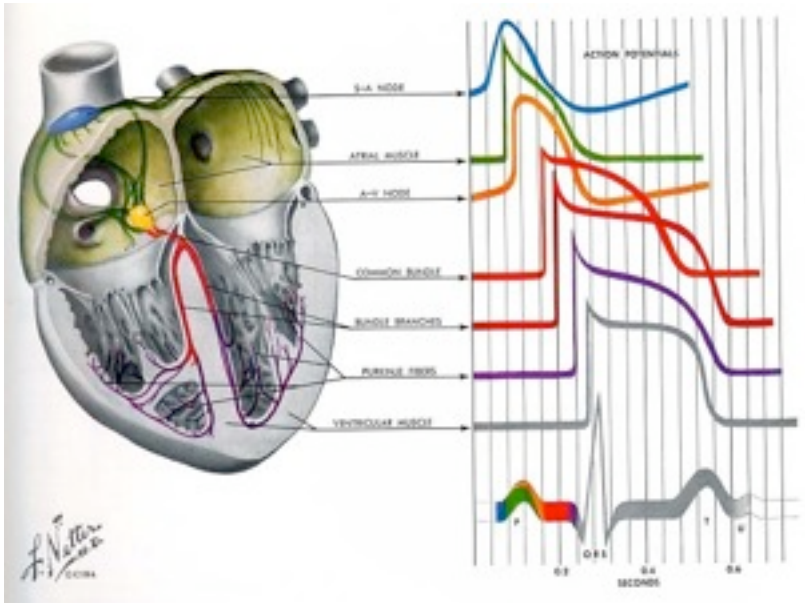
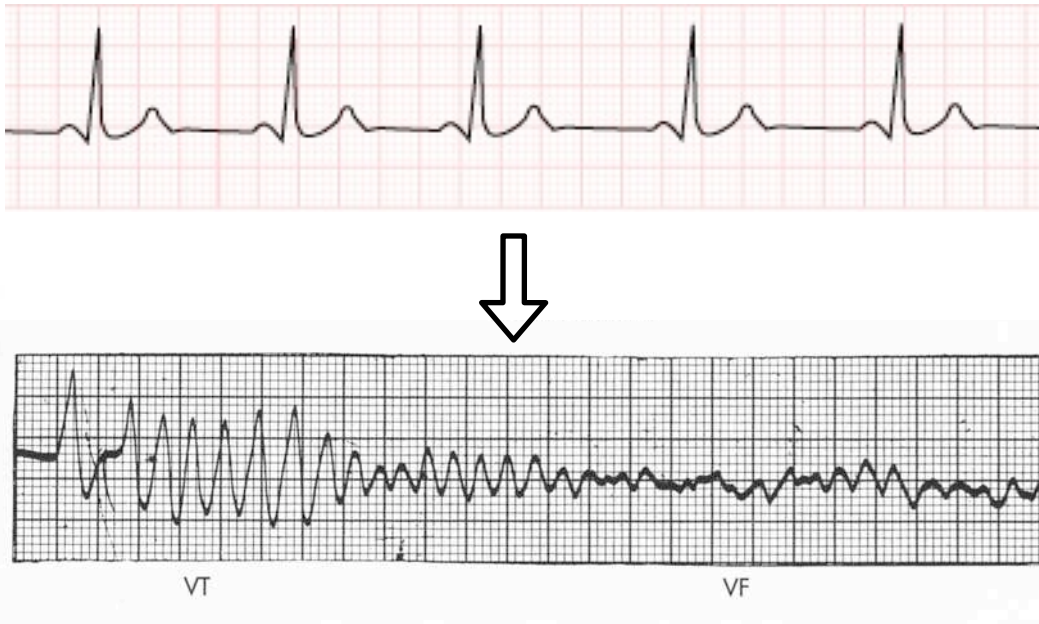
Multiscale computational modeling of cardiac action potentials

Trine Krogh-Madsen
Department of Medicine (Cardiology)
Institute for Computational Biomedicine
trk2002@med.cornell.edu
A-325

Cardiac arrhythmias



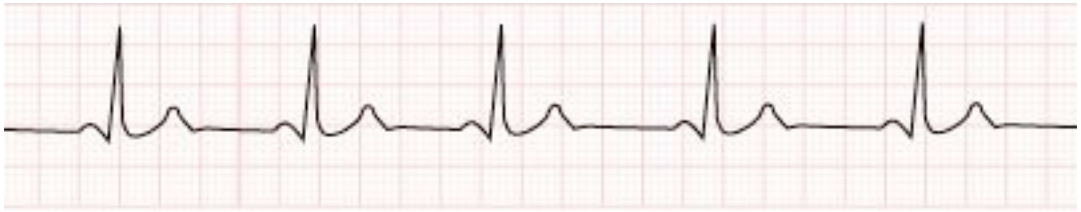


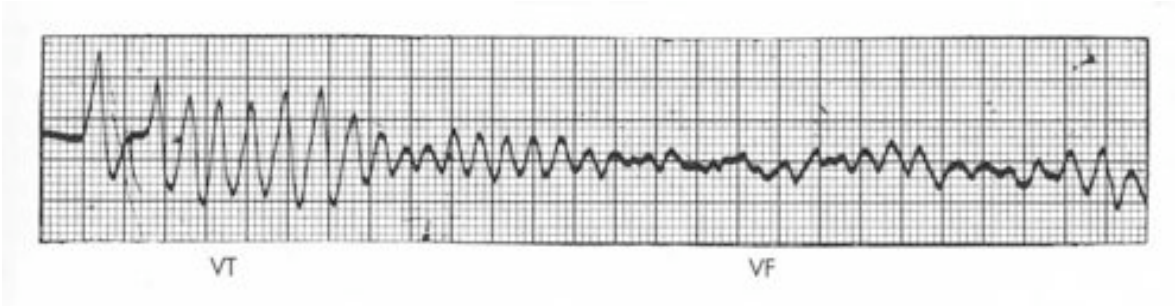
Sudden cardiac death:
~300,000 deaths/year

Ventricular tachycardia
- Rapid activation
- May impair pumping
- May degenerate to VF

Ventricular fibrillation
- Loss of synchronous activation
- Syncope, death

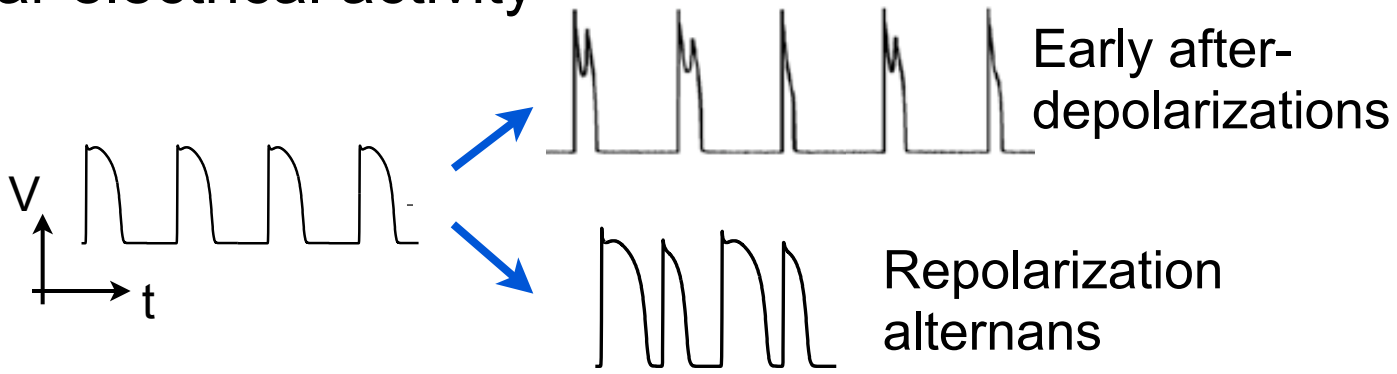
- How do cardiac arrhythmias initiate?
- How are they sustained?
- What can we do to prevent their occurrence?
- How can we terminate them?



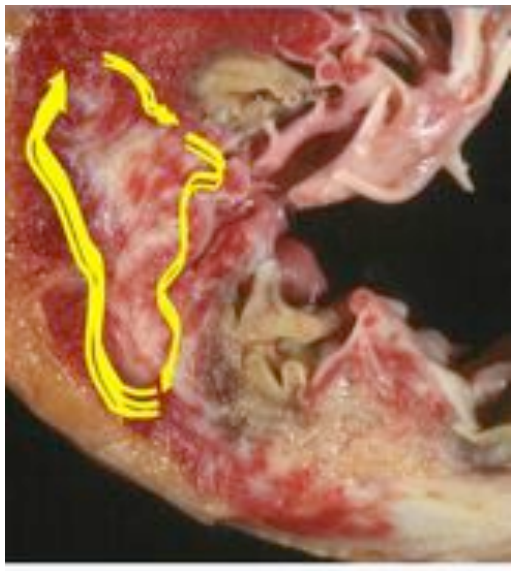


Initiation

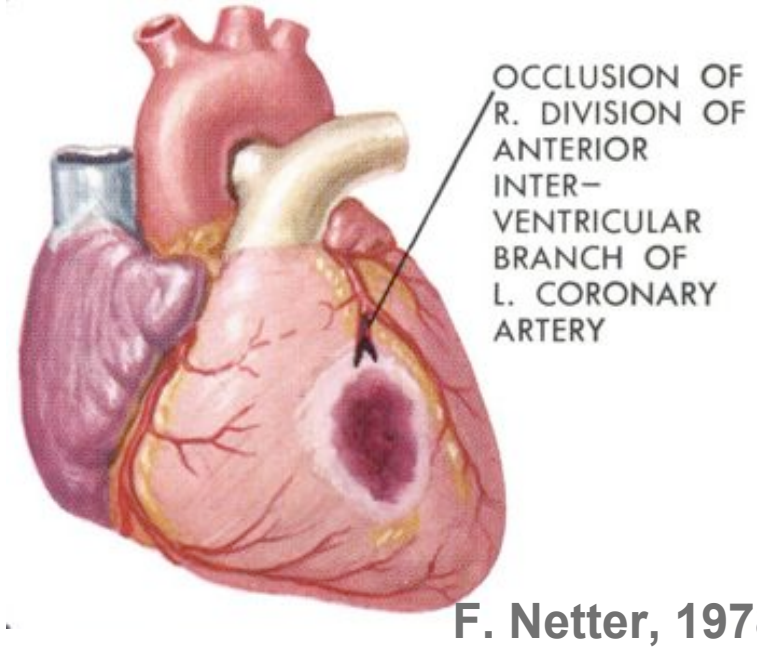
Abnormal cellular electrical activity



Structural heterogeneity



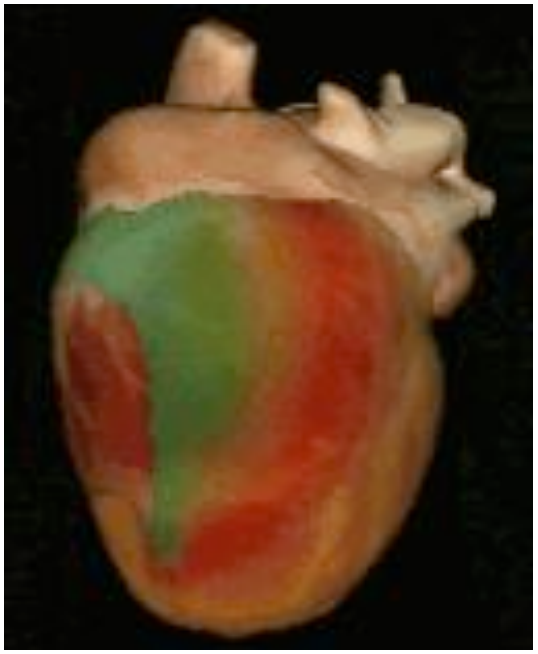
Bill Stevenson, KITP seminar, 2006.



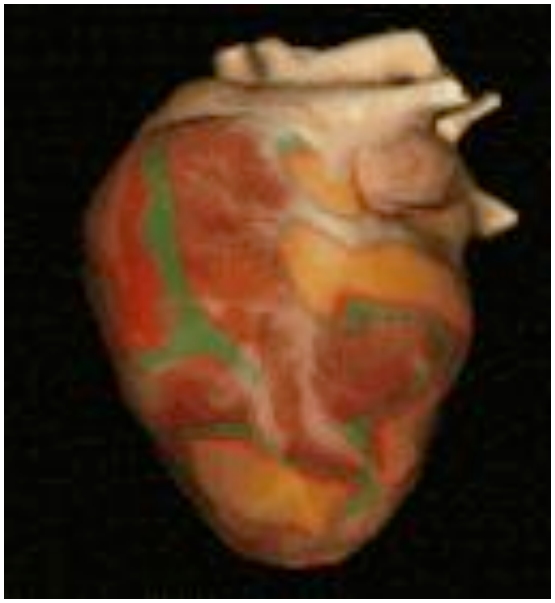
F. Netter, 1978

Cardiac arrhythmia mechanisms

Ventricular tachycardia



Ventricular fibrillation

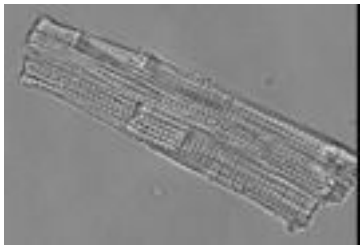


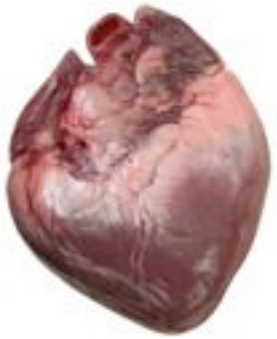
Defibrillation

thevirtualheart.org

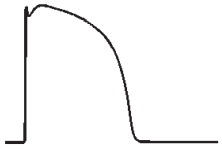
Multiscale phenomena

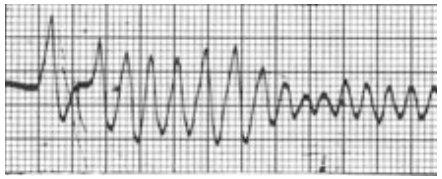
single channel → single cell → tissue, organ





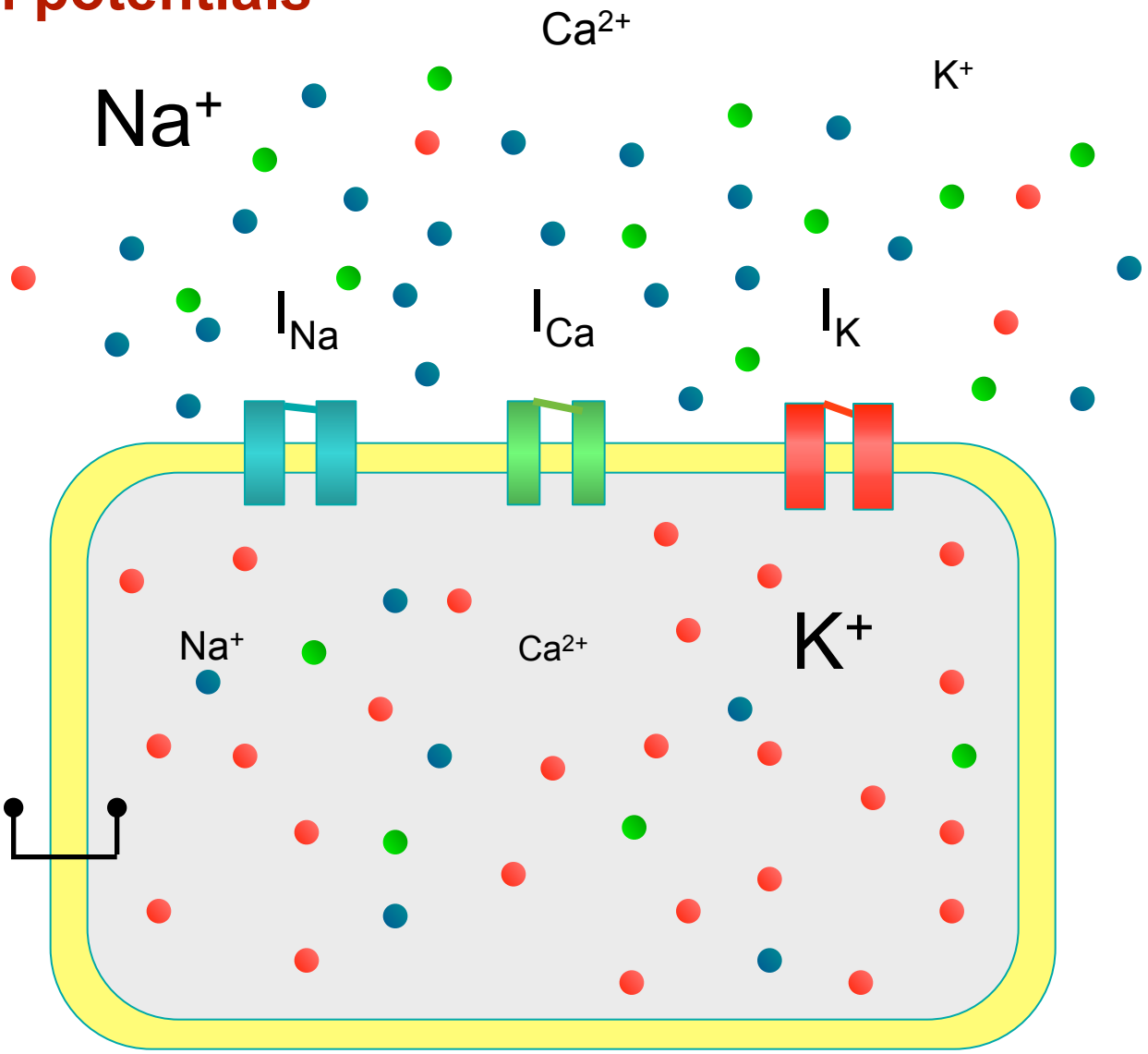
1 Å | 1 nm | 10 nm | 100 nm | 1 µm | 10 µm | 100 µm | 1 mm | 1 cm | 10 cm





