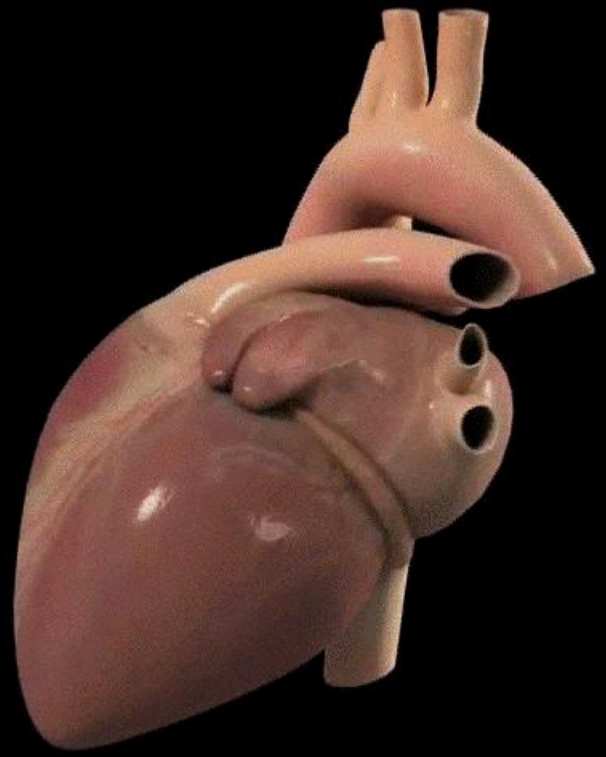
2011 NSF-CMACS Workshop on Atrial Fibrillation (4th day)



Flavio H. Fenton

Department of Biomedical Sciences
College of Veterinary Medicine,
Cornell University, NY
and
Max Planck Institute for Dynamics and
Self-organization, Goettingen, Germany

Lehman College,
Bronx, NY. Jan 3-7, 2011

Mathematical Model

All cardiac cell models in tissue are reaction-diffusion equations.

$$C_{\mathrm{m}} \frac{\partial V(t,\mathbf{x})}{\partial t} = \nabla \cdot (D(\mathbf{x}) \nabla V) - I_{\mathrm{ion}}(V,\mathbf{m}) - I_{\mathrm{stim}}(t,\mathbf{x})$$

$$\frac{\partial \mathbf{m}(t,\mathbf{x})}{\partial t} = \mathbf{f}(V,\mathbf{m})$$

Cell Modeling (Continuum Mathematical Model)

Nonlinear parabolic reaction-diffusion equations:

$$C_{\mathrm{m}}\partial_t V(t,\mathbf{x}) = \nabla\cdot(D(\mathbf{x})\nabla V) - I_{\mathrm{ion}}(V,\mathbf{m}) - I_{\mathrm{stim}}(t,\mathbf{x})$$
$$\partial_t \mathbf{m}(t,\mathbf{x}) = \mathbf{f}(V,\mathbf{m})$$

$V(t,\mathbf{x})$ membrane potential

$\mathbf{m}(t,\mathbf{x})$ gating variables, ionic concentrations

C_{m} membrane capacitance

D(x) conductivity tensor

Iion total ionic current across the membrane of the cell

Istim external stimulus current

Neumann boundary conditions on potential V:

$$n\cdot\nabla V = 0$$

Continuum Mathematical Model

Nonlinear parabolic reaction-diffusion equations:

$$C_{\mathrm{m}}\partial_t V(t,\mathbf{x}) = \nabla\cdot(D(\mathbf{x})\nabla V) - I_{\mathrm{ion}}(V,\mathbf{m}) - I_{\mathrm{stim}}(t,\mathbf{x})$$

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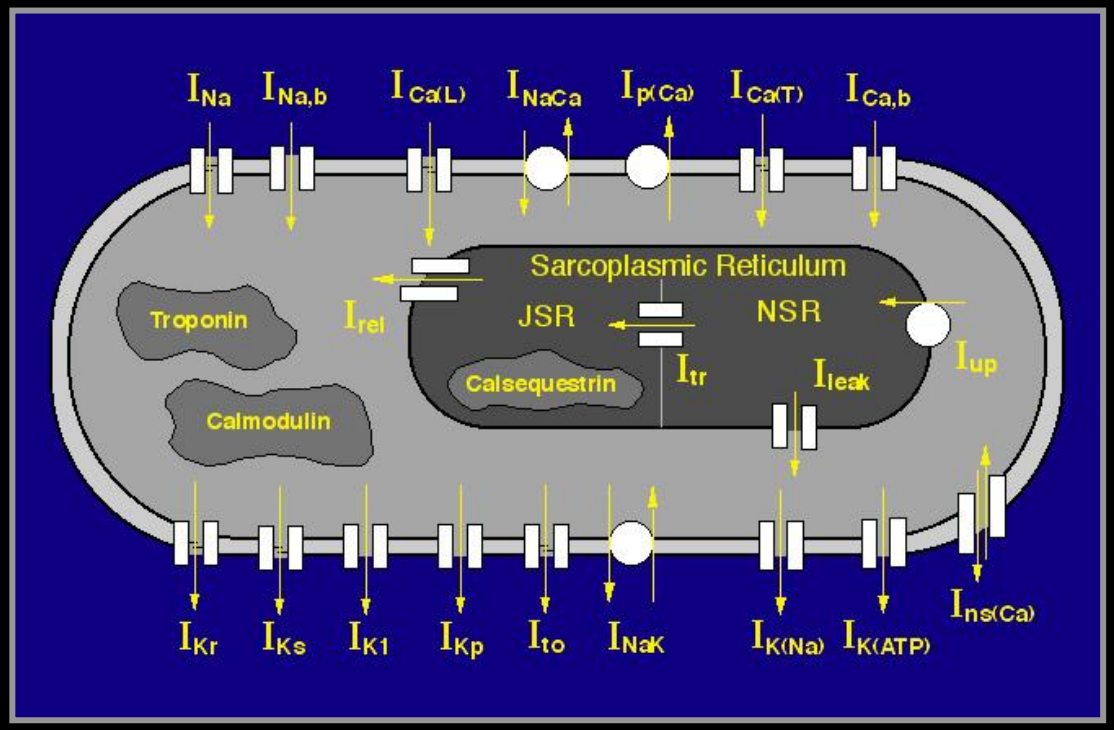
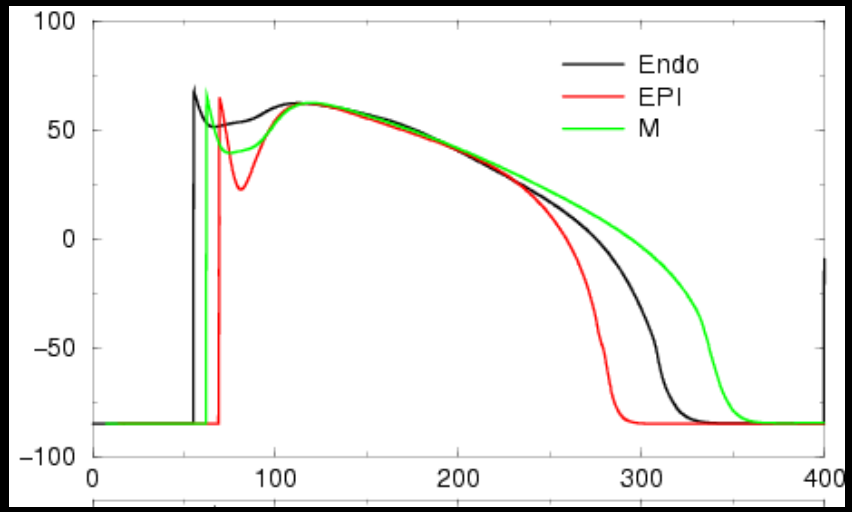


AP shape depends on the currents



Continuum Mathematical Model

Nonlinear parabolic reaction-diffusion equations:

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$$\partial_t \mathbf{m}(t,\mathbf{x}) = \mathbf{f}(V,\mathbf{m})$$

Examples:

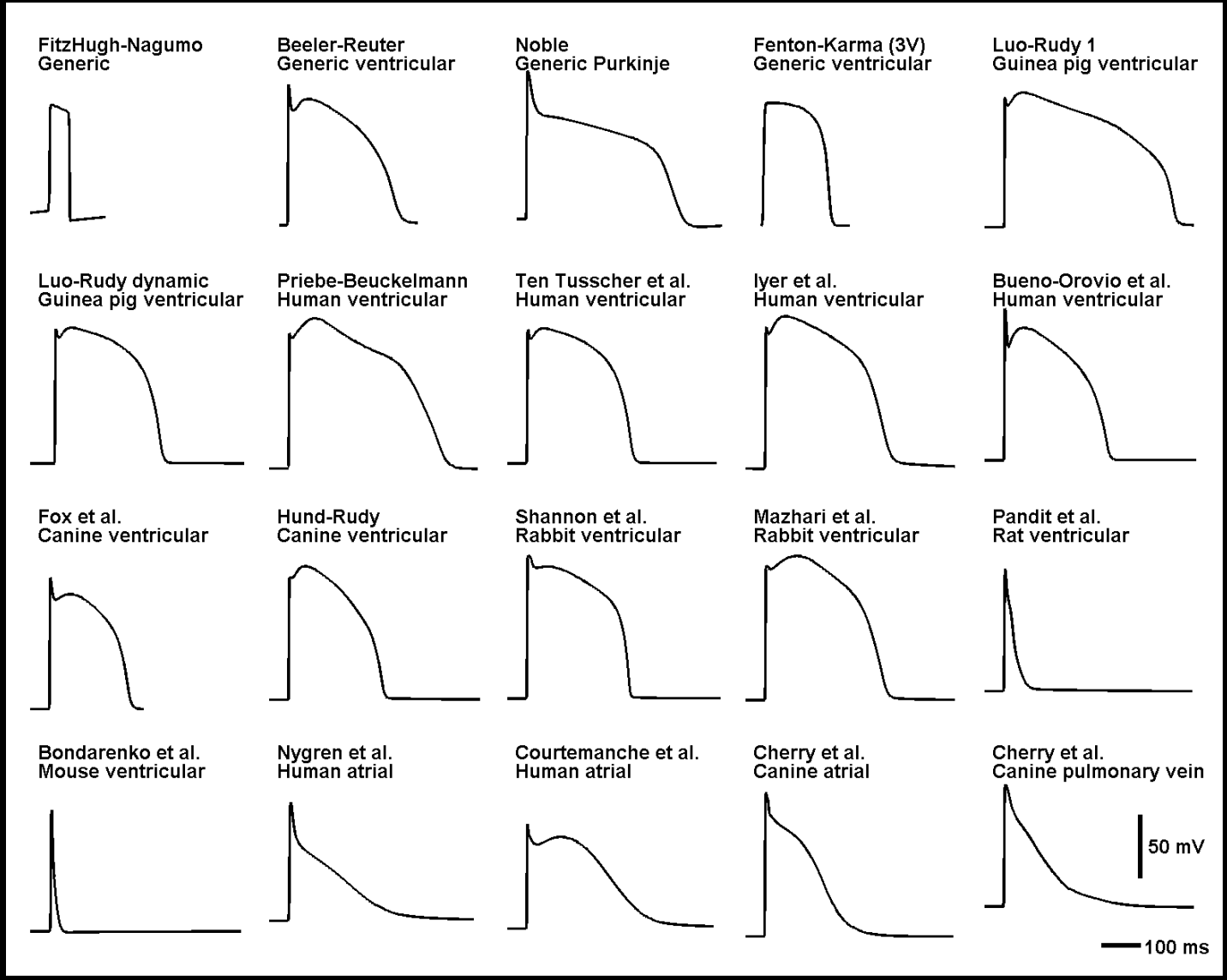
Ventricular:

- Luo-Rudy 1 (LR1) 8v
- Luo-Rudy d (LRd) 20v
- Fox et al. 13v

Atrial:

- Courtemanche. 19v
- Nygren. 29v

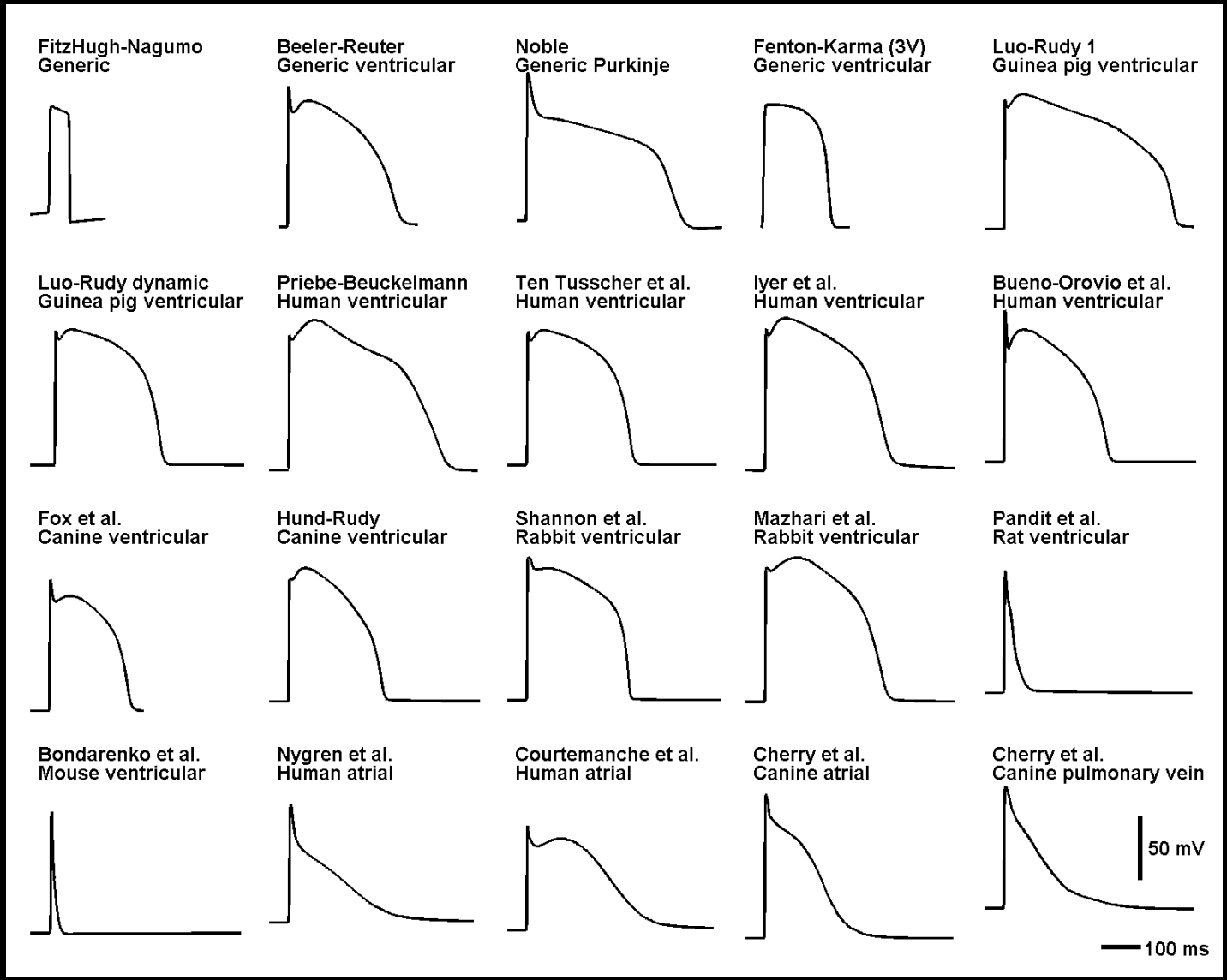
Many Models for Different Cell Types



Fenton FH, Cherry EM, 2008. Models of cardiac cell. Scholarpedia 3, 1868.

Many Models for Different Cell Types

Different mammalian hearts have different AP morphology and duration
Because they are different in size (various orders of magnitude)



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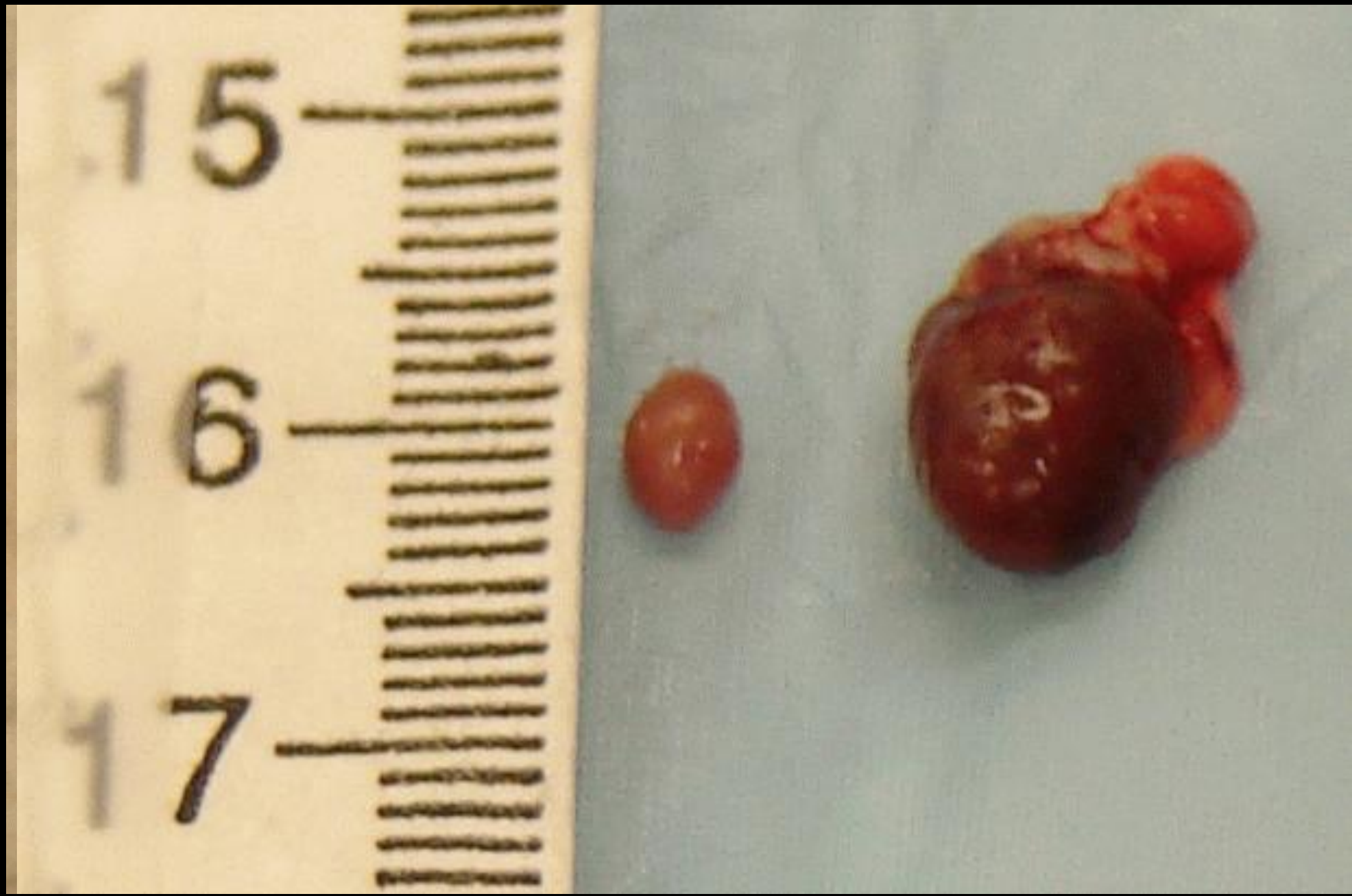

