Questions and Challenges in Tissue and Whole Organ Modeling

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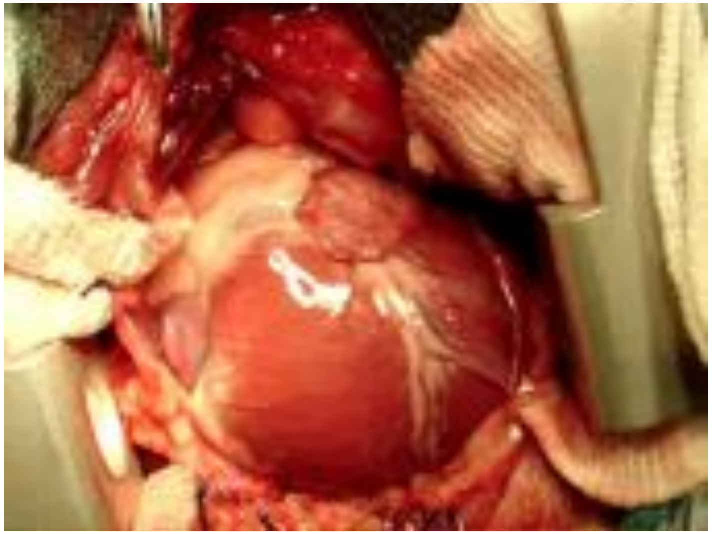
NSF-Expeditions Project CMACS
NSF-Frontiers Project CyberHeart

The Grand Challenge



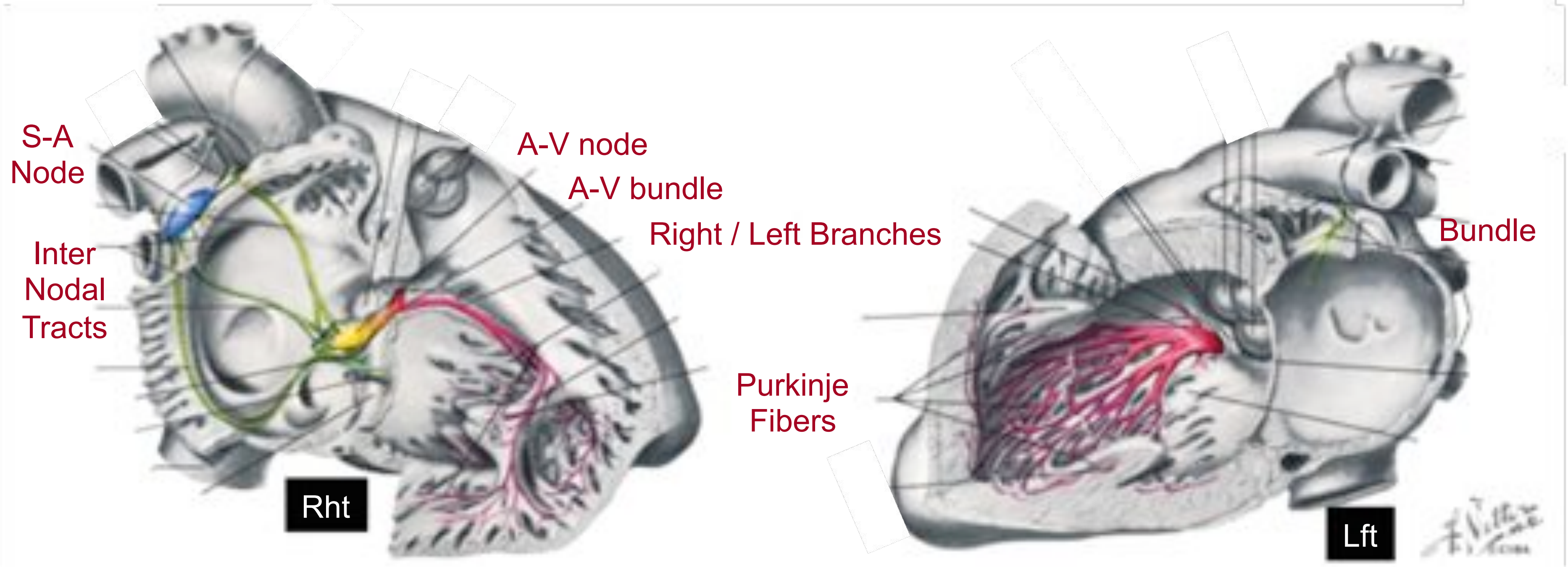
Error-Free Heart

Error-Prone Heart

Can we predict and control abnormal behavior?

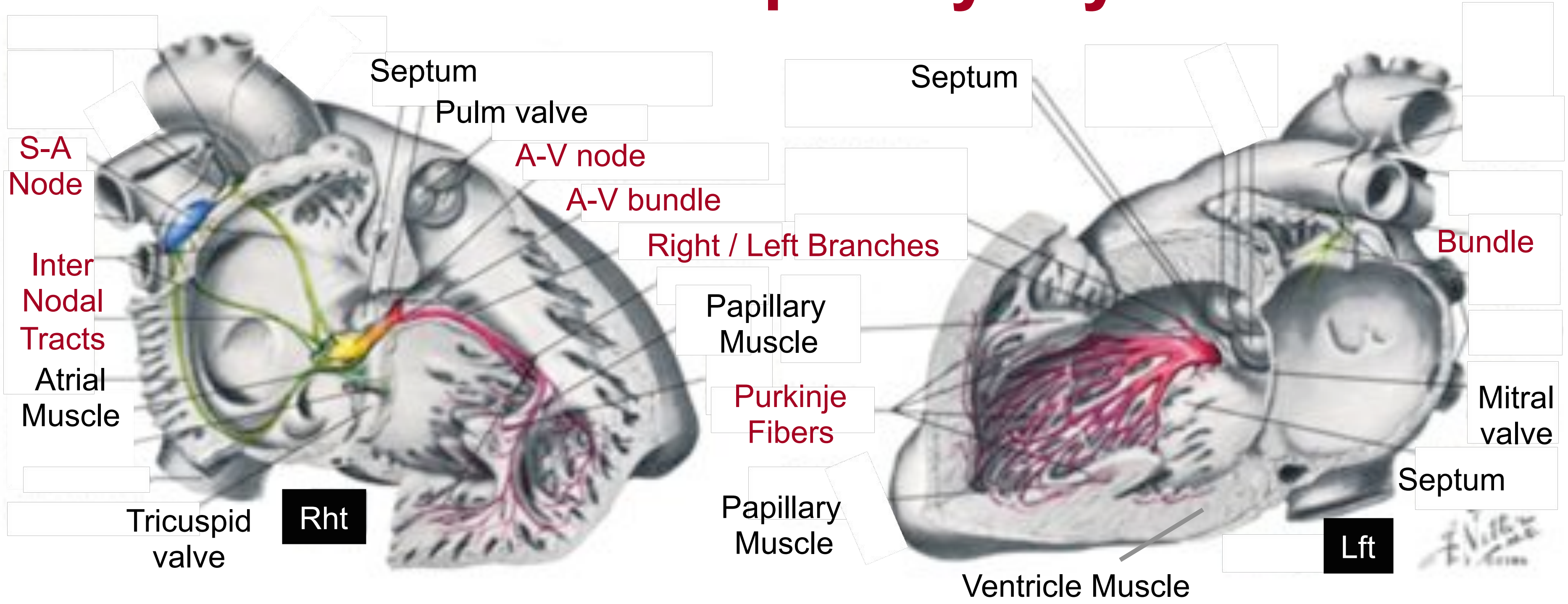
- **Abstraction, approximation and composition**

A Taste of Complexity: Systems



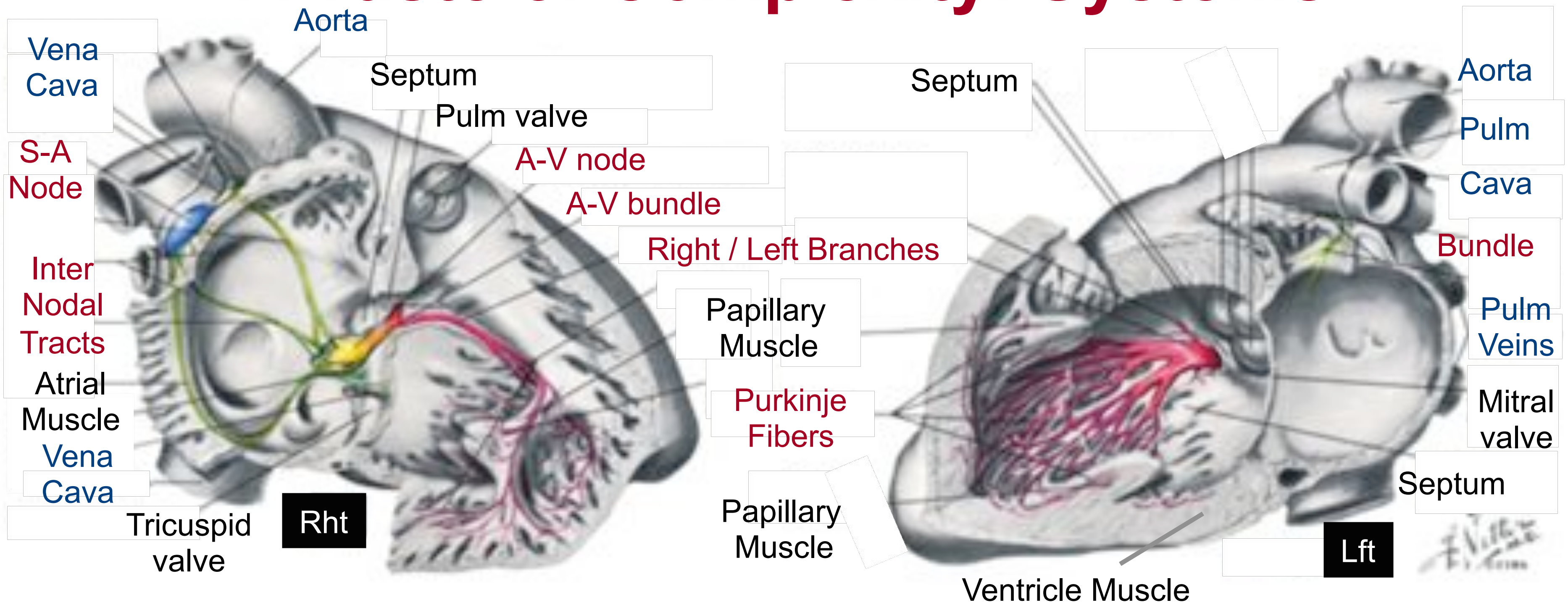
Electrical system: Responsible for synchroniztion

