Object-oriented scientific computing: Applications

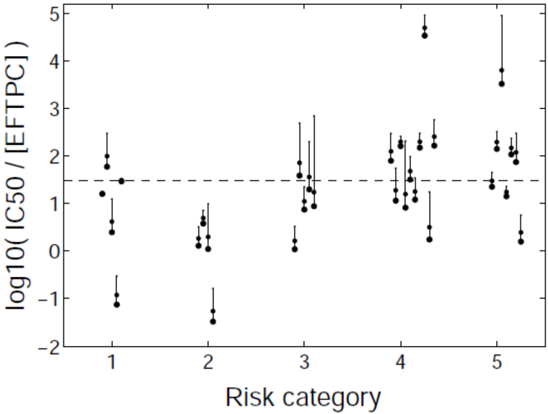
Pras Pathmanathan

Summer 2011

Solving ODEs: Cardiac drug risk assessment

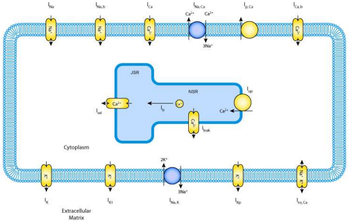
Solving ODEs: Cardiac drug risk assessment

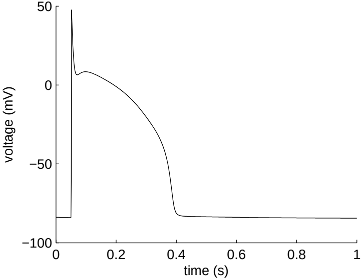
It costs about $1bn to get a drug to market, and cardiac side-effects are the leading cause of withdrawal from market.



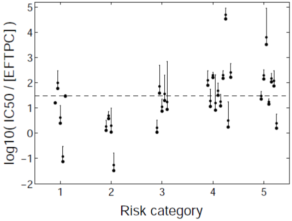
Solving ODEs: Cardiac drug risk assessment

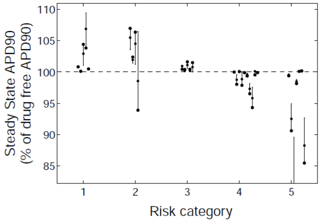
- Aim is to model electrical activity of a single cell
- ODE-based models have been developed since the 1950s
- 10s or even 100s of state-variables (ionic concentrations, probabilities of channel gates being open..)
- Model can be *phenomenological*, or *physiological* (or both)
- Can study affect of drugs





Solving ODEs: Cardiac drug risk assessment



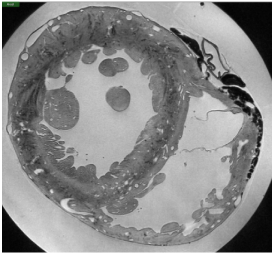


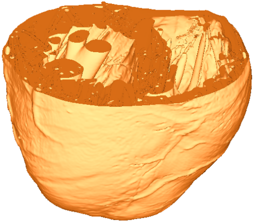
- Cell cycle models with multiple channel drug block can predict action potential duration change (ΔAPD)
- ΔAPD correlates much more nicely with side-effect risk than existing markers used in pharma industry

G.R. Mirams et al. *Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk*, Cardiovascular Research, 2011

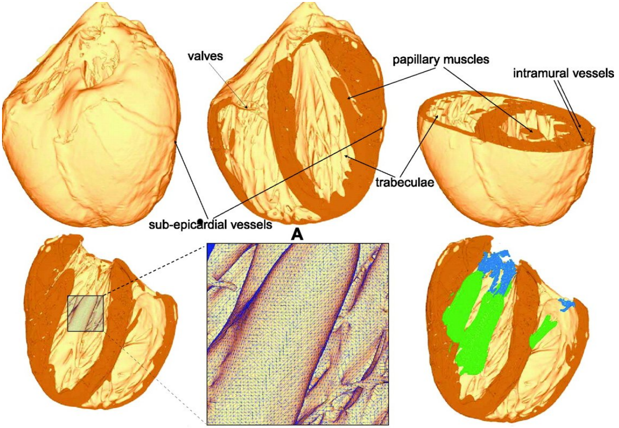
The heat equation and finite elements: electrical propagation in the heart

MR images to computational mesh





Hi-resolution geometrically detailed rabbit mesh



M. Bishop et al. *Development of an anatomically detailed MRI-derived rabbit ventricular model and assessment of its impact on simulations of electrophysiological function*, Heart and Circulatory Phys. 2010.