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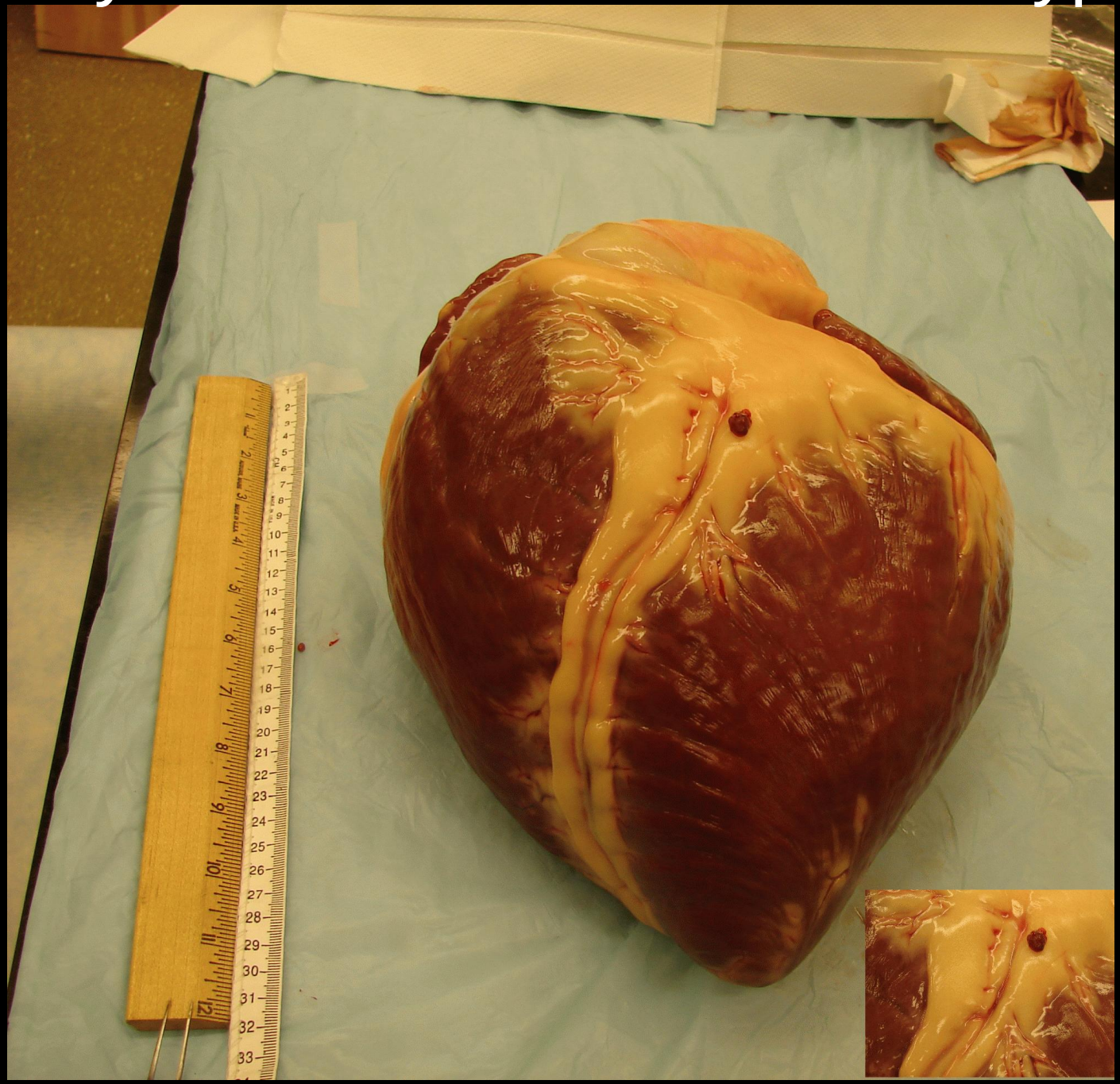

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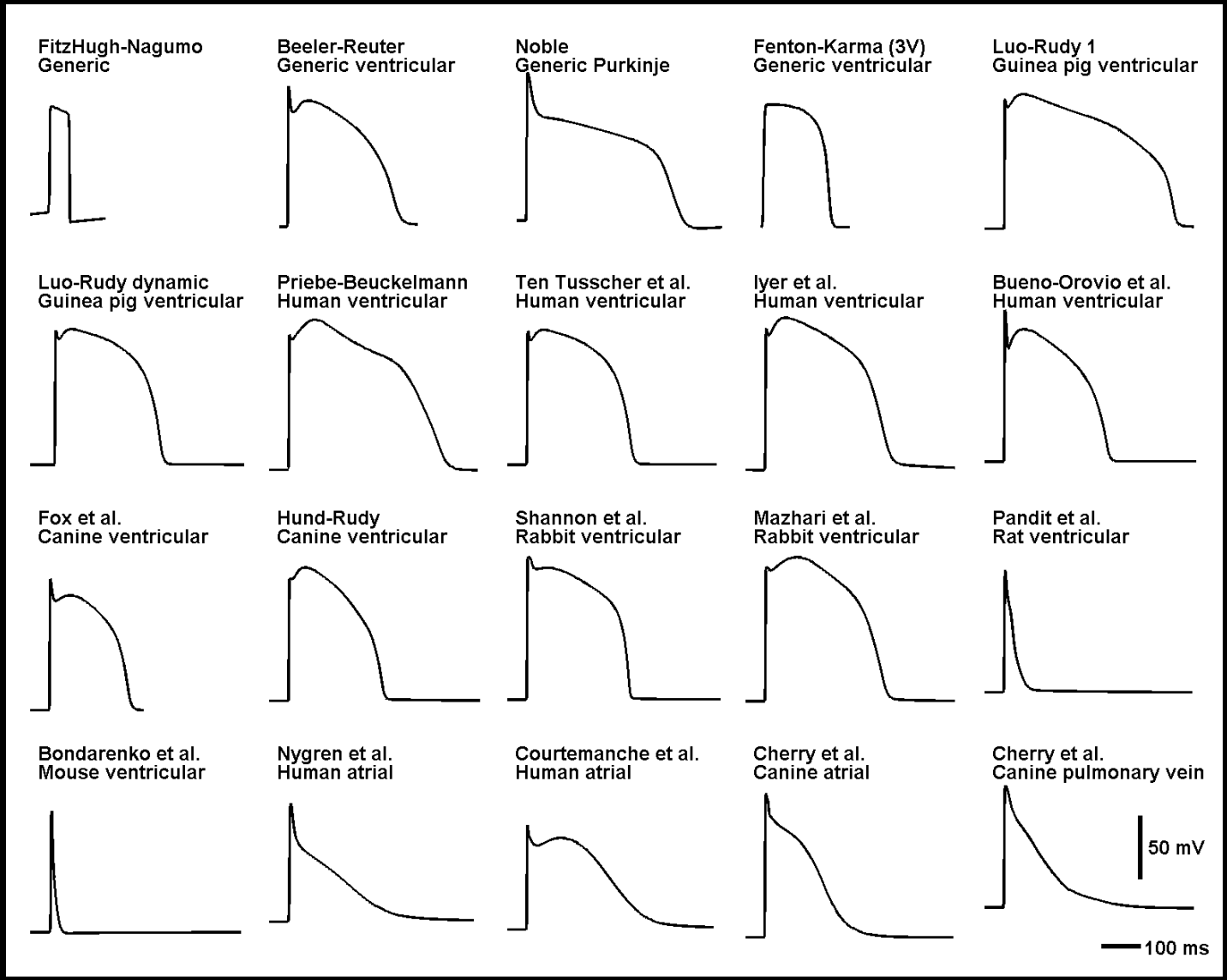
Implemented most (~40) of the published models in single cells and in tissue.



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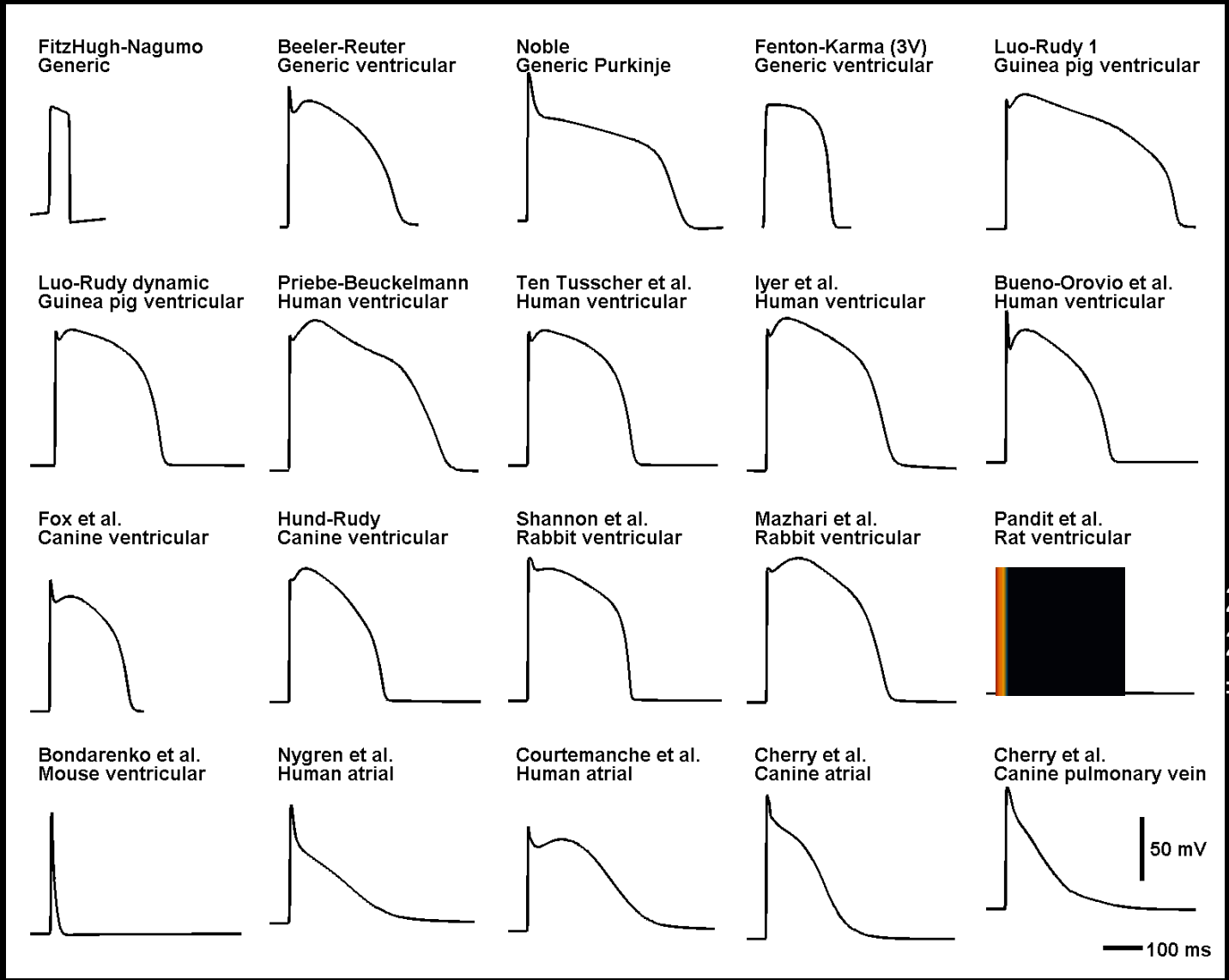

26 variables
2D (200x200x26 =1,040,000)

dt ~ .01ms
1s of simulation = 1,040,000*100000 =$1x10^{11}$

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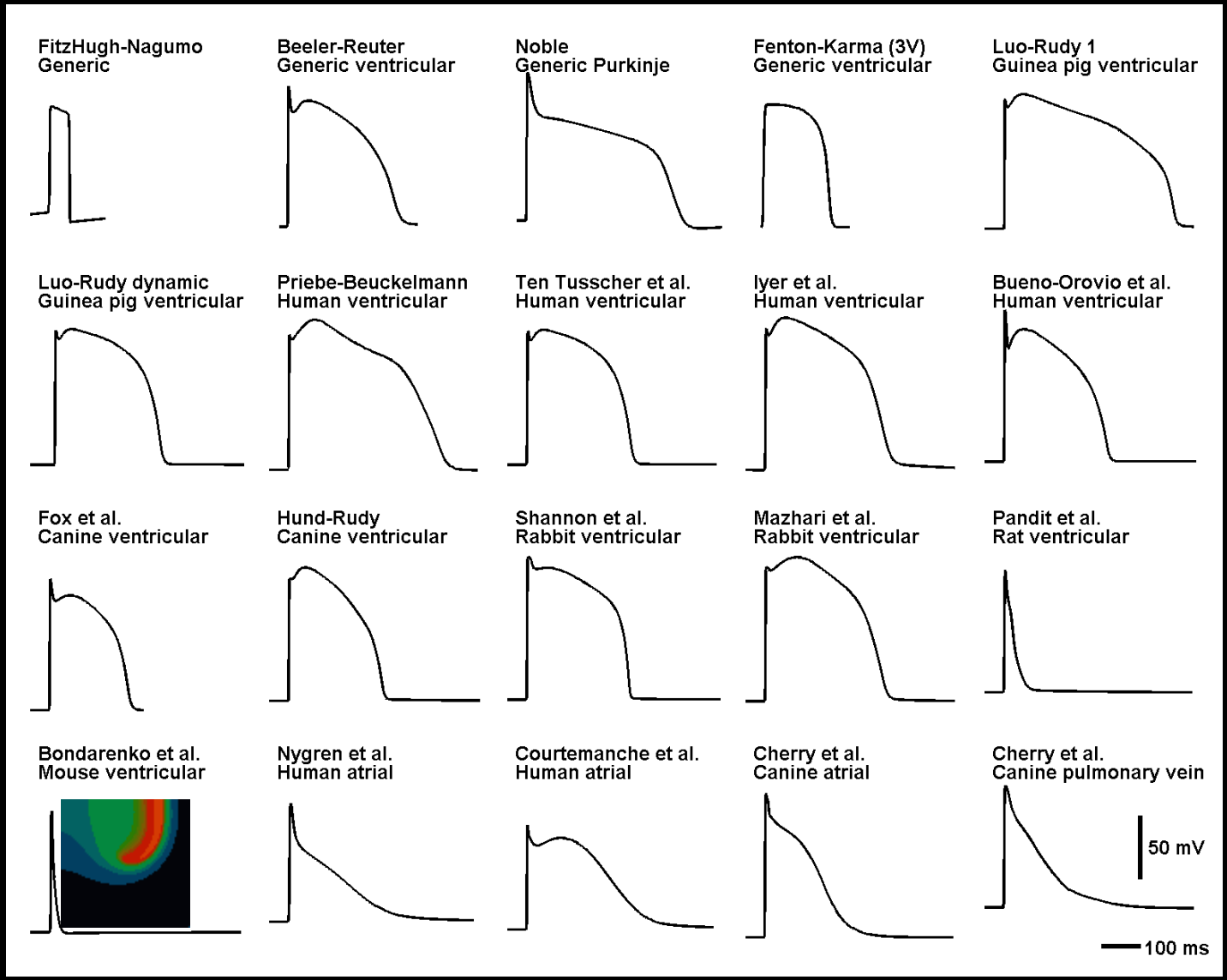

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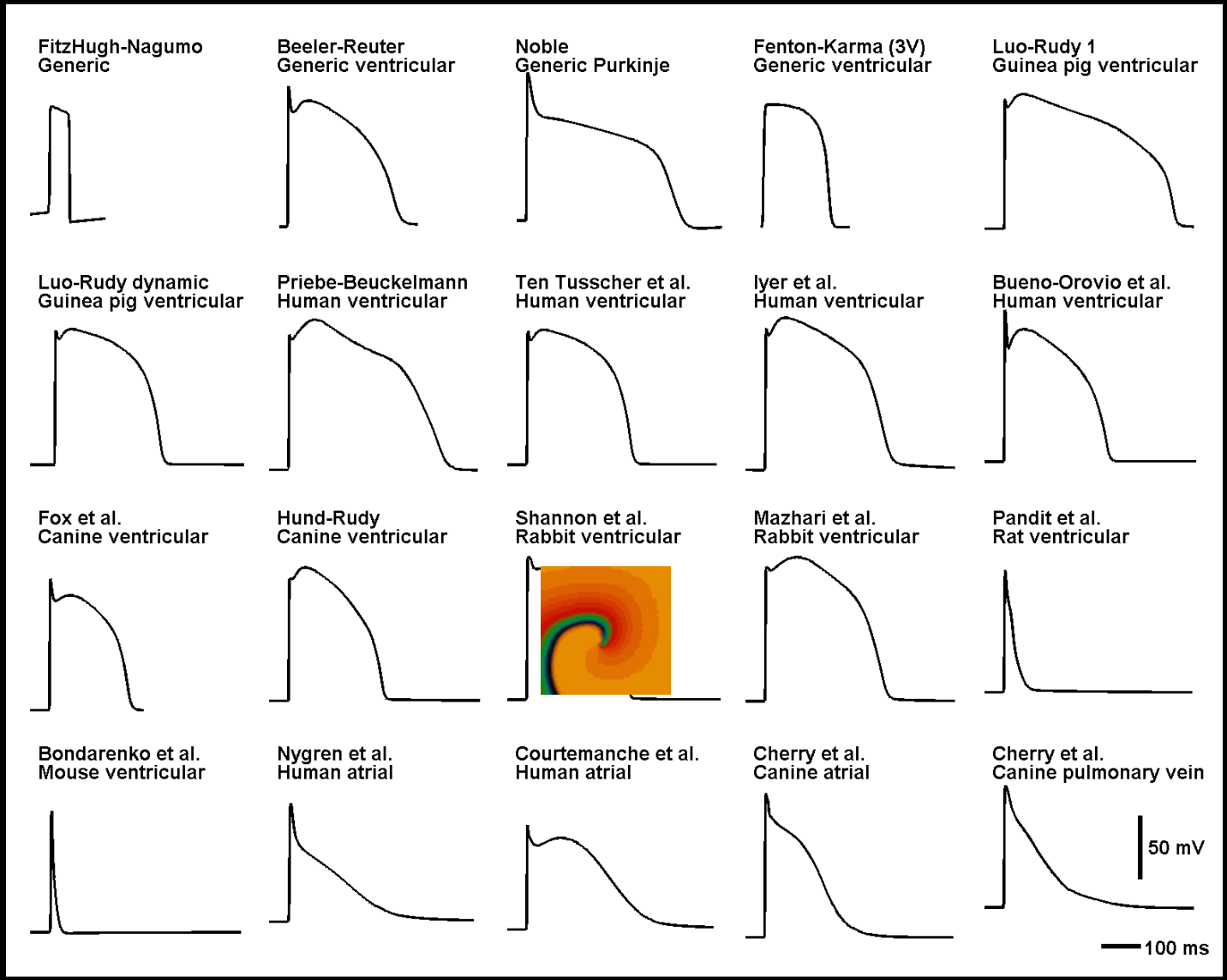