A Taste of Complexity: Systems



Mechanical system: responsible for contraction

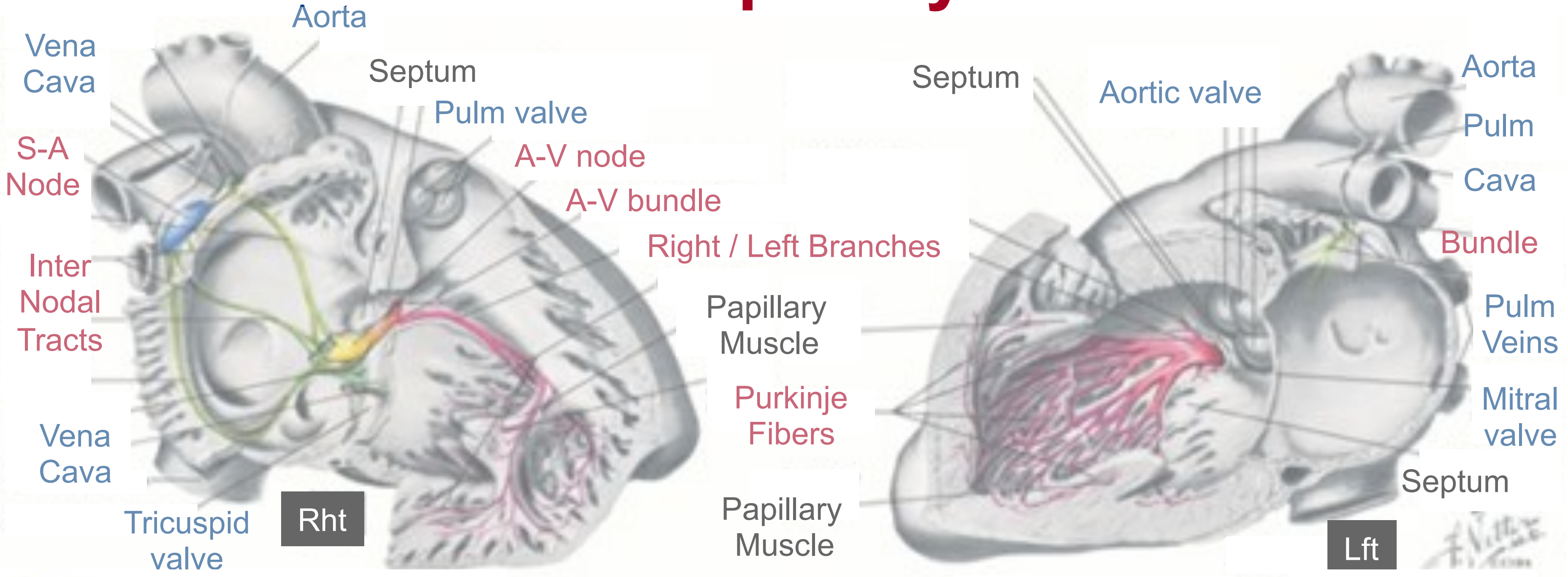
A Taste of Complexity: Systems

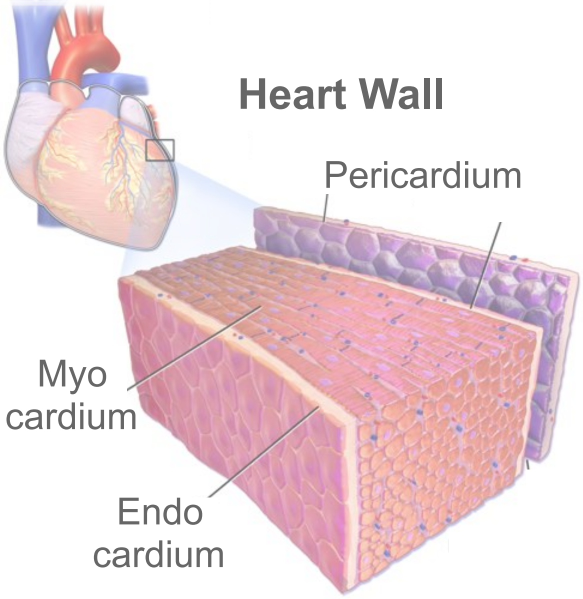


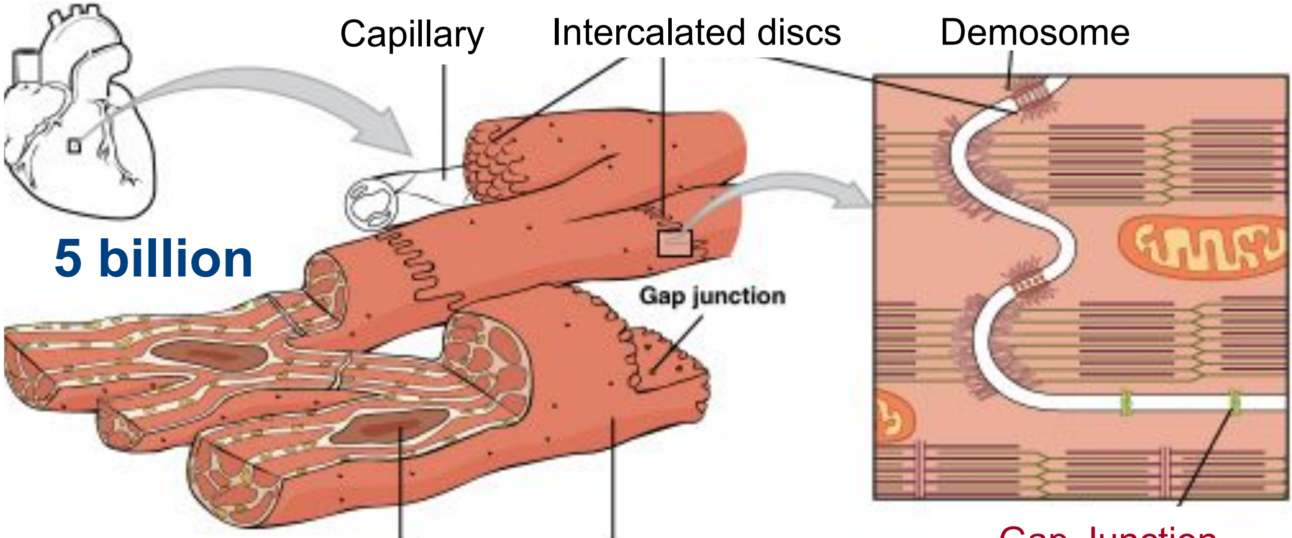
Vascular system: responsible for transportation

System abstraction: electrical, mechanical, vascular

A Taste of Complexity: Multiscale





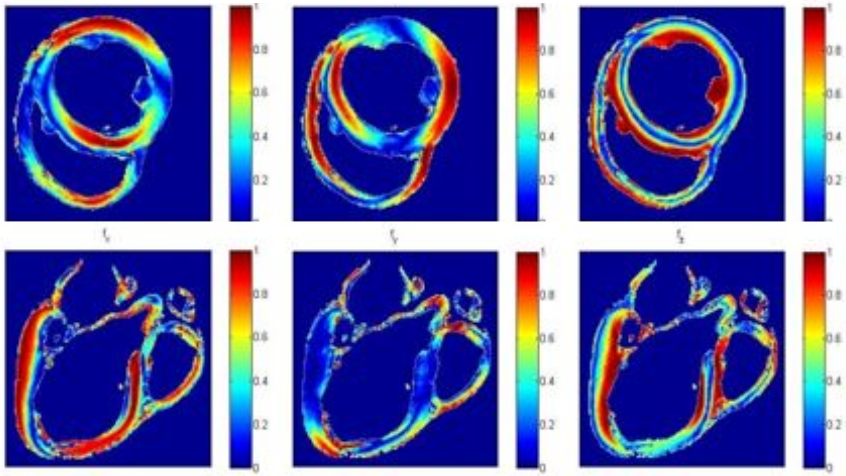


Cardiac Myocyte Cardiac Muscle Fiber

A Taste of Complexity: Tools

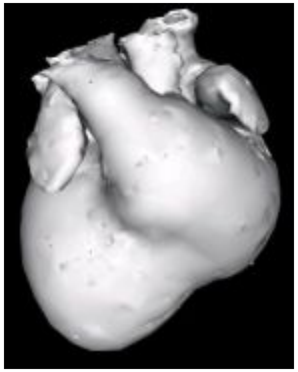
Complicated structure: Atrium

Canine heart: slices
(DTMRI @ 250 microns resolution)



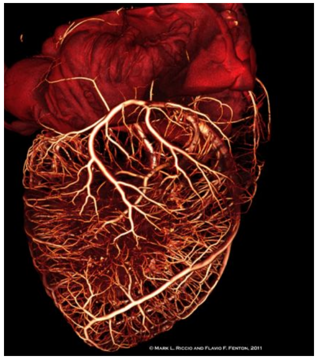
Ventricle

Matrix



Fibers

Vessels

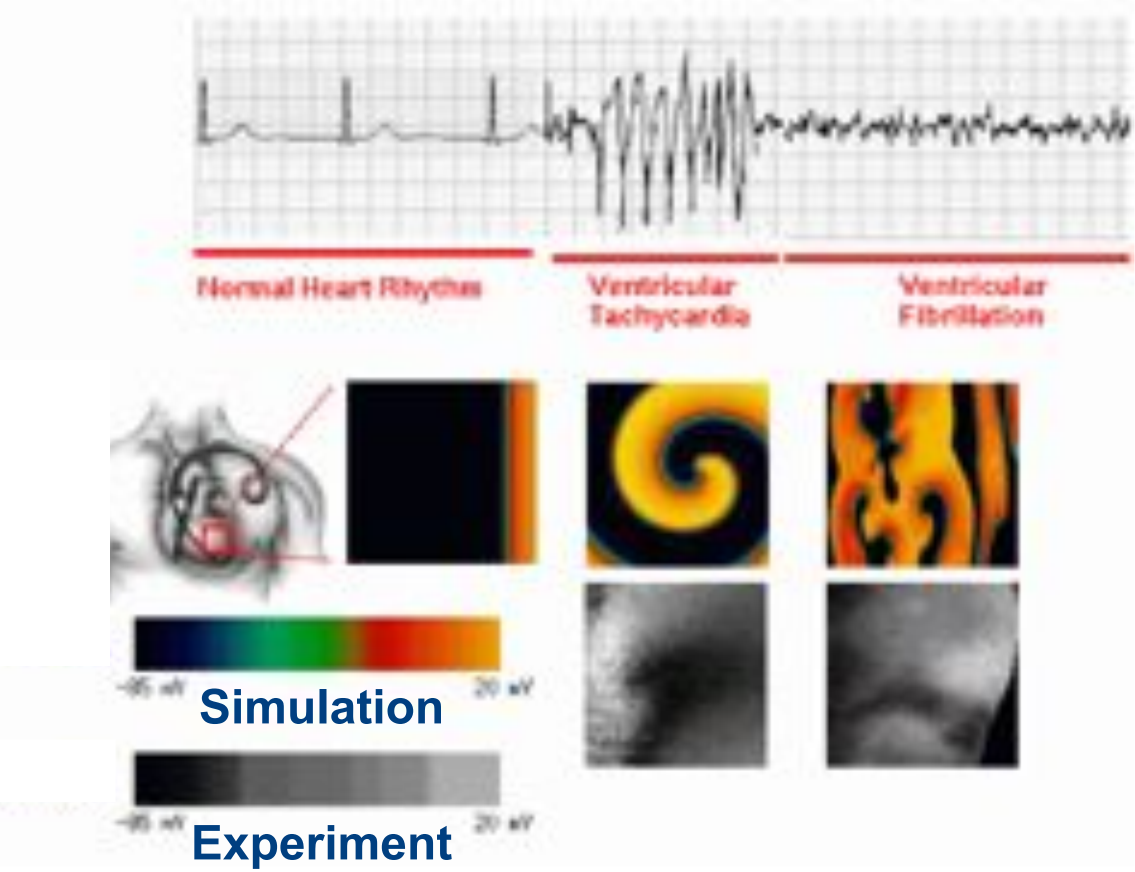


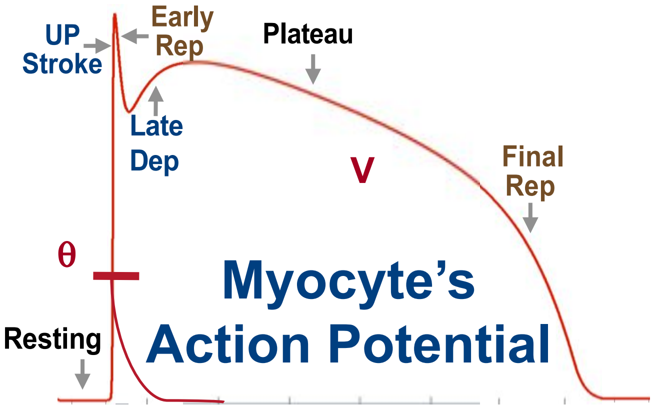
Pittsburgh NMR Center

MicroCT Cornell

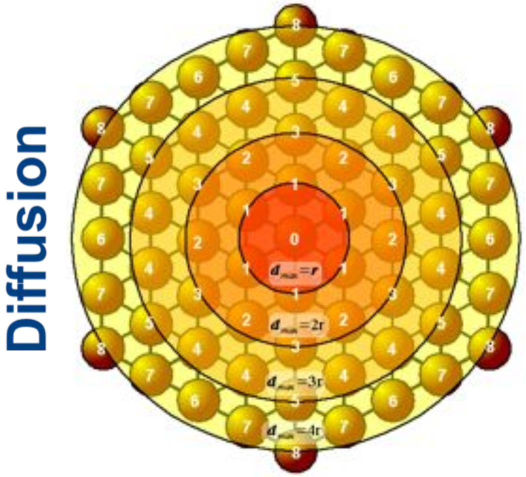
5 billion cells synchronize their contraction to create a heart beat!

From Cell to EKG and Tissue





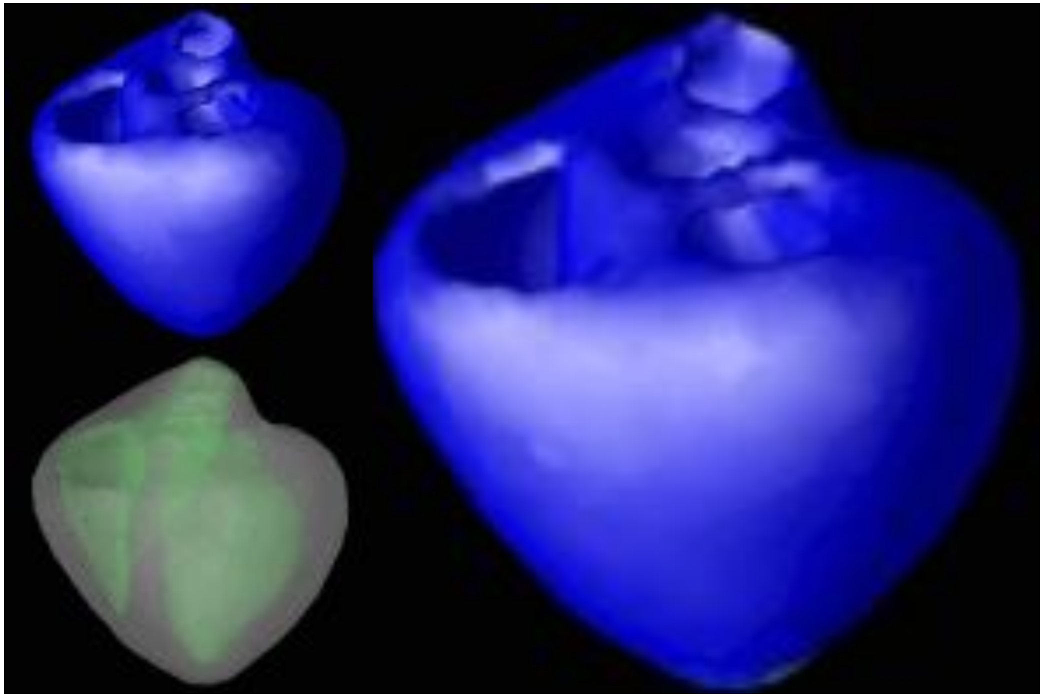
Myocyte's Action Potential

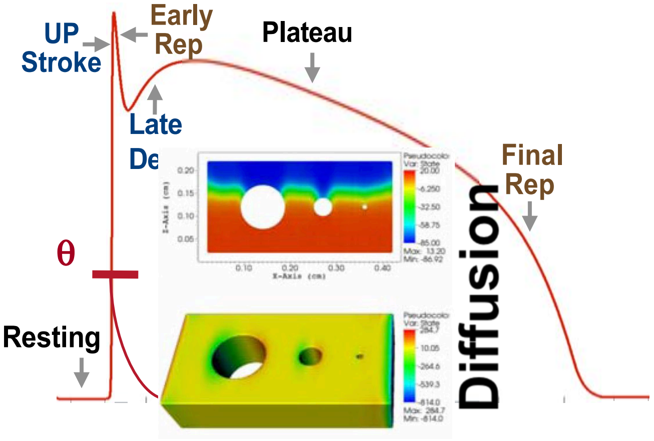


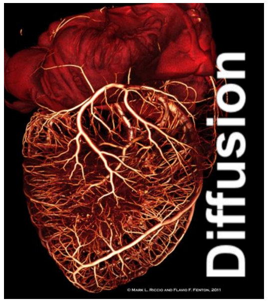
$$\frac{\partial V}{\partial t} = \nabla(D\nabla V) - I_{react}$$

