartbeat

• Hybrid IOA-based models [Bartocci et al. 2009]
  – Interaction semantics similar to those presented here.
  – 23mins for 1s (~ 2 heartbeats) for 10k (isotropic) cells with OpenMP implementation

• Timed IOA with data [Barbot et al., 2015]
  – Statistical verification

• This model
  – 64 (anisotropic) cells took 2252 secs for 6s in Matlab
Whole heart

What level of precision, where?
MODEL’S FORMAL PROPERTIES

[Abbas et al., HSCC 2016]
Connection to formal verification

- **in vitro**
- **Device-in-the-loop**
- **Heart-in-the-loop**
- **in silico**
Model the heart and ICD algorithms
Model the heart and ICD algorithms
Approach: Model the heart’s electrophysiology
Approach: Model the ICD measurement process
Approach: Model the ICD algorithms

Network of hybrid automata
Formalism: *(STORMED)* Hybrid automata

(Network of) hybrid automata admits finite bisimulation
Formalism: (STORMED) Hybrid automata

(Network of) hybrid automata admits finite bisimulation
**Formalism: (STORMED) Hybrid automata**

STORMED hybrid automata (HA)

admit finite bisimulation
Properties of Composition?

Etc.
General results

**Theorem 6.1**

The parallel composition of STORMED hybrid systems is STORMED if Collection Separability holds.

Etc.
Theorem 6.2
If the flows of a STORMED system are replaced by definable set-valued flows (such as produced by some reachability tools), the resulting system has a finite simulation.
First formal model of ICD sensing and detection algorithms
First result towards model checking of heart + ICD
O-MINIMAL SPECIFICATIONS
STORMED hybrid automata

• S: Separable guards (continuous flows have a minimum dwell time)
• T: Time-invariant, Semi-Group flows
• O: flows, resets, guards, and invariants are definable in an O-minimal theory
• R: Reset and flow Monotonicity
• Ends Delimited
O-minimal sets

In \( \mathbb{R} \), finite unions of intervals and points
O-minimal functions

Function $f$ is o-minimal if its graph $G = \{(t, f(t))\}$ is o-minimal
Frequency specifications

• Time-frequency analysis is a standard way of analyzing signals
• A rudimentary time-frequency analysis is the Short-Time Fourier Transform (STFT)
• Time-Frequency Logic augments STL with a STFT operator
Sample specifications

\[ c_\omega(\tau) = \int_{\tau-L/2}^{\tau+L/2} x(t)g_L(t-\tau)e^{-i2\pi\omega t} dt \]

\[ = \int_{\tau-L/2}^{\tau+L/2} x(t)g_L(t-\tau)\cos2\pi\omega t dt \]

\[ -i \int_{\tau-L/2}^{\tau+L/2} x(t)g_L(t-\tau)\sin2\pi\omega t dt \]

\[ = C_r(\tau + L/2) - C_r(\tau - L/2) - i[C_i(\tau + L/2) - C_i(\tau - L/2)] \]
MODEL VALIDATION FOR IN-SILICO PRE-CLINICAL TRIALS
Story so far

Device-in-the-loop

in vitro

Heart-in-the-loop

in silico
Story so far

- **in vitro**
- **Device-in-the-loop**
- **Heart-in-the-loop**
- **in silico**
Story so far

in vitro

Device-in-the-loop

Heart-in-the-loop

in silico
Clinical trials

- in vitro
- Device-in-the-loop
- Heart-in-the-loop
- in silico
In-Silico pre-clinical trials

Device-in-the-loop

Heart-in-the-loop

in vitro

in silico

Complete Generated Population

Synthetic Cohort Generation (Arrhythmias A, ..., J)

Generated Electrogram Waveforms

Atrial Signal

Ventricular Signal

Shock Signal

PAC

AF

VT

PVC

RVA

AV

SA

VF

RBB

LVA

SVT

PAC

AF

VT

PVC

RVA

AV

SA

VF

RBB

LVA

SVT
Model parameter distribution

- Identify model parameters from Electrophysiology testing patient data
- Fit a distribution to the experimental parameter data
- Sample from learned distribution to generate model instances.
What about aspects that can’t be learned from data?

• Fit black box model
  – E.g. markov model

• Use statistical substitute
  – E.g. rate of incorrect morphology discrimination is used to model morphology discriminator
Story so far

- **Device-in-the-loop**
- **Heart-in-the-loop**
- **in vitro**
- **in silico**
There and Back Again

“Adapted” by Houssam Abbas