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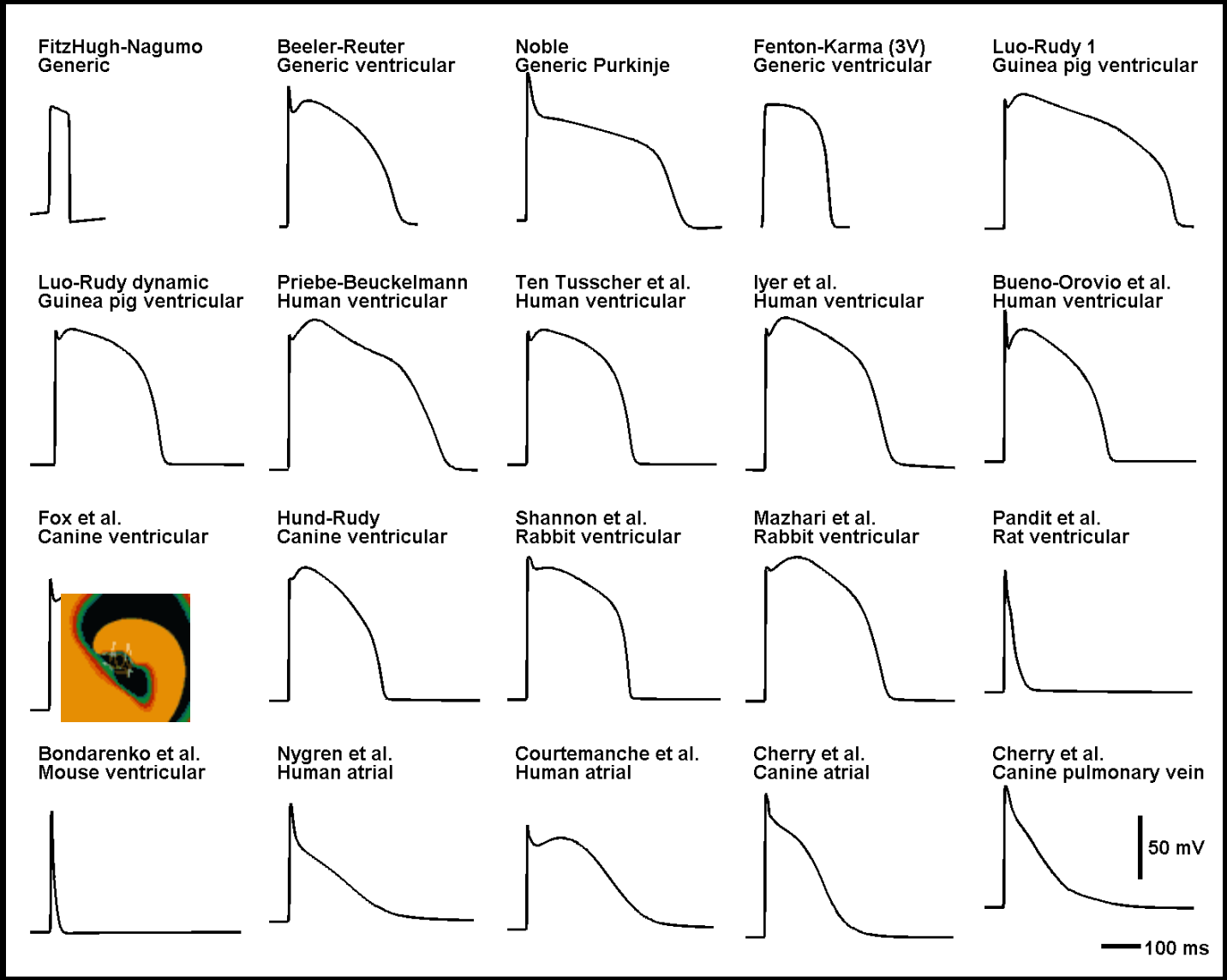

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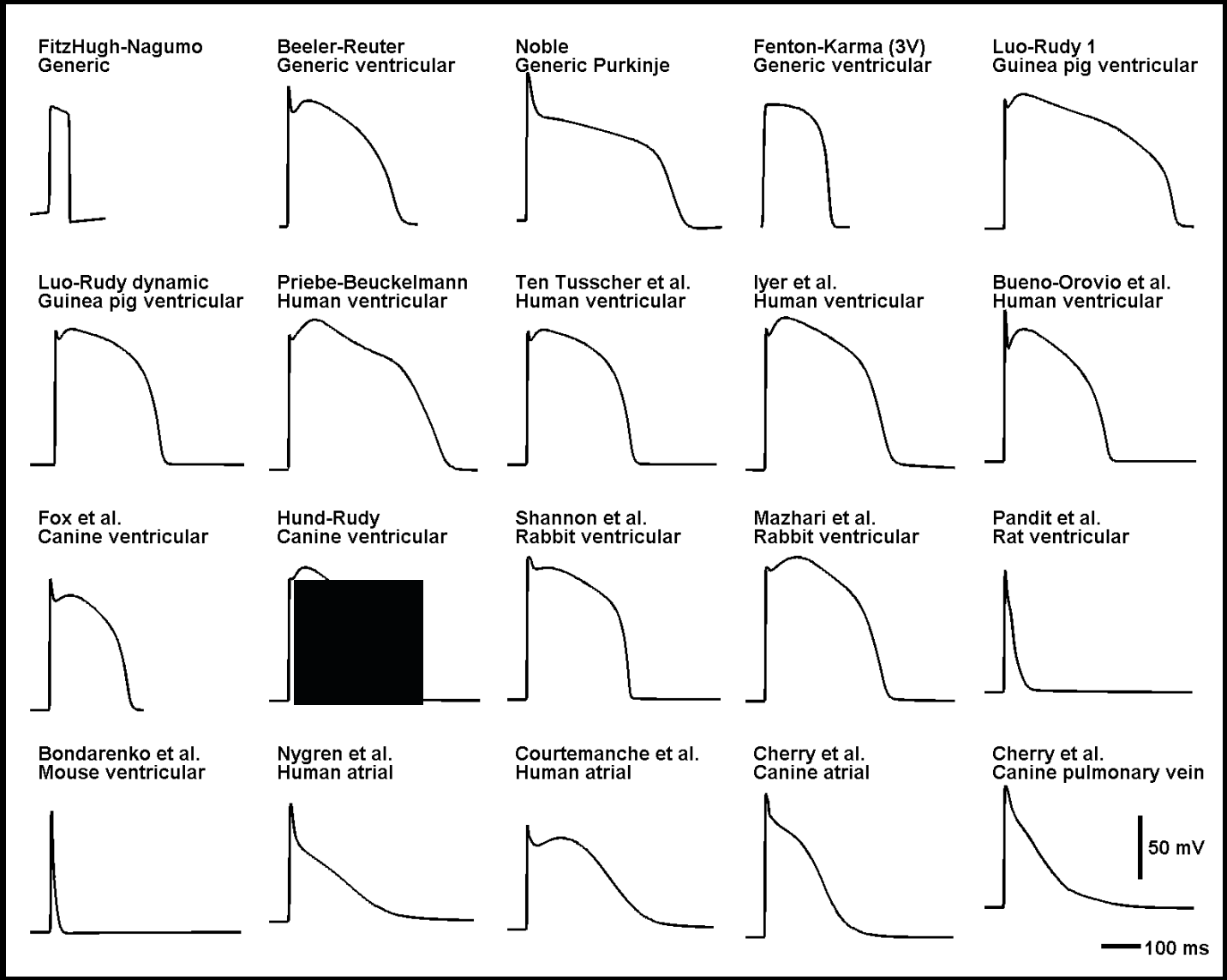

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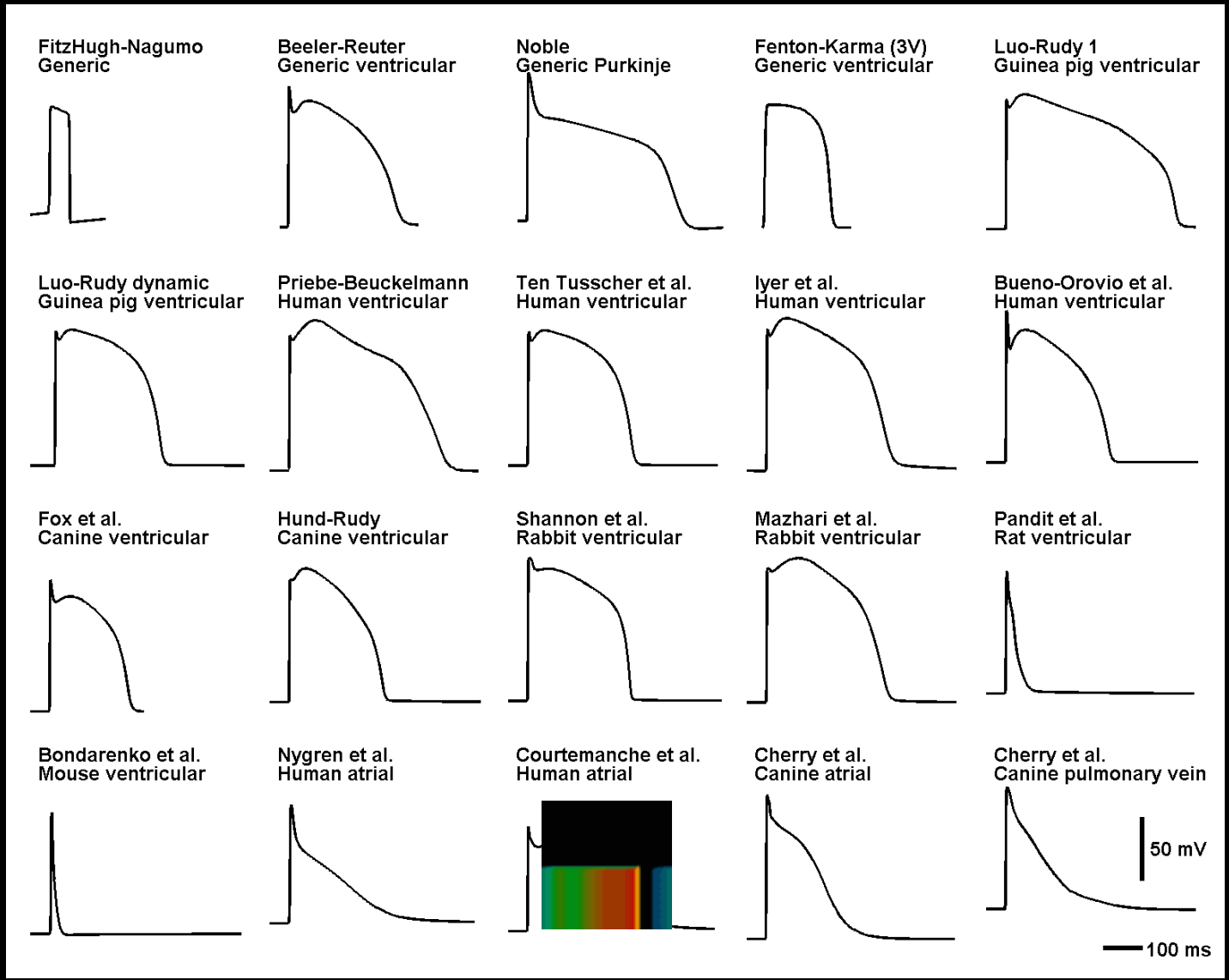

Remember
This and the
Next atrial models

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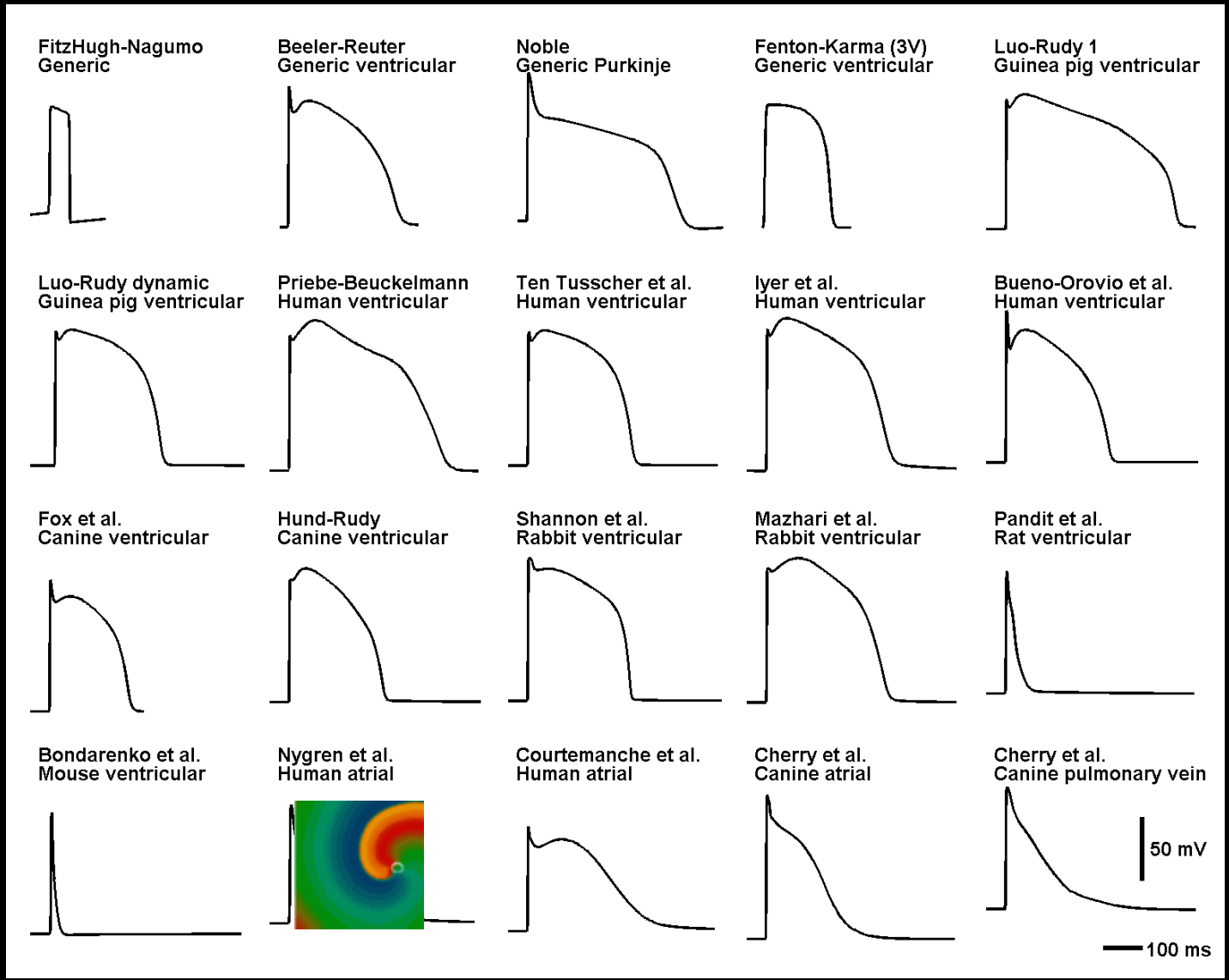

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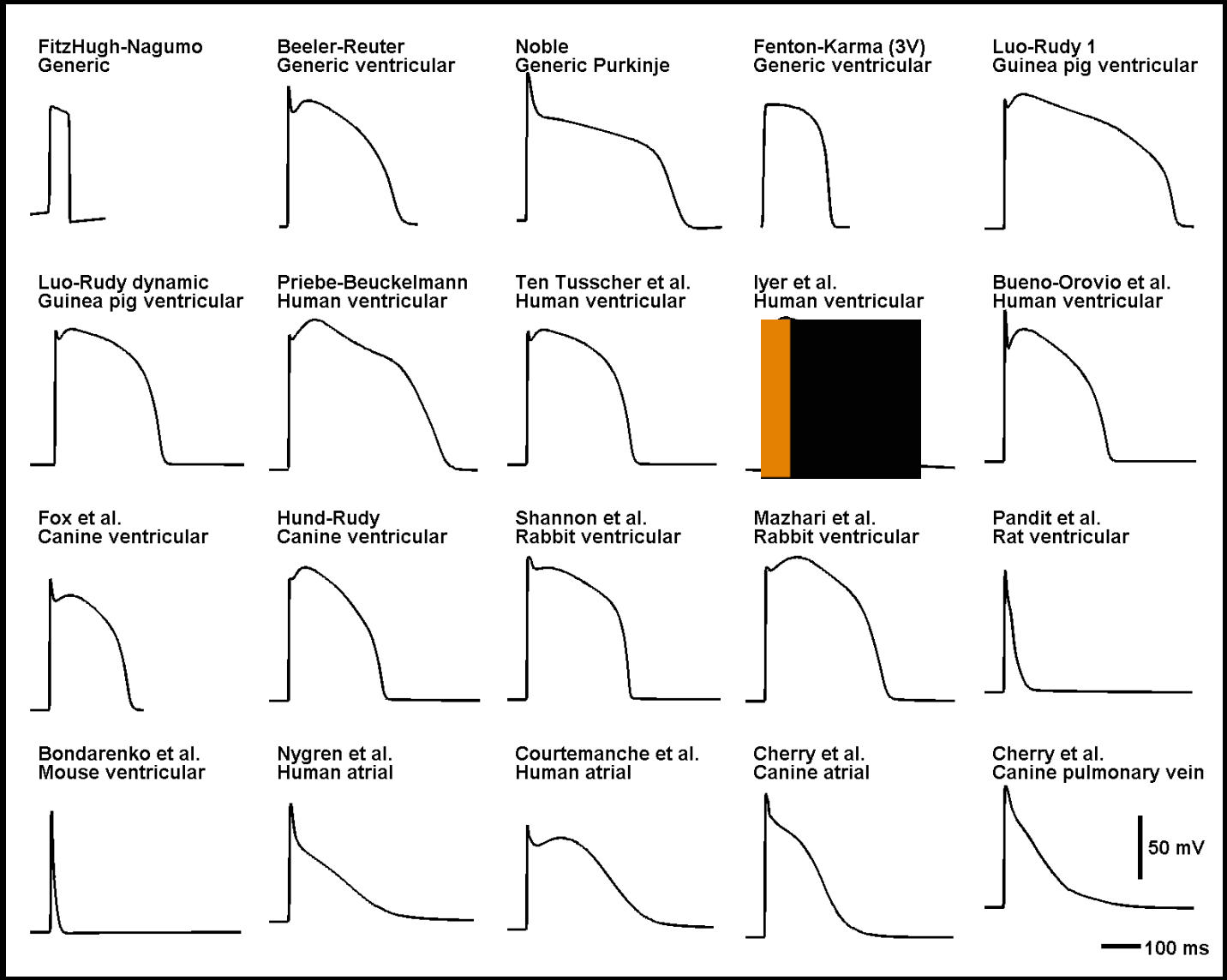


67 variables
2D (200x200x67 =2,680,000)

Imagine in 3D!