From Cell to Whole Heart

3D Model of a Pig Heart (FK 3V Model)



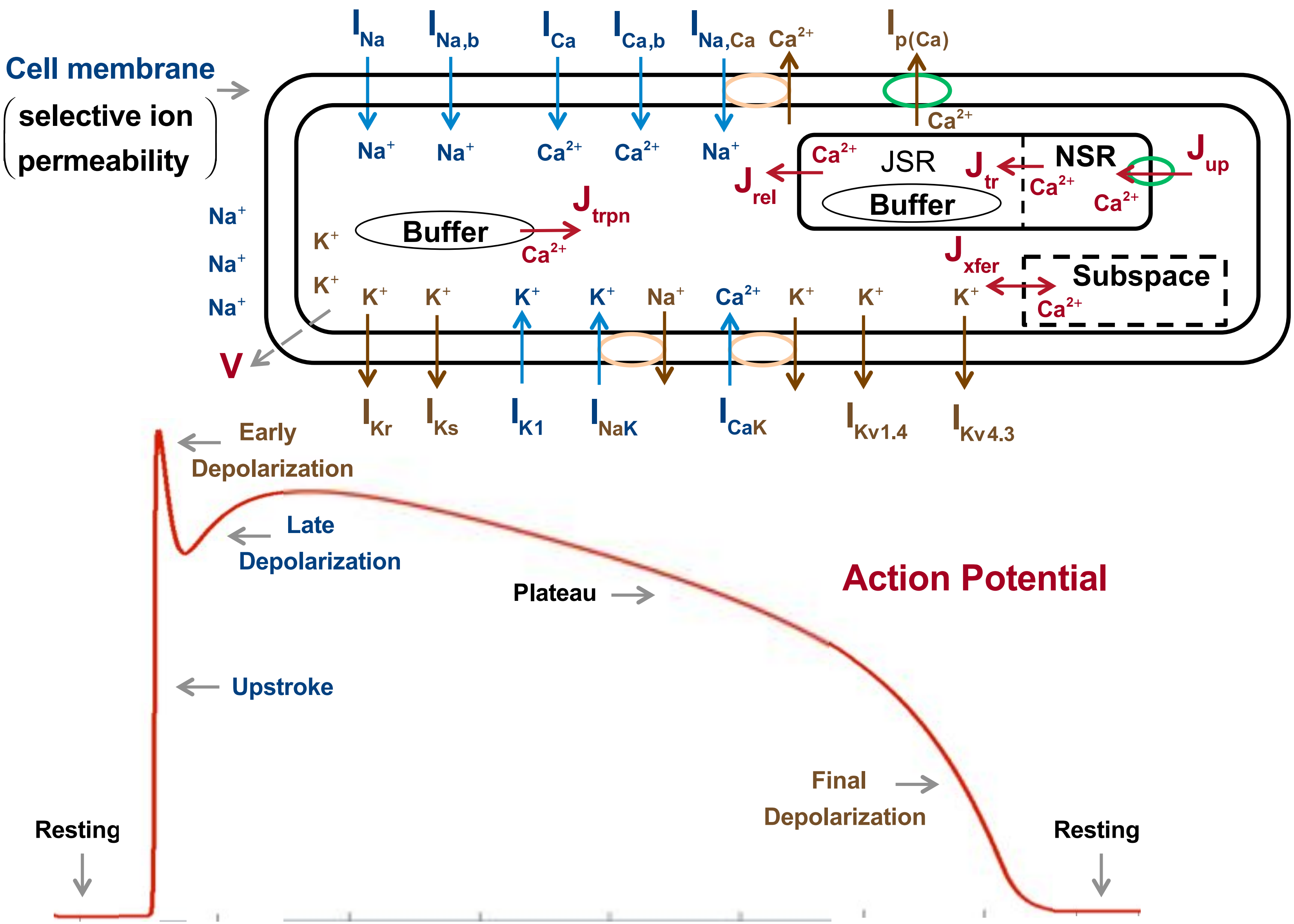




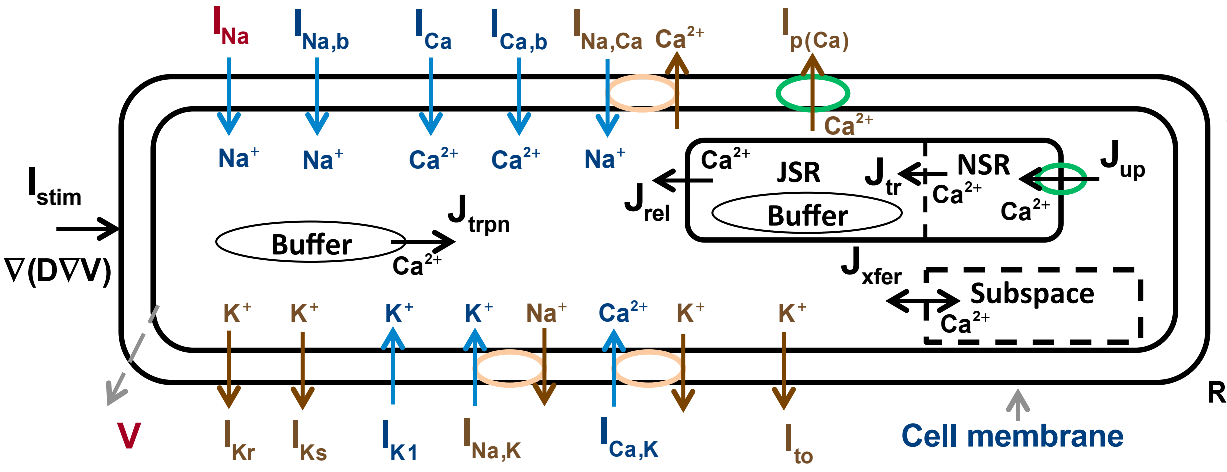
Topological approximations:

- 0D, 1D: EKG (no space), cable propagation
- 2D, 3D: tissue/organ, (an)isotropic, (no)veins, etc.

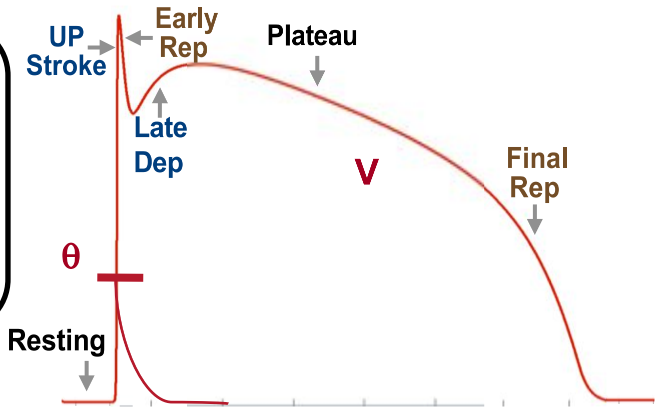
The Cell: Action-Potential



Cellular Approximation Challenge



The 67-variable IMW myocyte model



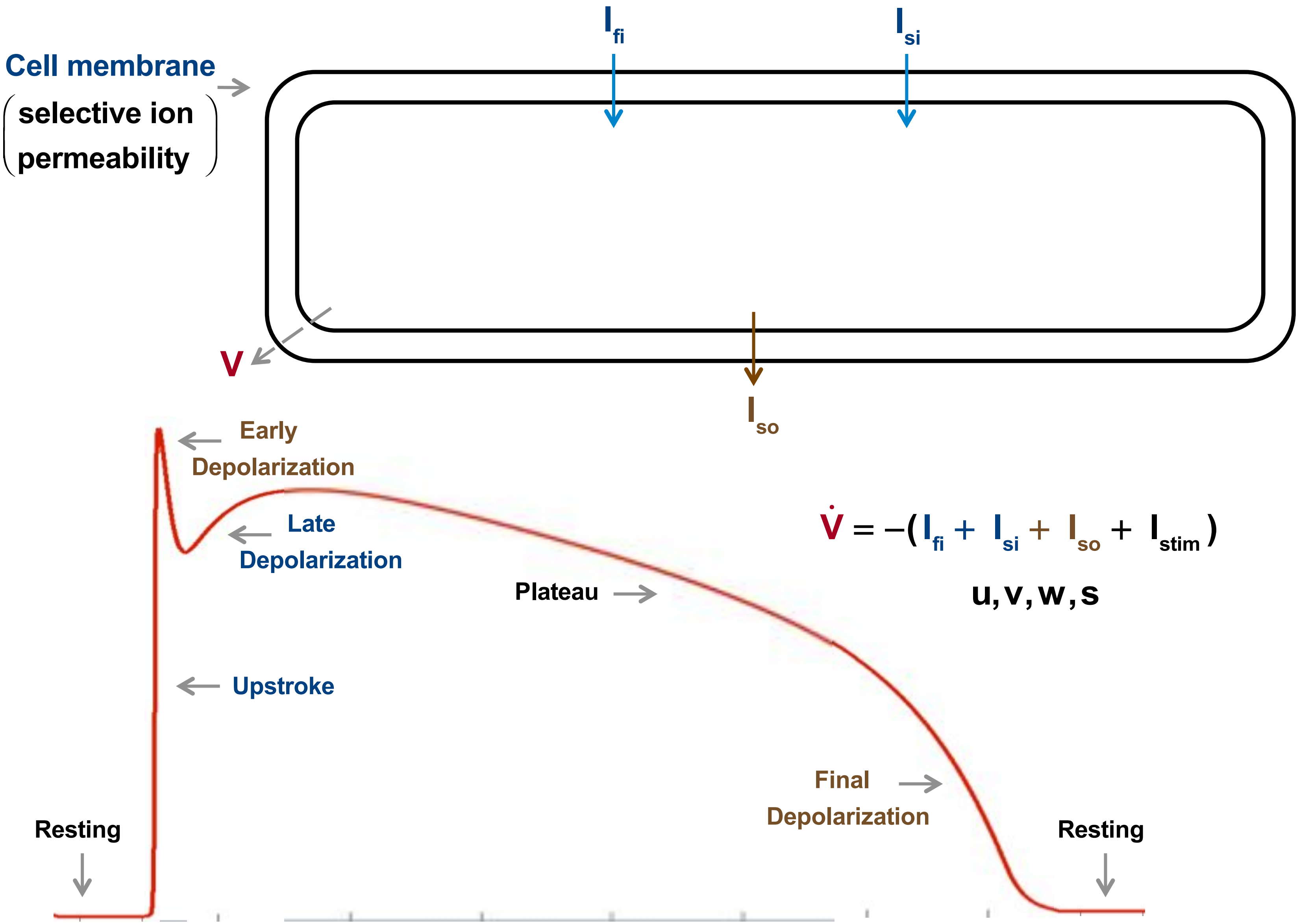
Myocyte Action Potential

$$\frac{\partial V}{\partial t} = -(\nabla(D\nabla V) + I_{Na} + I_{Ca} + I_{Ca,K} + I_{Kr} + I_{Ks} + I_{K1} + I_{Na,Ca} + I_{Na,K} + I_{to} + I_{p(Ca)} + I_{Cab} + I_{Nab})$$

Assumption: V is the only variable of interest

Can we construct simpler models?