10 µs | 100 µs | 1 ms | 10 ms | 100 ms | 1 s | 10 s | 100 s

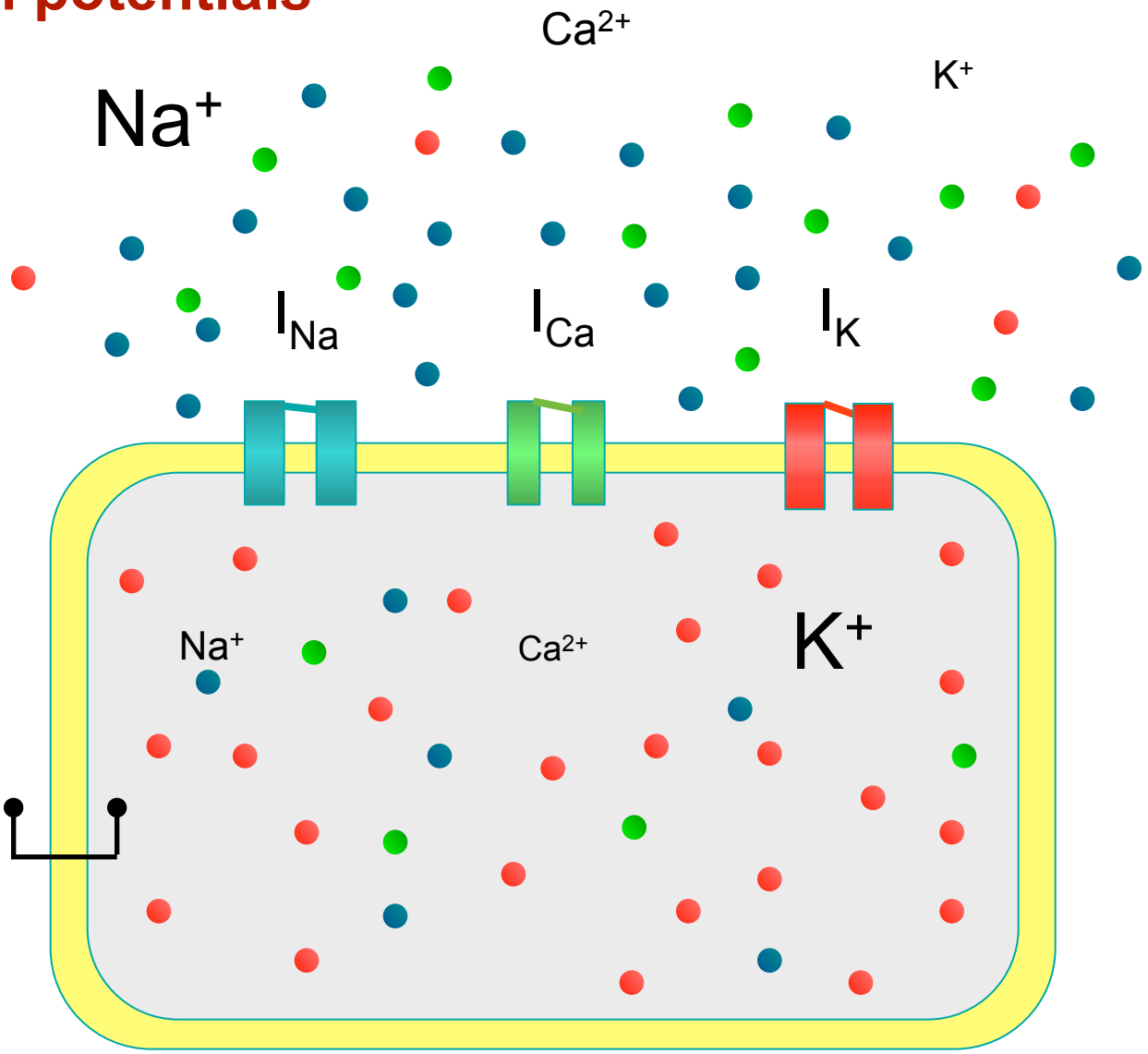
Cardiac action potentials



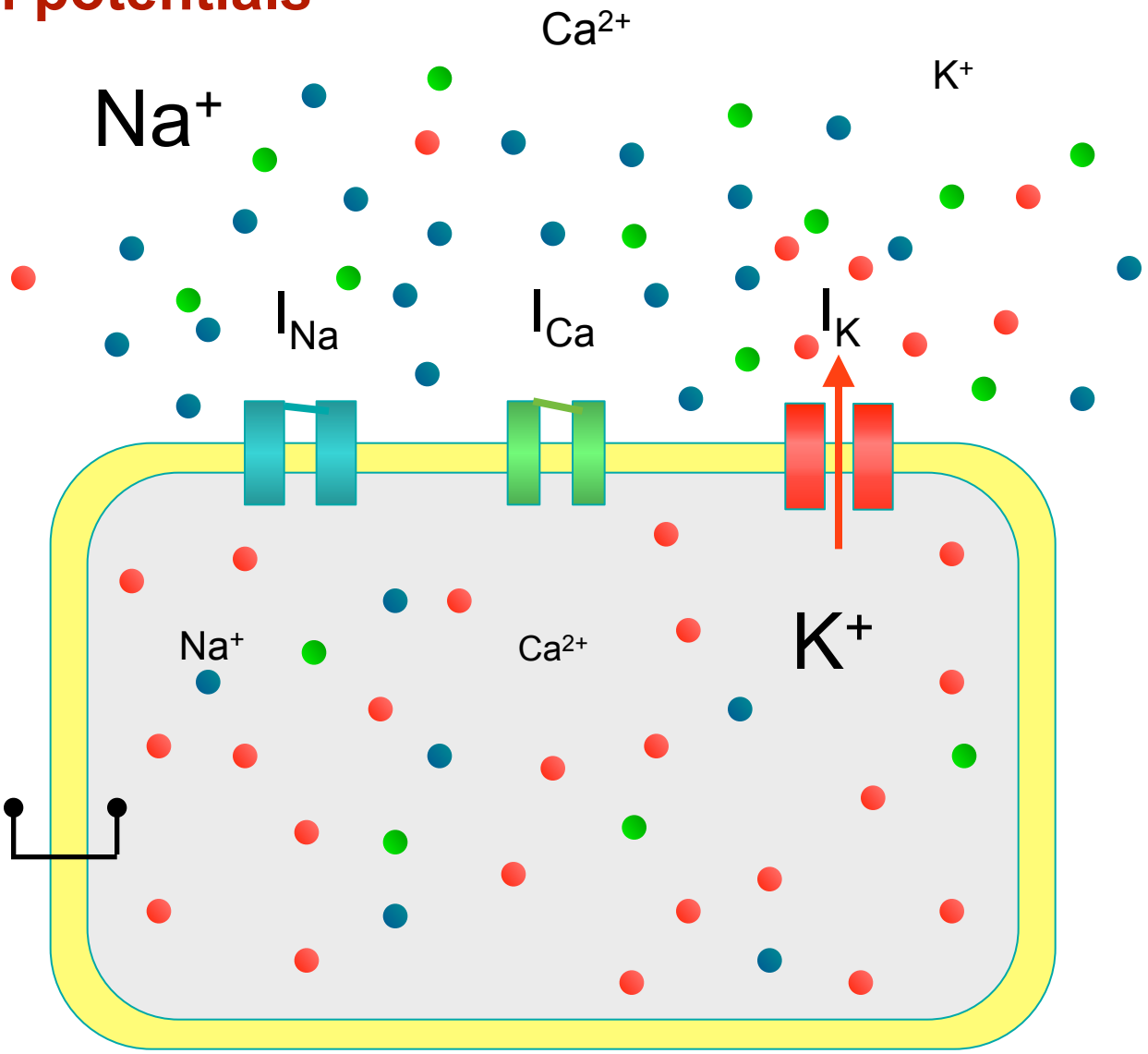
Transmembrane potential:
If ionic distribution neutral,
V = ? mV.

Cardiac action potentials

Transmembrane potential:
If ionic distribution neutral,
V = 0 mV.



Cardiac action potentials



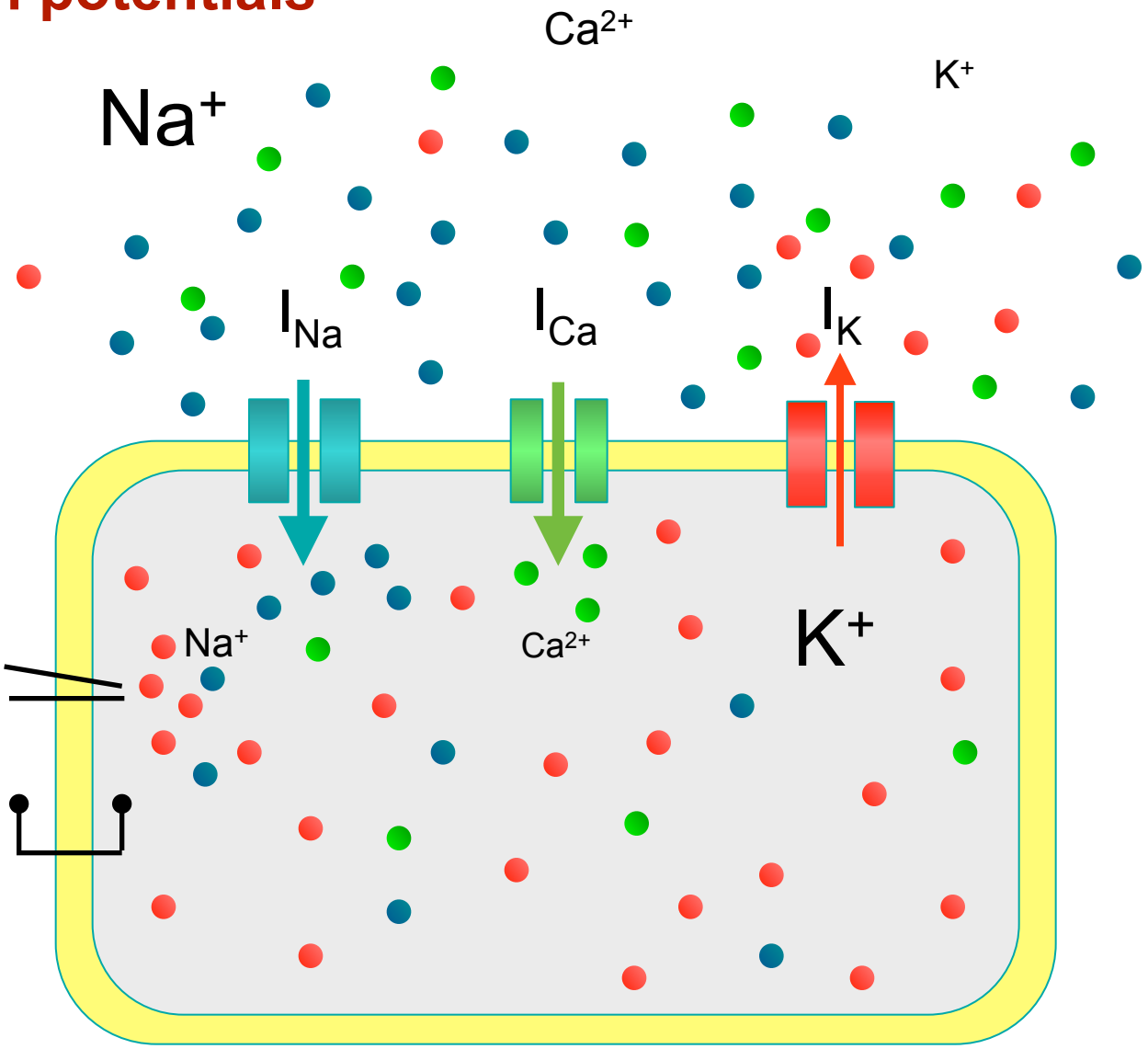
Cardiac cells rest at $V \approx -85\,mV$ with some K channels open.

Nernst potential (equilibrium potential for electrodiffusion):

$$E_K = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i} \approx -85\,mV$$

Cardiac action potentials

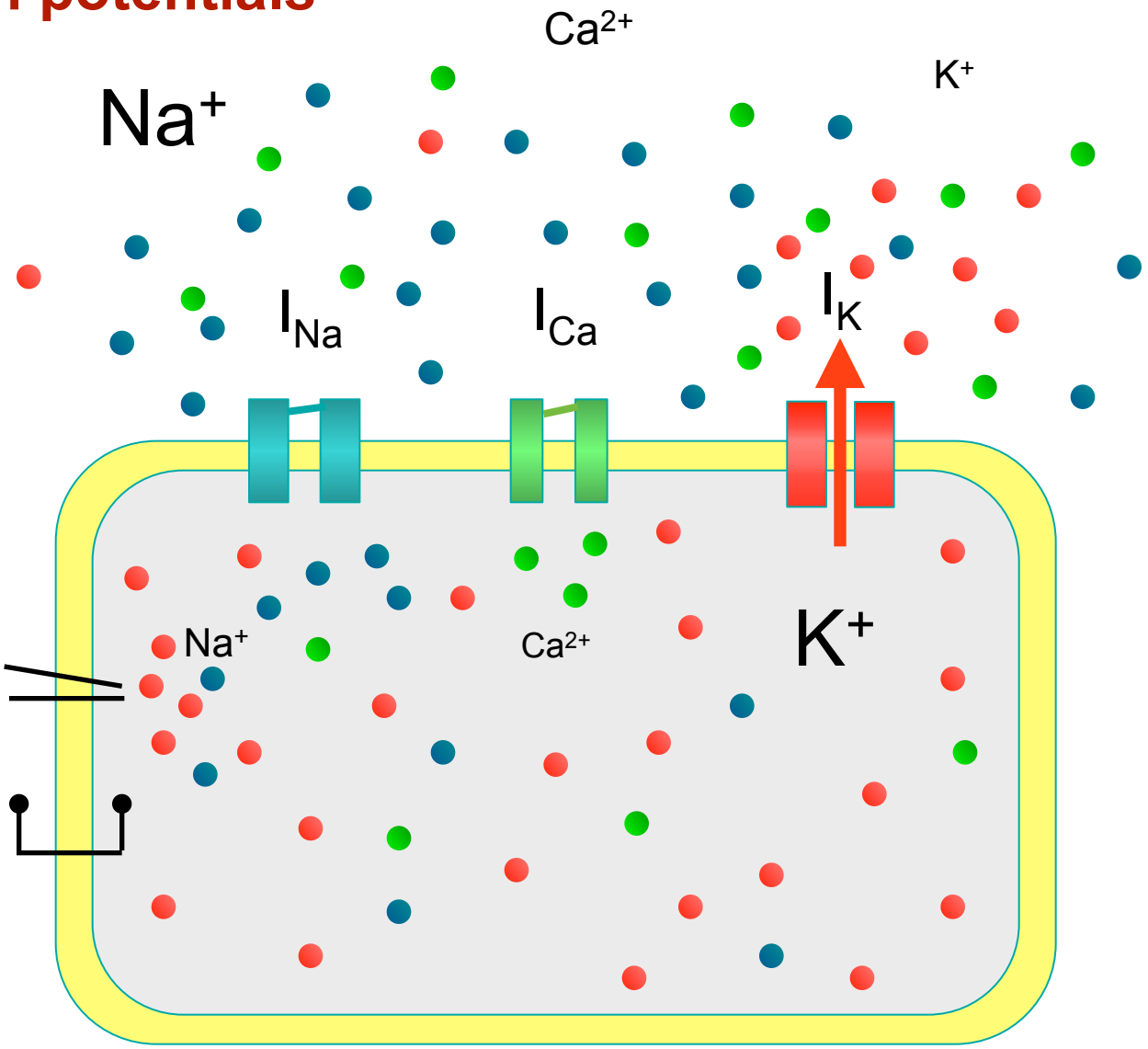
Injection of a stimulus current initiates depolarization, which cause Na^+ and Ca^+ channels to open and further depolarize the membrane, $V \approx +20\,mV$



($E_{Na} \approx +50\,mV$, $E_{Ca} \approx +30\,mV$)

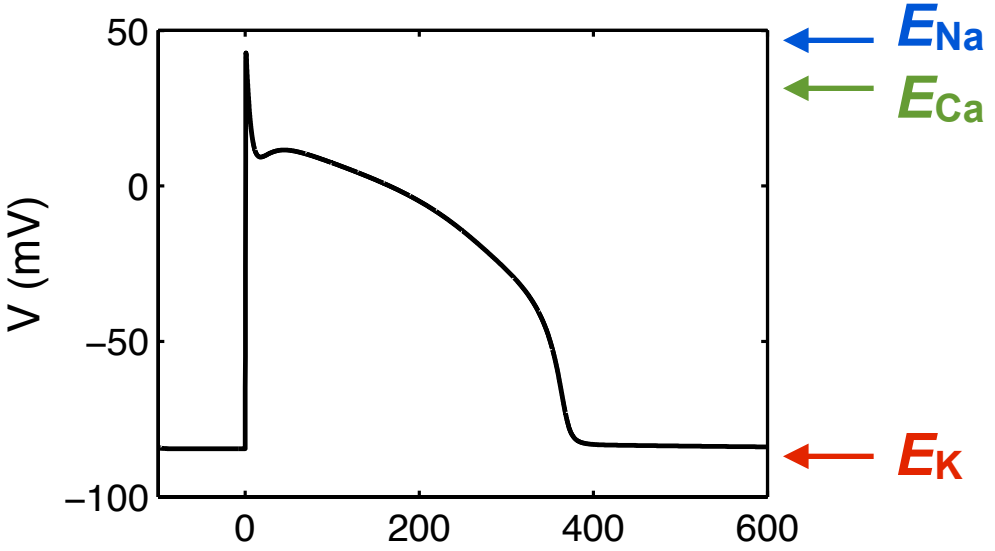
Cardiac action potentials

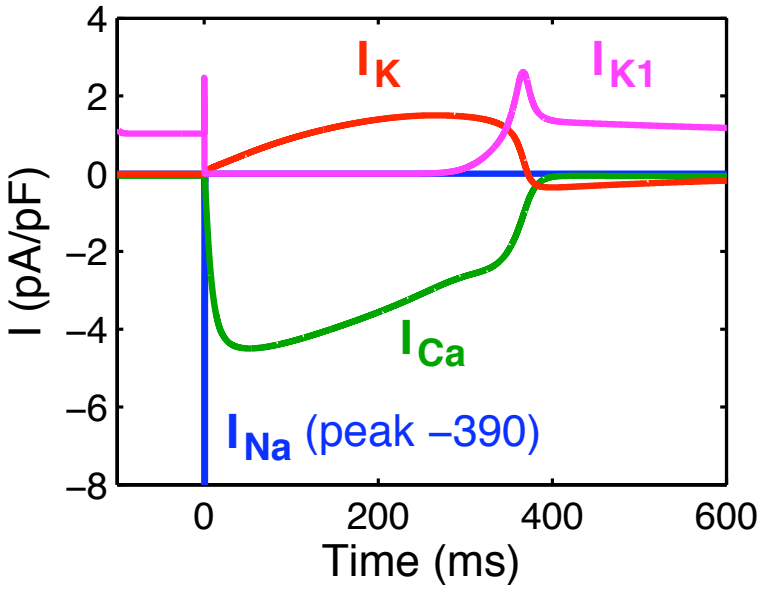
Na^+ and Ca^+ channels inactivate (close) with prolonged depolarization. K^+ channels open and cause repolarization to $V \approx -85\,mV$.



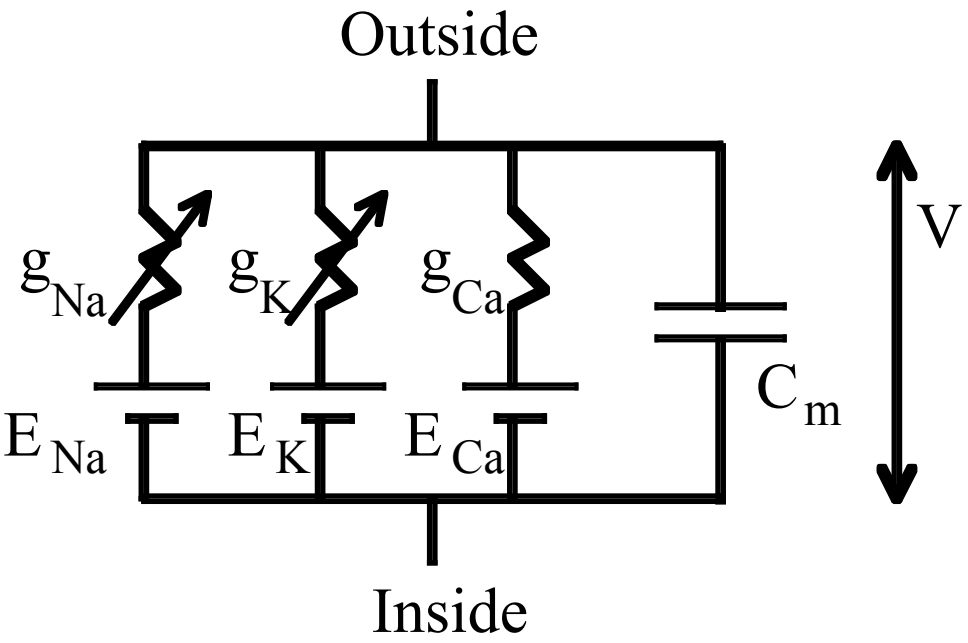
Cardiac action potentials

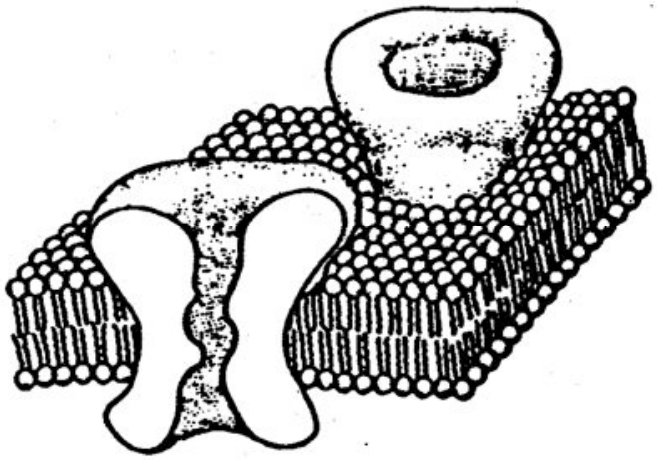
- Upstroke of ventricular AP is Na^+ mediated.
- A prolonged inward Ca^{2+} current prolongs the AP (plateau).
- Ca^{2+} influx triggers additional Ca^{2+} release from the sarcoplasmic reticulum.
- Cytoplasmic Ca^{2+} produces muscle contraction.
- Cardiac cells have many different types of K^+ channels.