Fenton FH, Cherry EM, 2008. Models of cardiac cell. Scholarpedia 3, 1868.

Number of equations to solve each iteration in time

1s = $1X10^{14}$ equations

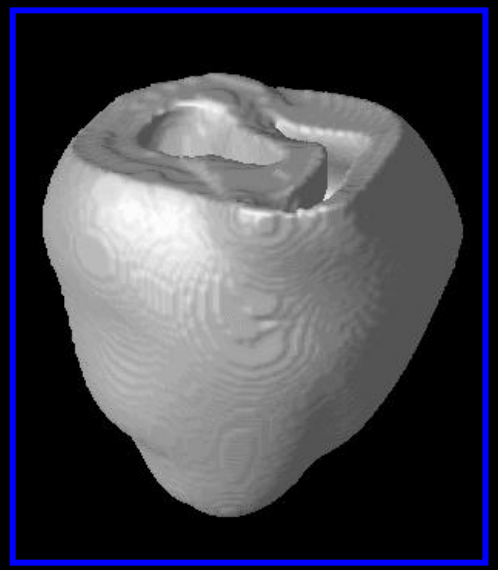
100 trillion operations

Dimensions:

3cm x 3cm x 3cm

~500,000 nodes

This is a rabbit



Human ventricles at least 3 times bigger

13,500,000 nodes

13,500,000*67 = 904,500,000

Almost a billion operations every time step (.01 ms)

Many Models for Different Cell Types

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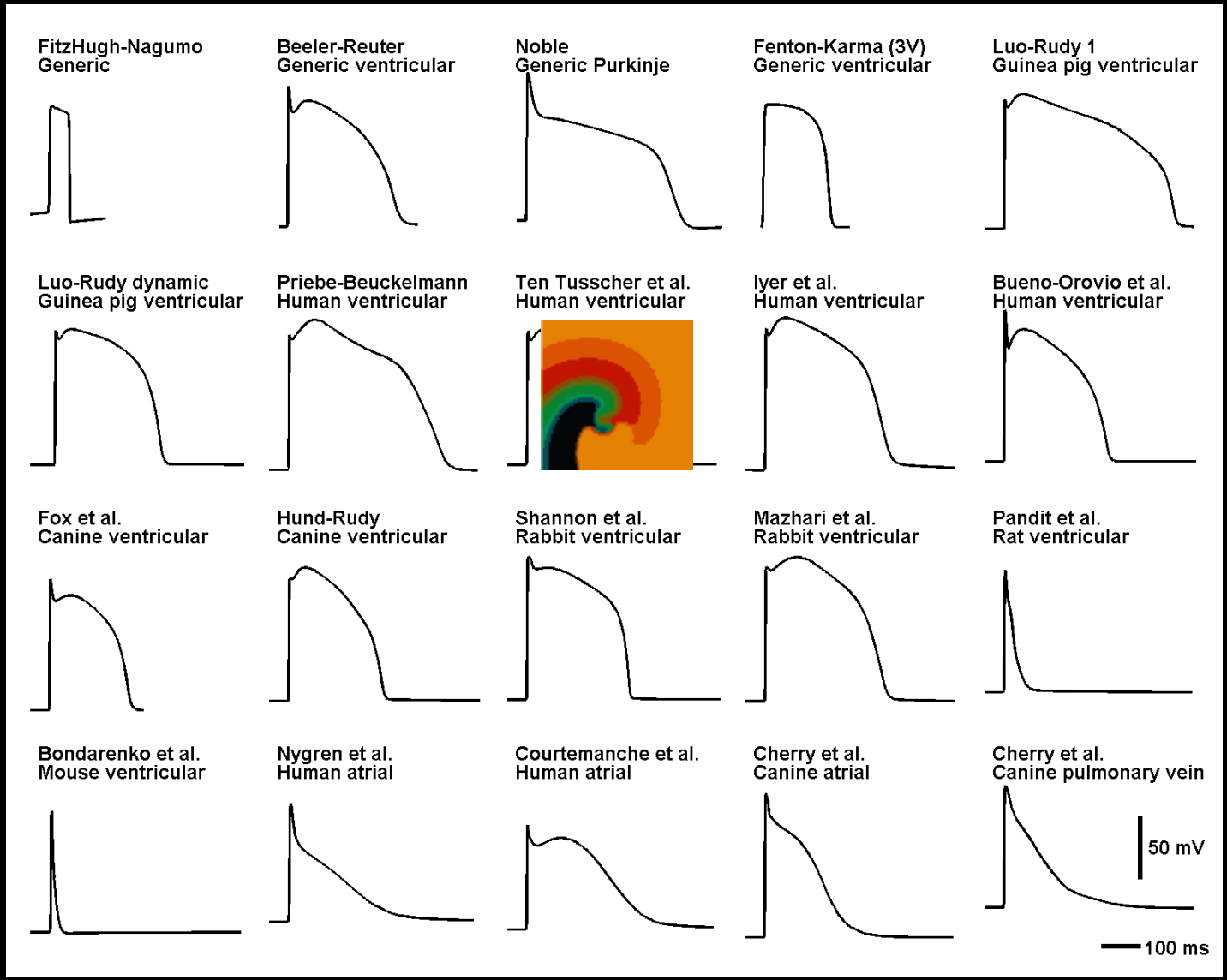

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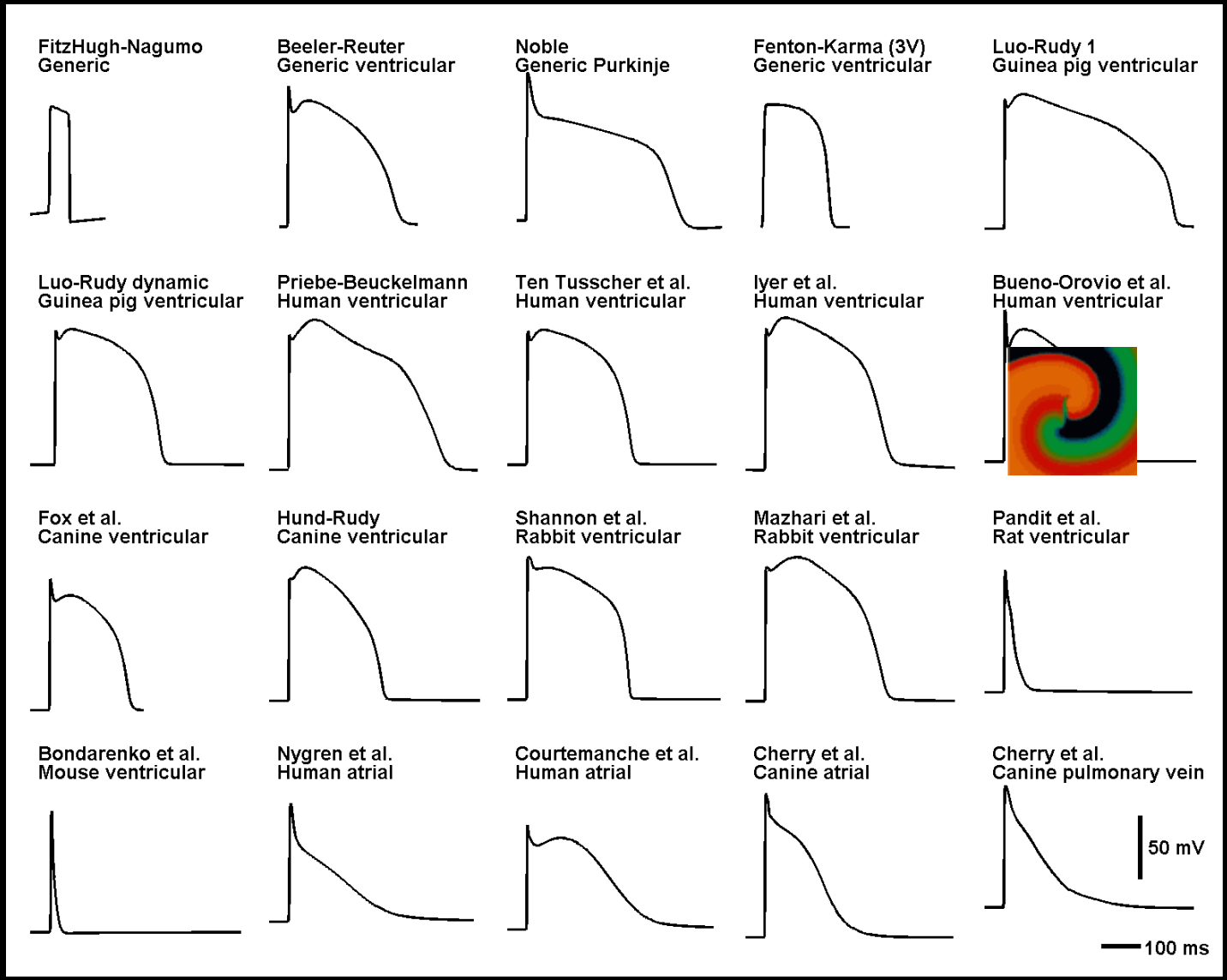


Fenton FH, Cherry EM, 2008. Models of cardiac cell. Scholarpedia 3, 1868.

Examples of differences in cardiac cell models of same type

Three comparisons

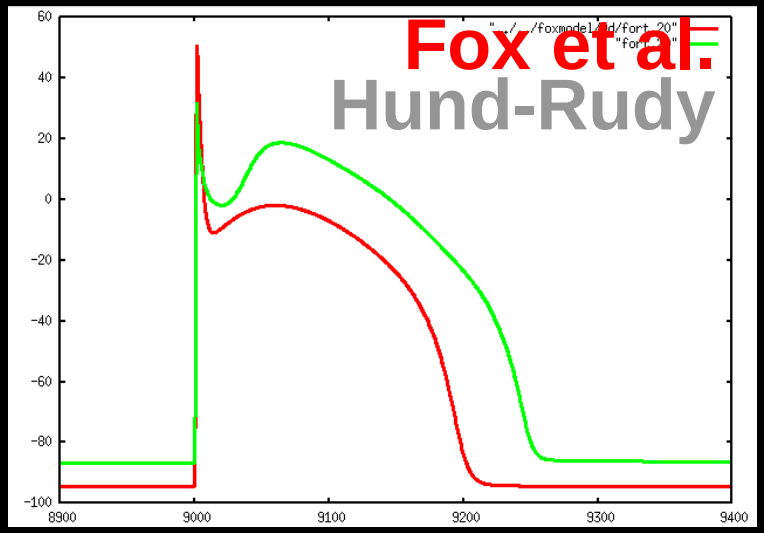
Comparing two canine cell models

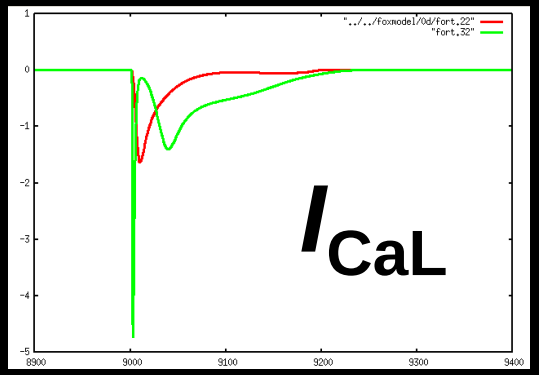
Two ionic models of canine ventricular myocytes:

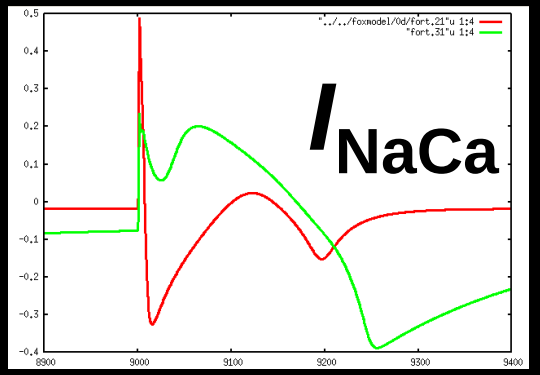
- Fox et al., 2002:
  - 13 variables.
  - 13 transmembrane currents.
  - Intracellular calcium handling includes single-compartment SR, buffering.
  - No other intracellular concentrations.
- Hund-Rudy, 2004:
  - 30 variables.
  - 14 transmembrane currents.
  - Intracellular calcium handling includes two-compartment SR, buffering, subspace, CaMKII autophosphorylation.
  - Intracellular Na+, K+, Cl- concentrations.

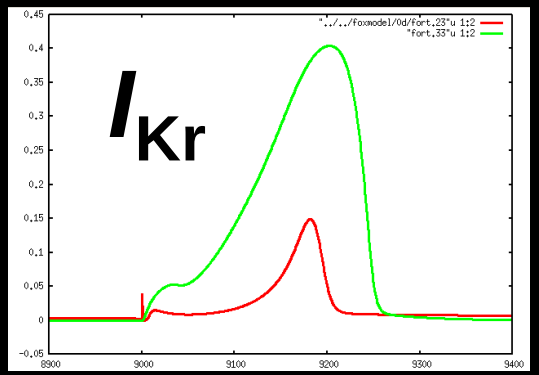
Fox JJ, McHarg JL, Gilmour RF. Am J Physiol Heart Circ Physiol 2002; 282: H516-H530.
Hund TJ, Rudy Y. Circulation 2004; 110: 3168-3174.

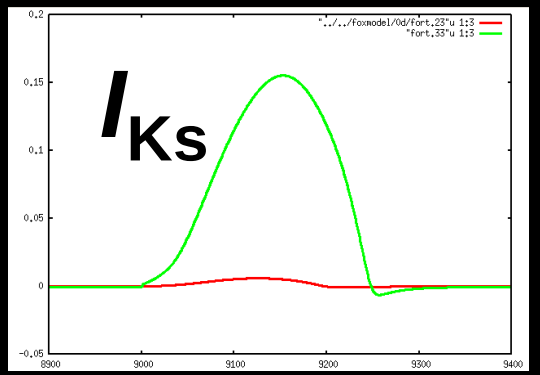
Cellular Dynamics

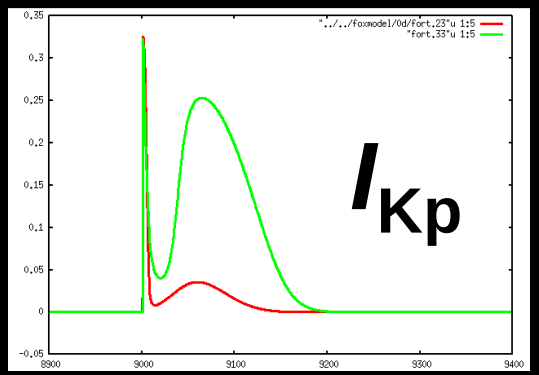


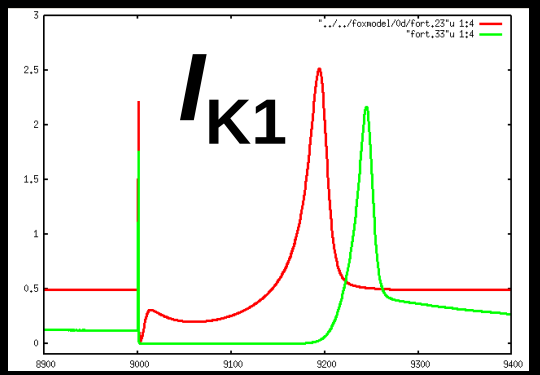








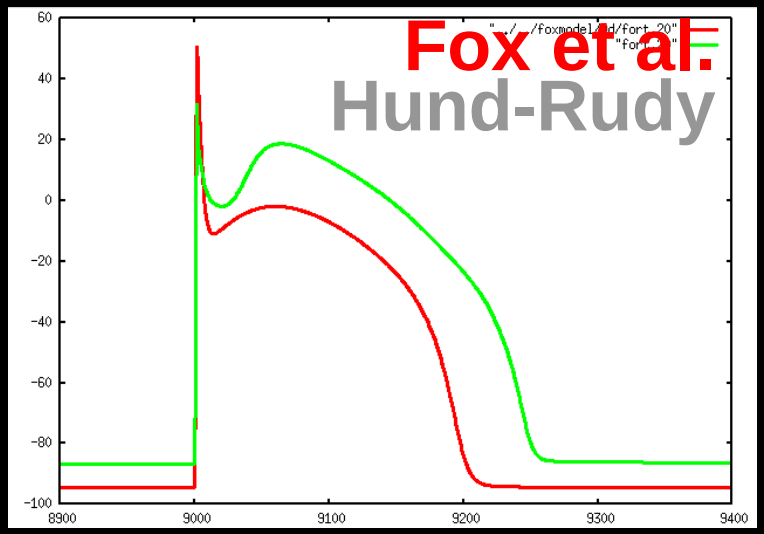


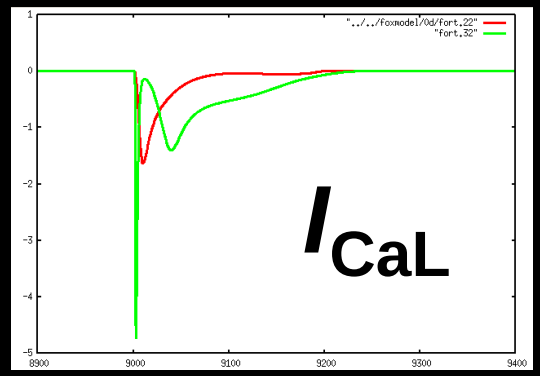


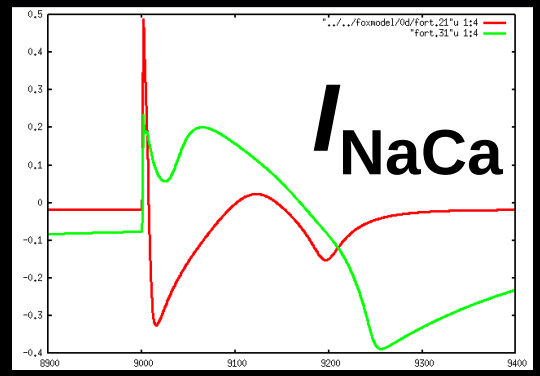
Fox et al.: larger amplitude (145 vs. 107mV), with smaller RMP (-95 vs. -87mV) and larger peak voltage (50 vs. 30mV).

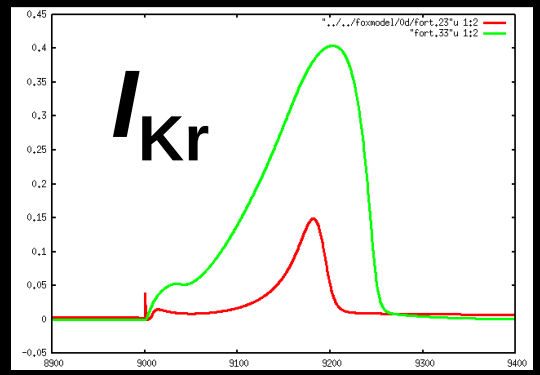
Hund-Rudy: more pronounced notch, longer AP.