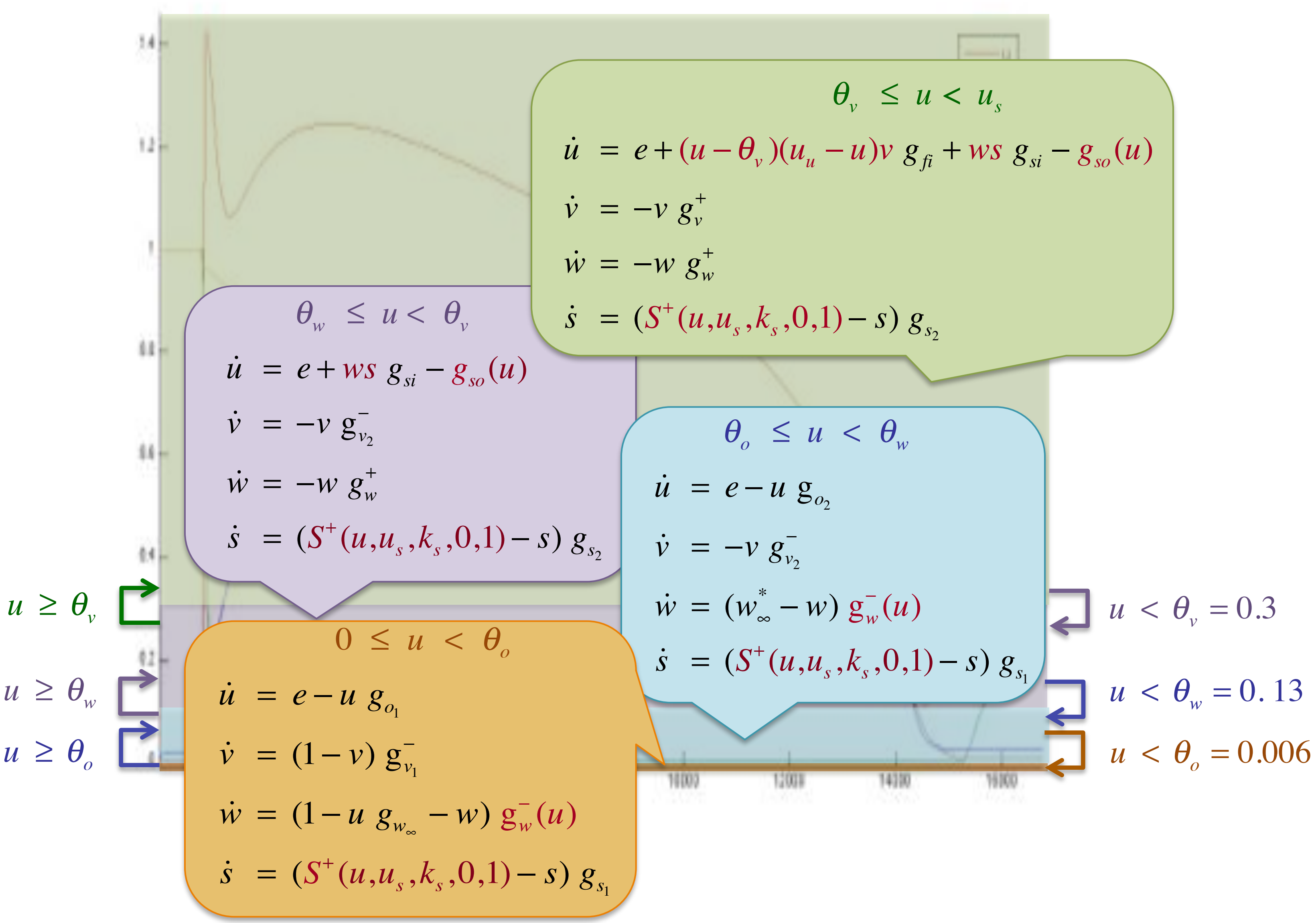
Cellular-Approx: Nonlinear HA-Model



$$\dot{V} = -(I_{fi} + I_{si} + I_{so} + I_{stim})$$

$$u, v, w, s$$

Cellular-Approx: Nonlinear HA-Model



$$\theta_v \leq u < u_s$$

$$\begin{aligned}
\dot{u} &= e + (u - \theta_v)(u_u - u)v\ g_{fi} + ws\ g_{si} - g_{so}(u) \\
\dot{v} &= -v\ g_v^+ \\
\dot{w} &= -w\ g_w^+ \\
\dot{s} &= (S^+(u, u_s, k_s, 0, 1) - s)\ g_{s_2}
\end{aligned}$$

$$\theta_w \leq u < \theta_v$$

$$\begin{aligned}
\dot{u} &= e + ws\ g_{si} - g_{so}(u) \\
\dot{v} &= -v\ g_{v_2}^- \\
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\end{aligned}$$

$$\theta_o \leq u < \theta_w$$

$$\begin{aligned}
\dot{u} &= e - u\ g_{o_2} \\
\dot{v} &= -v\ g_{v_2}^- \\
\dot{w} &= (w_\infty^* - w)\ g_w^-(u) \\
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\end{aligned}$$

$$0 \leq u < \theta_o$$

$$\begin{aligned}
\dot{u} &= e - u\ g_{o_1} \\
\dot{v} &= (1 - v)\ g_{v_1}^- \\
\dot{w} &= (1 - u\ g_{w_\infty} - w)\ g_w^-(u) \\
\dot{s} &= (S^+(u, u_s, k_s, 0, 1) - s)\ g_{s_1}
\end{aligned}$$

$u \geq \theta_v$

$u \geq \theta_w$

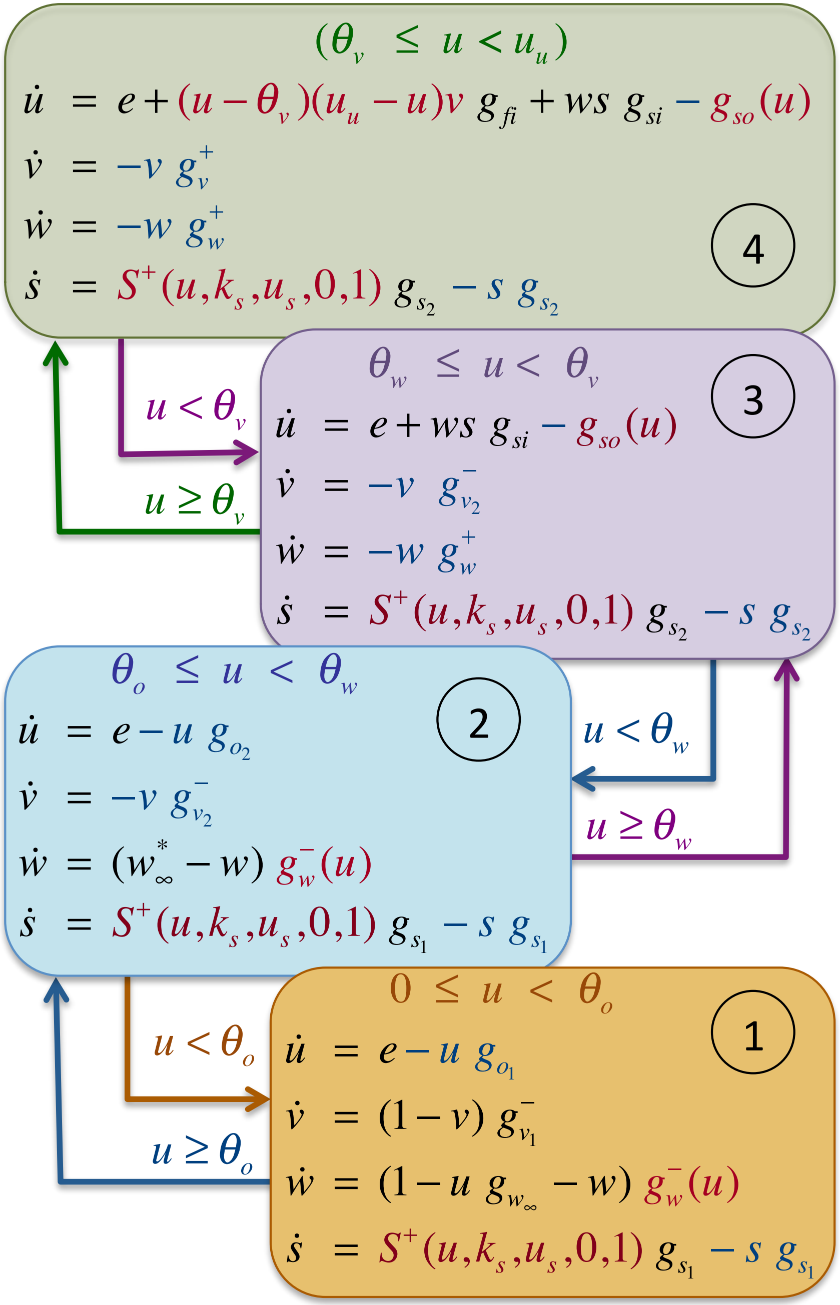
$u \geq \theta_o$

$u < \theta_v = 0.3$

$u < \theta_w = 0.13$

$u < \theta_o = 0.006$

Cellular-Approx: Nonlinear HA-Model



$(\theta_v \leq u < u_u)$

$$\begin{aligned}\dot{u} &= e + (u-\theta_v)(u_u - u)v\, g_{fi} + ws\, g_{si} - g_{so}(u)\\ \dot{v} &= -v\, g_v^+\\ \dot{w} &= -w\, g_w^+\\ \dot{s} &= S^+(u,k_s,u_s,0,1)\, g_{s_2} - s\, g_{s_2}\end{aligned}$$

④

$\theta_w \leq u < \theta_v$

③

$$\begin{aligned}\dot{u} &= e + ws\, g_{si} - g_{so}(u)\\ \dot{v} &= -v\; g_{v_2}^-\\ \dot{w} &= -w\; g_w^+\\ \dot{s} &= S^+(u,k_s,u_s,0,1)\, g_{s_2} - s\, g_{s_2}\end{aligned}$$

$\theta_o \leq u < \theta_w$

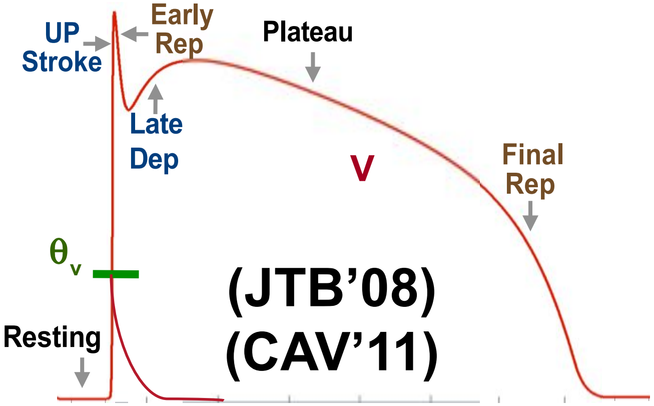
②

$$\begin{aligned}\dot{u} &= e - u\; g_{o_2}\\ \dot{v} &= -v\; g_{v_2}^-\\ \dot{w} &= (w_\infty^* - w)\; g_w^-(u)\\ \dot{s} &= S^+(u,k_s,u_s,0,1)\, g_{s_1} - s\, g_{s_1}\end{aligned}$$

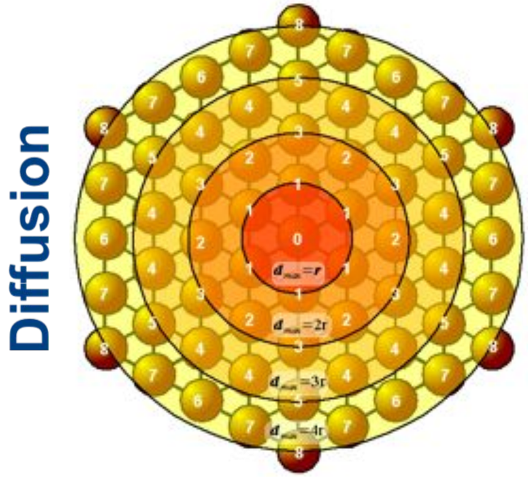
$0 \leq u < \theta_o$

①

$$\begin{aligned}\dot{u} &= e - u\; g_{o_1}\\ \dot{v} &= (1-v)\; g_{v_1}^-\\ \dot{w} &= (1 - u\; g_{w_\infty} - w)\; g_w^-(u)\\ \dot{s} &= S^+(u,k_s,u_s,0,1)\, g_{s_1} - s\, g_{s_1}\end{aligned}$$



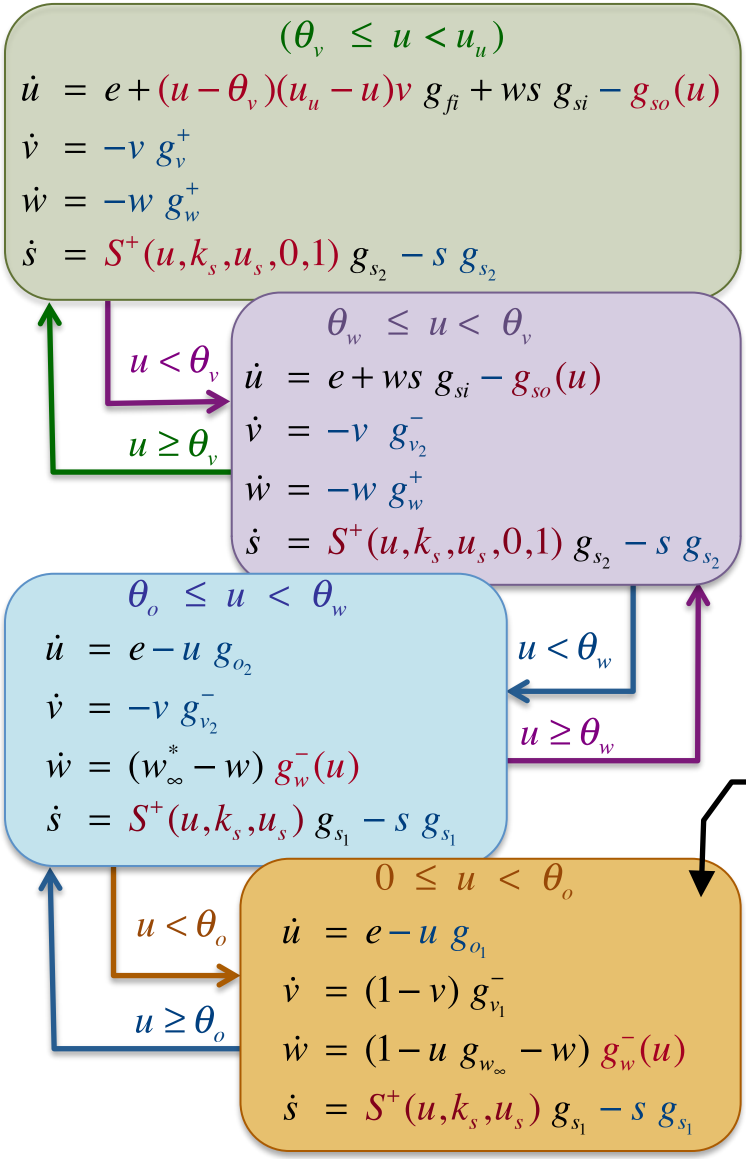
(JTB'08)
(CAV'11)



$$\frac{\partial u}{\partial t} = \nabla(D\nabla u) - (I_{fi} + I_{si} + I_{so})$$