The membrane as an electrical circuit





Equation for capacitor: $Q = C_m V$

Current across capacitor: $I_c = \mathrm{d}Q/\mathrm{d}t = C_m \mathrm{d}V/\mathrm{d}t$

Charge conservation: $I = I_c + I_{ion} = 0$

Hence, $\boxed{\mathrm{d}V/\mathrm{d}t = -I_{ion}/C_m,}$ where $I_{ion} = I_{Na} + I_K + I_{Ca}$

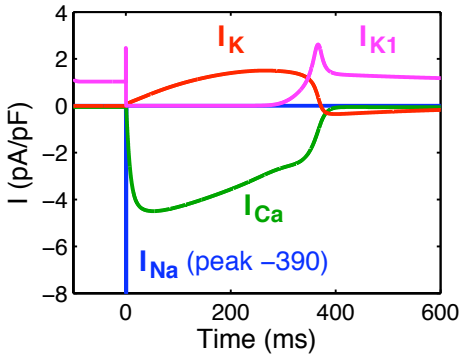
Examples of currents with voltage-gated conductances:

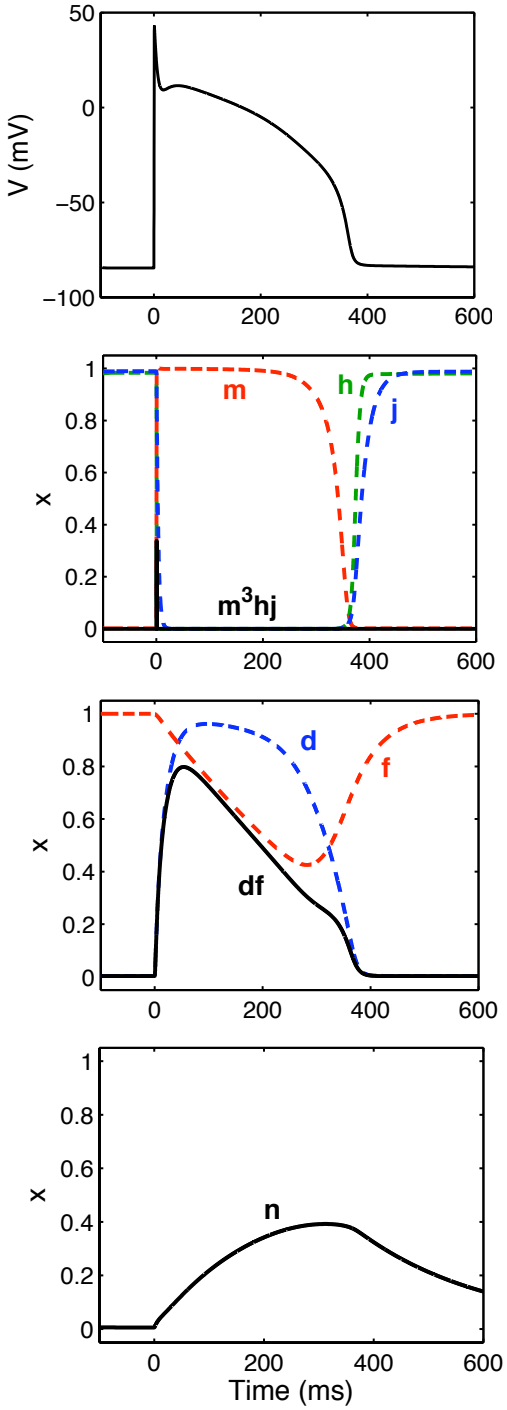
$$I_{Na} = g_{Na} m^3 h j (V - E_{Na})$$

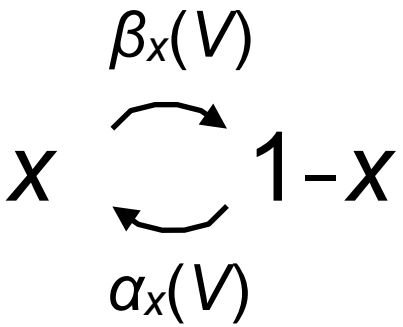
$$I_{Ca} = g_{Ca} d f (V - E_{Ca})$$

$$I_K = g_K n (V - E_K)$$

m, h, j, d, f, n represents the fraction of gates that are open ("gating variables")







x: fraction of gates that are open

$1-x$: fraction of gates that are closed

$\alpha_x(V)$: opening rate

$\beta_x(V)$: closing rate

ODE for gating variable:

$$\begin{aligned} dx/dt &= \alpha_x(1-x) - \beta_x x \\ &= -(\alpha_x + \beta_x)x + \alpha_x \\ &= (x_\infty - x)/\tau_x \end{aligned}$$

where $x_\infty = \alpha_x/(\alpha_x + \beta_x)$

$\tau_x = 1/(\alpha_x + \beta_x)$

Solution for constant *V*:

$$dx/dt = (x_\infty - x)/\tau_x$$

$$1/(x_\infty - x)\,dx = 1/\tau_x\,dt$$

$$\int_{x_0}^{x} 1/(x_\infty - x')\,dx' = \int_0^t 1/\tau_x\,dt'$$

$$[-\ln(x_\infty - x')]_{x_0}^{x} = t/\tau_x$$

$$\ln\frac{x_\infty - x}{x_\infty - x_0} = -t/\tau_x$$

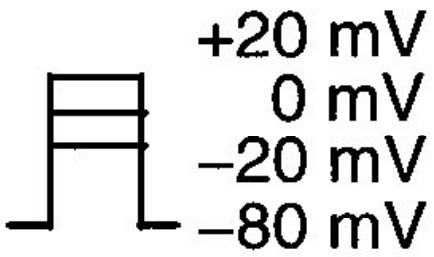
$$\frac{x_\infty - x}{x_\infty - x_0} = \exp(-t/\tau_x)$$

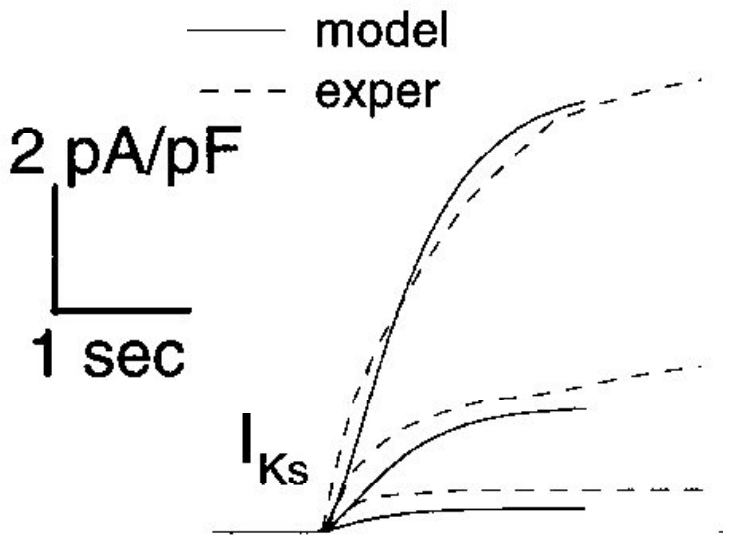
$$x = x_\infty - (x_\infty - x_0)\exp(-t/\tau_x)$$

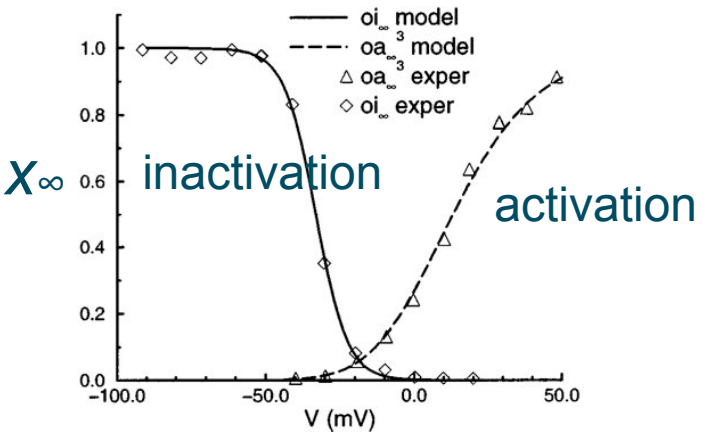
Solution for constant *V*:

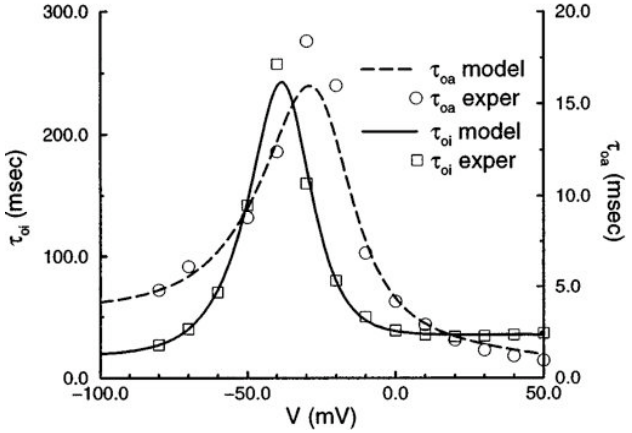
$$x = x_\infty - (x_\infty - x_0)\exp(-t/\tau_x)$$

Voltage clamp experiments:

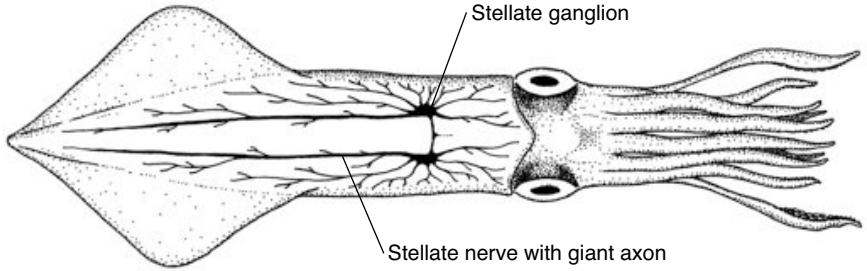




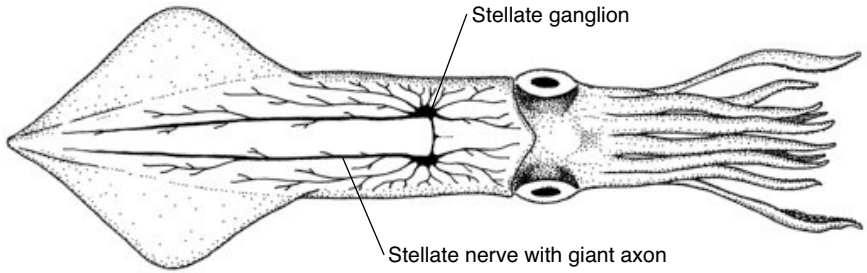


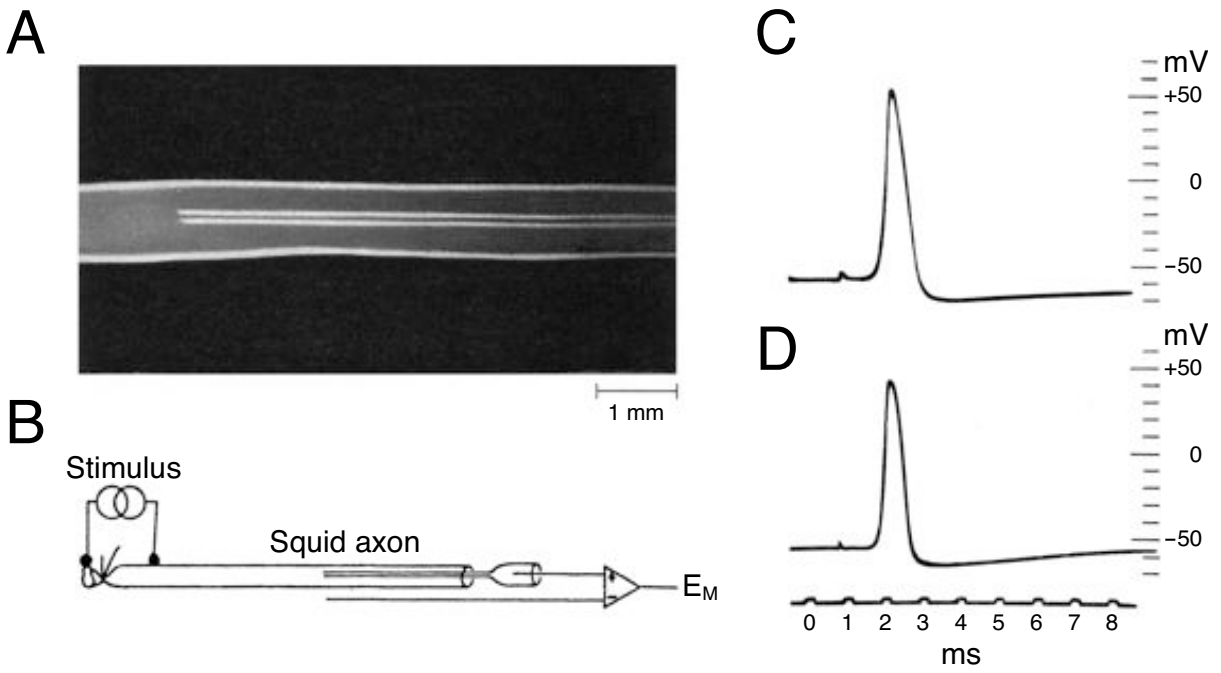


The Hodgkin-Huxley model of the squid giant axon



The axon is giant,
not the squid





Action potential recordings from squid giant axon

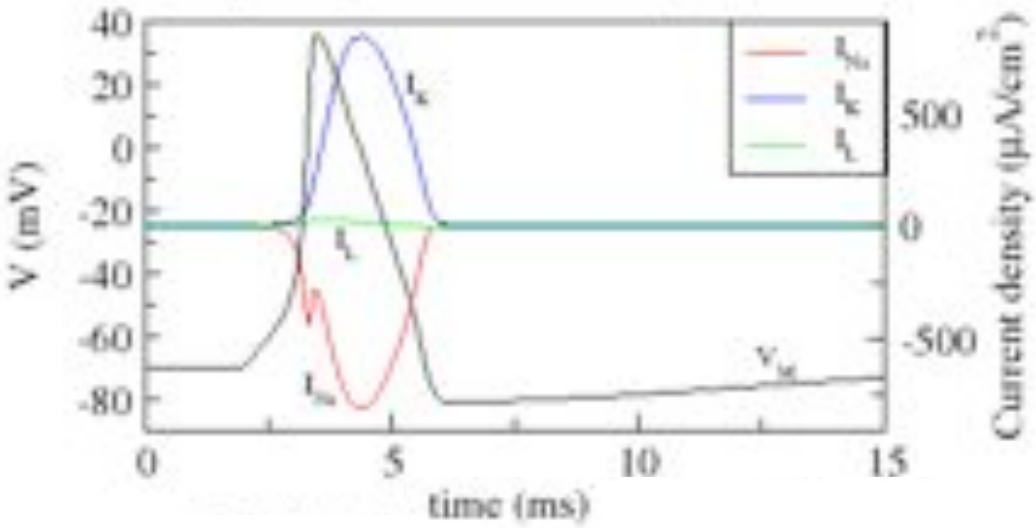
Full Hodgkin-Huxley model

$$\frac{dV}{dt} = -\frac{1}{C}[(\bar{g}_{\mathrm{Na}} m^3 h(V - E_{\mathrm{Na}}) + \bar{g}_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}) + \bar{g}_{\mathrm{L}}(V - E_{\mathrm{L}}) + I_{\mathrm{stim}}],$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m,$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h,$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n,$$



$$\alpha_m = 0.1(V+35)/(1-\exp(-(V+35)/10)),$$

$$\beta_m = 4\exp(-(V+60)/18),$$

$$\alpha_h = 0.07\exp(-(V+60)/20),$$

$$\beta_h = 1/(\exp(-(V+30)/10)+1),$$

$$\alpha_n = 0.01(V+50)/(1-\exp(-(V+50)/10)),$$

$$\beta_n = 0.125\exp(-(V+60)/80).$$

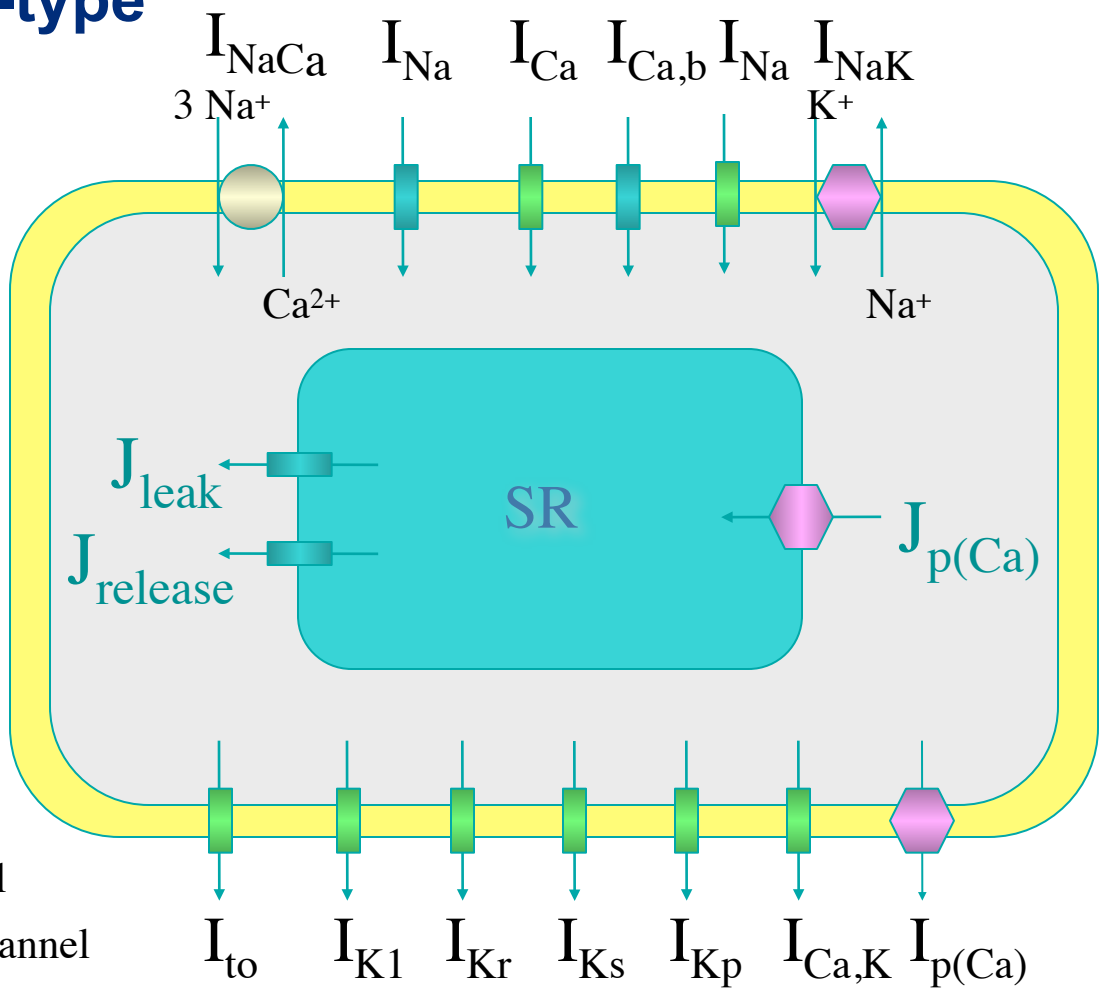
Single cardiac myocyte model example

Hodgkin-Huxley-type

$$\frac{dV}{dt} = -\sum I_i / C_m$$

$$I_i = g_i x (V - E_i)$$

$$x = f(V,t)$$



Pump

Exchanger

Voltage-gated ion channel

Non-voltage-gated ion channel

CVM model of the canine ventricular myocyte
13 state variables and ~60 parameters