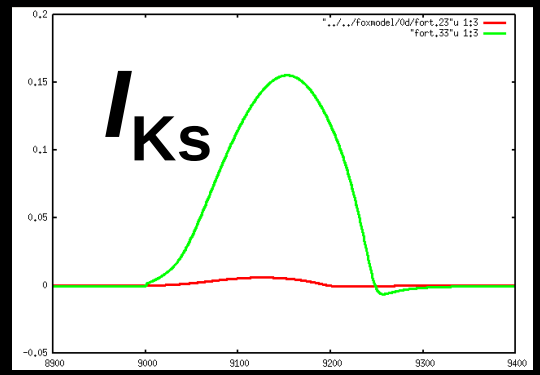
Cellular Dynamics



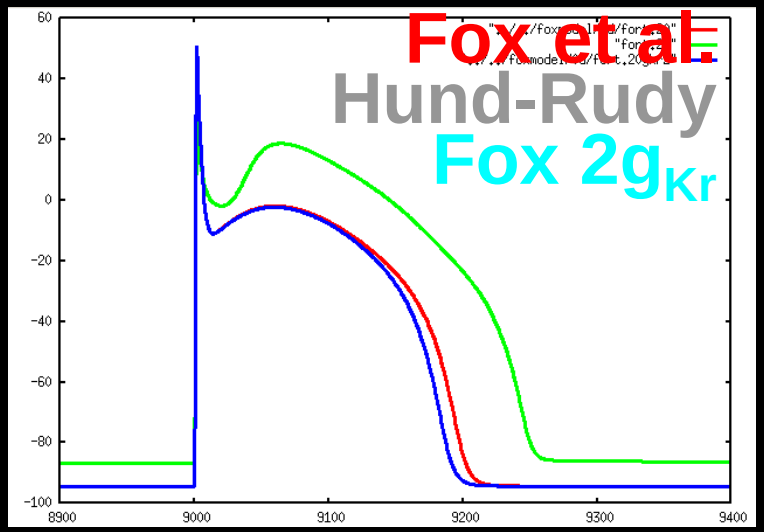


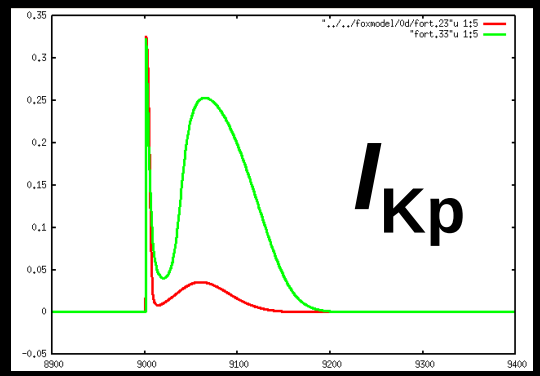


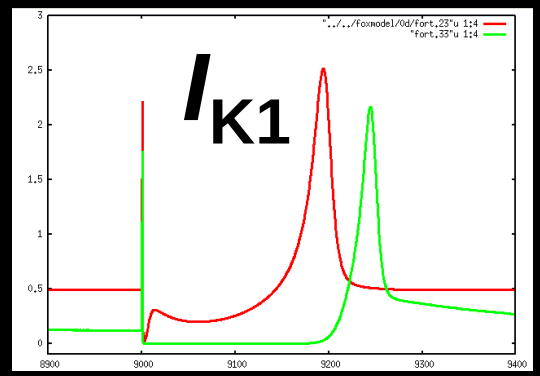




Increased I_{Kr} suppresses alternans.

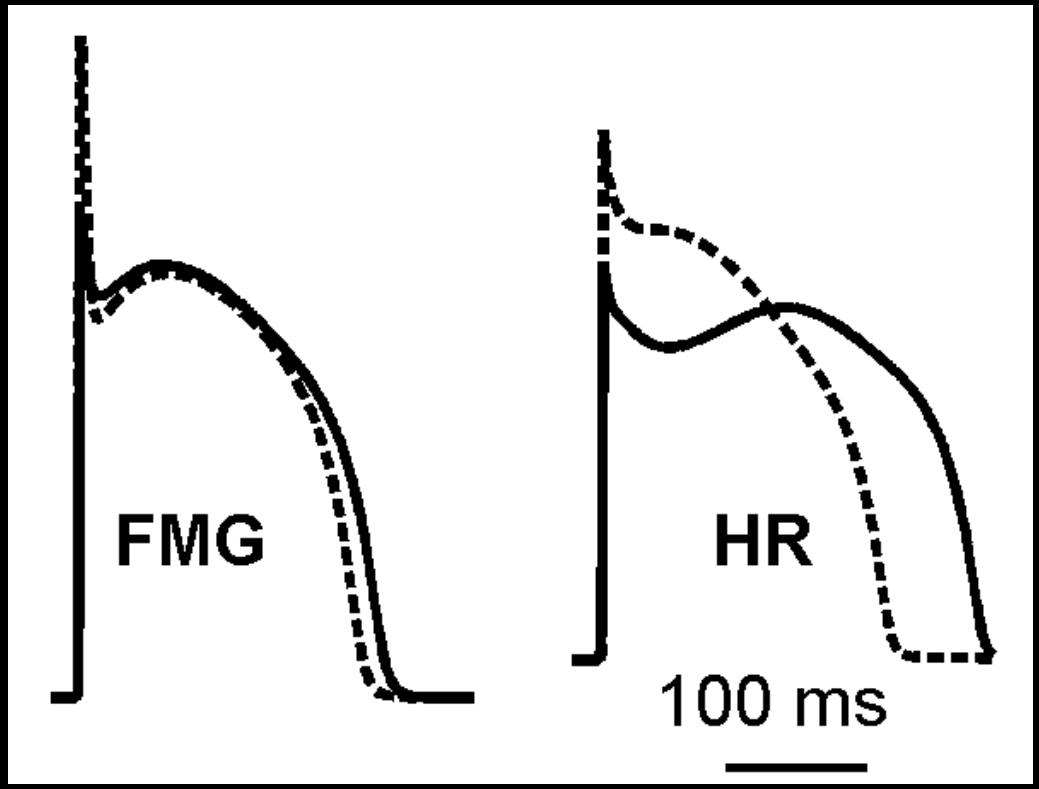






AP Morphology Changes in Tissue

- Action potentials in the Hund-Rudy model decrease in amplitude and *substantially change morphology* in tissue.



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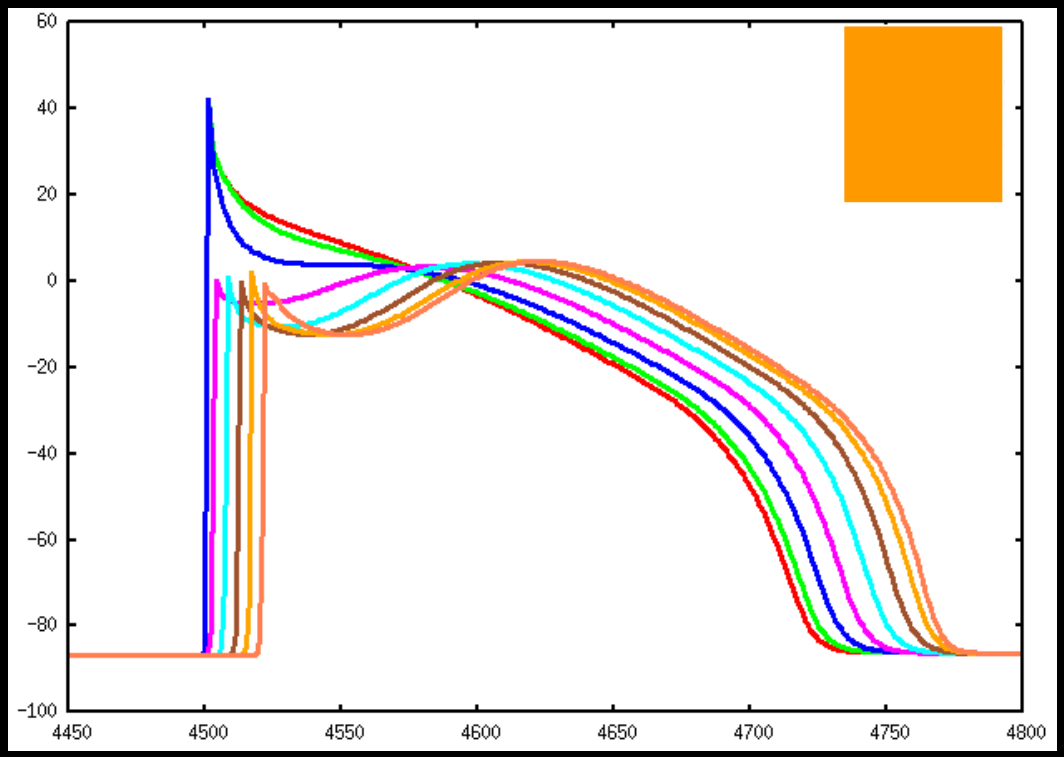
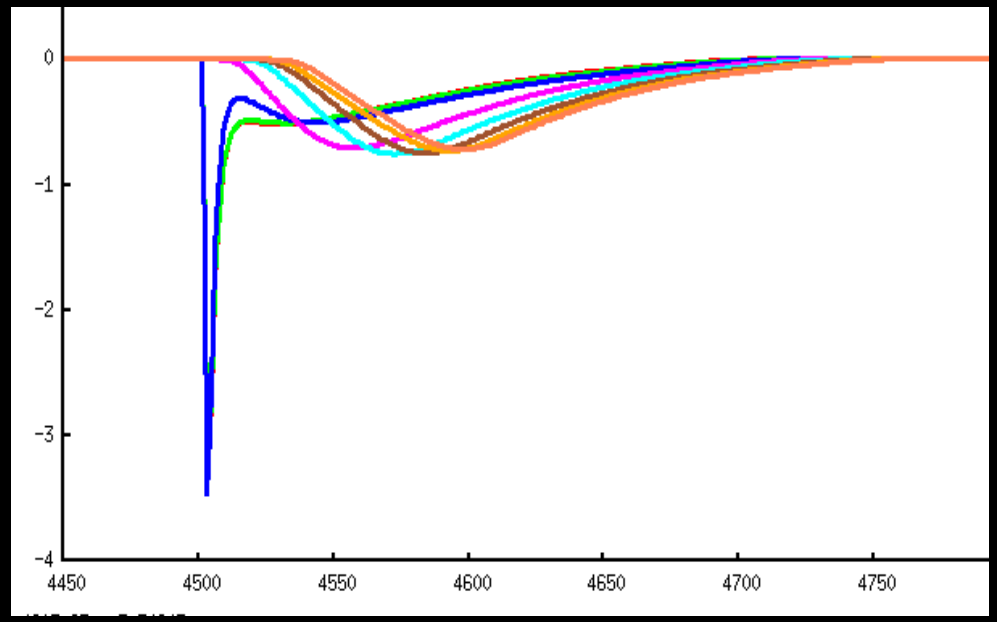
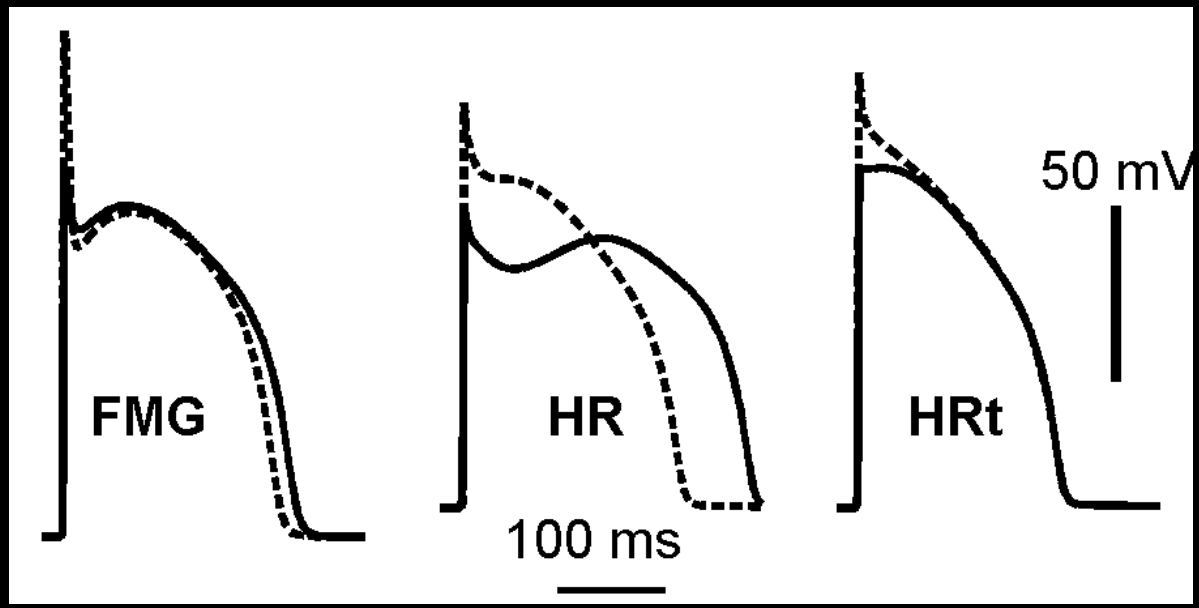


L-type Ca^{2+} current may be responsible!



HRt Model

- Hund-Rudy tissue model (HRt) restores L-type calcium current by increasing AP amplitude.



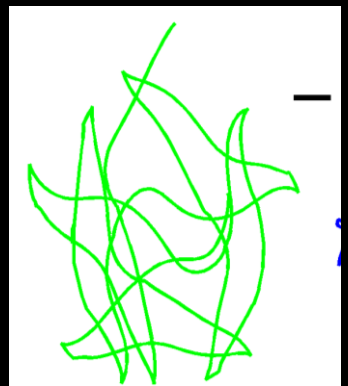
Spiral Waves in 2D

- Stable spirals.
- Similar tip trajectories.
- Hund-Rudy meanders more strongly.

Fox et al.

Hund-Rudy

18x18cm
Period: ~169 ms



15x15cm
Period: ~120 ms

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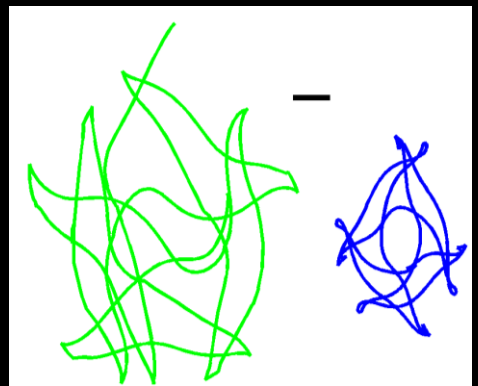
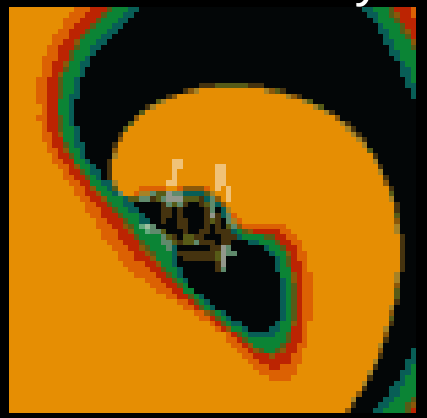


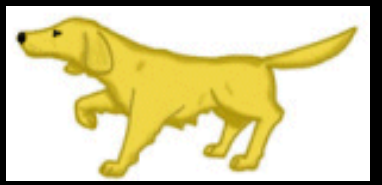
Hund-Rudy



15x15cm
Period: ~120 ms

Summary

- Good news:
  - Both models have similar CV restitution and max CV.
  - Both models have similar linear spiral trajectories in 2D.
  - Similar DI_{min}.
- Bad news: two different beasts!
  - Different alternans CL ranges, onset CLs.
  - Different values of dv/dt_{max}.
  - Different spiral periods.
  - Both CV restitutions are unrealistically flat.
  - Pronounced differences in AP morphology in tissue for Hund-Rudy model.
  - Spiral stability can depend on initial conditions.