PDEs are simulated as Finite Difference Equations

Cellular-Approx: Multi-Affine HA-Model



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\end{aligned}$$

$\theta_w \ \leq \ u < \ \theta_v$

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$\theta_o \ \leq \ u \ < \ \theta_w$

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\end{aligned}$$

$0 \ \leq \ u \ < \ \theta_o$

$$\begin{aligned}
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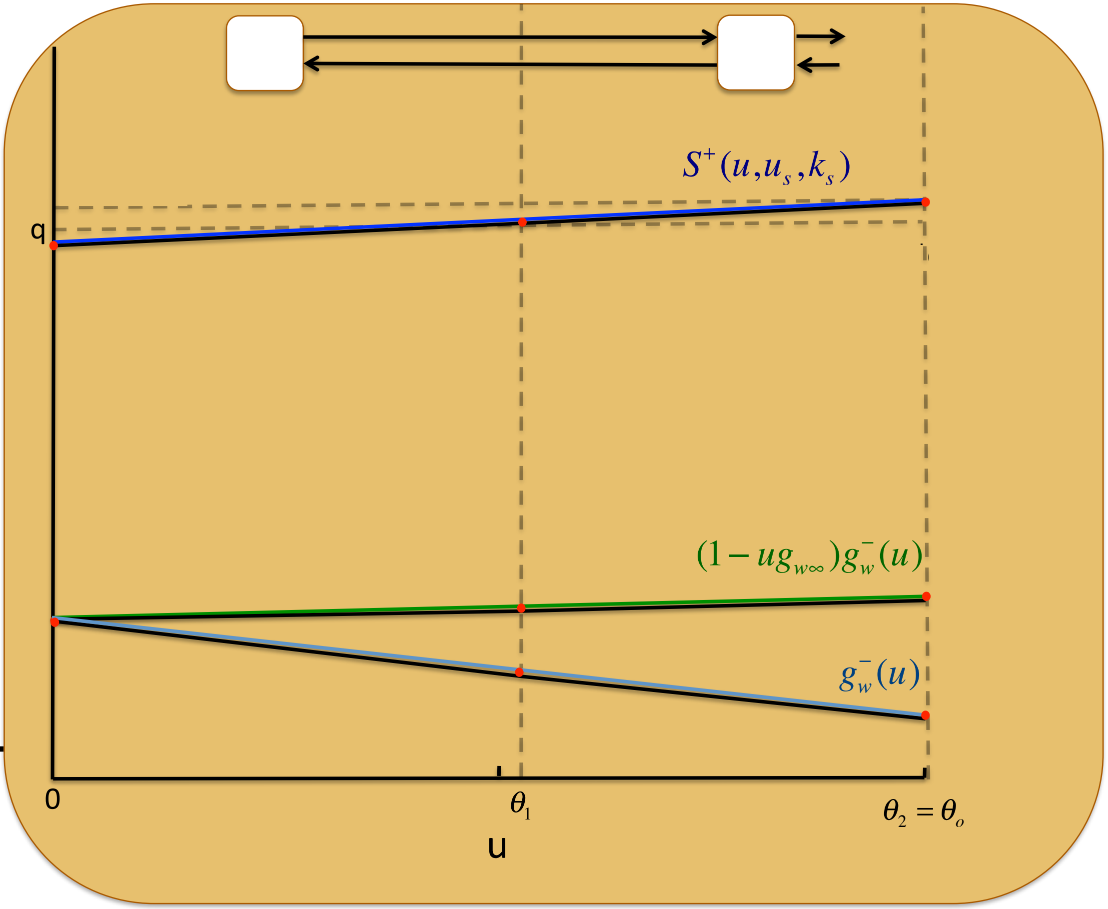
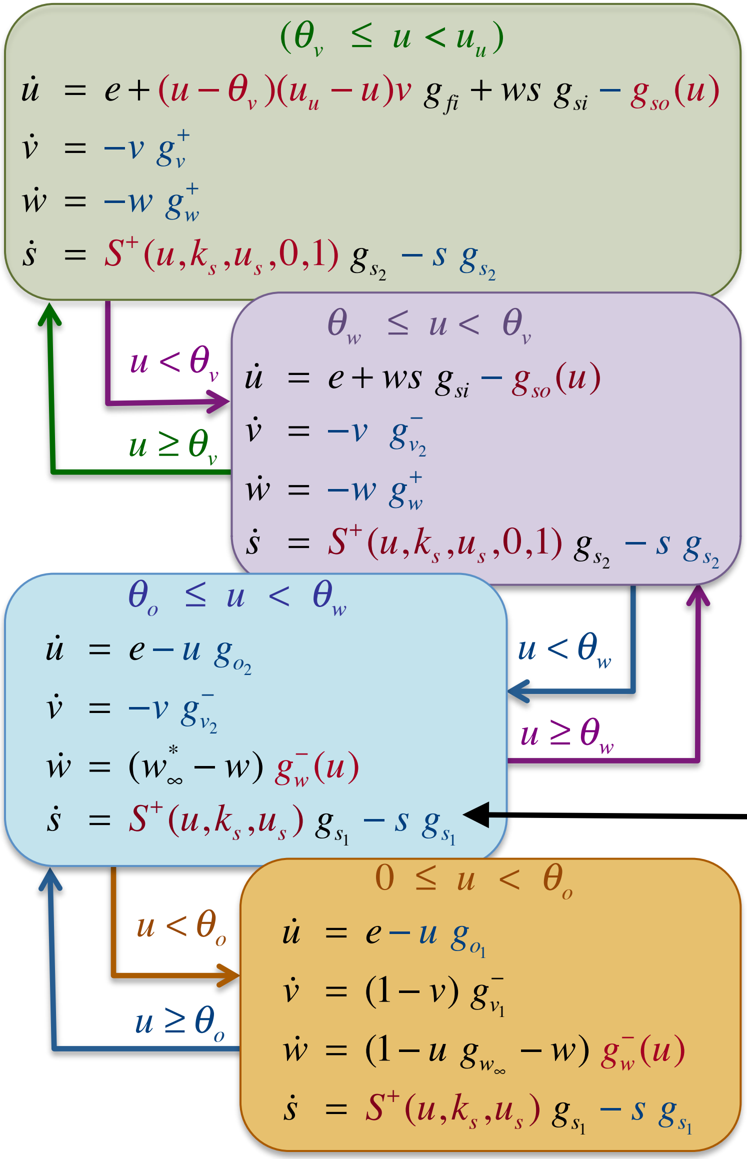


Cellular-Approx: Multi-Affine HA-Model



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\end{aligned}$$

$\theta_o \leq u < \theta_w$

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\dot{s} &= S^+(u, k_s, u_s)\ g_{s_1} - s\ g_{s_1}
\end{aligned}$$

$0 \leq u < \theta_o$

$$\begin{aligned}
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\dot{v} &= (1 - v)\ g_{v_1}^- \\
\dot{w} &= (1 - u\ g_{w_\infty} - w)\ g_w^-(u) \\
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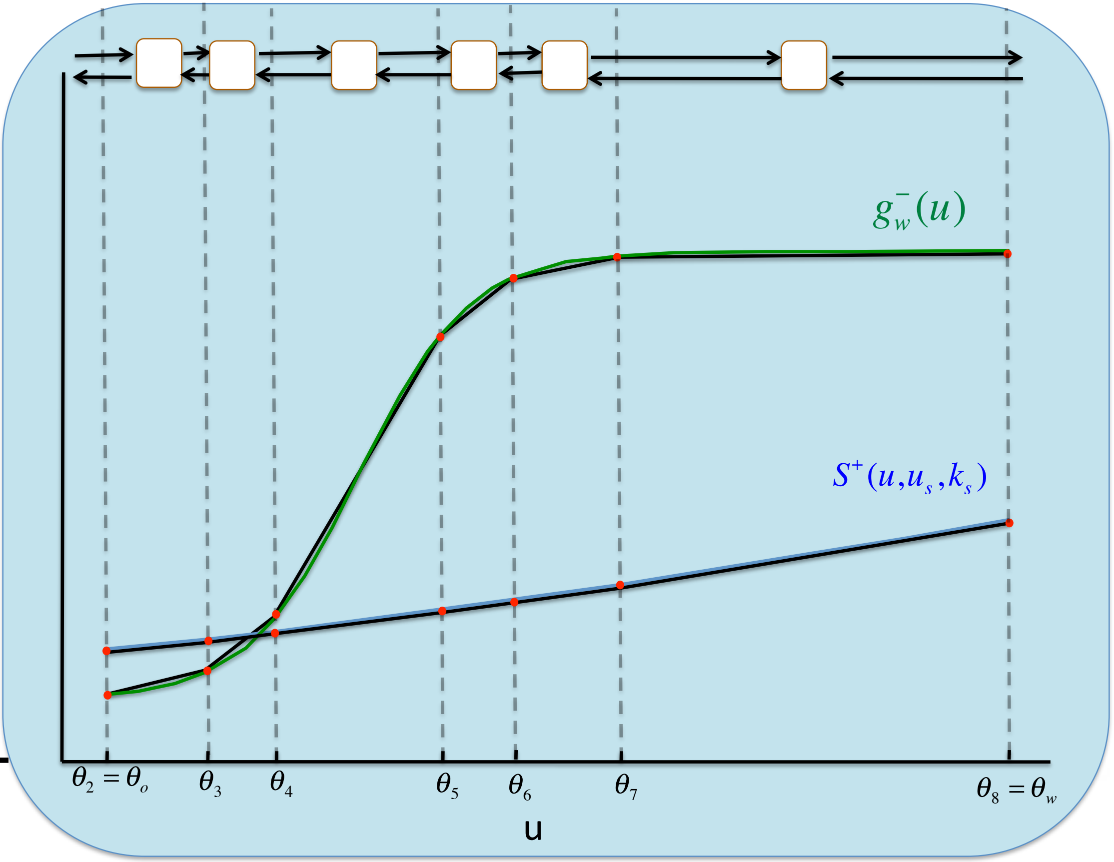

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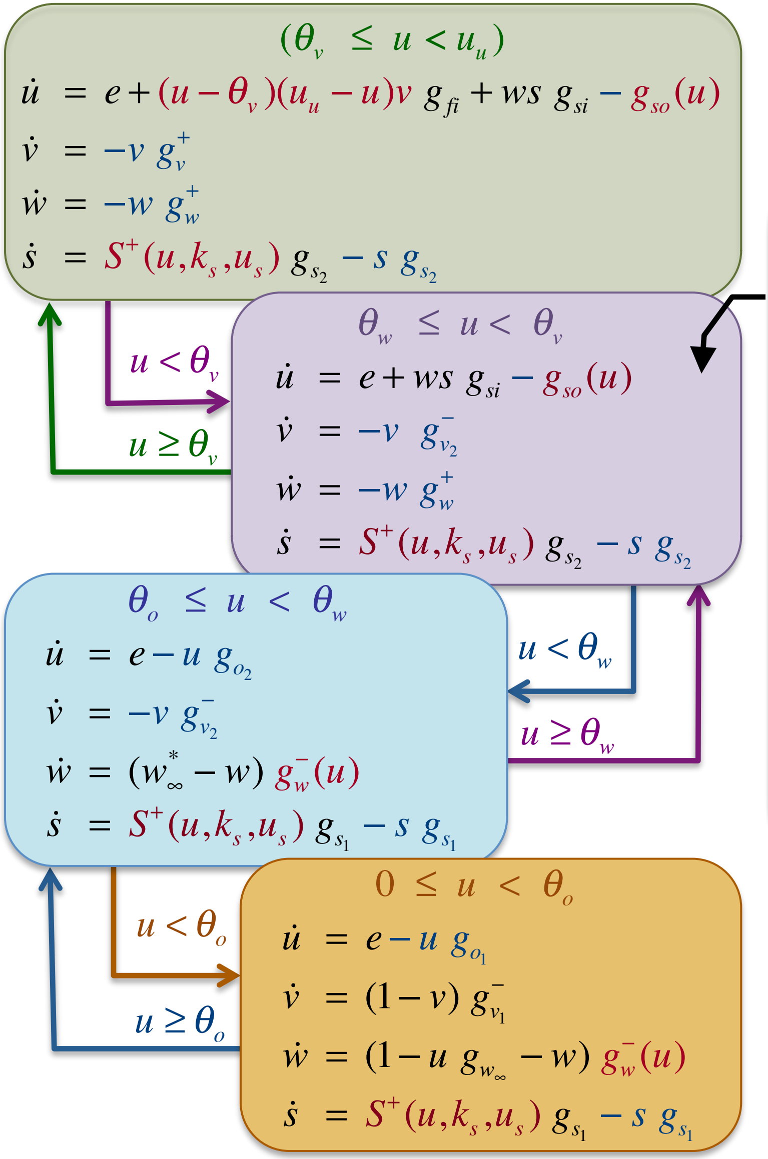

$(\theta_v \;\le\; u < u_u)$

$$\begin{aligned}\dot u &= e + (u-\theta_v)(u_u - u)v\; g_{fi} + ws\; g_{si} - g_{so}(u)\\ \dot v &= -v\; g_v^+\\ \dot w &= -w\; g_w^+\\ \dot s &= S^+(u,k_s,u_s)\; g_{s_2} - s\; g_{s_2}\end{aligned}$$

$u < \theta_v$

$u \ge \theta_v$

$\theta_w \;\le\; u < \;\theta_v$

$$\begin{aligned}\dot u &= e + ws\; g_{si} - g_{so}(u)\\ \dot v &= -v\;\; g_{v_2}^-\\ \dot w &= -w\; g_w^+\\ \dot s &= S^+(u,k_s,u_s)\; g_{s_2} - s\; g_{s_2}\end{aligned}$$