courtesy of R. Gilmour

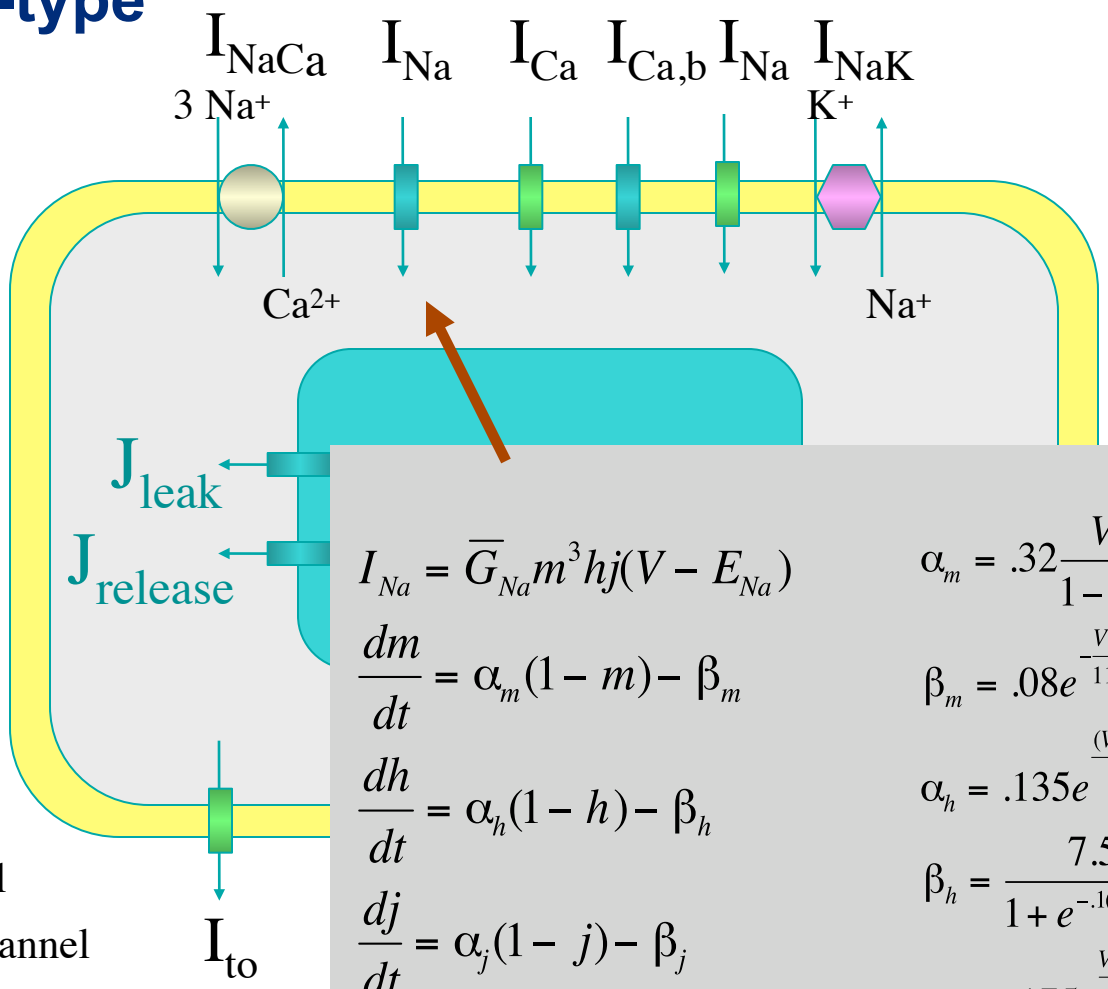
Single cardiac myocyte model example

Hodgkin-Huxley-type

$$\frac{dV}{dt} = -\sum I_i / C_m$$

$$I_i = g_i x (V - E_i)$$

$$x = f(V,t)$$



Pump

Exchanger

Voltage-gated ion channel

Non-voltage-gated ion channel

$$I_{Na} = \bar{G}_{Na} m^3 h j (V - E_{Na})$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h$$

$$\frac{dj}{dt} = \alpha_j (1 - j) - \beta_j$$

$$E_{Na} = \frac{RT}{F} \ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right)$$

$$\alpha_m = .32 \frac{V + 47.13}{1 - e^{-.1(V+47.13)}}$$

$$\beta_m = .08 e^{-\frac{V}{11}}$$

$$\alpha_h = .135 e^{\frac{(V+80)}{-6.8}}$$

$$\beta_h = \frac{7.5}{1 + e^{-.1(V+11)}}$$

$$\alpha_j = \frac{.175 e^{\frac{V+100}{-23}}}{1 + e^{.15(V+79)}}$$

$$\beta_j = \frac{.3}{1 + e^{-.1(V+32)}}$$

CVM mod
~13 state

Cell model evolution: Noble, 1962

The sodium current

$$I_{Na} = (400m^3h + 0{\cdot}14)(E_m - 40).$$

$$\alpha_h = 0{\cdot}17 \exp[(-E_m - 90)/20],$$

$$\beta_h = \left[\exp\left(\frac{-E_m - 42}{10}\right) + 1\right]^{-1},$$

$$\alpha_m = \frac{0{\cdot}1(-E_m - 48)}{\exp[(-E_m - 48)/15] - 1},$$

$$\beta_m = \frac{0{\cdot}12(E_m + 8)}{\exp[(E_m + 8)/5] - 1}.$$

The potassium current

$$I_K = (g_{K_1} + g_{K_2})(E_m + 100).$$

$$g_{K_1} = 1{\cdot}2 \exp[(-E_m - 90)/50] + 0{\cdot}015 \exp[(E_m + 90)/60].$$

$$g_{K_2} = 1{\cdot}2n^4,$$

$$\alpha_n = \frac{0{\cdot}0001(-E_m - 50)}{\exp[(-E_m - 50)/10] - 1},$$

$$\beta_n = 0{\cdot}002 \exp[(-E_m - 90)/80].$$

the anion conductance, g_{An}

$$g_{An} = I_{An}/(E_m - E_{An}),$$

Noble,
J Physiol, 1962.

Cell model evolution: Luo & Rudy, 1991

TABLE I. Formulations of Ionic Currents

Inward currents

Fast sodium current

$I_{Na} = 23 \cdot m^3 \cdot h \cdot j \cdot (V - E_{Na})$

For $V \geq -40$ mV

$\alpha_h = \alpha_j = 0.0$, $\beta_h = 1/(0.13[1 + \exp[(V + 10.66)/-11.1]])$

$\beta_j = 0.3 \cdot \exp(-2.535 \cdot 10^{-7} V)/[1 + \exp[-0.1(V + 32)]]$

For $V < -40$ mV

$\alpha_h = 0.135 \cdot \exp[(80 + V)/-6.8]$, $\beta_h = 3.56 \cdot \exp(0.079V) + 3.1 \cdot 10^5 \cdot \exp(0.35V)$

$\alpha_j = [-1.2714 \cdot 10^5 \cdot \exp(0.2444V) - 3.474 \cdot 10^{-5} \cdot \exp(-0.04391V)] \cdot (V + 37.78)/[1 + \exp[0.311 \cdot (V + 79.23)]]$

$\beta_j = 0.1212 \cdot \exp(-0.01052V)/[1 + \exp[-0.1378(V + 40.14)]]$

For all range of V

$\alpha_m = 0.32(V + 47.13)/[1 - \exp[-0.1(V + 47.13)]]$, $\beta_m = 0.08 \cdot \exp(-V/11)$

Slow inward current

$I_s = 0.09 \cdot d \cdot f \cdot (V - E_s)$, $E_s = 7.7 - 13.0287 \cdot \ln[Ca_i]$

$\alpha_d = 0.095 \cdot \exp[-0.01(V - 5)]/[1 + \exp[-0.072(V - 5)]]$

$\beta_d = 0.07 \cdot \exp[-0.017(V + 44)]/[1 + \exp[0.05(V + 44)]]$

$\alpha_f = 0.012 \cdot \exp[-0.008(V + 28)]/[1 + \exp[0.15(V + 28)]]$

$\beta_f = 0.0065 \cdot \exp[-0.02(V + 30)]/[1 + \exp[-0.2(V + 30)]]$

Calcium uptake: $d[Ca_i]/dt = -10^{-4} \cdot I_s + 0.07(10^{-4} - [Ca_i])$

Outward currents

Time-dependent potassium current

$I_x = \overline{G}_x \cdot X \cdot X_i \cdot (V - E_x)$, $\overline{G}_x = 0.282 \cdot \sqrt{[K]_o/5.4}$

$X_i = 2.837 \cdot [\exp[0.04(V + 77)] - 1]/[(V + 77) \cdot \exp[0.04(V + 35)]]$ for $V > -100$ mV and $X_i = 1$ for $V \leq -100$ mV

$\alpha_x = 0.0005 \cdot \exp[0.083(V + 50)]/[1 + \exp[0.057(V + 50)]]$

$\beta_x = 0.0013 \cdot \exp[-0.06(V + 20)]/[1 + \exp[-0.04(V + 20)]]$

Time-independent potassium current

$I_{K1} = \overline{G}_{K1} \cdot K1_\infty \cdot (V - E_{K1})$, $\overline{G}_{K1} = 0.6047 \cdot \sqrt{[K]_o/5.4}$

$\alpha_{K1} = 1.02/[1 + \exp[0.2385 \cdot (V - E_{K1} - 59.215)]]$

$\beta_{K1} = [0.49124 \cdot \exp[0.08032 \cdot (V - E_{K1} + 5.476)] + \exp[0.06175 \cdot (V - E_{K1} - 594.31)]]/$
$[1 + \exp[-0.5143 \cdot (V - E_{K1} + 4.753)]]$

Plateau potassium current

$I_{Kp} = 0.0183 \cdot Kp \cdot (V - E_{Kp})$, $E_{Kp} = E_{K1}$

$Kp = 1/[1 + \exp[(7.488 - V)/5.98]]$

Background current

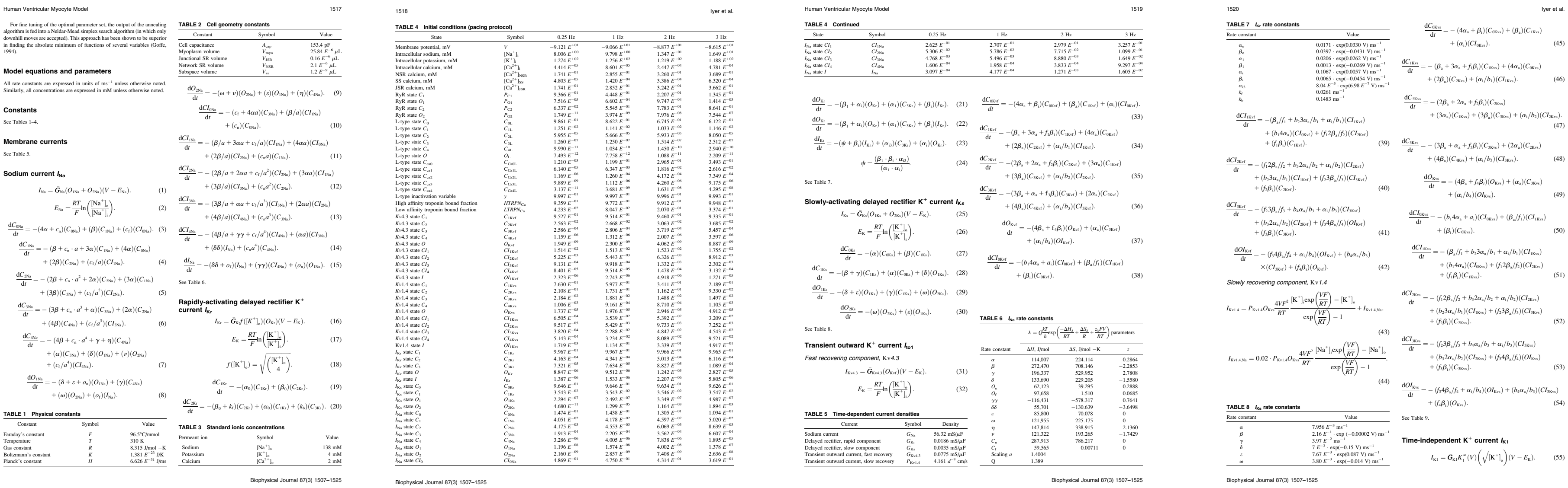
$I_b = 0.03921 \cdot (V + 59.87)$

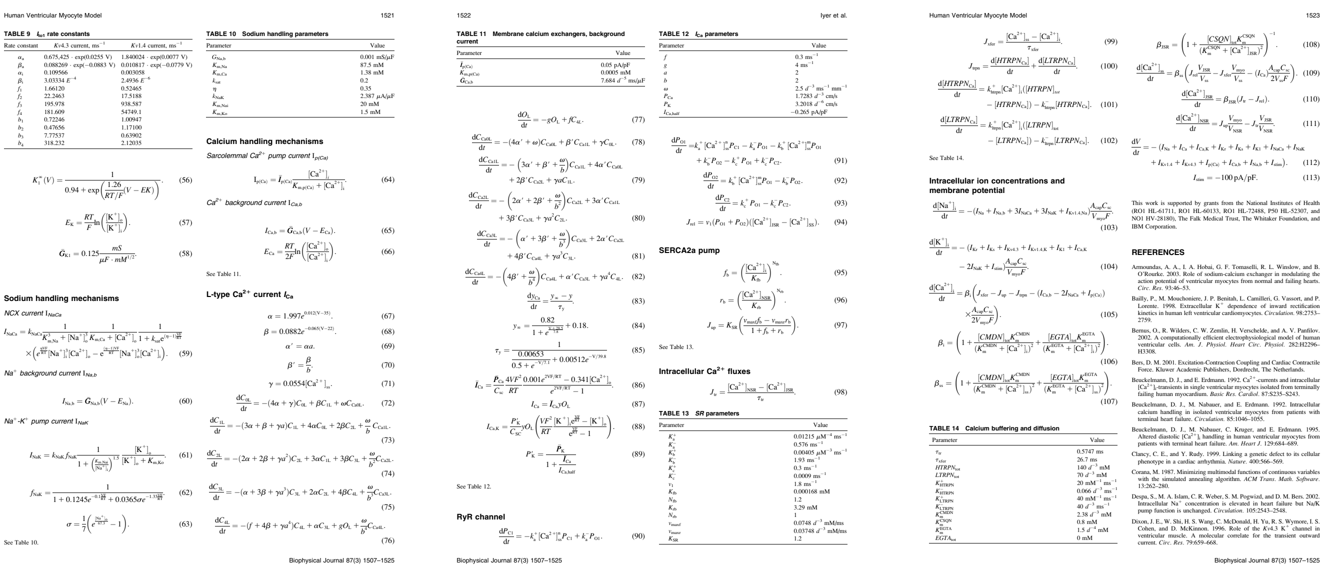
Total time-independent potassium current

$I_{K1} = I_{K1} + I_{Kp} + I_b$

Luo & Rudy,
Circ Res, 1991.

Cell model evolution: Iyer et al. 2004

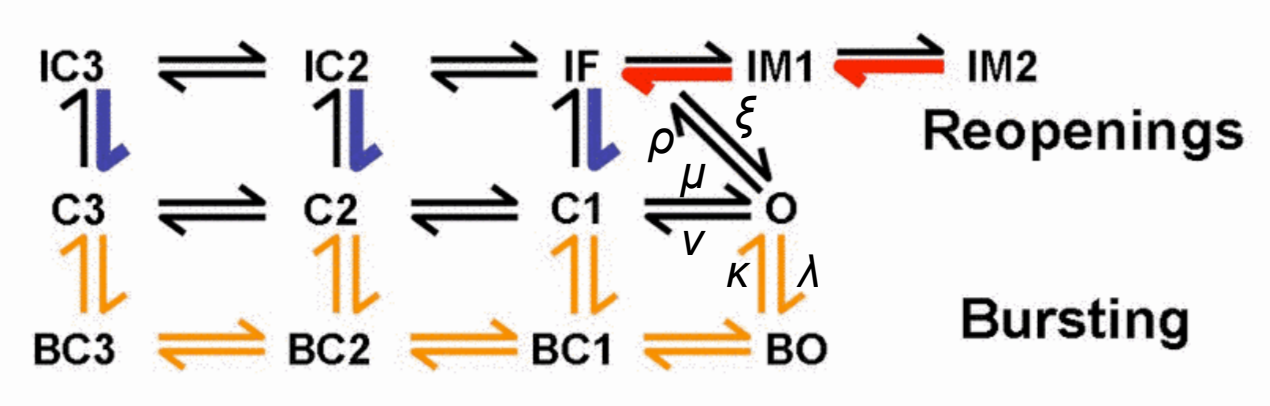




Iyer et al., Biophys J, 2004.