Models of same type with even larger difference in dynamics

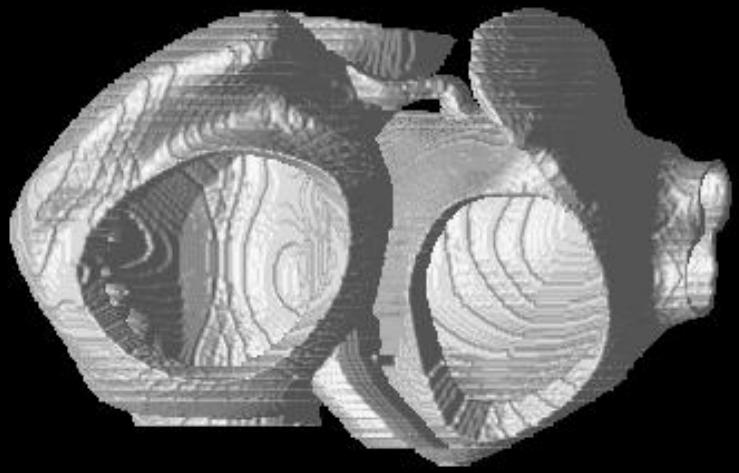
- Human Atrial models

Anatomically Realistic Model of Human Atria

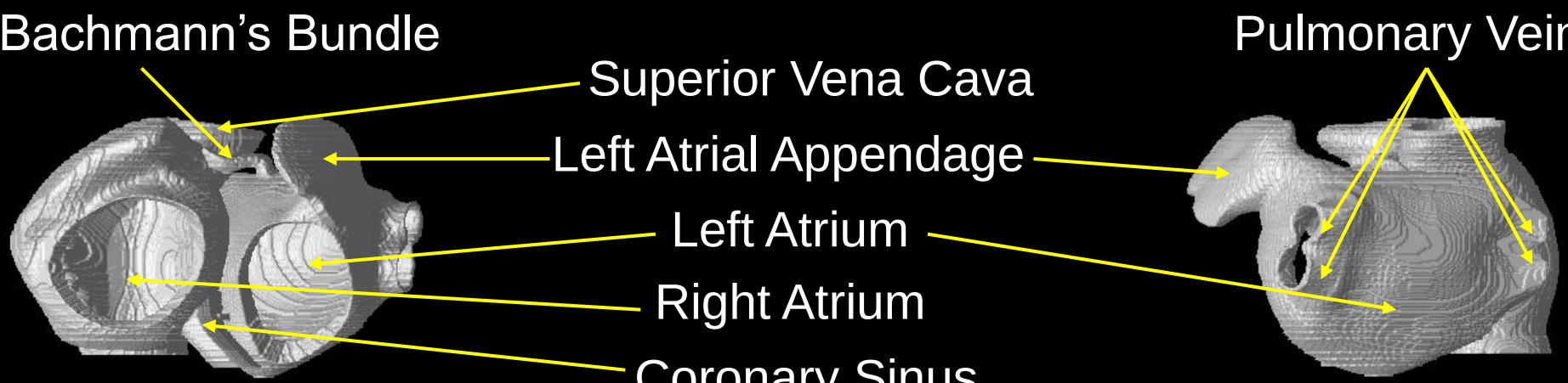
Dimensions:

7.5cm x 7cm x 5.5cm

2.5 million nodes



Harrild and Henriquez, 2000
+ coronary sinus



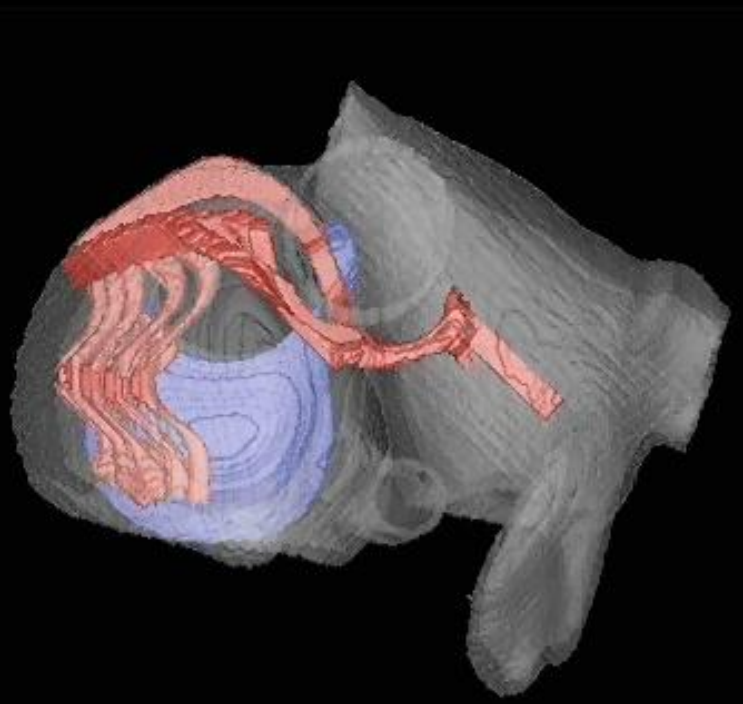
Bundle Conductivities

Healthy atria

Fast CV: 150 cm/

Bulk CV: 60 cm/s

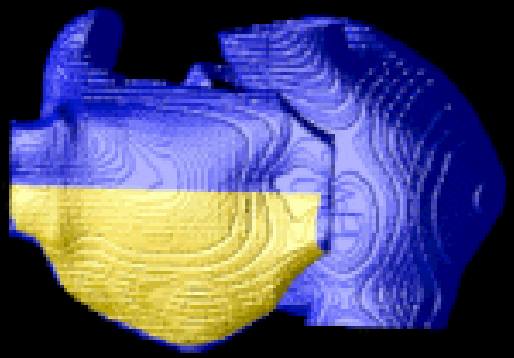
Slow CV: 35 cm/s



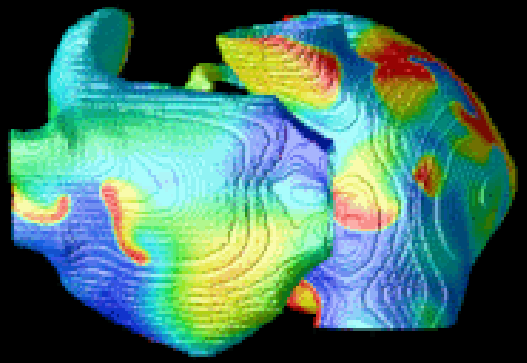
Example of Simulated AT and AF

Reentry in the Atrial Model

Nygren et al model
Atrial Tachycardia



Courtemanche et al
Atrial Fibrillation



Models of same type with even larger difference in dynamics

- Human Atrial models
- Human Ventricular models

Computational models for human ventricular APs

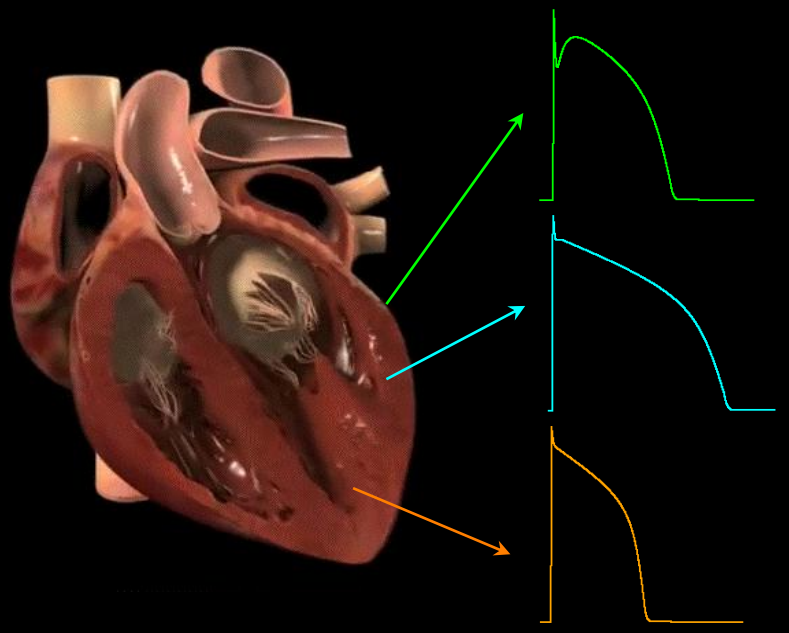
- Priebe L, Beuckelmann DJ (PB):
  - "Simulation study of cellular properties in heart failure." *Circ Res* 82: 1206-1223 (1998).
  - 22 variables.
  - Epicardial cells only.
- Ten Tusscher KHWJ, Noble D, Noble PJ, Panfilov AV (TNNP):
  - "A model for human ventricular tissue." *Am J Physiol Heart Circ Physiol* 286: H1573-H1589 (2003).
  - 17 variables.
  - Epicardial, endocardial and midmyocardial cells.
- Iyer V, Mazhari R, Winslow RL (IMW):
  - "A computational model of the human left-ventricular epicardial myocyte." *Biophys J* 87: 1507-1525 (2004).
  - **67 variables.**
  - Epicardial cells only.

Minimal model for human ventricular action potentials in tissue

3V → 4V

(3V-SIM) makes use of the minimum number of equations (3 variables) capable of reproducing published physiological data:

+ thresholds for excitation.
+ $dv/dt|_{max}$ in tissue.
+ APD_{min} and DI_{min}.
+ APD and CV restitution curves.
+ AP morphology.



Minimal model for human ventricular action potentials in tissue

Why?

3V → 4V

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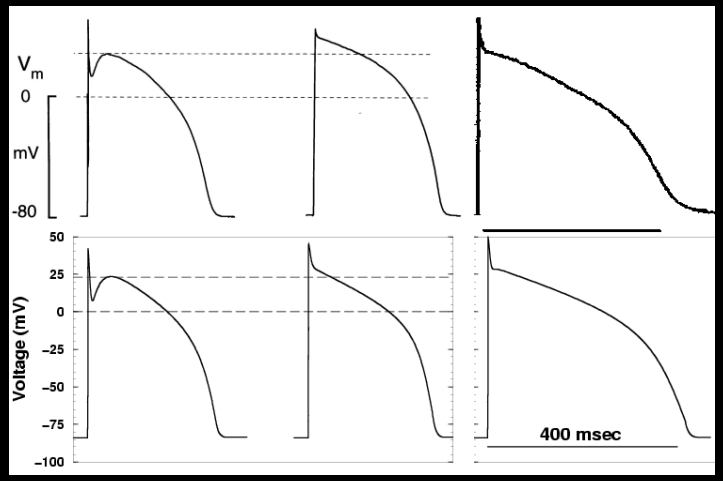
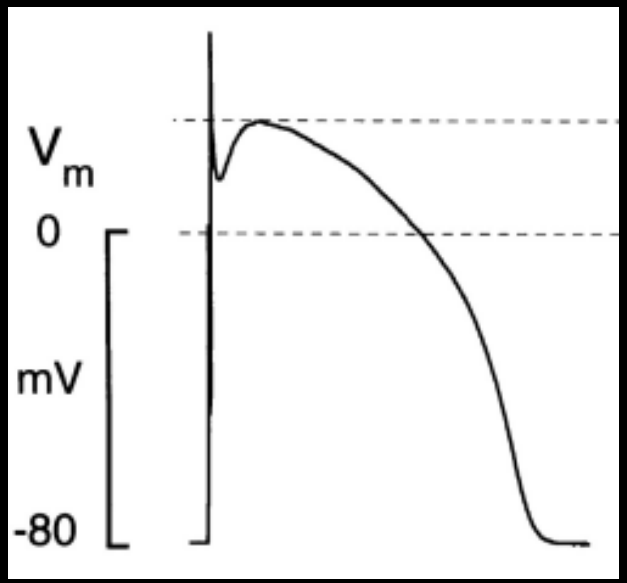


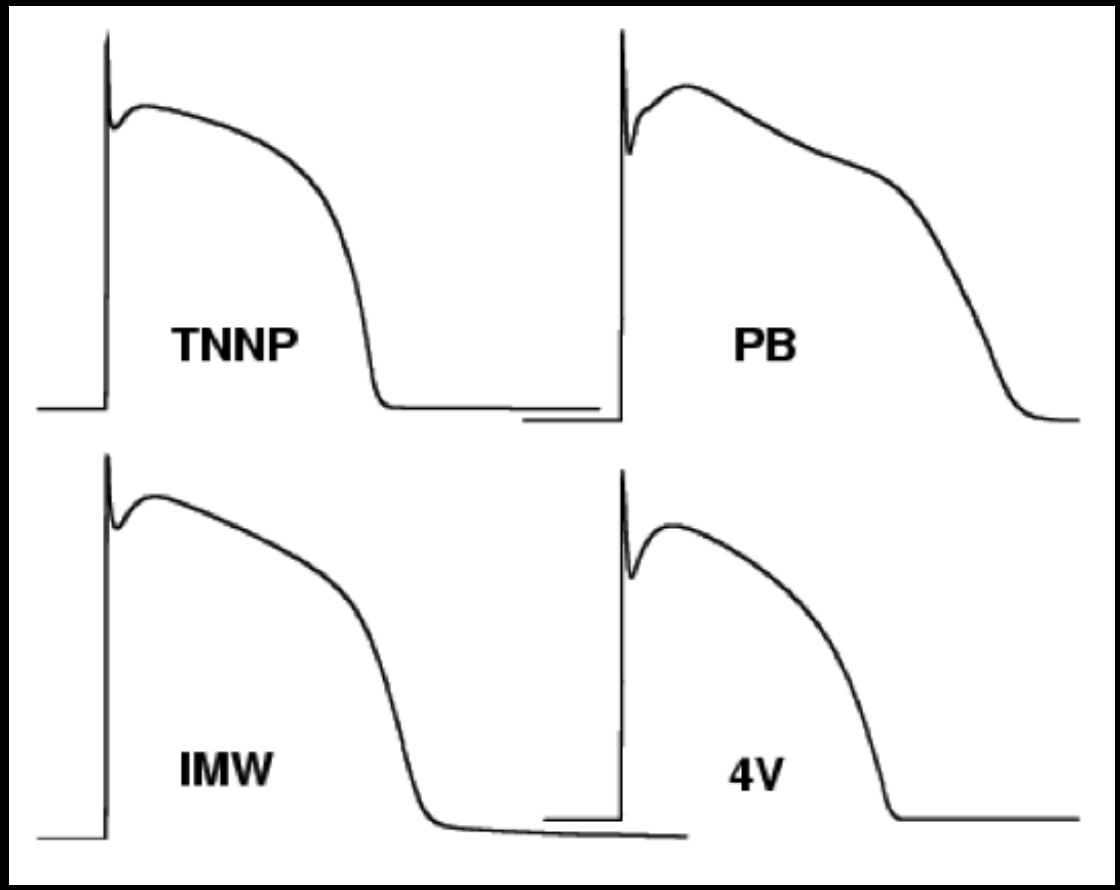
Nabaur et al,
Circulation 93: 169-177, 1996.
Drouin et al
J Am Coll Cardiol 26: 185-92, 1995.
Li et al,
Am J Physiol 275: H369-H377, 1998.
JCE Vol 15 1357-1363 Dic. 2004

AP morphology (epicardial single cell)

- AP shapes are qualitatively and quantitatively different depending on the ionic model.



Experimental epicardial AP.
(M. Näbauer *et al.*, Circulation 1996, 93: 168-177.)



Simulated epicardial APs for the different ionic models.

AP morphology (epicardial single cell)

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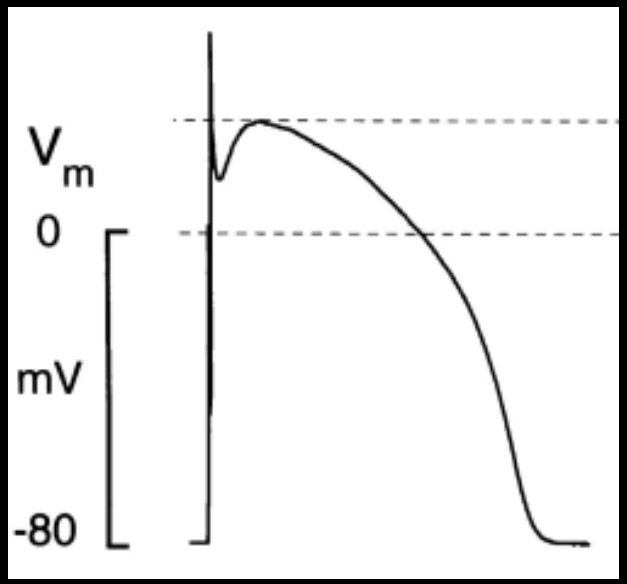

Experimental epicardial AP.
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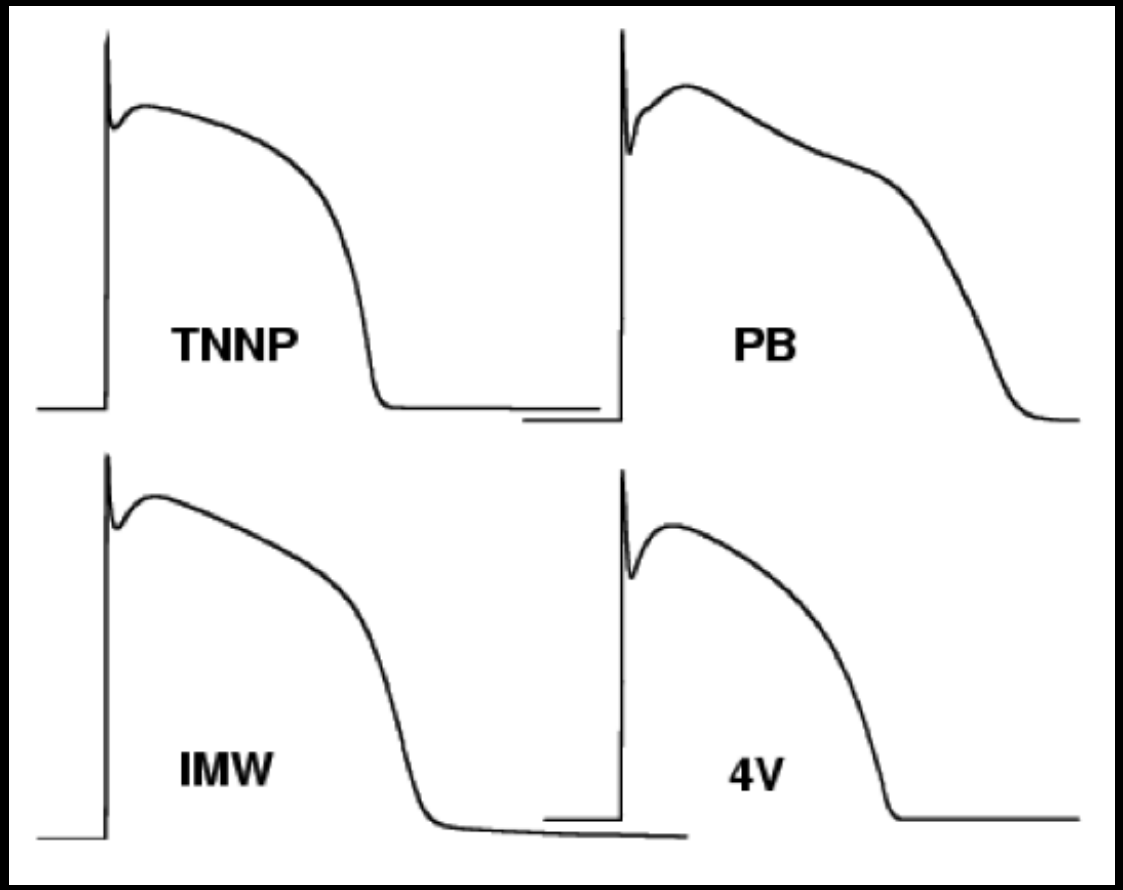


Simulated epicardial APs for the different ionic models.

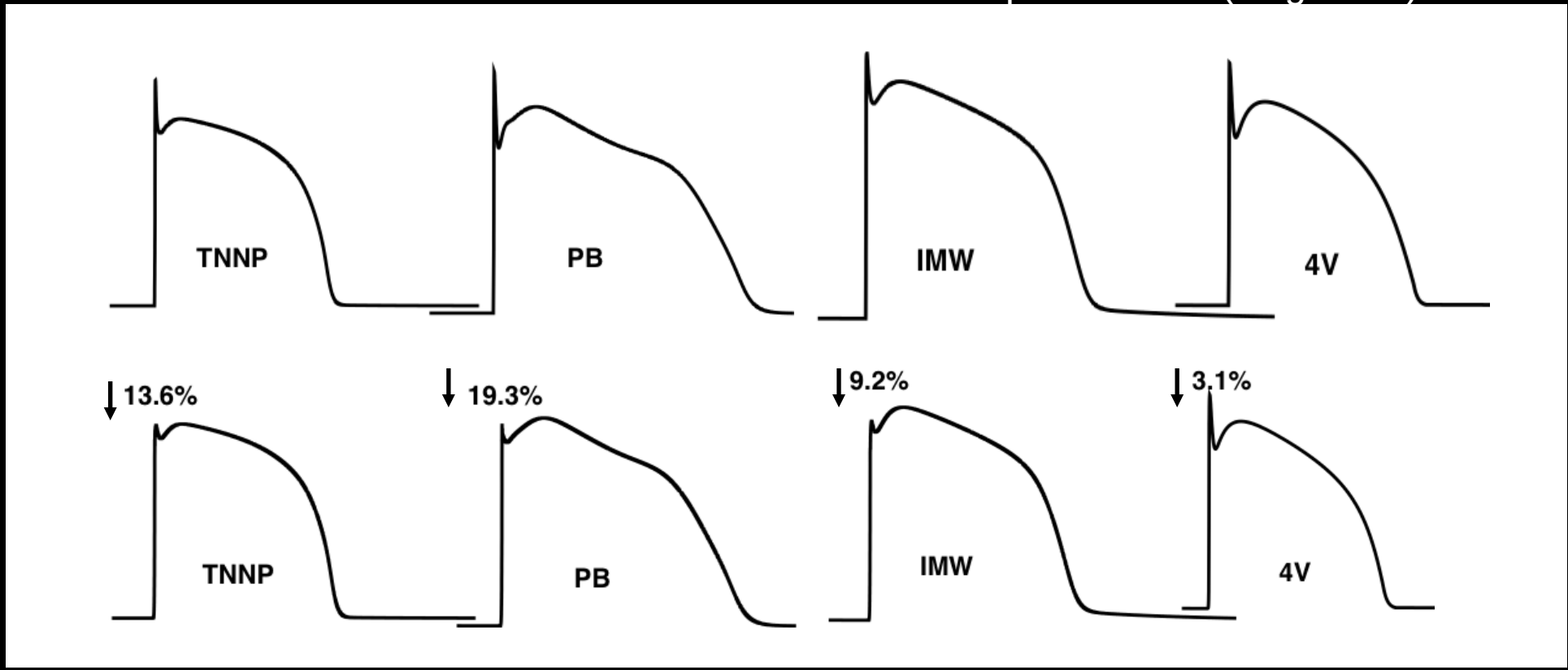
ratio of 8084:70:31:1
IMW :PB :TNNP: 4V

	TNNP	PB	IMW	4V
Time to simulate 10 s	**4.1 s**	**9.2 s**	**17 min**	**0.13 s**

AP morphology (epicardial 1D tissue)

- PB, TNNP and IMW model APs lose a considerable fraction of the phase 0 amplitude when coupled into tissue.