$u < \theta_w$

$u \ge \theta_w$

$\theta_o \;\le\; u \;<\; \theta_w$

$$\begin{aligned}\dot u &= e - u\; g_{o_2}\\ \dot v &= -v\; g_{v_2}^-\\ \dot w &= (w_\infty^* - w)\; g_w^-(u)\\ \dot s &= S^+(u,k_s,u_s)\; g_{s_1} - s\; g_{s_1}\end{aligned}$$

$u < \theta_o$

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$0 \;\le\; u \;<\; \theta_o$

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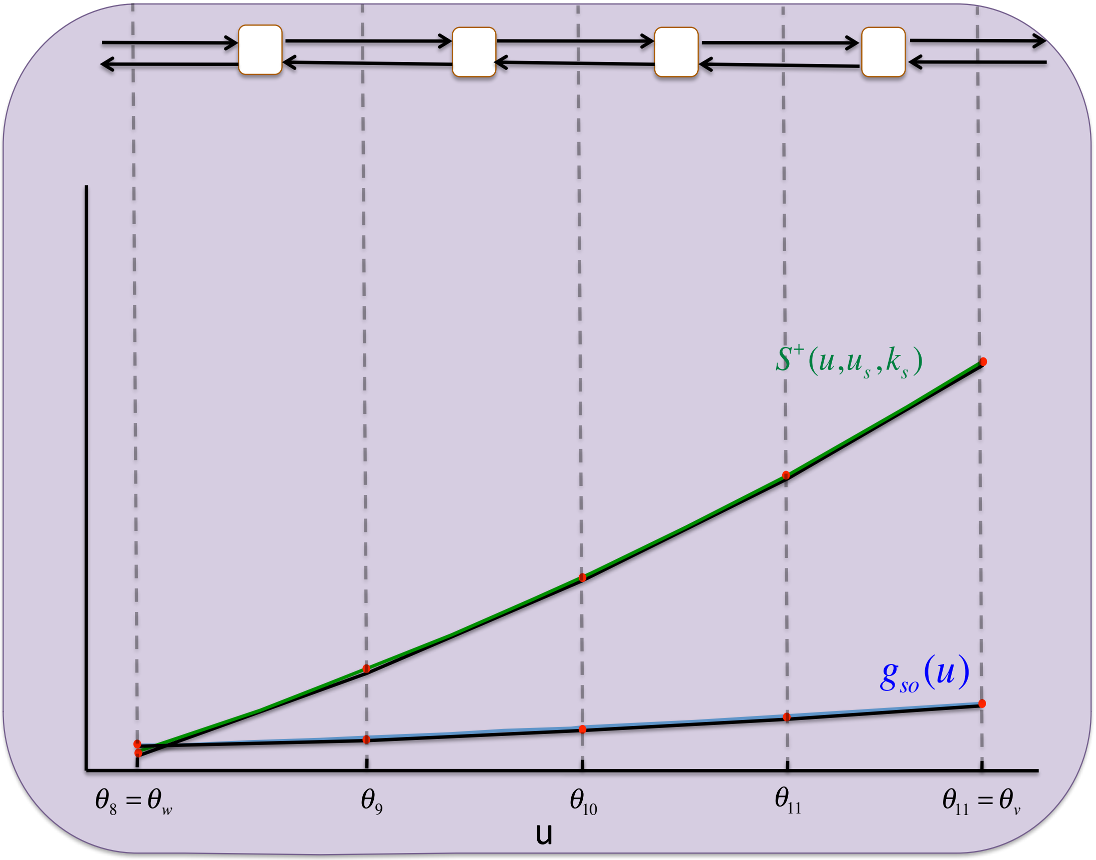

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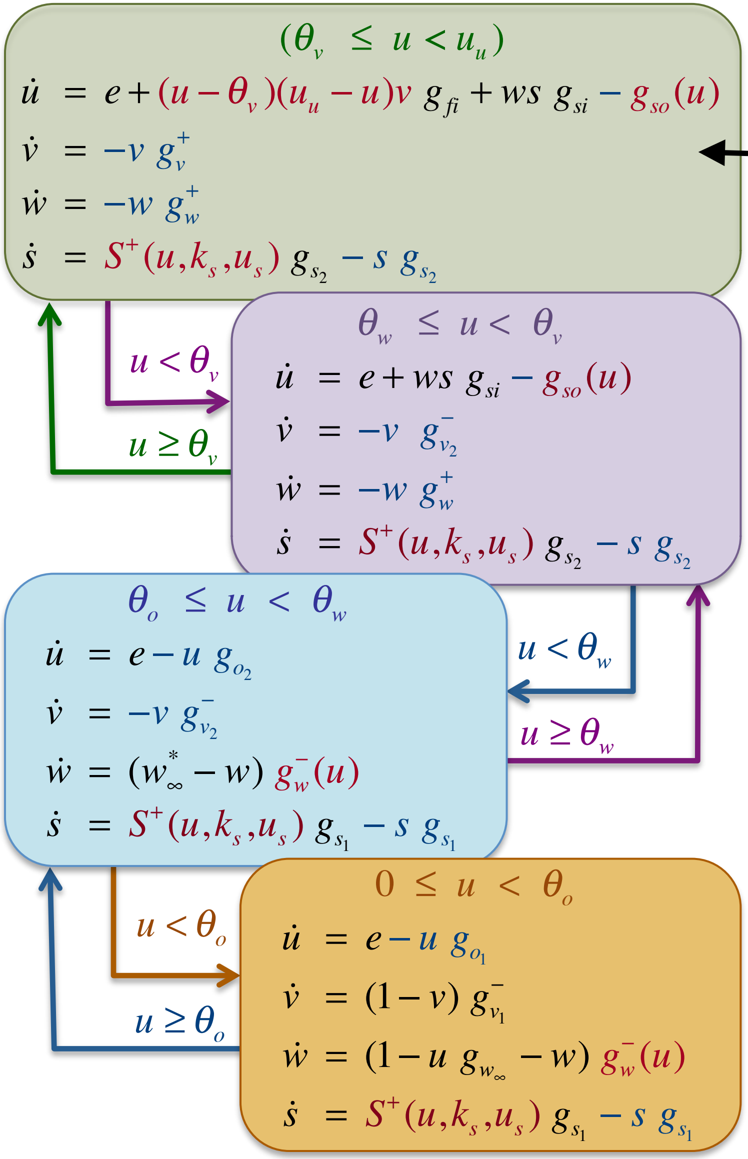

$$(\theta_v \le u < u_u)$$

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$u < \theta_v$

$u \ge \theta_v$

$$\theta_w \le u < \theta_v$$

$$\begin{aligned}\dot{u} &= e + ws\ g_{si} - g_{so}(u)\\ \dot{v} &= -v\ g_{v_2}^-\\ \dot{w} &= -w\ g_w^+\\ \dot{s} &= S^+(u,k_s,u_s)\ g_{s_2} - s\ g_{s_2}\end{aligned}$$

$u < \theta_w$

$u \ge \theta_w$

$$\theta_o \le u < \theta_w$$

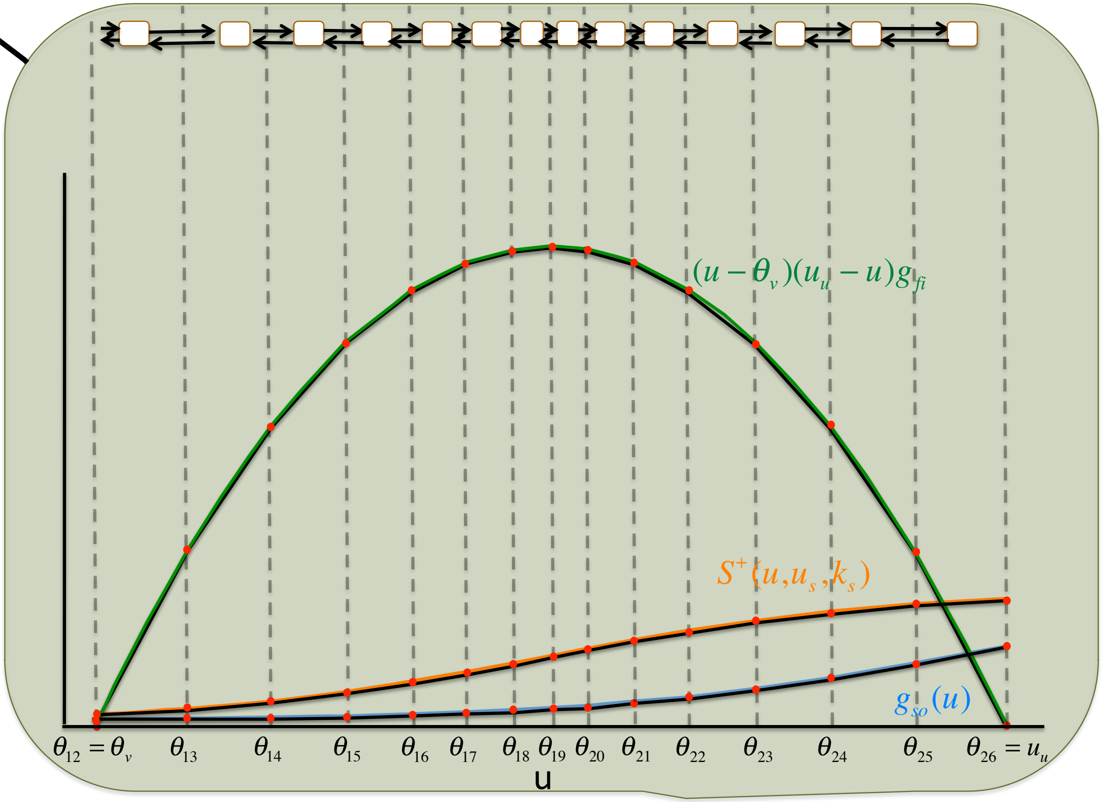
$$\begin{aligned}\dot{u} &= e - u\ g_{o_2}\\ \dot{v} &= -v\ g_{v_2}^-\\ \dot{w} &= (w_\infty^* - w)\ g_w^-(u)\\ \dot{s} &= S^+(u,k_s,u_s)\ g_{s_1} - s\ g_{s_1}\end{aligned}$$

$u < \theta_o$

$u \ge \theta_o$

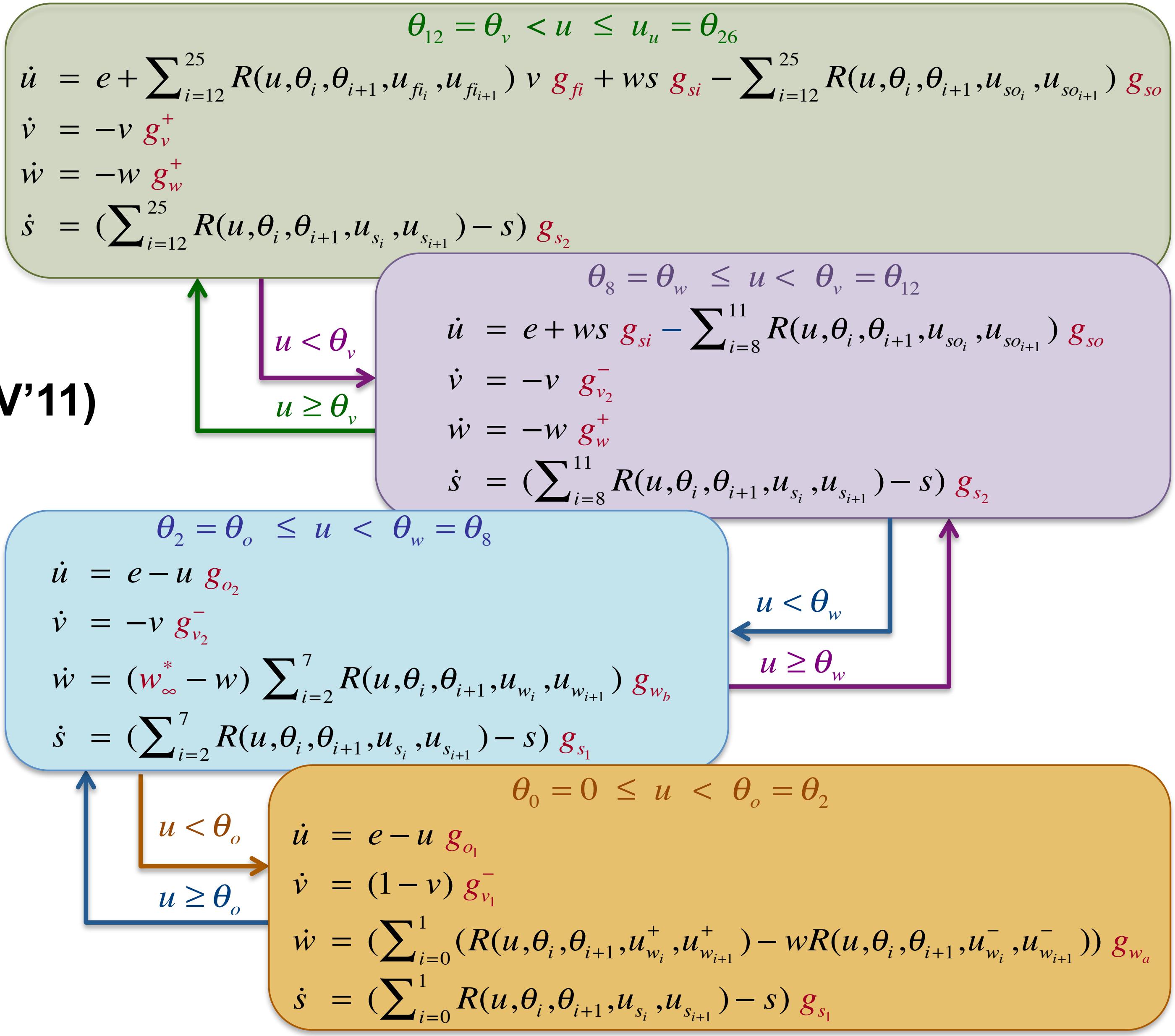
$$0 \le u < \theta_o$$

$$\begin{aligned}\dot{u} &= e - u\ g_{o_1}\\ \dot{v} &= (1-v)\ g_{v_1}^-\\ \dot{w} &= (1 - u\ g_{w_\infty} - w)\ g_w^-(u)\\ \dot{s} &= S^+(u,k_s,u_s)\ g_{s_1} - s\ g_{s_1}\end{aligned}$$