Markov model example: I_{Na}

$$I_{Na} = g_{Na}(O+BO)(V-E_{Na})$$



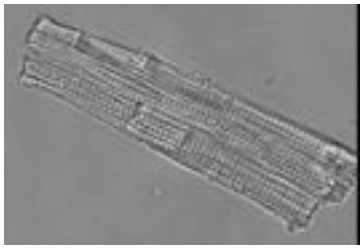
$$dO/dt = \kappa BO - \lambda O + \mu C1 - \nu O + \xi IF - \rho O$$
$$dBO/dt = \ldots$$
$$\vdots$$

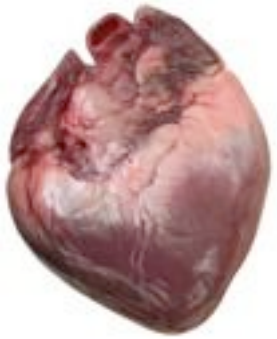
13 ODEs
(vs 4 for HH)

- May reproduce experimental data better than HH
- Integration time step usually small
- Many parameters

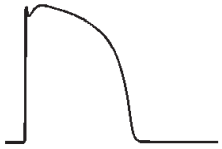
Multiscale phenomena

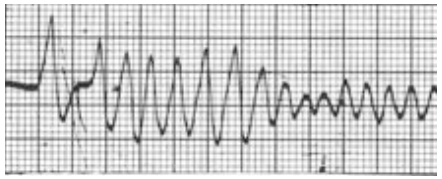
single channel → single cell → tissue, organ





1 Å | 1 nm | 10 nm | 100 nm | 1 µm | 10 µm | 100 µm | 1 mm | 1 cm | 10 cm

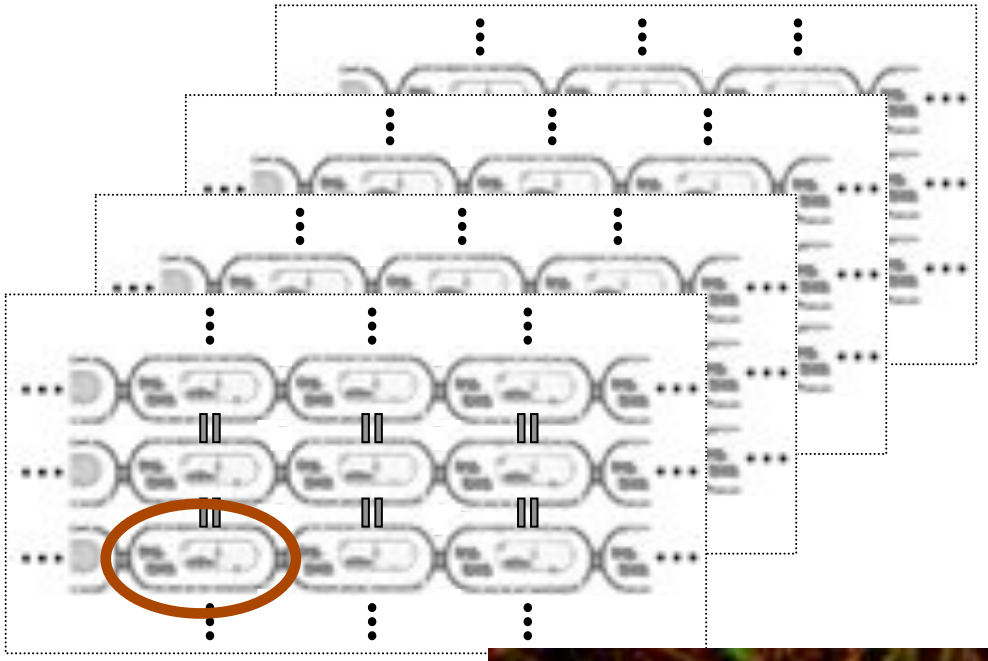


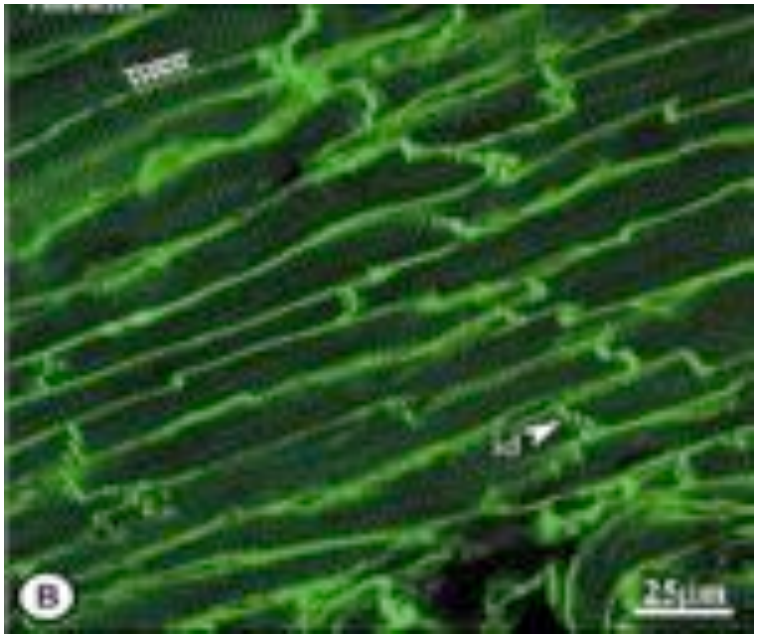


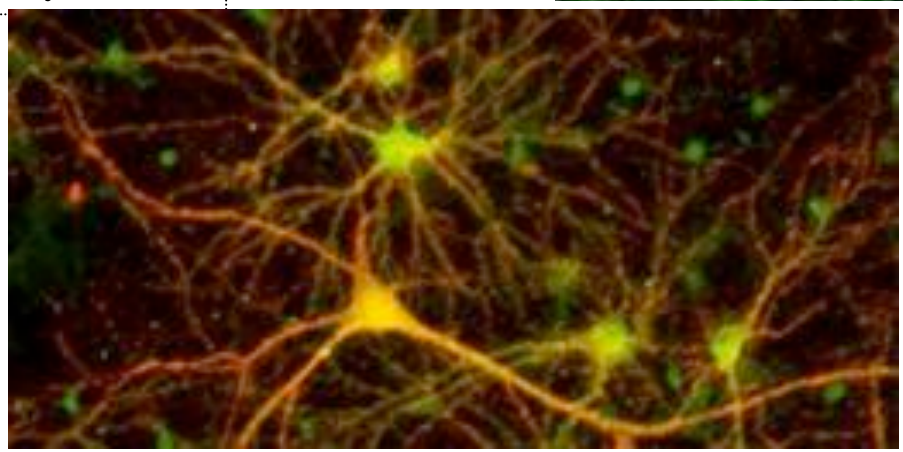
10 µs | 100 µs | 1 ms | 10 ms | 100 ms | 1 s | 10 s | 100 s

Three-dimensional virtual cardiac tissue

Virtual cells coupled by Ohmic resistances (gap junctions)

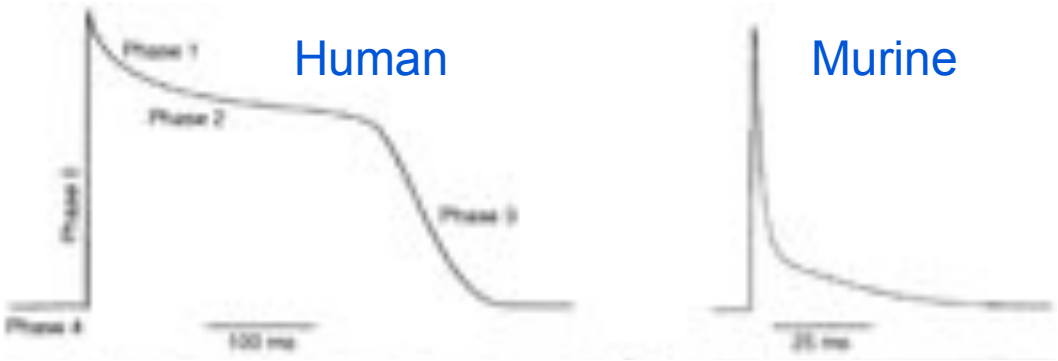






Why use computational modeling for cardiac electrophysiology?

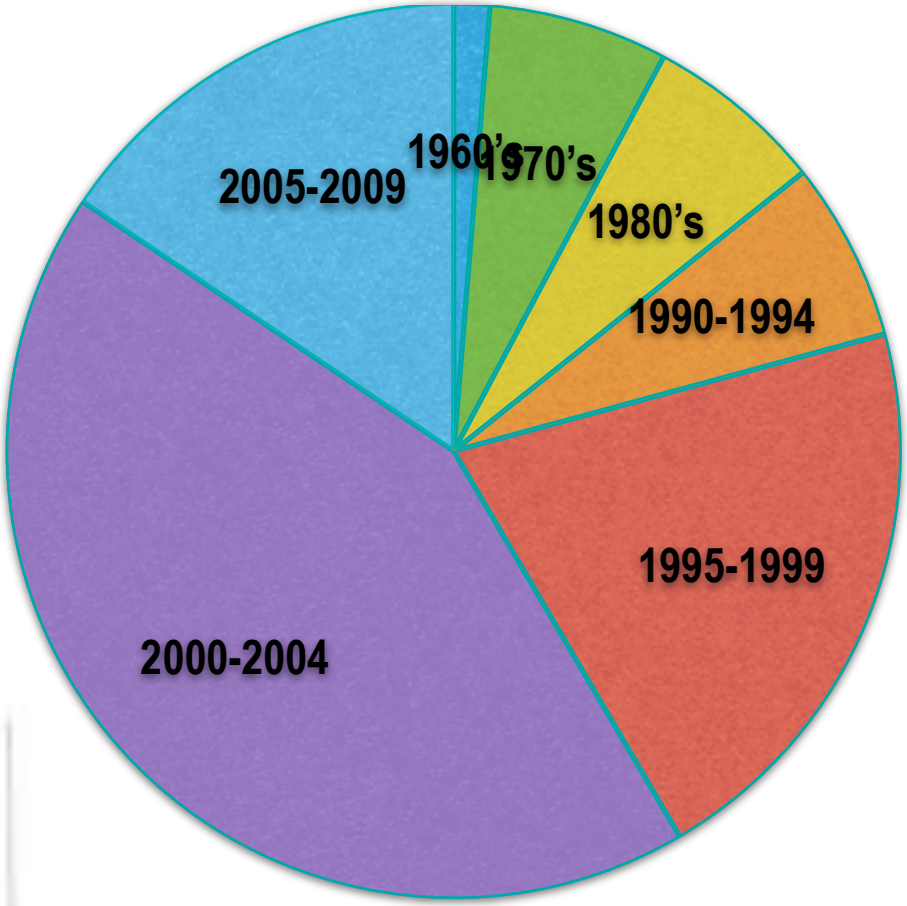
- Rodent cardiac myocytes have fundamentally different channel expression levels (especially repolarizing currents). Therefore, transgenic models are not always appropriate.
- Modeling allows one to monitor each component simultaneously – not possible in experiments.
- Dynamics can be observed at resolutions that are unattainable experimentally or clinically.
- It is often faster and cheaper to do so.

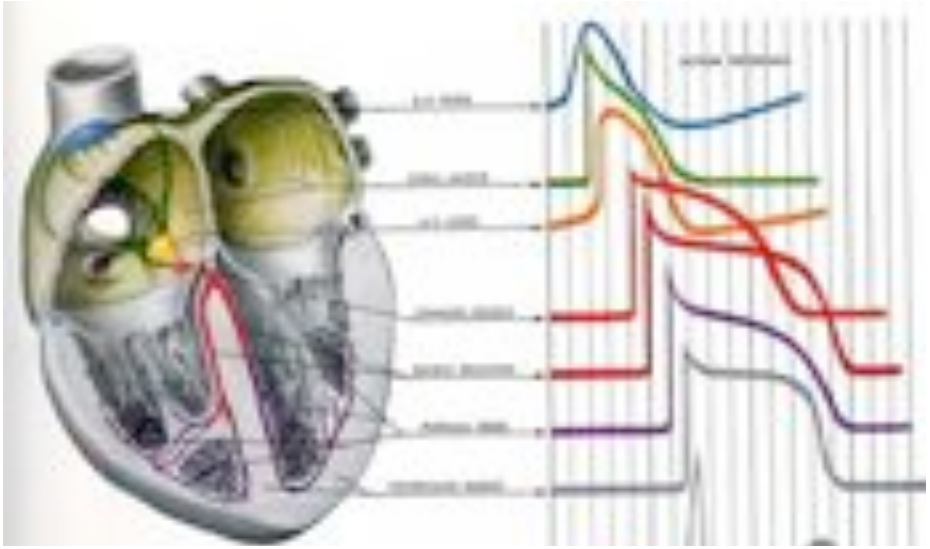


Nerbonne.
Trends Cardiovasc. Med.
2004.

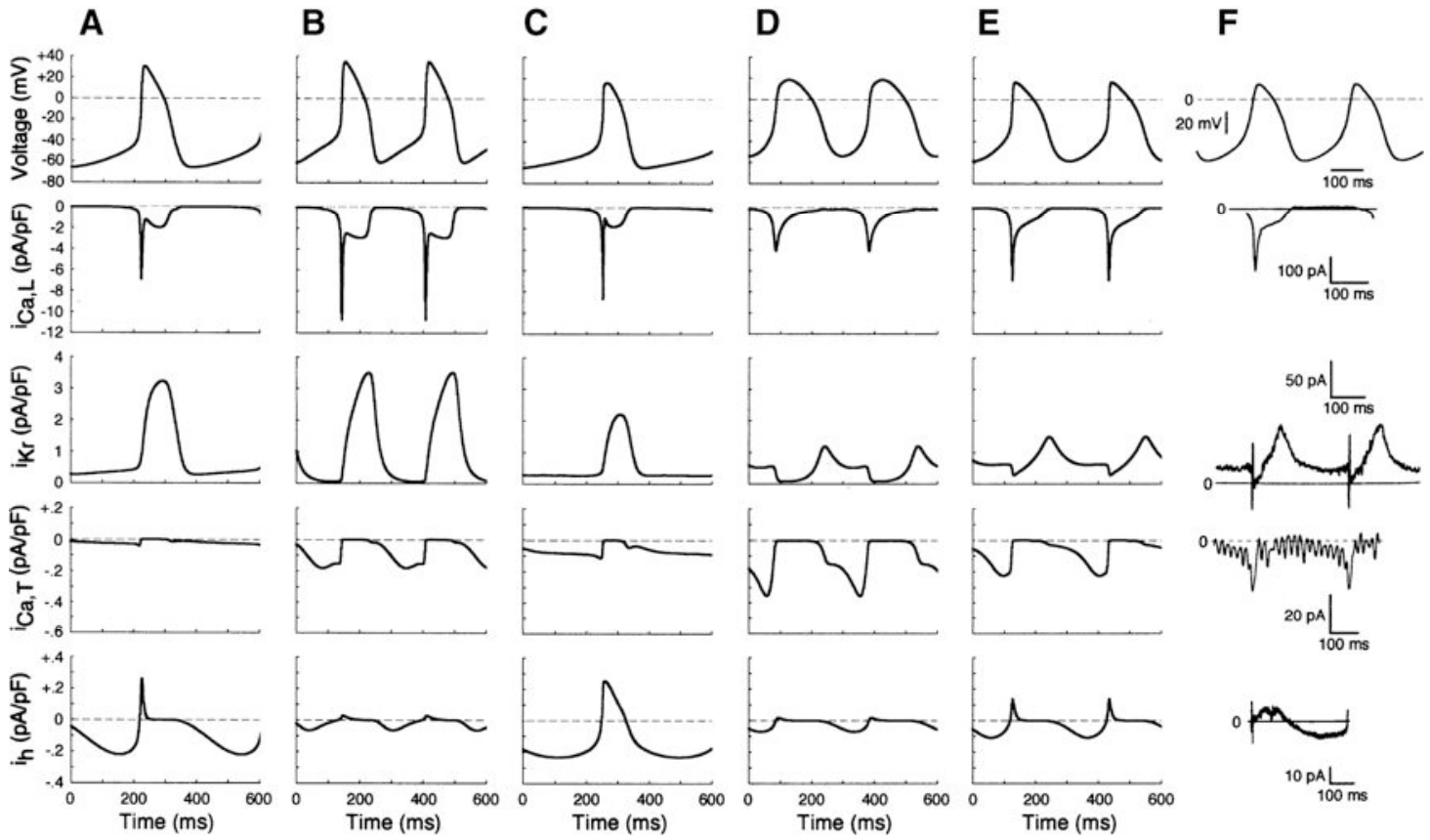
Cardiac ionic model surge

- Surge in development of cell models
- 66 in total (at CellML)
- Different species, regions, pathologies
- Multiple models for the same species/ region/condition





Five different rabbit SAN models

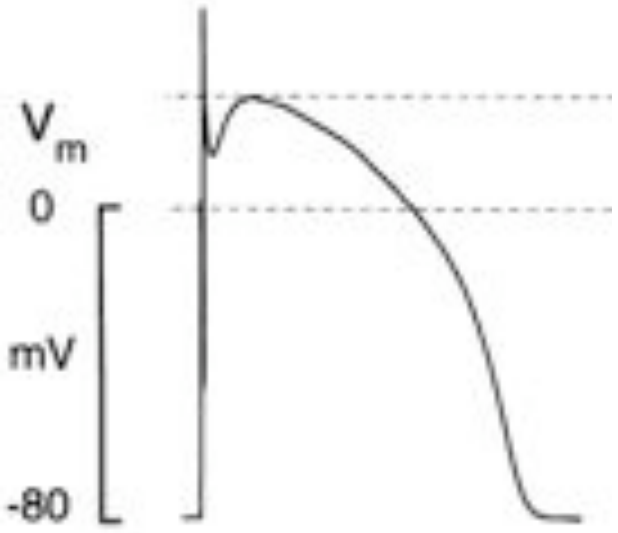


Different models, different action potential shapes and duration

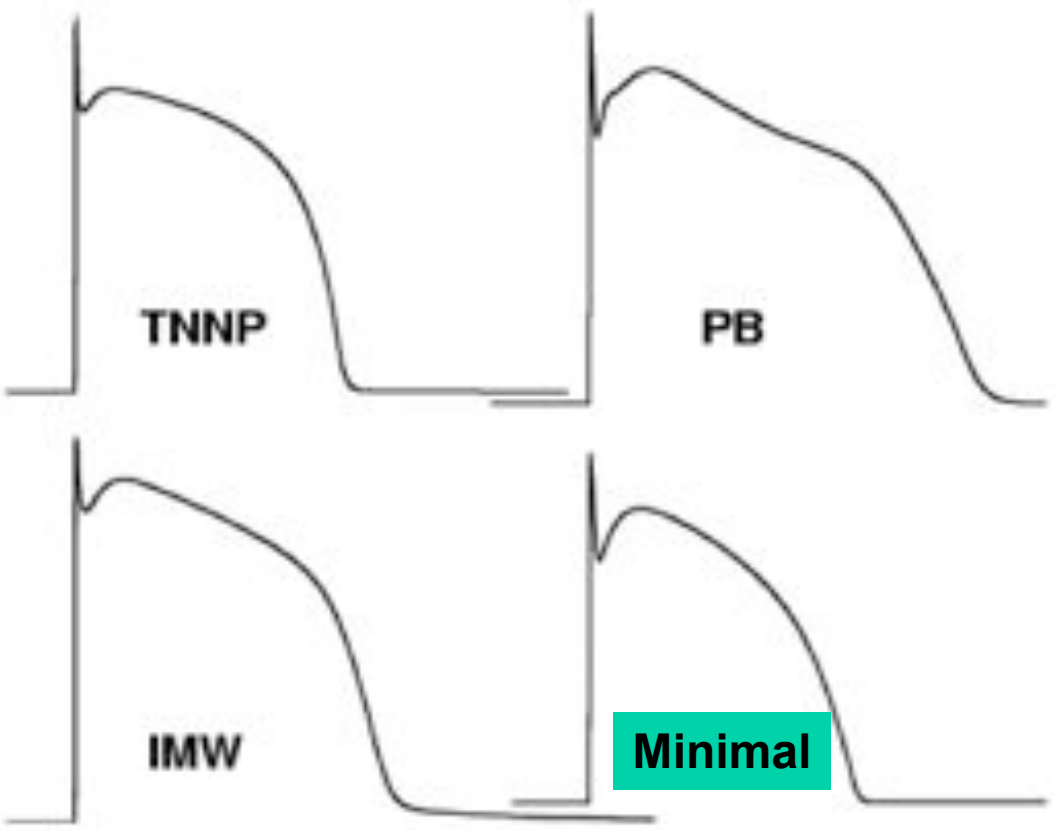
Kurata et al. (2002) AJP 283, H2074-2101.