The monodomain equation

Equations governing activation of a single cell: let $V \equiv V(t)$ be the transmembrane voltage, $\mathbf{u} \equiv \mathbf{u}(t)$ be cellular state variables

$$\begin{aligned} C\frac{\mathrm{d}V}{\mathrm{d}t} &= -I_{\mathrm{ion}}(\mathbf{u}, V) \\ \frac{\mathrm{d}\mathbf{u}}{\mathrm{d}t} &= f(\mathbf{u}, V) \end{aligned}$$

The 'monodomain equations' for activity in tissue: $V \equiv V(t, \mathbf{x})$, $\mathbf{u} \equiv \mathbf{u}(t, \mathbf{x})$

$$\begin{aligned} C\frac{\partial V}{\partial t} &= \frac{1}{\chi}\nabla \cdot (\sigma \nabla V) - I_{\mathrm{ion}}(\mathbf{u}, V) \\ \frac{\partial \mathbf{u}}{\partial t} &= f(\mathbf{u}, V) \end{aligned}$$

The monodomain equation

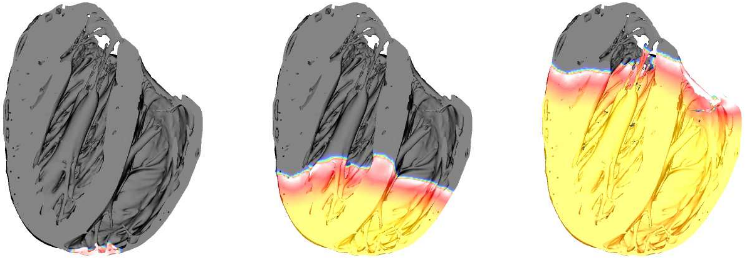
Equations governing activation of a single cell: let $V \equiv V(t)$ be the transmembrane voltage, $\mathbf{u} \equiv \mathbf{u}(t)$ be cellular state variables

$$\begin{aligned} C\frac{\mathrm{d}V}{\mathrm{d}t} &= -I_{\mathrm{ion}}(\mathbf{u}, V) \\ \frac{\mathrm{d}\mathbf{u}}{\mathrm{d}t} &= f(\mathbf{u}, V) \end{aligned}$$

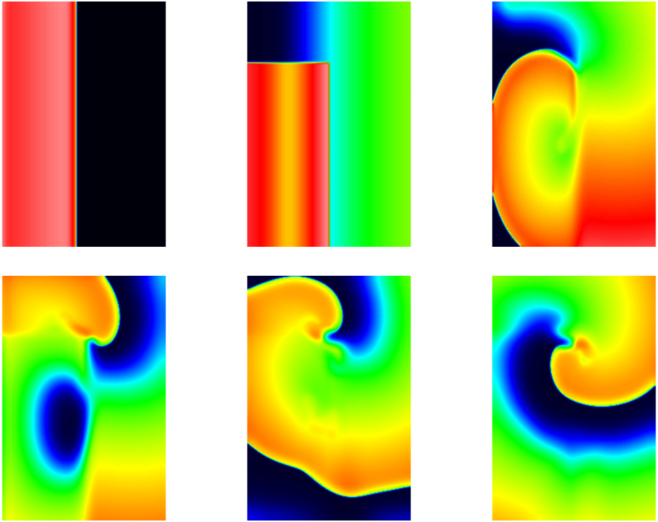
The 'monodomain equations' for activity in tissue: $V \equiv V(t, \mathbf{x})$, $\mathbf{u} \equiv \mathbf{u}(t, \mathbf{x})$

$$\begin{aligned} C\frac{\partial V}{\partial t} &= \frac{1}{\chi}\nabla \cdot (\sigma \boldsymbol{\nabla} V) - I_{\mathrm{ion}}(\mathbf{u}, V) \\ \frac{\partial \mathbf{u}}{\partial t} &= f(\mathbf{u}, V) \end{aligned}$$

Apical stimulation



Arrhythmic activity on a 2D mesh



Arrhythmic activity on a realistic geometry