Cellular-Approx: Multi-Affine HA-Model

(CAV’11)



$$\theta_{12} = \theta_v < u \leq u_u = \theta_{26}$$

$$\begin{aligned}
\dot{u} &= e + \sum_{i=12}^{25} R(u,\theta_i,\theta_{i+1},u_{fi_i},u_{fi_{i+1}})\ v\ g_{fi} + ws\ g_{si} - \sum_{i=12}^{25} R(u,\theta_i,\theta_{i+1},u_{so_i},u_{so_{i+1}})\ g_{so} \\
\dot{v} &= -v\ g_v^+ \\
\dot{w} &= -w\ g_w^+ \\
\dot{s} &= (\sum_{i=12}^{25} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s)\ g_{s_2}
\end{aligned}$$

$$\theta_8 = \theta_w \leq u < \theta_v = \theta_{12}$$

$$\begin{aligned}
\dot{u} &= e + ws\ g_{si} - \sum_{i=8}^{11} R(u,\theta_i,\theta_{i+1},u_{so_i},u_{so_{i+1}})\ g_{so} \\
\dot{v} &= -v\ g_{v_2}^- \\
\dot{w} &= -w\ g_w^+ \\
\dot{s} &= (\sum_{i=8}^{11} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s)\ g_{s_2}
\end{aligned}$$

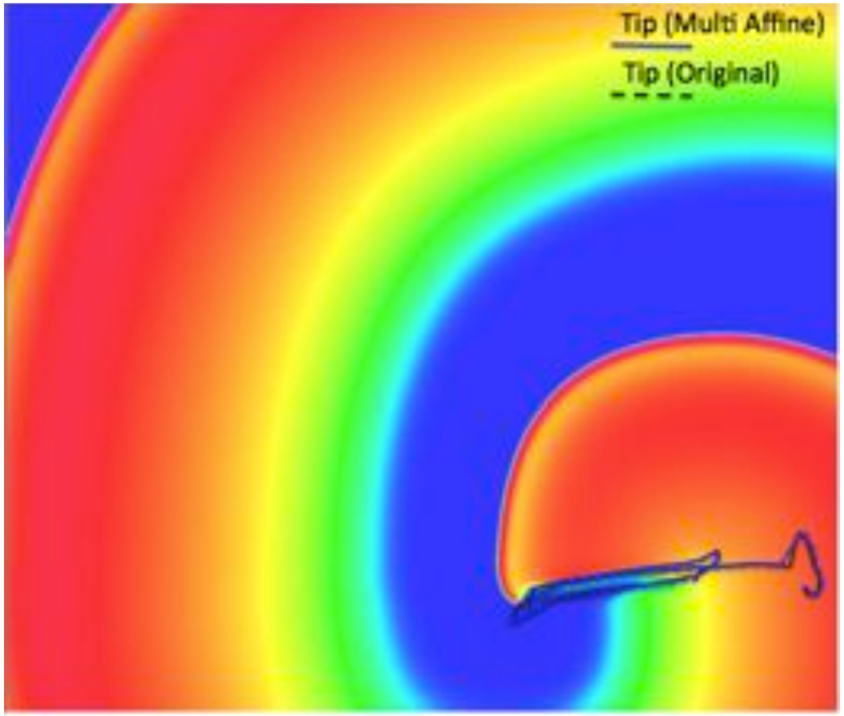
$$\theta_2 = \theta_o \leq u < \theta_w = \theta_8$$

$$\begin{aligned}
\dot{u} &= e - u\ g_{o_2} \\
\dot{v} &= -v\ g_{v_2}^- \\
\dot{w} &= (w_\infty^* - w) \sum_{i=2}^{7} R(u,\theta_i,\theta_{i+1},u_{w_i},u_{w_{i+1}})\ g_{w_b} \\
\dot{s} &= (\sum_{i=2}^{7} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s)\ g_{s_1}
\end{aligned}$$

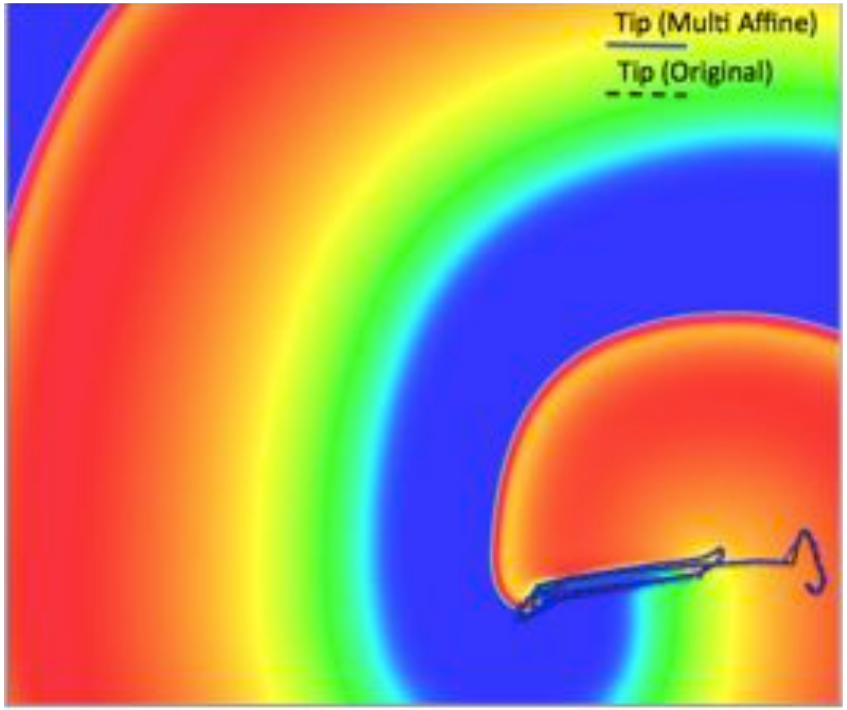
$$\theta_0 = 0 \leq u < \theta_o = \theta_2$$

$$\begin{aligned}
\dot{u} &= e - u\ g_{o_1} \\
\dot{v} &= (1 - v)\ g_{v_1}^- \\
\dot{w} &= (\sum_{i=0}^{1} (R(u,\theta_i,\theta_{i+1},u_{w_i}^+,u_{w_{i+1}}^+) - wR(u,\theta_i,\theta_{i+1},u_{w_i}^-,u_{w_{i+1}}^-))\ g_{w_a} \\
\dot{s} &= (\sum_{i=0}^{1} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s)\ g_{s_1}
\end{aligned}$$

Nonlinear vs Multi-Affine HA Model

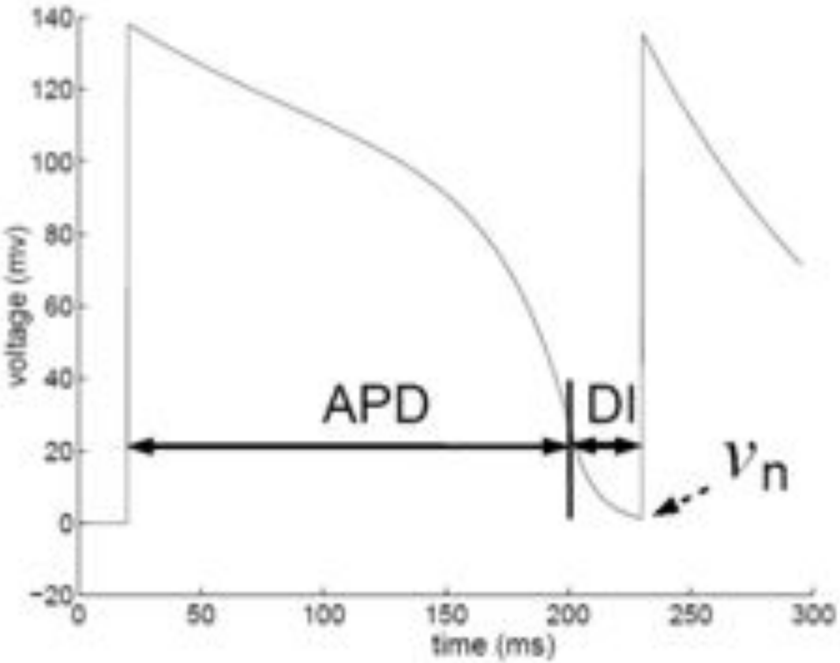


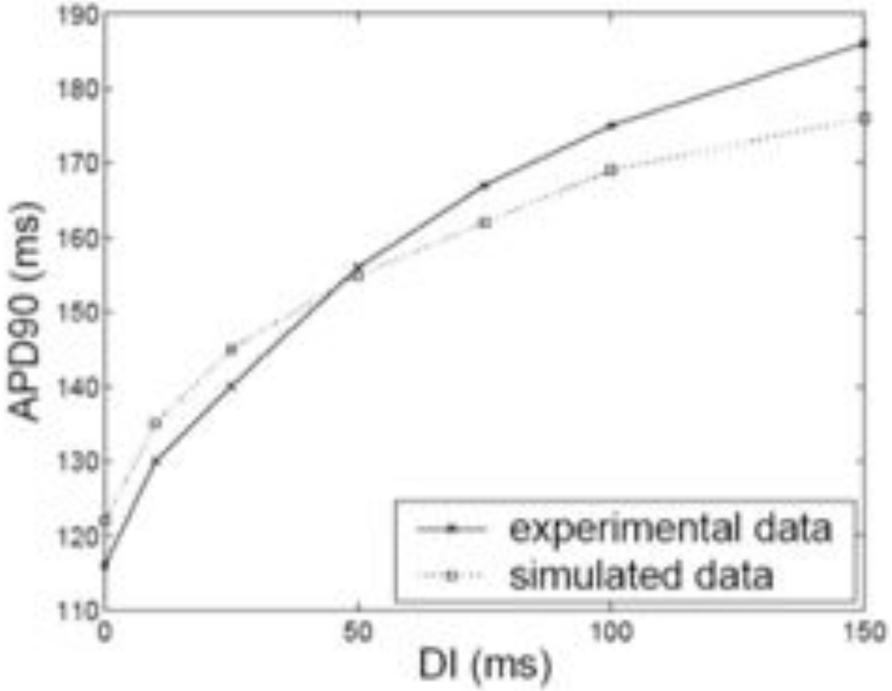
(a) Original MRM



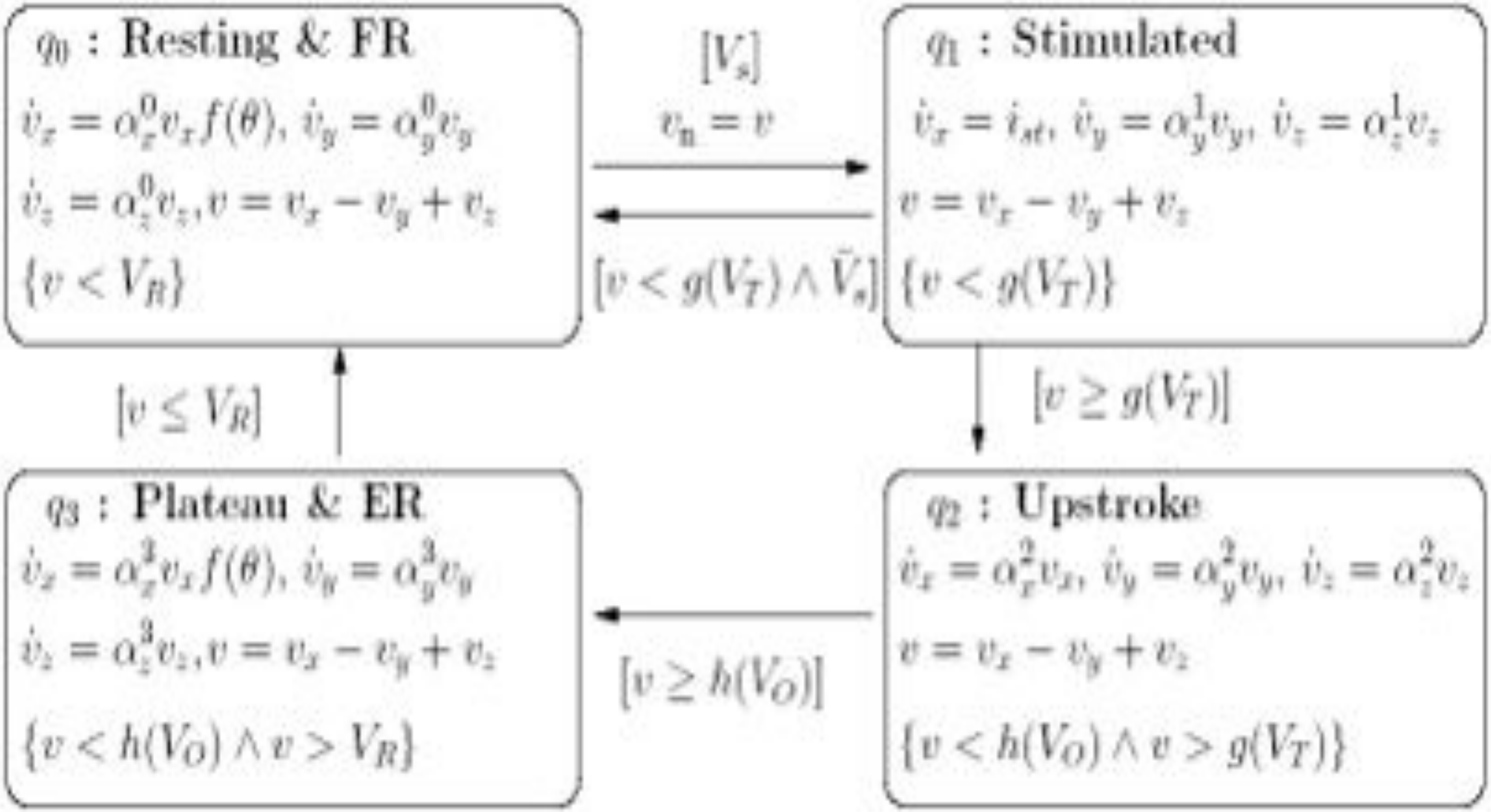
(b) Multi Affine (26 ramps)