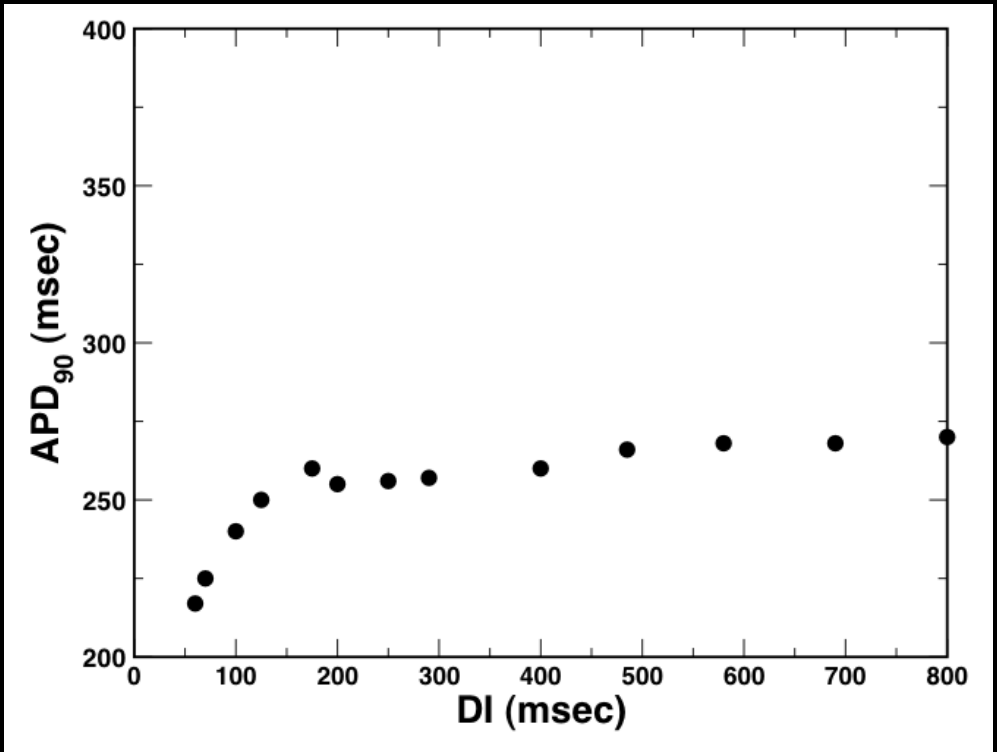
Simulated epicardial AP (single cell).

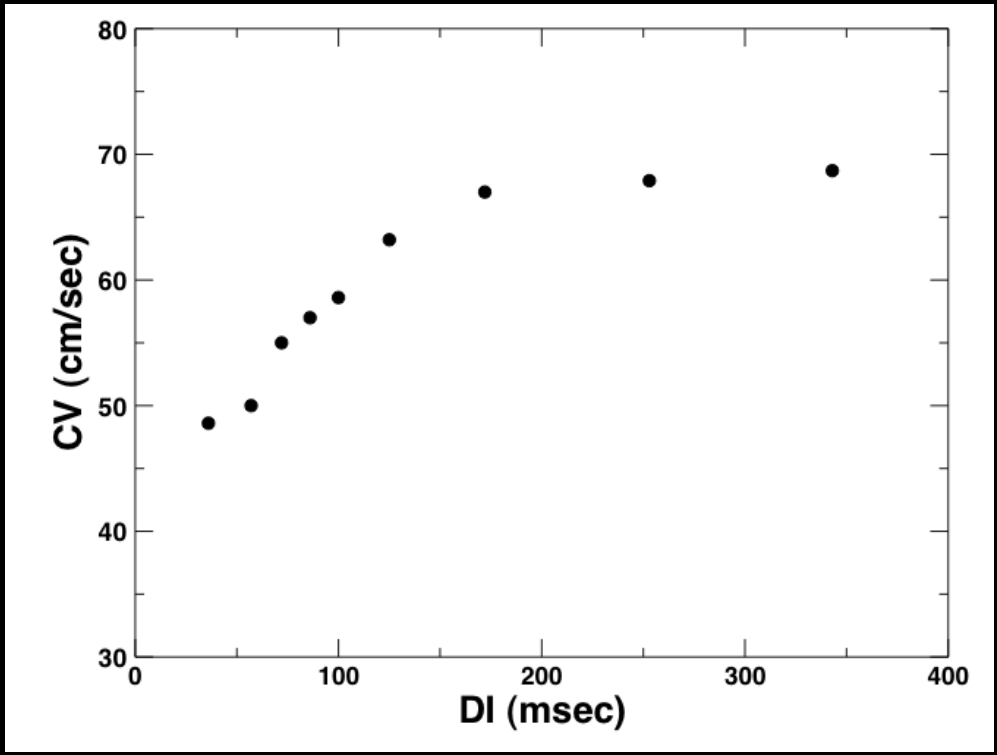


Simulated epicardial AP (tissue).

APD and CV restitutions in 1D tissue (epicardium)

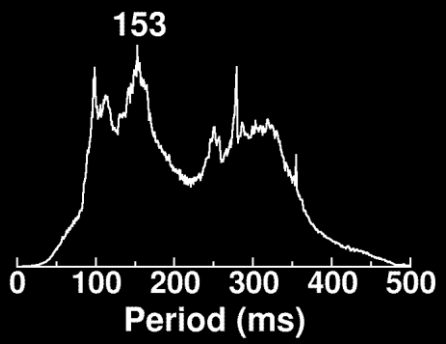
- APD restitution: APD larger for PB and Iyer *et al.* models.
- CV restitution: using published data, the diffusion coefficient for the human ventricular myocyte is estimated to be $D=1.16 cm^2/s$. For this value, the detailed ionic models fail to reach experimental CV_{max}.

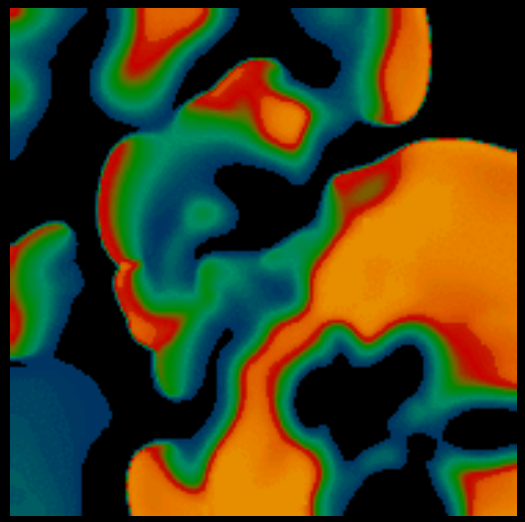




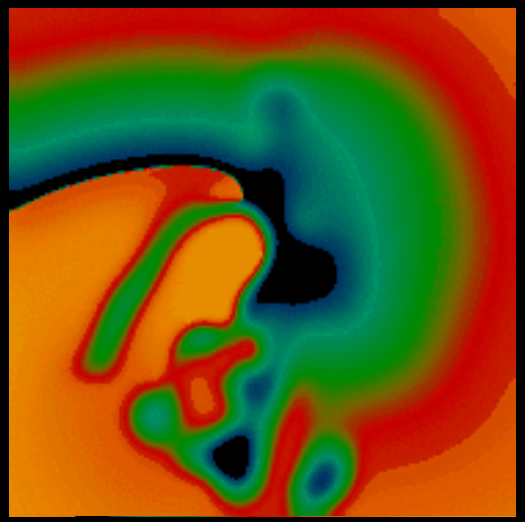
Experimental Data (APD): J. M. Morgan *et al.*, J. Am. Coll. Cardiol. 1992, 19: 1244-1253.
Experimental Data (CV): S. Girouard *et al.*, Circulation 1996, 93: 603-613.

Dynamics in homogeneous 2D-tissue (epicardium)

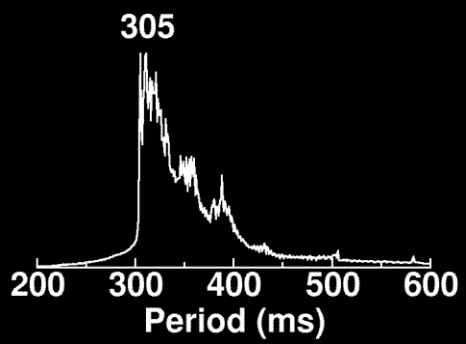


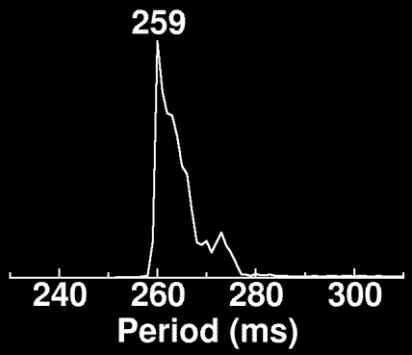


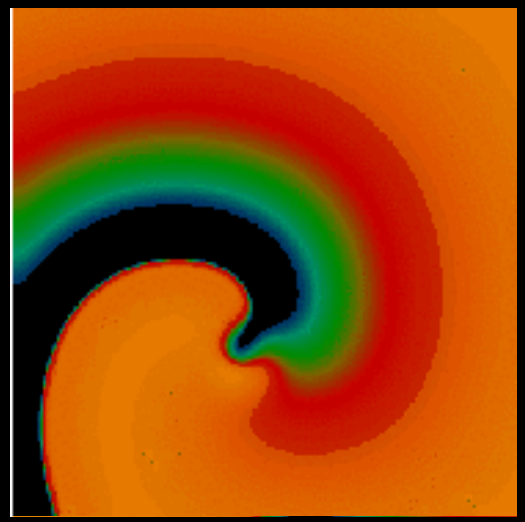
Iyer et al.



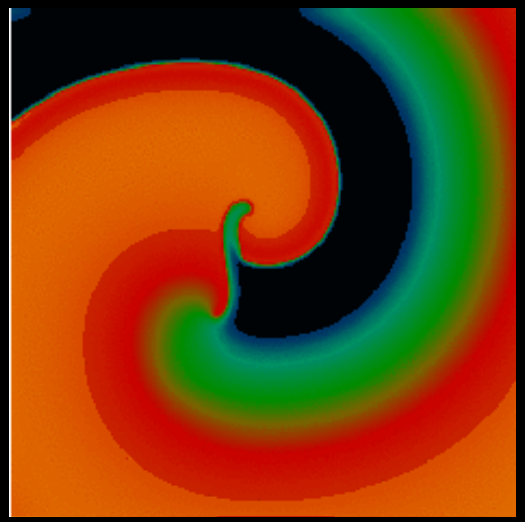
Priebe and Beuckelmann



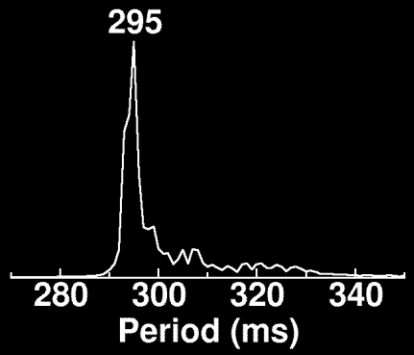




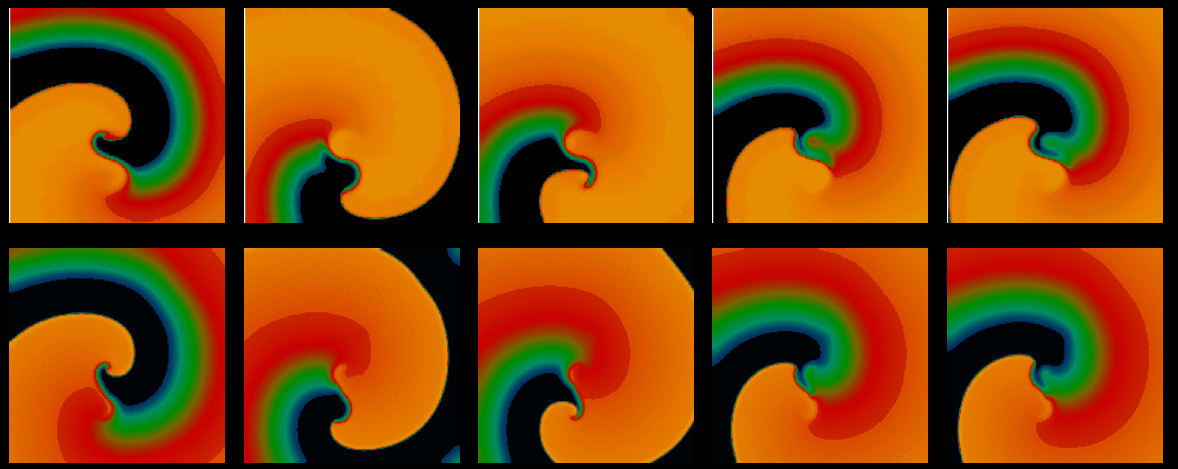
Ten Tusscher et al.



Minimal model

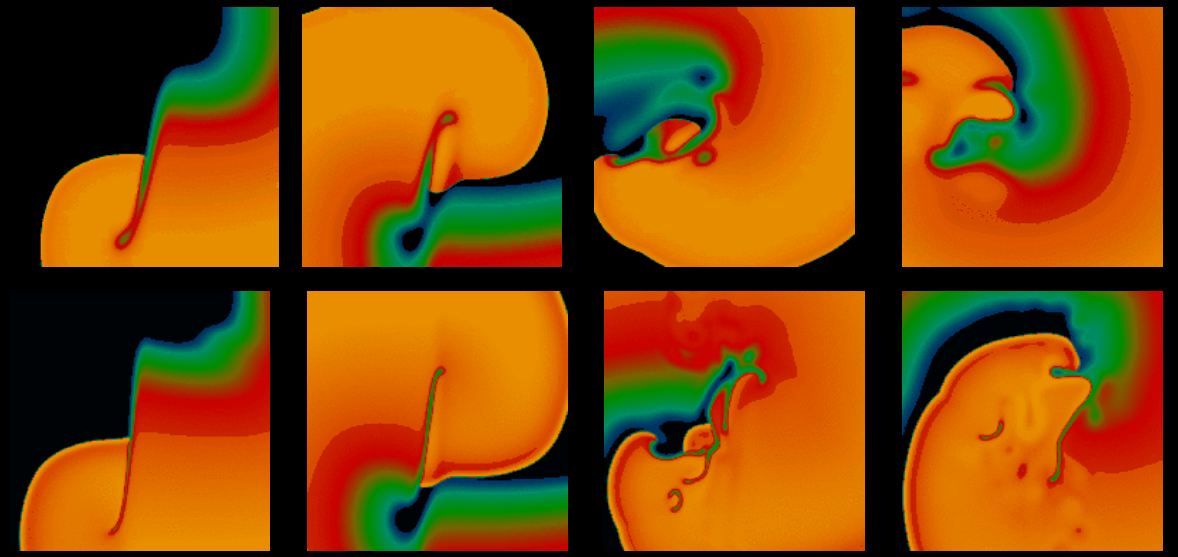


Simplified model fitted to experiments
Why not to other models?



TNNP

4v-sim



PB

4v-sim

Mathematical Model

All cardiac cell models in tissue are reaction-diffusion equations.

$$C_{\mathrm{m}} \frac{\partial V(t,\mathbf{x})}{\partial t} = \nabla \cdot (D(\mathbf{x}) \nabla V) - I_{\mathrm{ion}}(V,\mathbf{m}) - I_{\mathrm{stim}}(t,\mathbf{x})$$

$$\frac{\partial \mathbf{m}(t,\mathbf{x})}{\partial t} = \mathbf{f}(V,\mathbf{m})$$

$V(t,\mathbf{x})$ membrane potential

$\mathbf{m}(t,\mathbf{x})$ gating, concentrations

C_{m} membrane capacitance

$D(\mathbf{x})$ conductivity tensor

I_{ion} total ionic current ($I_{Na}+I_K+I_{Ca}$)

I_{ion} external stimulus current

We will describe now the 3V and 4V models (FK-models)

3V Cell Model Equations

Example: a simple 3 current phenomenological model.

The model consists of 3 variables: the membrane voltage **V**, a fast ionic gate **v**, and a slow ionic gate **w**.