Four different human ventricular cell models

AP shapes are different (qualitatively and quantitatively).



Experimental epicardial AP. (M. Näbauer *et al.*, Circulation 1996).



Simulated epicardial APs for the different ionic models.

Cherry, KITP seminar 2006

Why do different models of the same species and regions disagree?

- Some models are simply better than others:
  - Uses better data
  - Uses more data from particular species/region
- The models are equally good/bad:
  - Differences reflect electrophysiological heterogeneity
  - Differences reflect different age, sex, etc.

Model component heritage

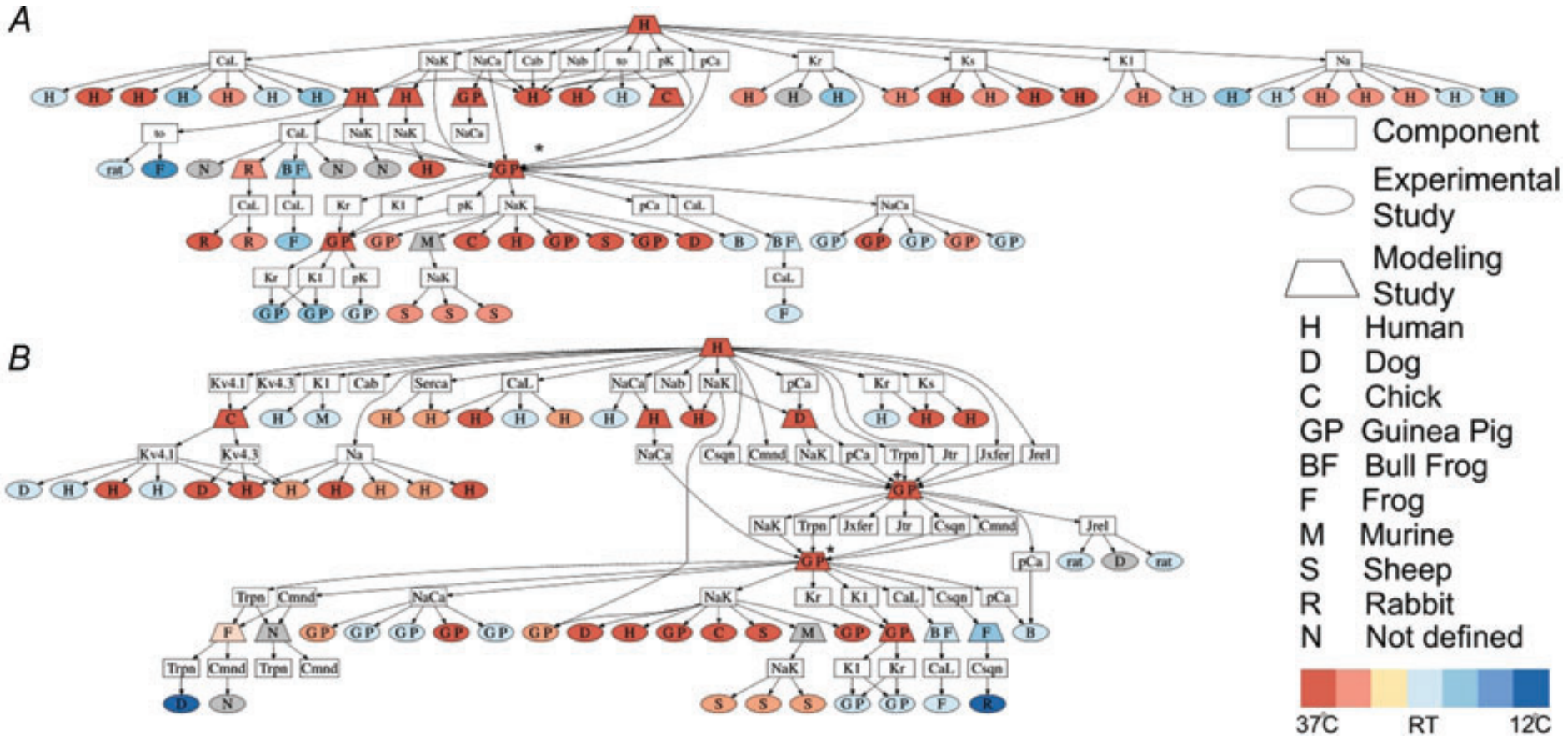


Figure 1. Phylogenetic schematic for the ten Tusscher *et al.* (2004; *A*) and the Iyer *et al.* (2004; *B*) cell models (*B*), showing the links between modelling (trapeziums) and experimental studies (ellipses)
Modelling studies are broken up into components (boxes), with connections (arrows) between components and published studies. ∗ Luo & Rudy (1994) model; and + Jafri *et al.* (1998) model.

Niederer et al.,
Exp Physiol, 2009.

Other modeling considerations

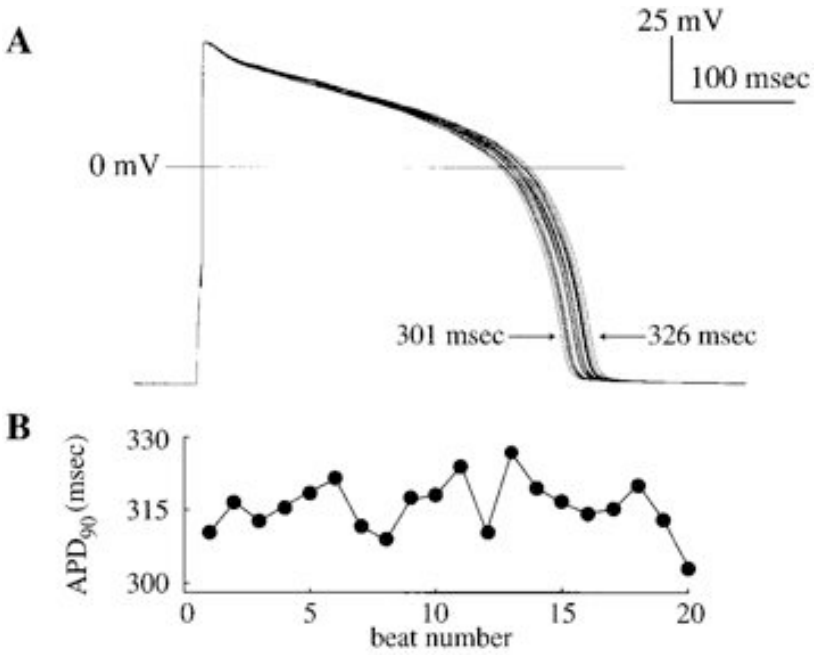
- Models are validated for specific conditions. They may not be valid for your numerical experiments (fast rates, temperature, concentrations, drugs, age, sex).
- A model can give a “right” result for the wrong reason.
- The more complicated the model (more variables and parameters), the more realistically it may behave. However,
- the more complicated the model, the harder it is to pin-point cause-and-effect relationships and the more components may be wrong.
- *Math instead of mice vs. insights from math/physics*

$$\frac{d\mathbf{x}}{dt} = f(\mathbf{x}, t)$$

Multiscale modeling example: single-channel noise

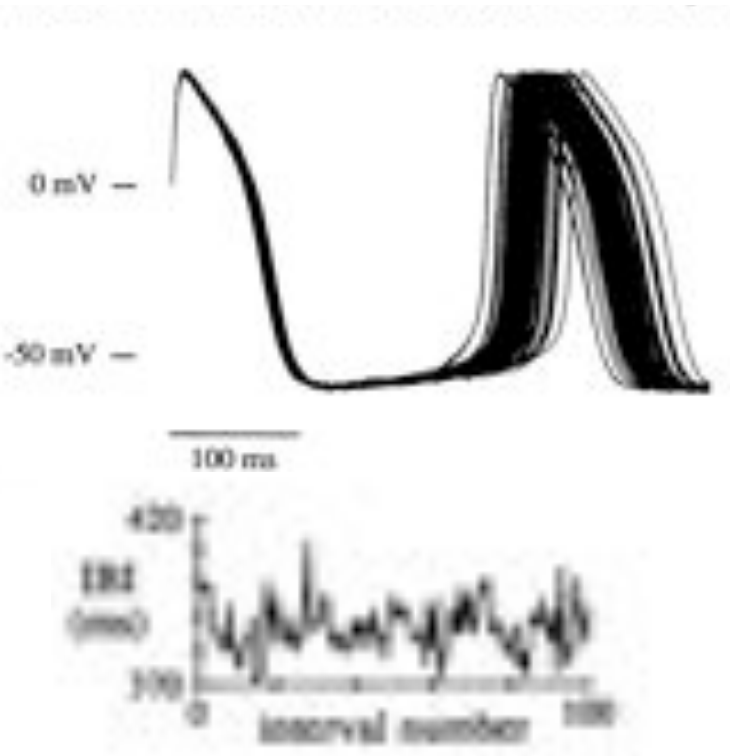
Beat-to-beat variability in cardiac action potentials

GP ventricular myocytes



Zaniboni et al., Am J Physiol, 2000

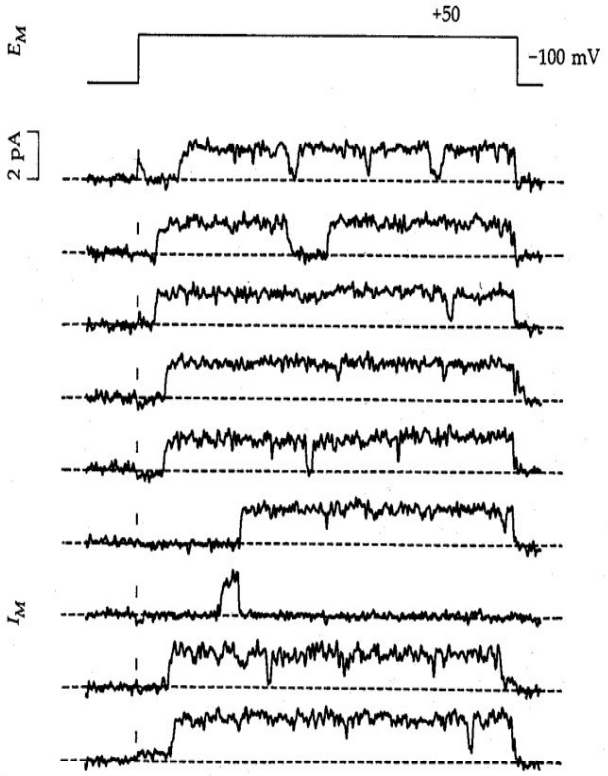
Rabbit SAN myocytes

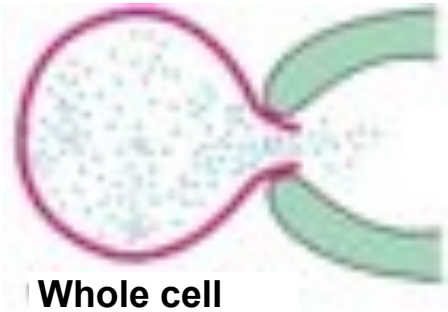


Wilders & Jongsma, Biophys J, 1993

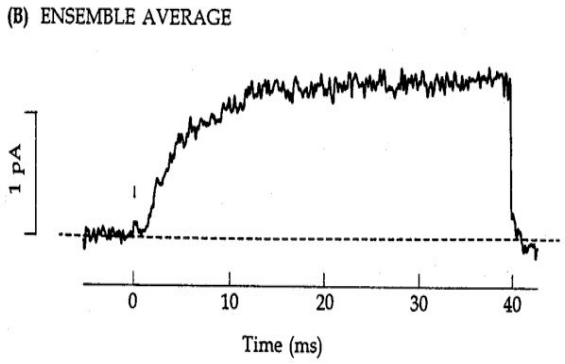
Multiscale modeling example: single-channel noise

Excised patch





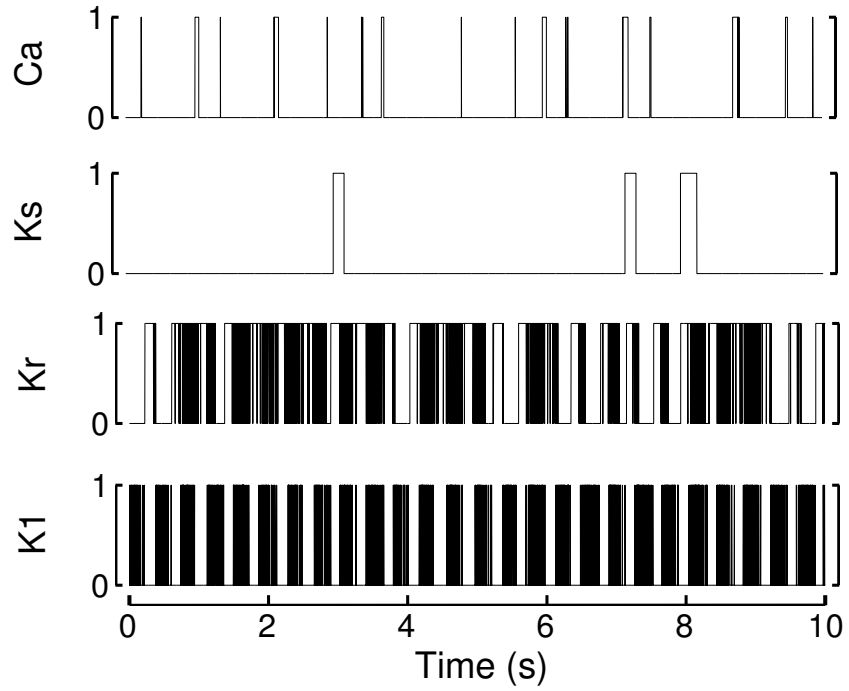
Whole cell

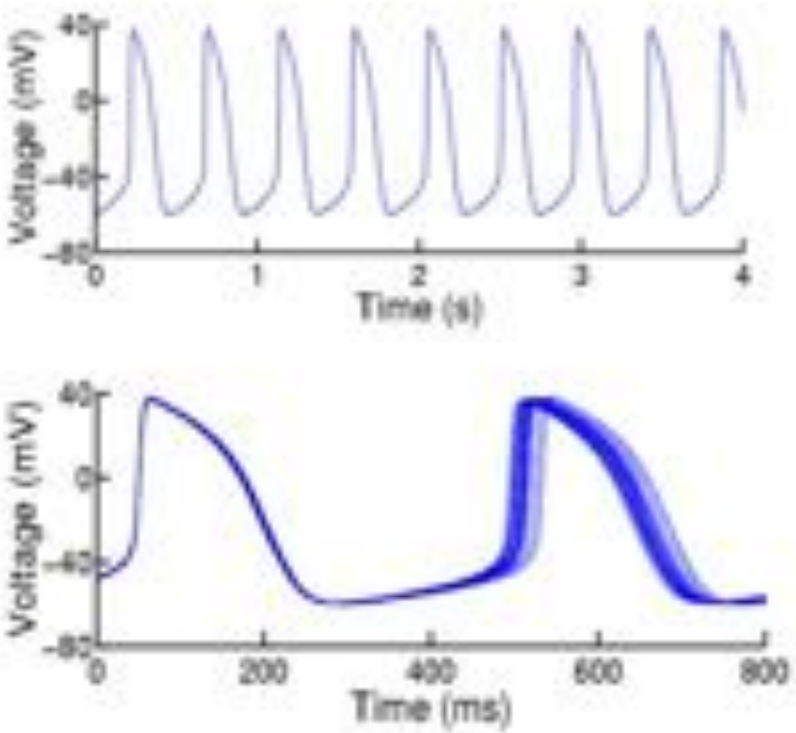


Unitary events add up to give the macroscopic current.

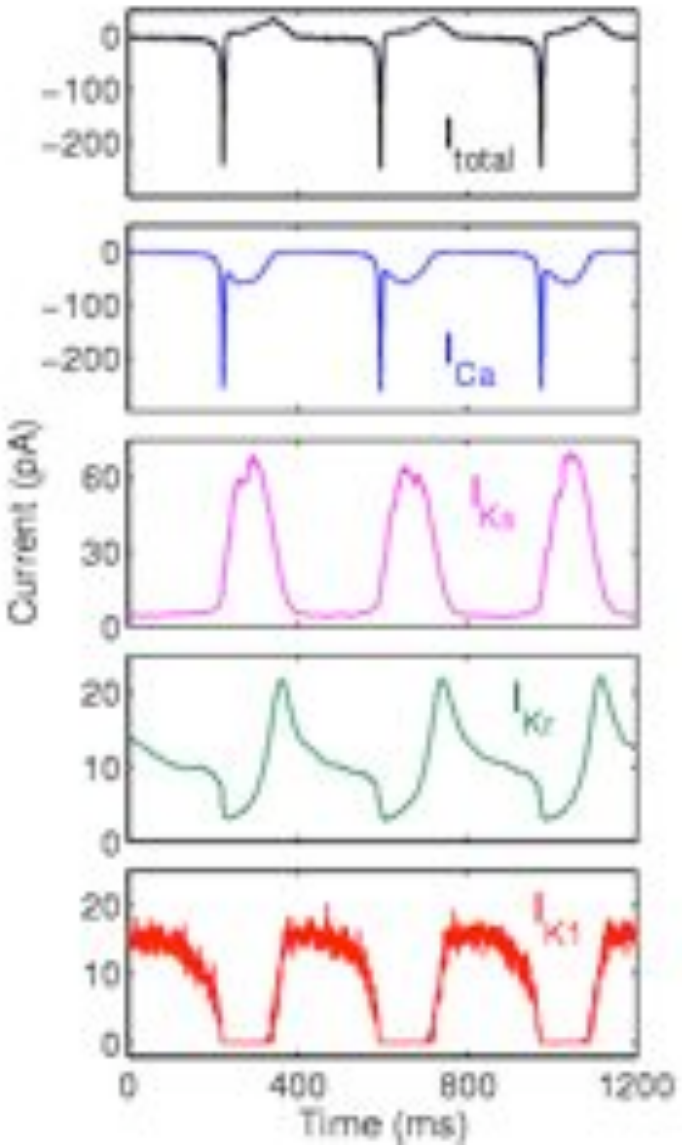
Multiscale modeling example: single-channel noise

