Cardiac Action Potential Reconstruction

CSRC/HESI/SPS/FDA Meeting
CiPA Update

In Silico CiPA Workstream

December 11, 2014

Agenda: In Silico Modeling

- Moderators:
  - **Thomas Colatsky (FDA/CDER), David Gutstein (Merck)**
- Overview and scientific approach
  - **Natalia Trayanova & Tom O'Hara (Johns Hopkins University)**
- Development and validation of the model
  - **Zhihua Li & Sara Dutta (FDA/CDER)**
- Proarrhythmia metrics
  - **Gary Mirams (University of Oxford)**
- Building a community resource
  - **Donna Lochner (FDA/CDRH)**
- Discussion

What Computer Models Can Do

What computer models can do:

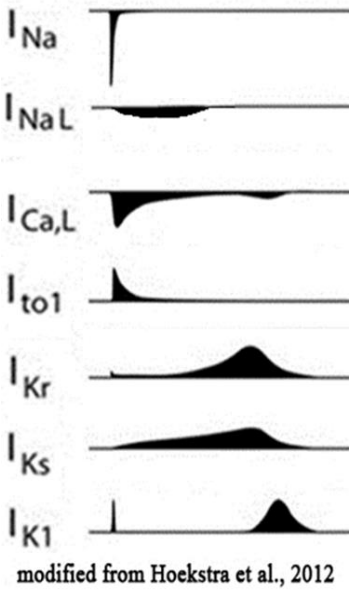
- **Conceptualize and quantify a system**
- **Organize current knowledge and identify gaps**
- **Test competing hypotheses**
- **Identify the key factors controlling response**
- **Estimate system variables that cannot be directly measured**
- **Predict system response under new conditions**

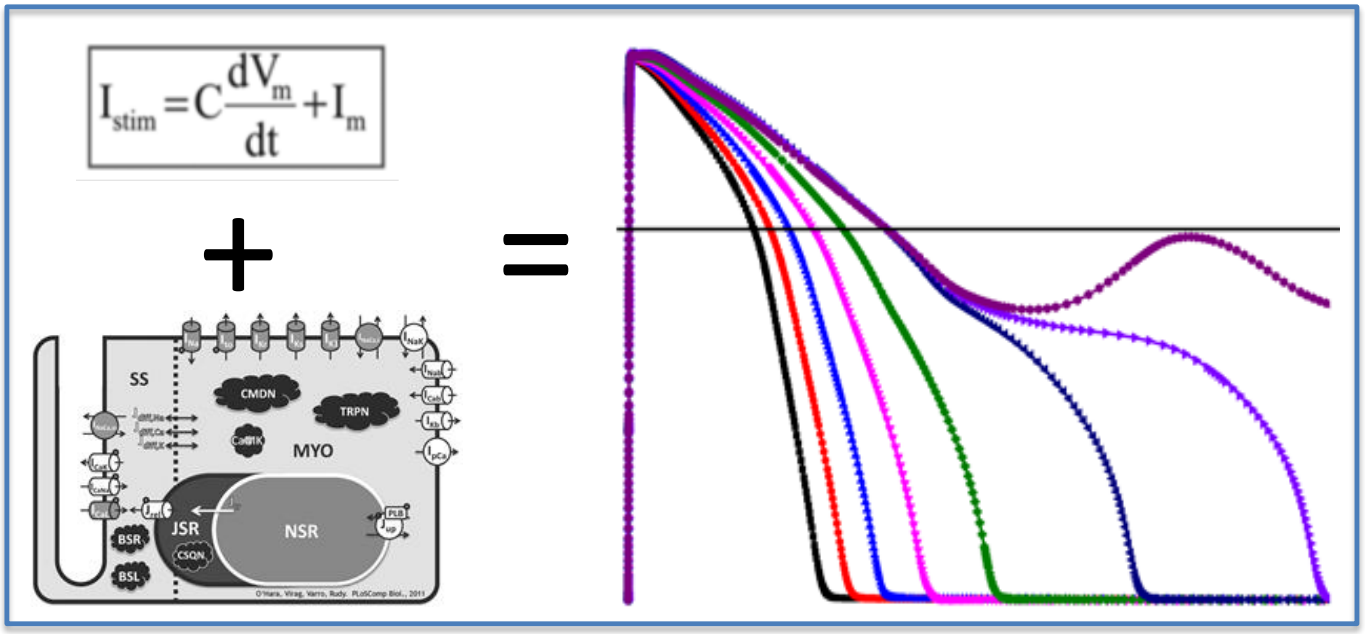
How cardiac models are developed:

- **Derived from detailed sets of experimental data for each individual ion channel studied in isolation (voltage, time)**
- **Assembled, verified in the context of known cell behaviors**
- **Data sources, assumptions are transparent and assessable**

Reconstructing the Cardiac Action Potential

(adapted from presentation by Gary Gintant – this meeting)





(a) Voltage clamp studies on individual ionic currents:

- **I = f(v, t)**
- **Drug effects**

(b) Mathematical descriptions capturing channel behavior in the context of cell physiology (calcium, pumps, transporters)

(c) Components integrated and verified to reproduce cellular AP behaviors under various conditions

In Silico Workstream: Background

- **Initial workshop held in July 2013 to discuss the in silico modeling approach in CiPA**
  - Modeling experts (academic, industry, FDA), including:
    - J. Jeremy Rice (IBM), Blanca Rodriguez, Gary Mirams (U Oxford), Colleen Clancy (UC Davis), Carolyn Cho, Alice Chain (Merck), Yoram Rudy (Washington U), Molly Maleckar (Simula)
- **Key questions asked:**
  - Is there a consensus computer model we can use?
  - How should drug-channel interactions be represented? (static vs. dynamic)
  - Is there a metric that can be used to quantify (or at least rank) proarrhythmia risk?
  - What simulation experiments are needed to define the metric and validate the model?

Key Requirements Defined

- **Keep the model relatively simple**
- **Preserve an immediate and direct relation to experimentally derived and verifiable data sets**
- **Provide access to the models as a community resource, without a need for specialized hardware/software**

2013 In Silico Workshop Outcomes

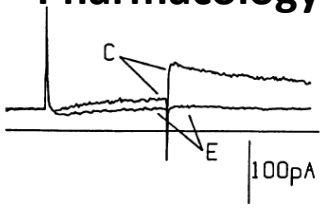
- **Identified the utility of using a single cell model vs. more complex 2D or 3D models (including ECGs)**
  - Less model uncertainty - fewer free parameters
  - More transparent - assumptions easier to understand
  - Can function as an assay to generate a proarrhythmia metric
- **O'Hara Rudy human ventricular myocyte model selected**
  - No consensus model of the cardiac cell exists
  - No single cardiac myocyte model has been broadly validated within the context of use proposed in CiPA
  - O'Hara-Rudy model was considered the "gold standard" for simulating the human ventricular myocyte action potential
    - Built using "essential" experimental data from human hearts
    - Validated using human myocyte electrophysiology
    - Expected to increase human-specific accuracy of results

Initial In Silico Strategy

- **Download and run publicly available O'Hara-Rudy model**
- **Generate "virtual" concentration-response curves for a provisional set of drug targets**
  - Assume IC50s accurately reflect ion channel pharmacology
  - Represent channel block as a decrease in maximal conductance
- **Repeat studies using experimental pharmacology data and evaluate model performance**
  - Use published IC50 data sets for drugs with different levels of TdP risk
    - Mirams et al. (2011): 31 drugs
    - Kramer et al (2013) 55 drugs (32 torsadogenic, 23 non-torsadogenic)
  - Run provisional studies on the 29 drugs selected by CiPA using available pharmacology data
  - Evaluate possible metrics (including those in Mirams et al., 2011)
  - Evaluate the need for more complex (dynamic) models to represent drug-channel interactions, and develop as required
- **Wait for new pharmacology data to be generated by the CiPA Ion Channel WG using standardized protocols → repeat evaluations**

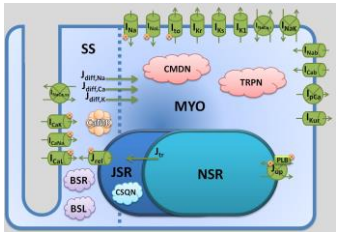
Challenges

Ion Channel Pharmacology



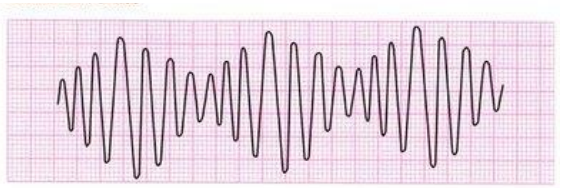
INPUT

O'Hara-Rudy Model



DATA INTEGRATION

TdP Risk Classification



CALIBRATION /OUTPUT

- **Do the test systems used to generate data adequately replicate native channel biophysics and pharmacology?**
- **Are the measurements of drug effects consistent, reliable and sufficiently quantitative?**
- **Can data be extrapolated to more physiologically relevant conditions: e.g. temperature, exposure times, protein binding?**
- **How exact are the risk categories for calibrating the model?**
- **How can we ensure model accuracy in light of new data?**

Computer Models Are Just One Type of Model

- **A model is an approximation of a real system containing the most essential variables needed to predict an outcome of interest**
- **Models are used when it is impossible or impractical to measure the outcomes directly**
- **A variety of models are already used routinely during drug development and review to support decision making, e.g.:**
  - Cell and animal models: product safety and efficacy
  - Clinical trial models: patient response in a larger populations
- **In all cases, models are "black boxes" and must:**
  - Utilize "good" data
  - Be appropriately tested/verified to establish their credibility
  - Have a well defined context of use, including a clear understanding of:
    - the boundary conditions that constrain their utility
    - the assumptions governing their development and use

Agenda: In Silico Modeling

10:55-12:35pm

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