The variables are used to produce 3 independent phenomenological ionic currents.

$$
\begin{aligned}
I_{fi}(V;\mathbf{v}) &= -\mathbf{v}\, p\,(V-V_c)(V-V_m)/\tau_d \\
I_{so}(V) &= (V-V_o)\,(1-p)/\tau_o + p/\tau_r \\
I_{si}(V;\mathbf{w}) &= -\mathbf{w}\,\left(1+\tanh\left[k\,(V-V_c^{si})\right]\right)/(2\tau_{si})
\end{aligned}
$$

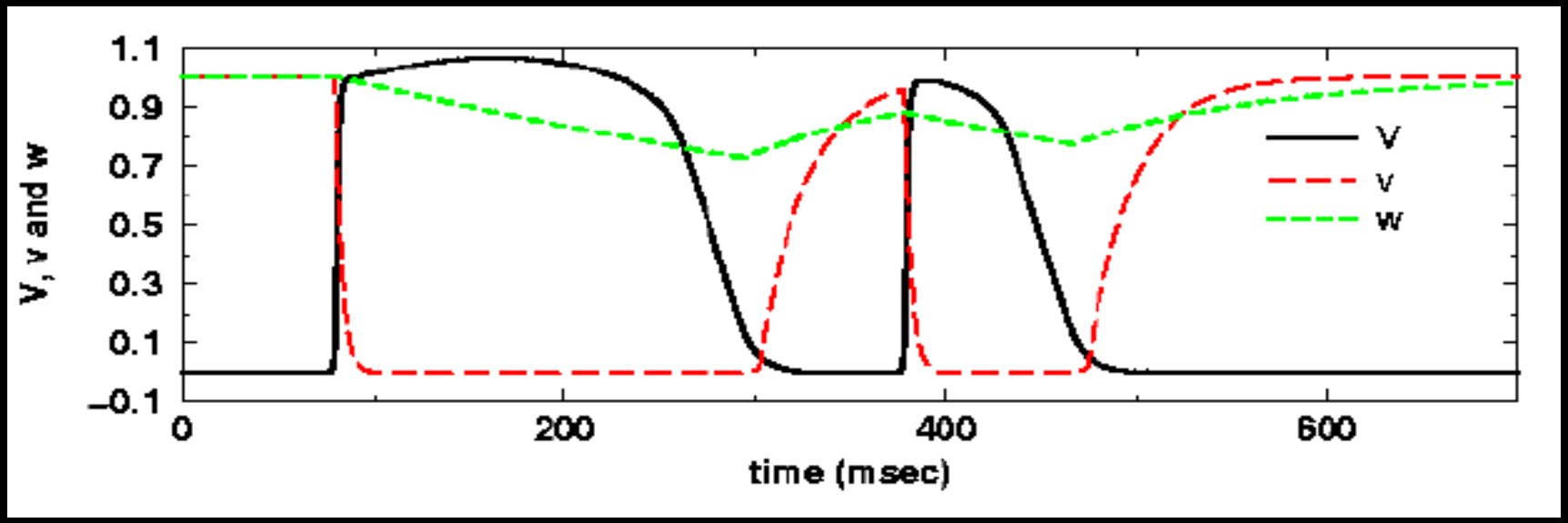
3V Cell Model Equations

The equations for the 3 variables are:

$$\begin{aligned} \partial_t V(\vec{x},t) &= \nabla\cdot(\tilde{D}\nabla V) - I_{\text{ion}} \\ \partial_t \mathbf{v}(t) &= (1-p)\,(1-\mathbf{v})/\tau_{\mathbf{v}}^{-}(V) \;-\; p\,\mathbf{v}/\tau_{\mathbf{v}}^{+} \\ \partial_t \mathbf{w}(t) &= (1-p)\,(1-\mathbf{w})/\tau_{\mathbf{w}}^{-} \;-\; p\,\mathbf{w}/\tau_{\mathbf{w}}^{+} \end{aligned}$$

where $\tau_{\mathbf{v}}^{-}(V) = (1-q)\,\tau_{\mathbf{v}1}^{-} + q\,\tau_{\mathbf{v}2}^{-}$

$$p = \begin{cases} 1 & \text{if } V \geq V_c \\ 0 & \text{if } V < V_c \end{cases} \quad \text{and} \quad q = \begin{cases} 1 & \text{if } V \geq V_{\mathbf{v}} \\ 0 & \text{if } V < V_{\mathbf{v}} \end{cases}$$



Comparison with Other Models

The equations for the 3 variables are:

$$\begin{aligned}
\partial_t V(\vec{x},t) &= \nabla\cdot(\tilde{D}\nabla V) - I_{\text{ion}} \\
\partial_t \mathbf{v}(t) &= (1-p)\,(1-\mathbf{v})/\tau_{\mathbf{v}}^{-}(V) \;-\; p\,\mathbf{v}/\tau_{\mathbf{v}}^{+} \\
\partial_t \mathbf{w}(t) &= (1-p)\,(1-\mathbf{w})/\tau_{\mathbf{w}}^{-} \;-\; p\,\mathbf{w}/\tau_{\mathbf{w}}^{+}
\end{aligned}$$

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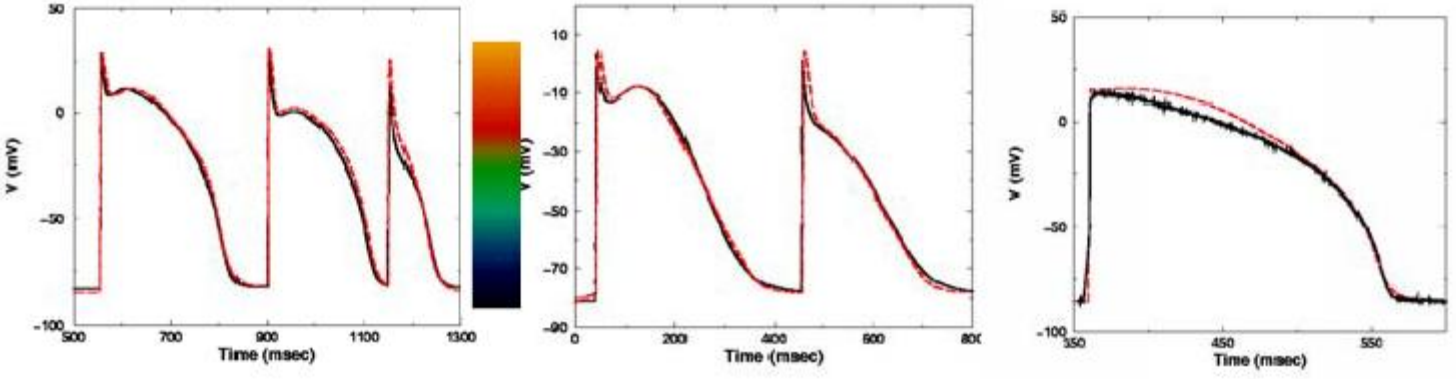


Beeler-Reuter Courtemanche Rabbit experiment

4V Cell Model Equations

$$\partial_t u = \nabla(\tilde{D}\nabla u) - (J_{fi} + J_{so} + J_{si}) \quad (1)$$
$$\partial_t v = (1-m)(v_\infty - v)/\tau_v^- - mv/\tau_v^+ \quad (2)$$
$$\partial_t w = (1-p)(w_\infty - w)/\tau_w^- - pw/\tau_w^+ \quad (3)$$
$$\partial_t s = ((1+\tanh(k_s(u-u_s)))/2 - s)/\tau_s \quad (4)$$

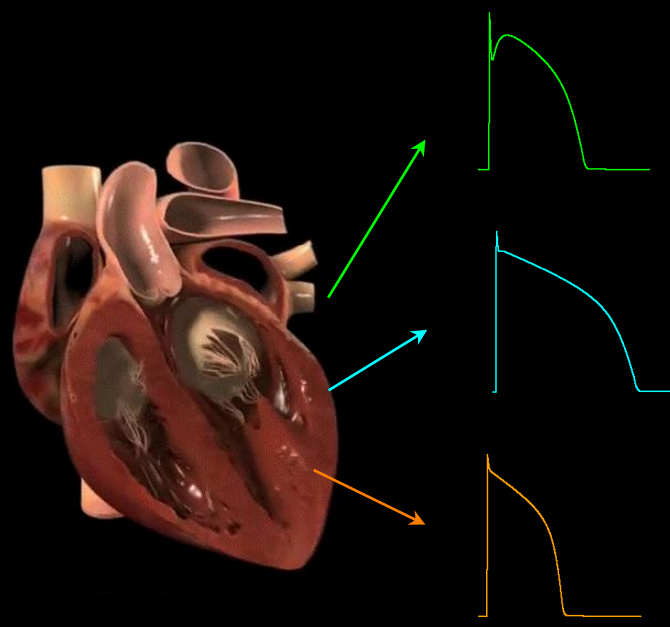
$$J_{fi} = -vm(u-u_m)(u_u - u)/\tau_{fi} \quad (5)$$
$$J_{so} = (u-u_o)(1-p)/\tau_o + p/\tau_{so} \quad (6)$$
$$J_{si} = -pws/\tau_{si} \quad (7)$$

$$\tau_v^- = (1-q)\tau_{v1}^- + q\tau_{v2}^- \quad (8)$$
$$\tau_w^- = \tau_{w1}^- + (\tau_{w2}^- - \tau_{w1}^-)(1+\tanh(k_w^-(u-u_w^-)))/2 \quad (9)$$
$$\tau_{so} = \tau_{so1} + (\tau_{so2} - \tau_{so1})(1+\tanh(k_{so}(u-u_{so})))/2 \quad (10)$$
$$\tau_s = (1-p)\tau_{s1} + p\tau_{s2} \quad (11)$$
$$\tau_o = (1-r)\tau_{o1} + r\tau_{o2} \quad (12)$$

$$v_\infty = \begin{cases} 1 & u < u_q \\ 0 & u \geq u_q \end{cases} \quad (13)$$
$$w_\infty = (1-r)(1-u/\tau_{w_\infty}) + rw_\infty^* \quad (14)$$

$$m = \begin{cases} 0 & u < u_m \\ 1 & u \geq u_m \end{cases} \qquad p = \begin{cases} 0 & u < u_p \\ 1 & u \geq u_p \end{cases} \quad (15)$$

$$q = \begin{cases} 0 & u < u_q \\ 1 & u \geq u_q \end{cases} \qquad r = \begin{cases} 0 & u < u_r \\ 1 & u \geq u_r \end{cases} \quad (16)$$



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$$\frac{\partial \mathbf{m}(t,\mathbf{x})}{\partial t} = \mathbf{f}(V,\mathbf{m})$$

Cardiac tissue modeling

Nonlinear parabolic reaction-diffusion equations:

$$C_{\mathrm{m}}\partial_t V(t,\mathbf{x}) = \nabla\cdot(D(\mathbf{x})\nabla V) - I_{\mathrm{ion}}(V,\mathbf{m}) - I_{\mathrm{stim}}(t,\mathbf{x})$$
$$\partial_t \mathbf{m}(t,\mathbf{x}) = \mathbf{f}(V,\mathbf{m})$$

$V(t,\mathbf{x})$ membrane potential

$\mathbf{m}(t,\mathbf{x})$ gating variables, ionic concentrations

C_{m} membrane capacitance

D(x) conductivity tensor

Iion total ionic current across the membrane of the cell

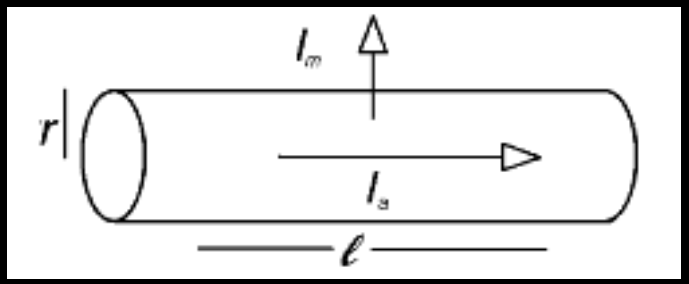
Istim external stimulus current

Neumann boundary conditions on potential V:

$$n\cdot\nabla V = 0$$

How to couple cardiac cells to represent tissue?

The Cable Equation



I_membrane
I_axial

$$I_m 2\pi r l = [I_a(x+l) - I_a(x)]\pi r^2 \approx -\left(\frac{\partial i_a}{\partial x}\right)\pi l r^2 \quad (1)$$

Any cahnge on the axial current, produces a change on the membrane current.

$$\left(\frac{\partial V_m}{\partial x}\right) = -\rho i_a \quad (2)$$

The flow of current along the cable is proportional to the voltage gradient (Ohm's law).

Q = CV ; dQ_m/dt = I_m = C dV_m/dt and I_m = I_c + I_ion

$$I_m = I_c + I_{ion} = C_m\left(\frac{\partial V_m}{\partial t}\right) + I_{ion} \quad (3)$$

Combinando Eq 1,2 y 3 obtenemos:

$$\left(\frac{\partial V_m}{\partial t}\right) = r\left(\frac{\partial^2 V_m/\partial x^2}{2\rho C_m}\right) - \frac{I_{ion}}{C_m} = D\left(\frac{\partial^2 V_m}{\partial x^2}\right) - \frac{I_{ion}}{C_m} \quad (4)$$

Fenton et al.
BioSystems 64 (2002) 73–96

Cardiac tissue modeling

Nonlinear parabolic reaction-diffusion equations:

$$C_{\mathrm{m}}\partial_t V(t,\mathbf{x}) = \nabla\cdot(D(\mathbf{x})\nabla V) - I_{\mathrm{ion}}(V,\mathbf{m}) - I_{\mathrm{stim}}(t,\mathbf{x})$$
$$\partial_t \mathbf{m}(t,\mathbf{x}) = \mathbf{f}(V,\mathbf{m})$$

$$\left(\frac{\partial V_{\mathrm{m}}}{\partial t}\right) = r\left(\frac{\partial^2 V_{\mathrm{m}}/\partial x^2}{2\rho C_{\mathrm{m}}}\right) - \frac{I_{\mathrm{ion}}}{C_{\mathrm{m}}} = D\left(\frac{\partial^2 V_{\mathrm{m}}}{\partial x^2}\right) - \frac{I_{\mathrm{ion}}}{C_{\mathrm{m}}} \quad (4)$$

Como resolver estas equaciones Numericamente?

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + (a - V)(V - 1)V - v$$

$$\frac{\partial v}{\partial t} = \epsilon(\beta V - \gamma v - \delta)$$

$$\left(\frac{\partial V_m}{\partial t}\right) = r\left(\frac{\partial^2 V_m / \partial x^2}{2\rho C_m}\right) - \frac{I_{ion}}{C_m} = D\left(\frac{\partial^2 V_m}{\partial x^2}\right) - \frac{I_{ion}}{C_m} \quad (4)$$

Integration

- Given an ODE, $\frac{\mathrm{d}V}{\mathrm{d}t} = f(V)$

  we can develop an integration method to evolve the solution in time using Taylor series:

$$V(t+\Delta t) = V(t) + \Delta t \frac{\mathrm{d}V(t)}{\mathrm{d}t} + \frac{\Delta t^2}{2} \frac{\mathrm{d}^2 V(t)}{\mathrm{d}t^2} + O\left(\Delta t^3\right)$$

- A first-order approximation of the derivative can be obtained as:

$$\frac{V(t+\Delta t) - V(t)}{\Delta t} = \frac{\mathrm{d}V(t)}{\mathrm{d}t} + O\left(\Delta t\right)$$

Integration

- Thus, for simplicity, we can approximate the derivative to first order as

$$\frac{V(t+\Delta t)-V(t)}{\Delta t}=\frac{\mathrm{d}V}{\mathrm{d}t}=f(V)$$

$$V(t+\Delta t)=V(t)+\Delta t\ f(V)$$

- We can represent V(t) as V^i and V(t+Δt) as V^{i+1}. Then

$$V^{i+1}=V^i+\Delta t\ f(V)$$

- Note that we need to begin with an initial condition V^0 (usually resting membrane potential).

Integration in Tissue

- In tissue, the equation of interest includes a spatial derivative:

$$\frac{\mathrm{d}V(x,t)}{\mathrm{d}t} = f\big(V(x,t)\big) + D\frac{\partial^2 V(x,t)}{\partial x^2}$$

- In this case we also need an approximation for the spatial derivative.

Integration in Tissue

- In this case we combine the following:

$$V(x+\Delta x,t)=V(x,t)+\Delta x\frac{\partial V(x,t)}{\partial x}+\frac{\Delta x^2}{2}\frac{\partial^2 V(x,t)}{\partial x^2}+O\left(\Delta x^3\right)$$

$$V(x-\Delta x,t)=V(x,t)-\Delta x\frac{\partial V(x,t)}{\partial x}+\frac{\Delta x^2}{2}\frac{\partial^2 V(x,t)}{\partial x^2}-O\left(\Delta x^3\right)$$

- Summing, we get the following:

$$V(x+\Delta x,t)+V(x-\Delta x,t)=2V(x,t)+\Delta x^2\frac{\partial^2 V(x,t)}{\partial x^2}-O\left(\Delta x^4\right)$$

- and to second order

$$\frac{\partial^2 V(x,t)}{\partial x^2}=\frac{V(x+\Delta x,t)-2V(x,t)+V(x-\Delta x,t)}{\Delta x^2}$$

Integration in Tissue

- We can use the following approximation to advance the solution in time (first order in time, second order in space):

$$V_i^{n+1} = V_i^n + \Delta t\, f(V_i^n) + \frac{\Delta t}{\Delta x^2}\left(V_{i+1}^n - 2V_i^n + V_{i-1}^n\right)$$

  where V_i^n represents the i^{th} point in space and the n^{th} time step.

- Note that now we need both an initial condition V(x,0) and boundary conditions V(0,t), e.g.

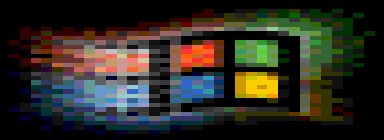
$$\frac{\partial V(0,t)}{\partial x} = 0, \quad \frac{\partial V(L_x,t)}{\partial x} = 0$$

Simulations in 1D (FHN-model)

http://thevirtualheart.org/java/fhn1d.html

Simulations in 2D (FHN-model)

http://thevirtualheart.org/java/2dfhn.html



3V Cell Model Equations

The model consists of 3 variables: the membrane voltage **v**, a fast ionic gate **v**, and a slow ionic gate **w**.

$$
\begin{aligned}
I_{fi}(V;\mathbf{v}) &= -\mathbf{v}\, p\,(V-V_c)(V-V_m)/\tau_d \\
I_{so}(V) &= (V-V_o)\,(1-p)/\tau_o + p/\tau_r \\
I_{si}(V;\mathbf{w}) &= -\mathbf{w}\,\left(1+\tanh\left[k\,(V-V_c^{si})\right]\right)/(2\tau_{si})
\end{aligned}
$$

$$
\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + (a-V)(V-1)V - v
$$

$$
\frac{\partial v}{\partial t} = \epsilon(\beta V - \gamma v - \delta)
$$

The equations for the 3 variables are:

$$
\begin{aligned}
\partial_t V(\vec{x},t) &= \nabla\cdot(\tilde{D}\nabla V) - I_{\text{ion}} \\
\partial_t \mathbf{v}(t) &= (1-p)\,(1-\mathbf{v})/\tau_{\mathbf{v}}^{-}(V) - p\,\mathbf{v}/\tau_{\mathbf{v}}^{+} \\
\partial_t \mathbf{w}(t) &= (1-p)\,(1-\mathbf{w})/\tau_{\mathbf{w}}^{-} - p\,\mathbf{w}/\tau_{\mathbf{w}}^{+}
\end{aligned}
$$

where $\tau_{\mathbf{v}}^{-}(V) = (1-q)\,\tau_{\mathbf{v}1}^{-} + q\,\tau_{\mathbf{v}2}^{-}$

$$
p = \begin{cases} 1 & \text{if } V \geq V_c \\ 0 & \text{if } V < V_c \end{cases}
\quad \text{and} \quad
q = \begin{cases} 1 & \text{if } V \geq V_{\mathbf{v}} \\ 0 & \text{if } V < V_{\mathbf{v}} \end{cases}
$$

3V Cell Model Equations