Single channel noise → irregularity of beating

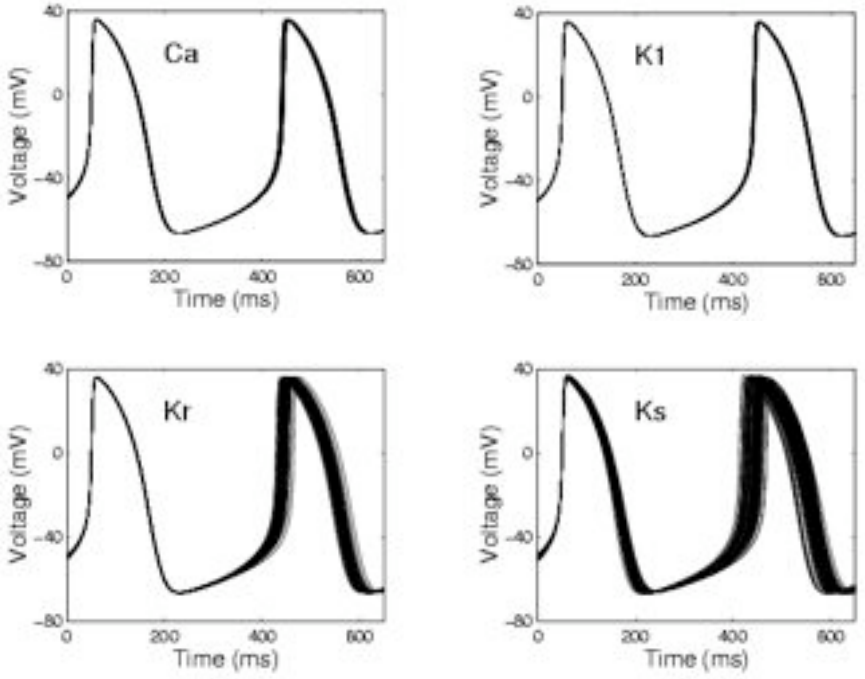




Multiscale modeling example: single-channel noise



One current stochastic at a time



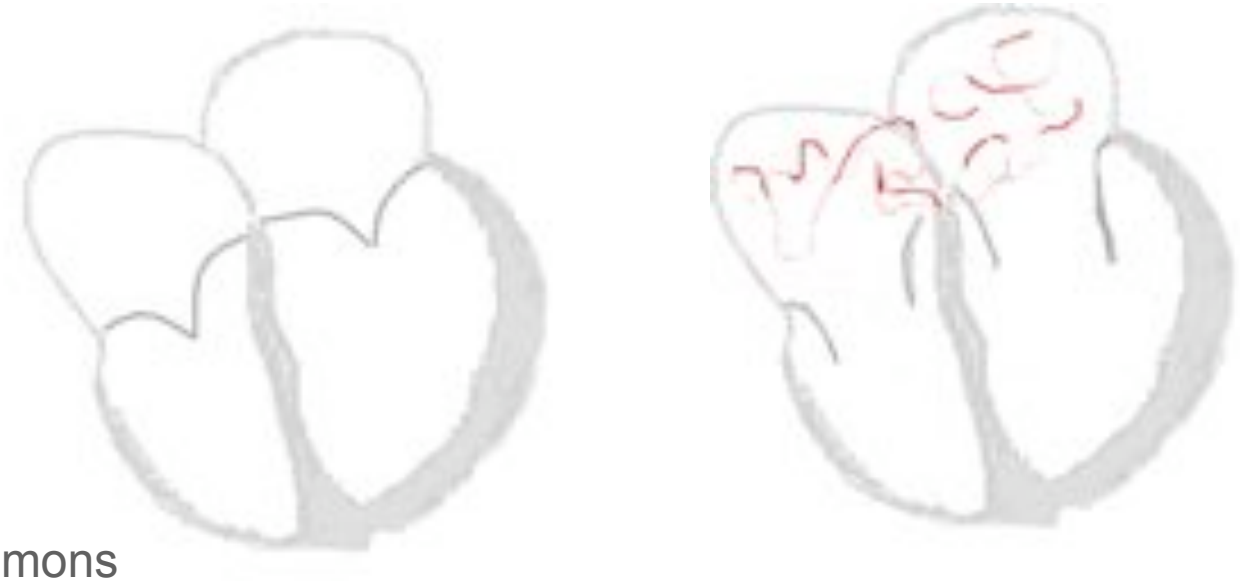
IKs: few channels, slow gating

Multiscale modeling example: atrial fibrillation maintenance

Atrial fibrillation:

- Rapid, irregular activation of the atria
- Loss of synchronized atrial contraction
- Rapid, irregular ventricular rate
- The most common sustained arrhythmia: more than 10% of population over the age of 80
- Associated with significant mortality and morbidity

Sinus rhythm

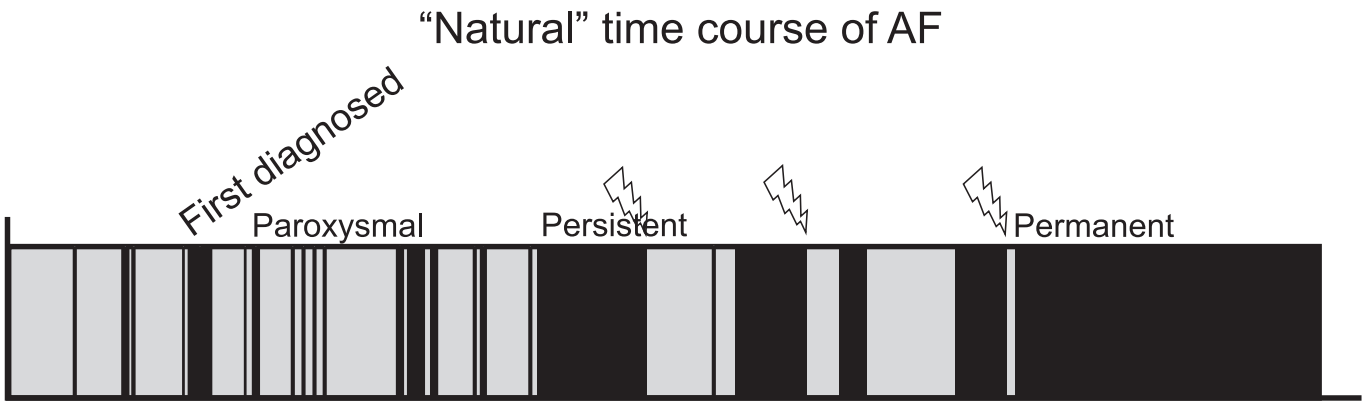


AF

Wikimedia Commons

Multiscale modeling example: AF maintenance

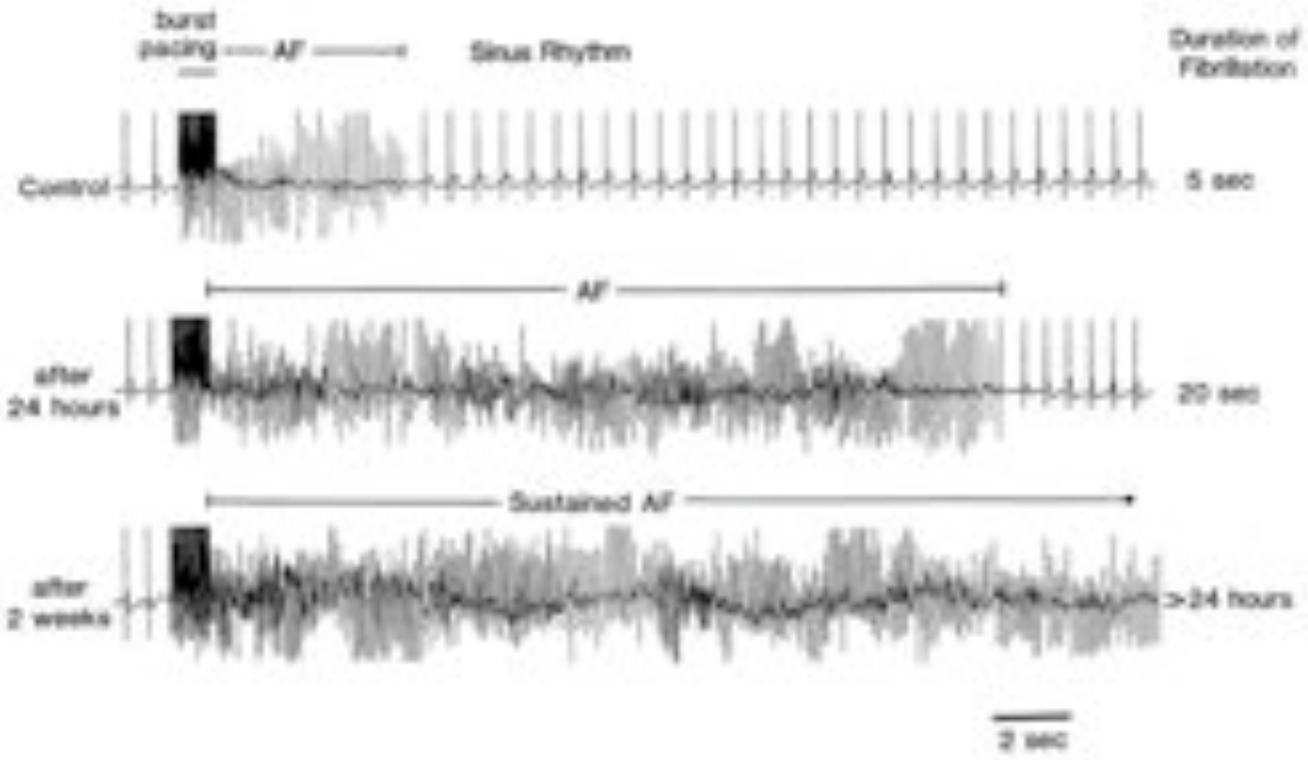
- In patients with chronic AF, fibrillatory episodes are of increased duration and frequency of occurrence
- This is due to ionic, structural, and contractile remodeling processes.

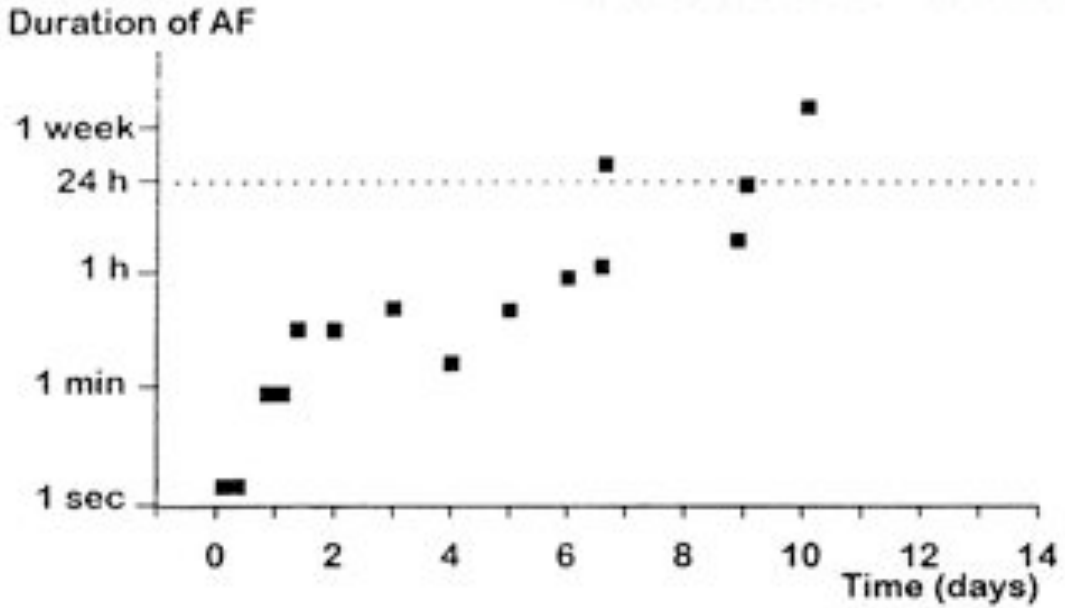


Schotten et al.,
Physiol Rev, 2011

Multiscale modeling example: AF maintenance

"AF begets AF"

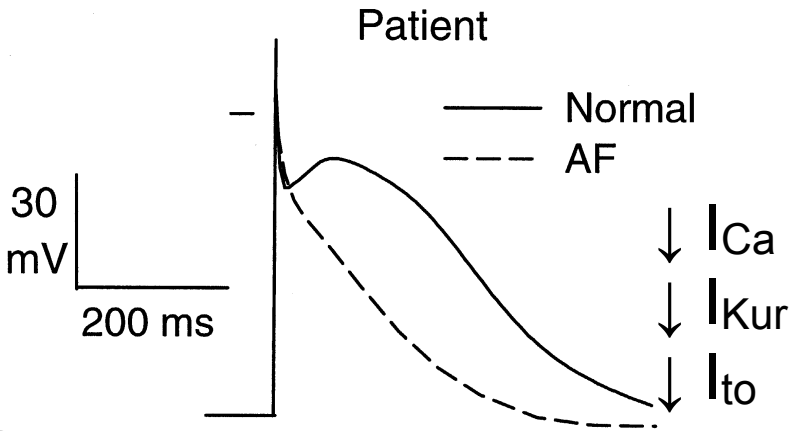




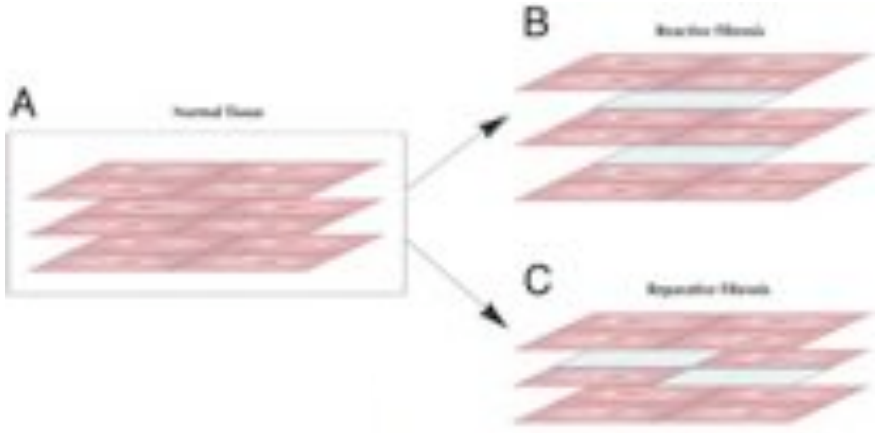
Wijffels et al., Circulation, 1995.

Multiscale modeling example: AF maintenance

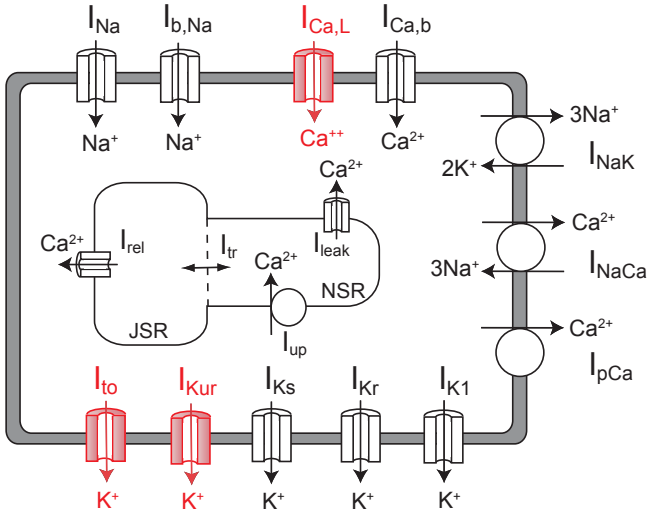
Ionic and structural remodeling

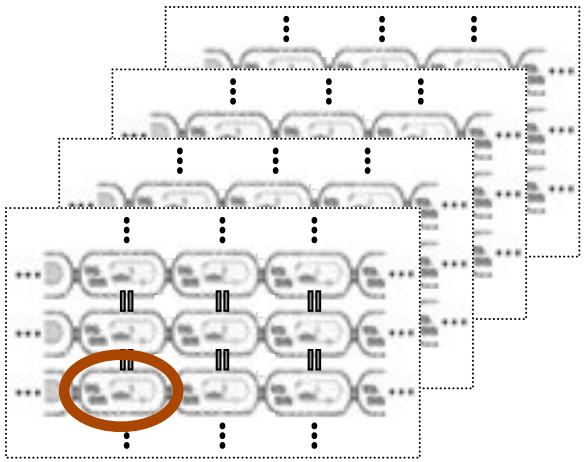


Courtemanche et al.,
Cardiovascular Research, 1999.



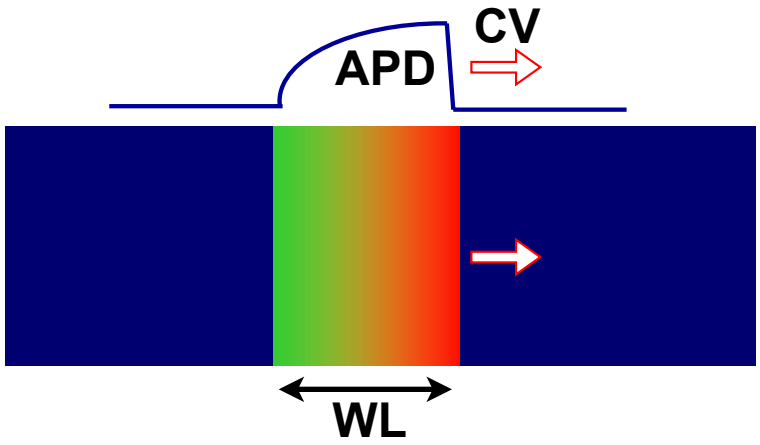
Burstein & Nattel,
J. American College of Cardiology, 2005.





Multiscale modeling example: AF maintenance

Effects of remodeling on wavelength

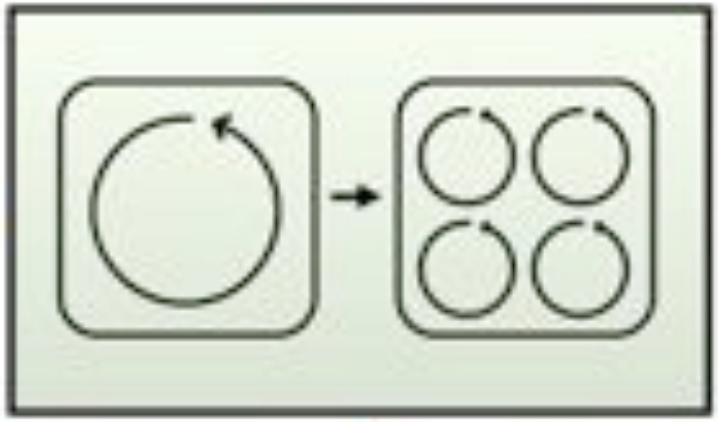


Wavelength: WL = CV · APD

↓CV
↓APD
⇨ ↓WL ⇨ multiple waves can fit in the atria

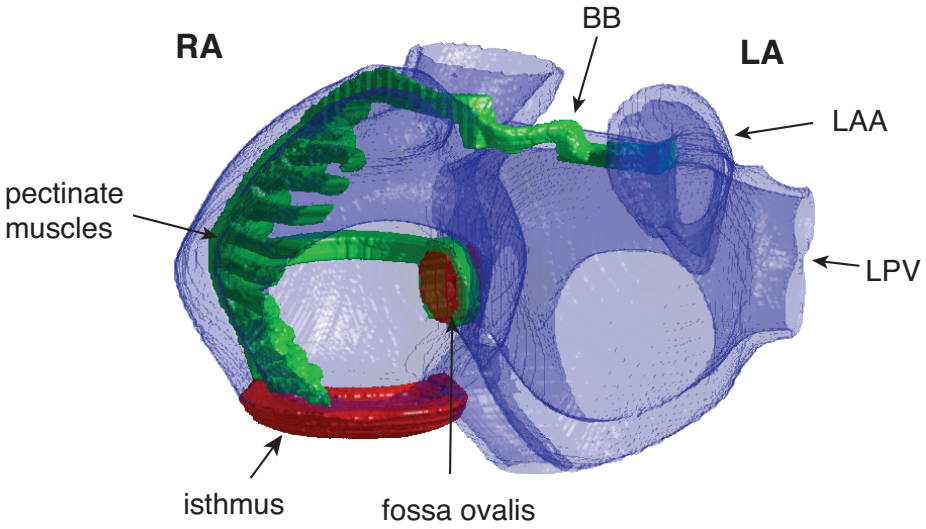
⇩

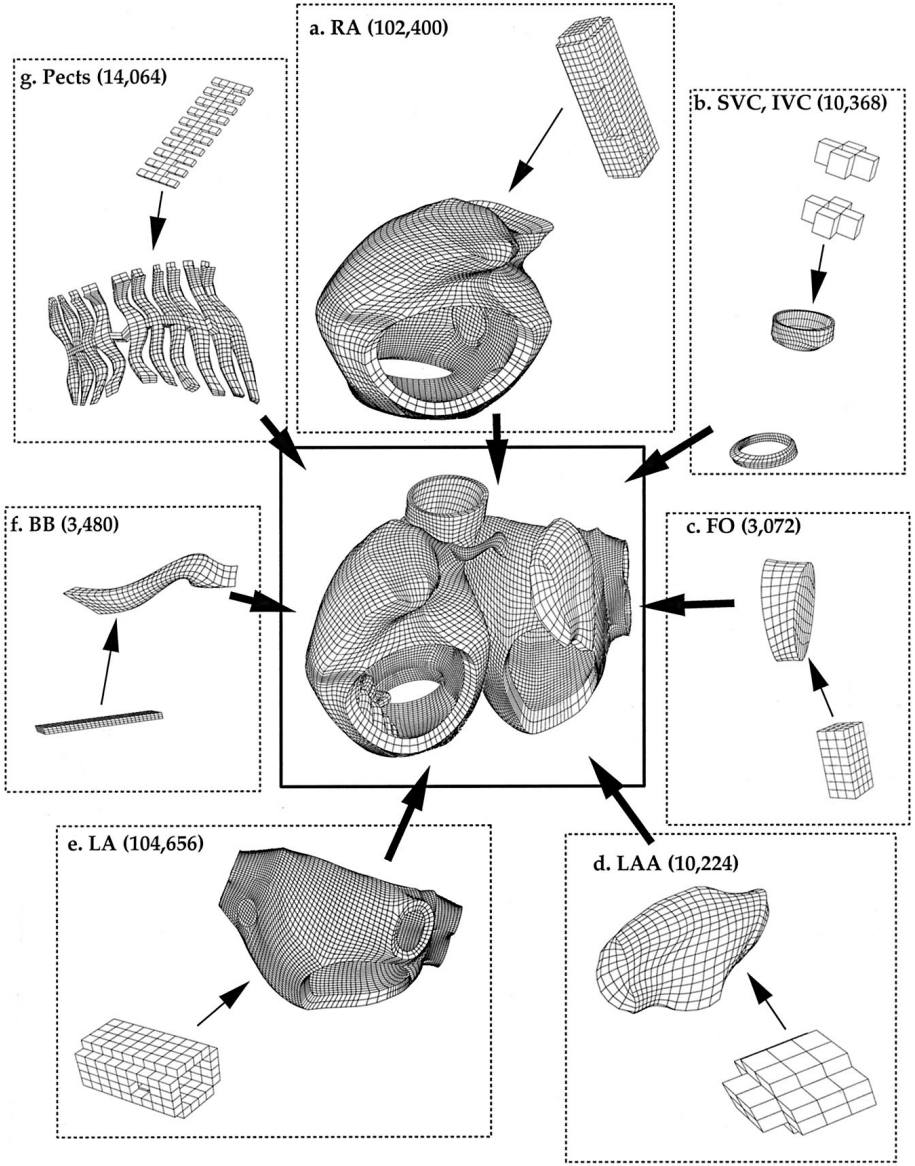
Substrate for multiple circuit reentry



Multiscale modeling example: AF maintenance

Anatomical structure





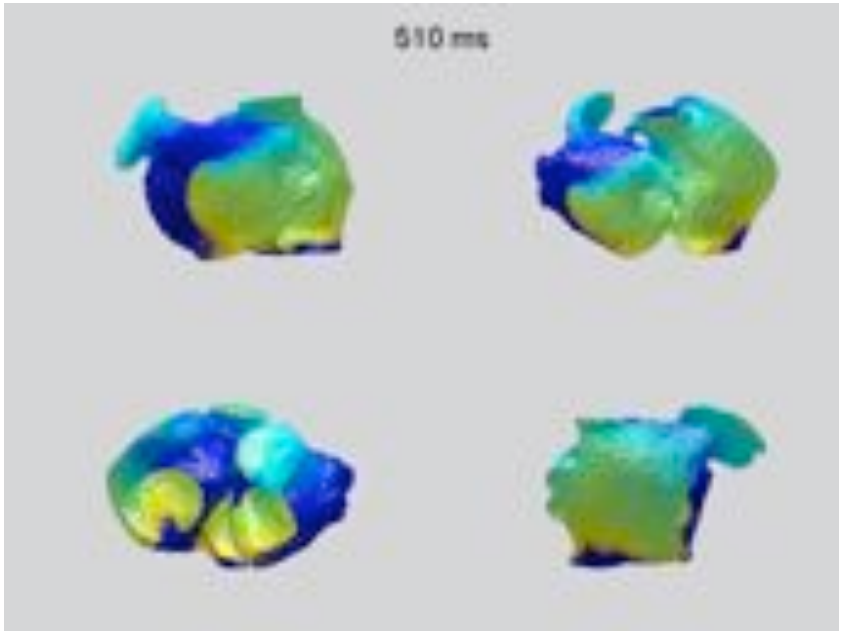
~2,000,000 virtual cells.

Computationally demanding, but easily parallelized.

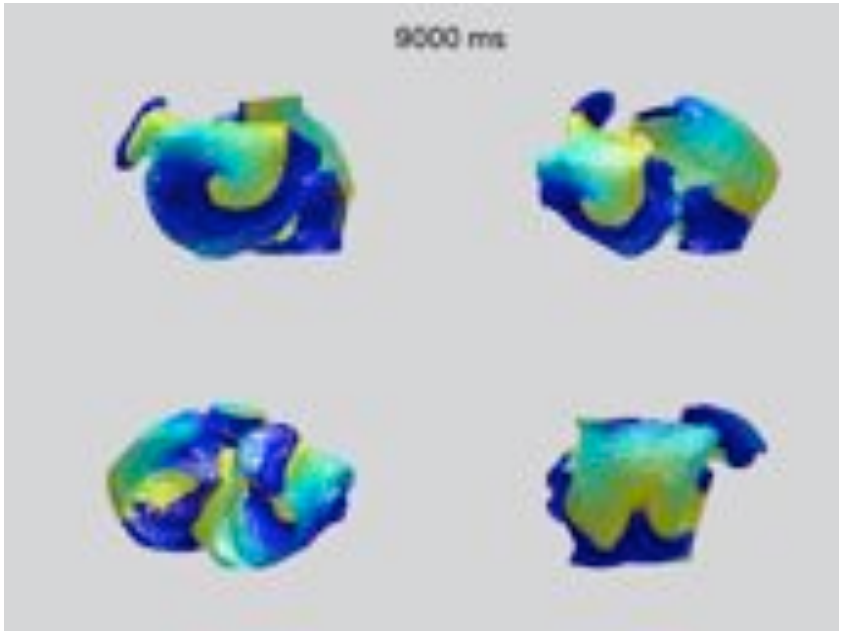
Harrild & Henriquez
Circ Res, 2000.

Multiscale modeling example: AF maintenance

No remodeling

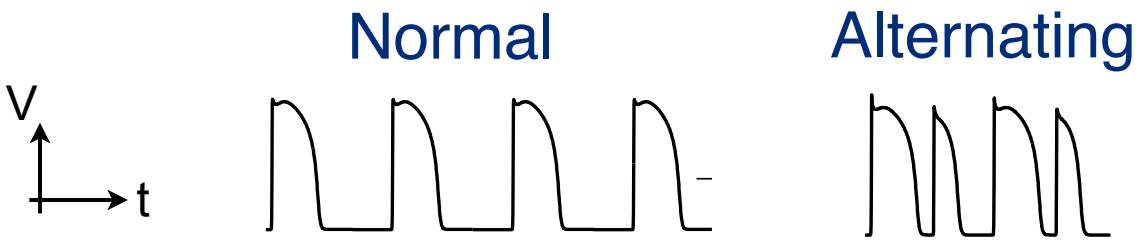


Ionic and structural remodeling

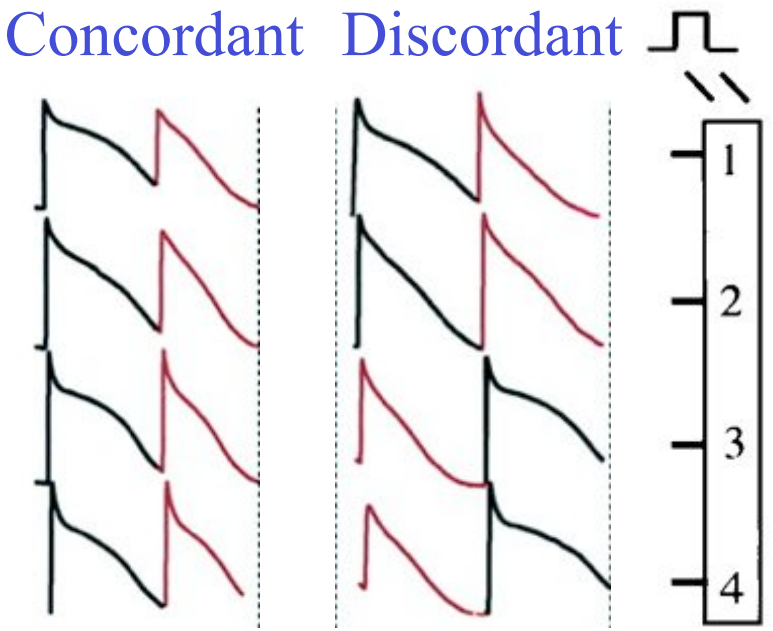


Alternans and alternans control

Repolarization alternans: a beat-to-beat alternation in action potential duration



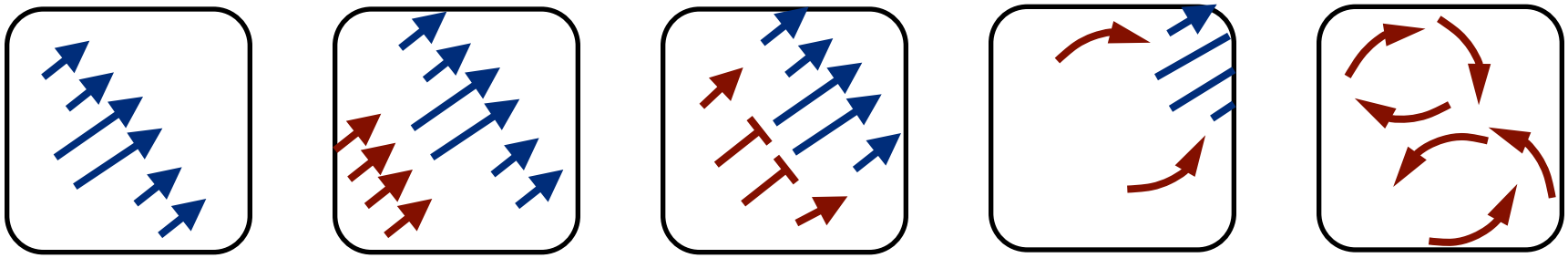
Alternans and arrhythmogenesis



Fox et al. Circ Res 2002

Alternans can induce large repolarization gradients across the heart, ultimately causing unidirectional block.

This may cause life-threatening ventricular tachyarrhythmias.



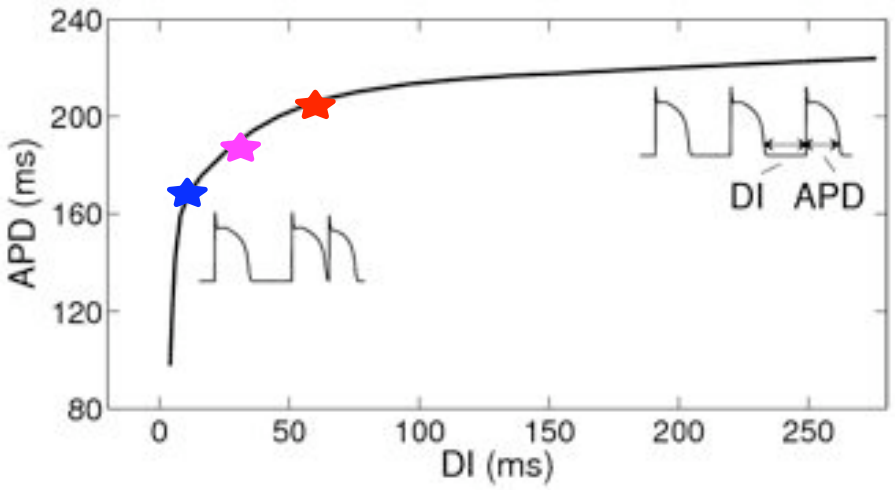
Alternans control

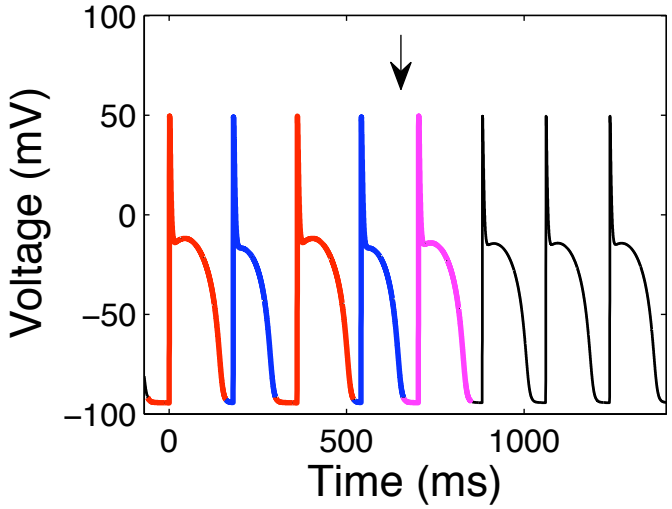
Basic concept: eliminate alternans by applying (small) electrical stimuli at well-timed intervals

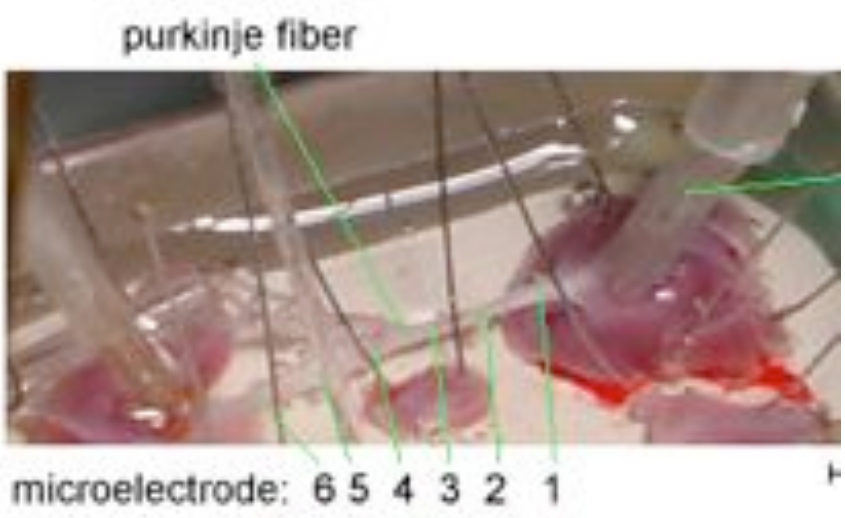
$$\mathrm{BCL}_{n+1} = \begin{cases} \mathrm{BCL}^{\star} & \text{for} \quad \Delta\mathrm{BCL}_{n+1} > 0, \\ \mathrm{BCL}^{\star} + \Delta\mathrm{BCL}_{n+1} & \text{for} \quad \Delta\mathrm{BCL}_{n+1} \leq 0, \end{cases}$$

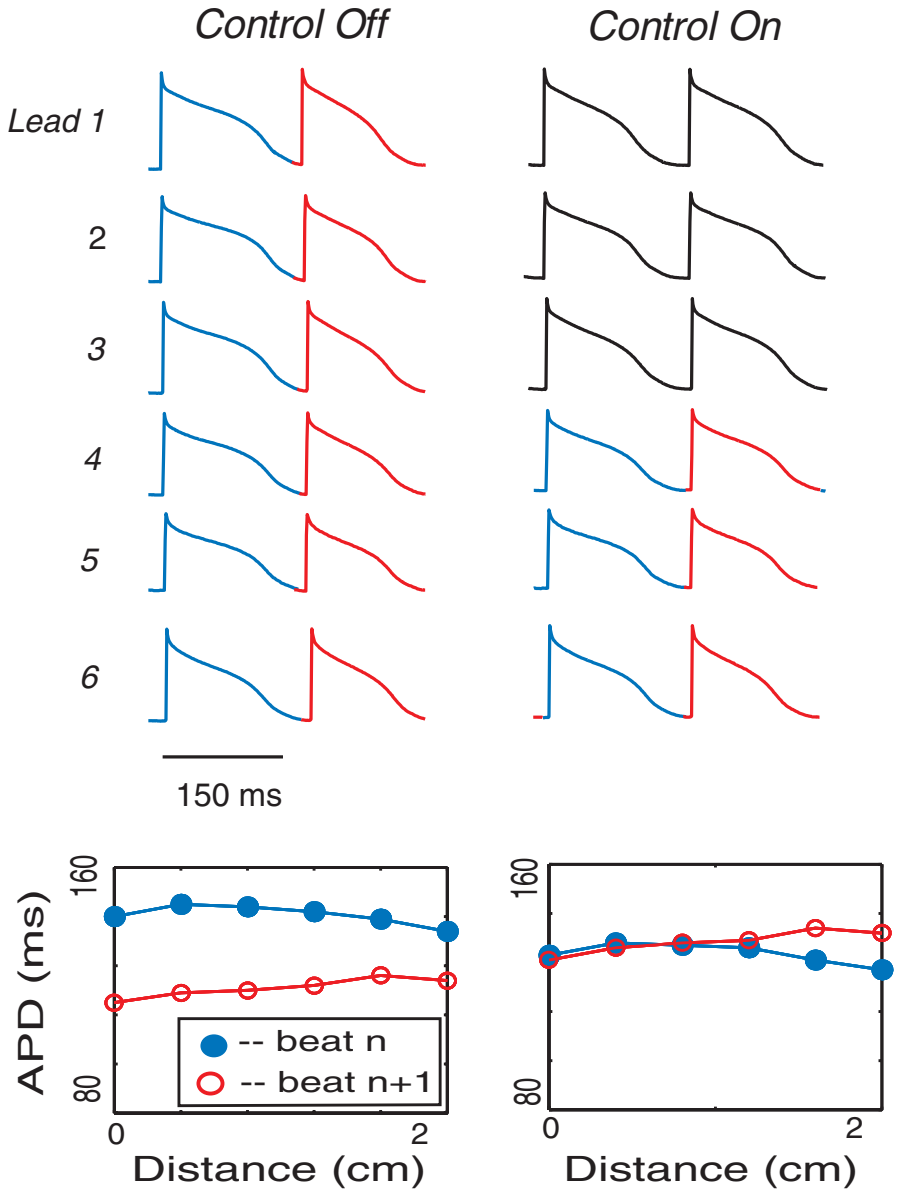
with

$$\Delta\mathrm{BCL}_{n+1} = \frac{\gamma}{2}(\mathrm{APD}_{n+1} - \mathrm{APD}_{n}),$$









Alternans control works well in single cells but is only effective over ~1 cm in tissue.

Christini et al., Physical Review Letters, 2006

Summary

- The cardiac action potential is generated by diffusion of ions through specific ion channels in the cell membrane
- Voltage-gated channel dynamics may be described quantitatively by HH-type equations or by Markov models
- Computational models can be used to explain mechanisms of experimentally or clinically observed phenomena