Cellular-Approx: Restitution



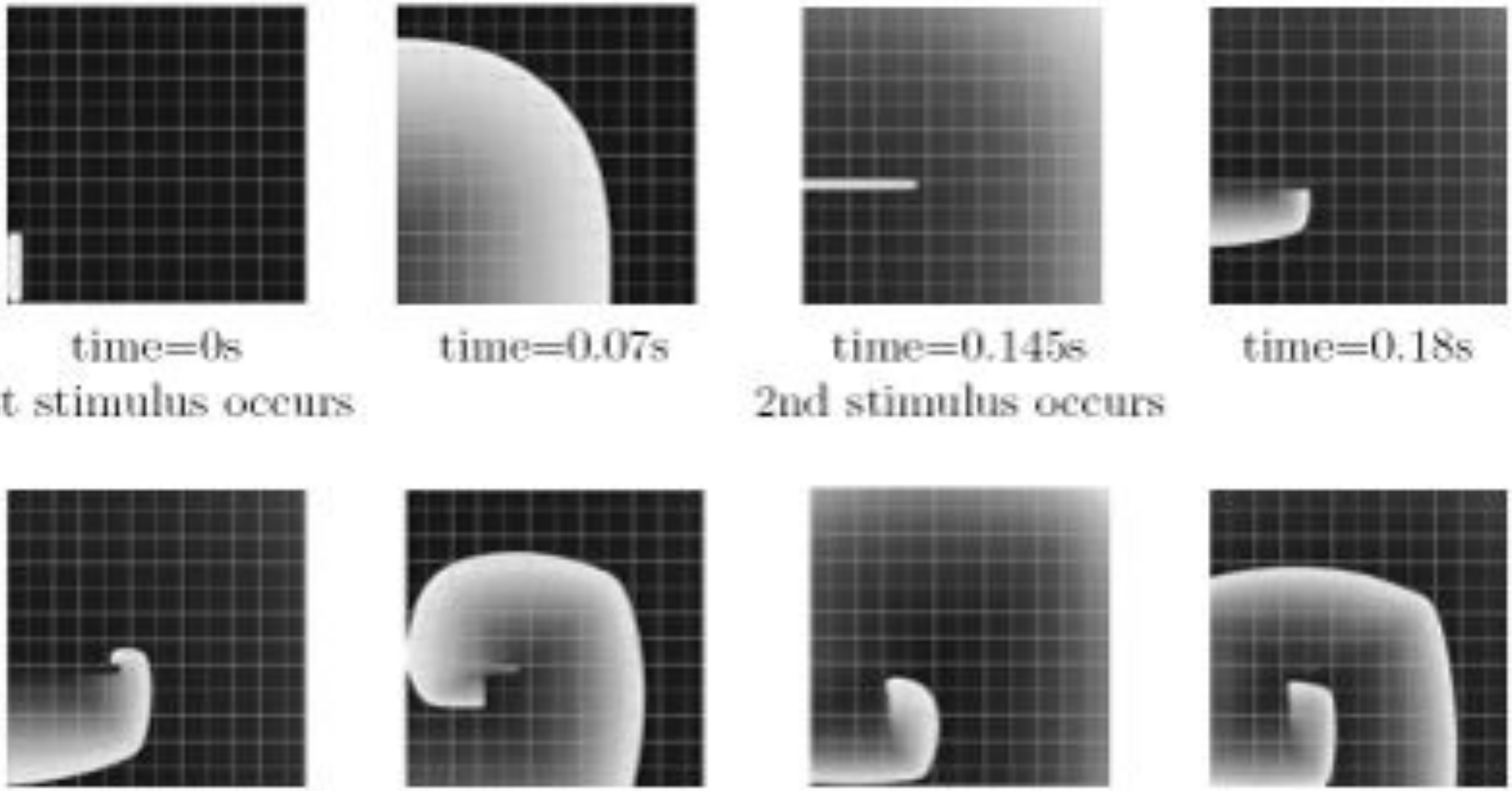


Cellular-Approx: Cycle-Linear HA-Model



(CMSB’05)

Cellular-Approx: Cycle-Linear HA-Model



time=0s
1st stimulus occurs

time=0.07s

time=0.145s
2nd stimulus occurs

time=0.18s

time=0.21s

time=0.27s

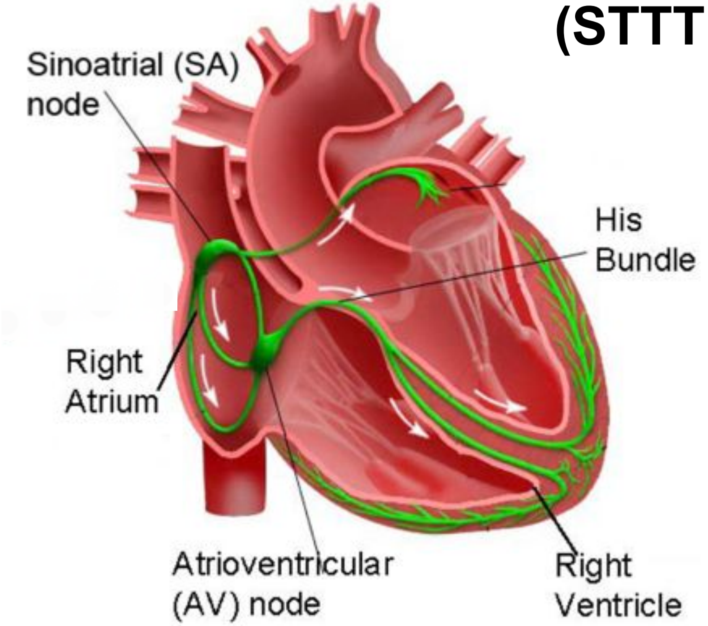
time=0.34s

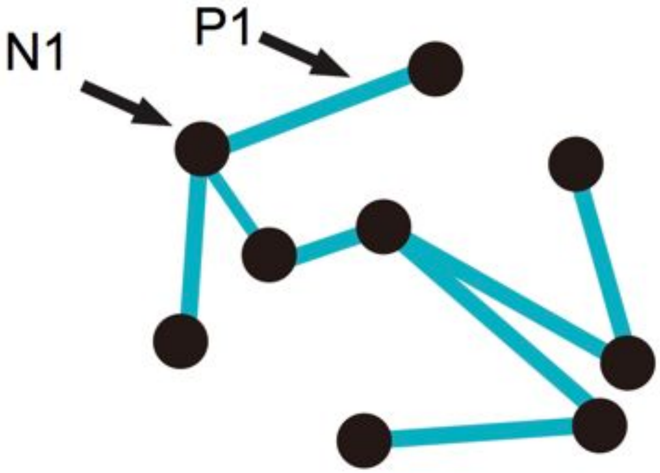
time=0.55s

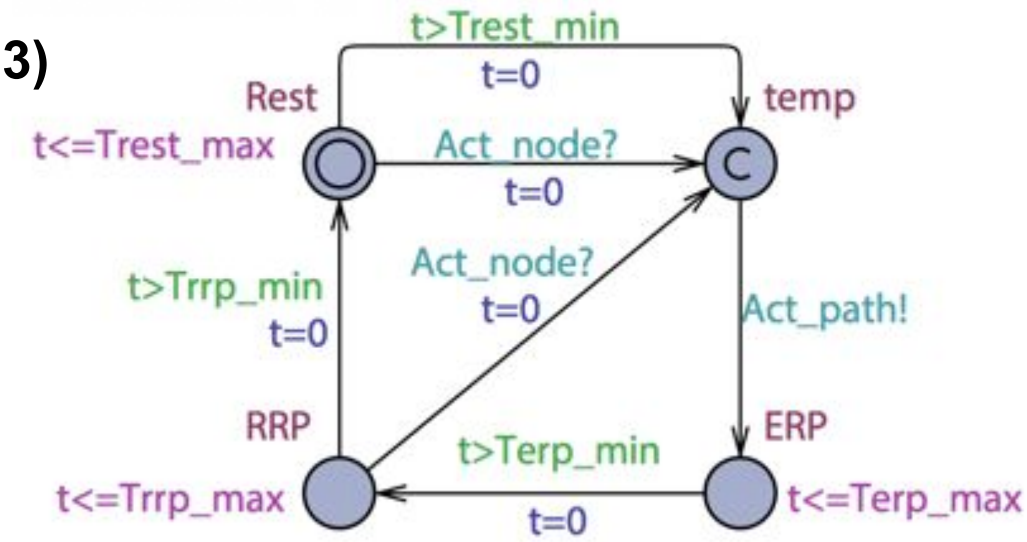
(CMSB’05)

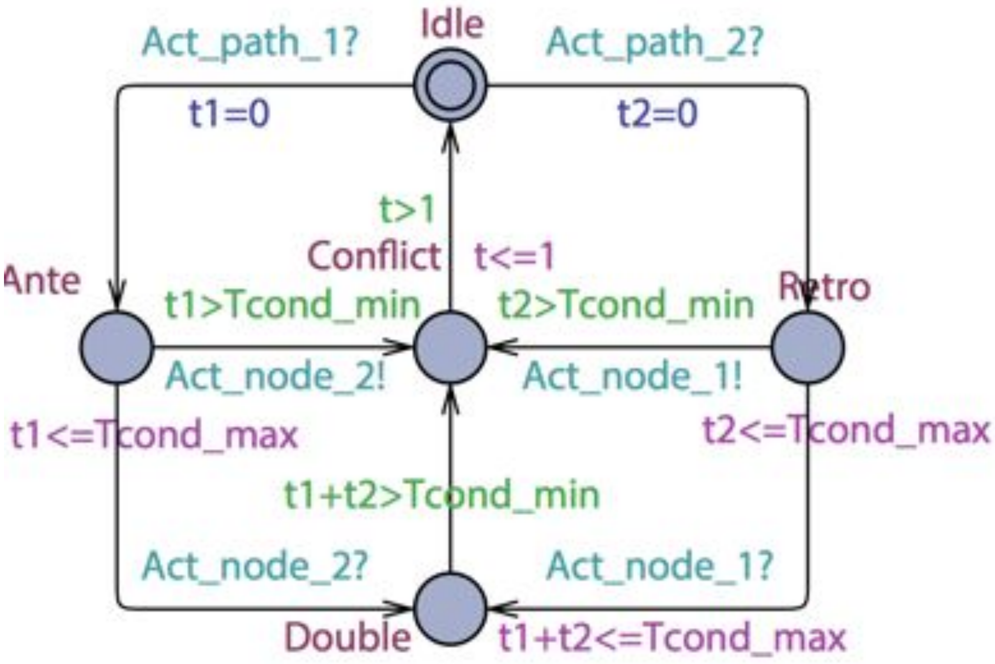
Cellular-Approx: Timed-Automata

(STTT'13)



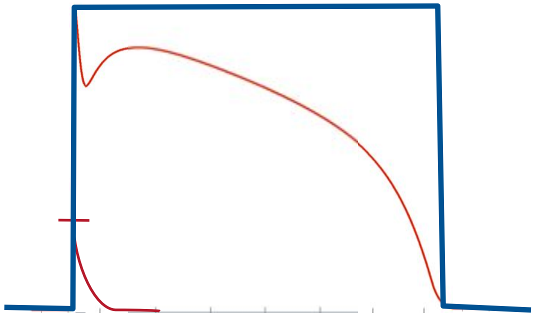




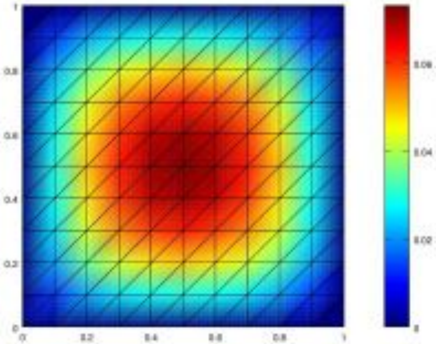


Cellular Approx: Cellular-Automata

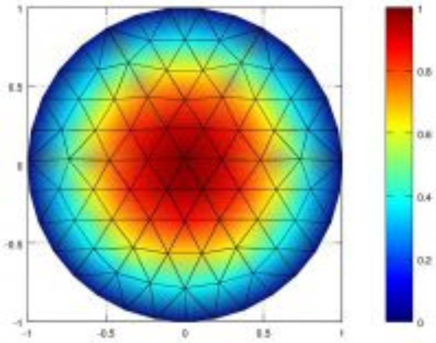
– **Waves take the form of lattice!** Curvature, velocity,..



Action Potential

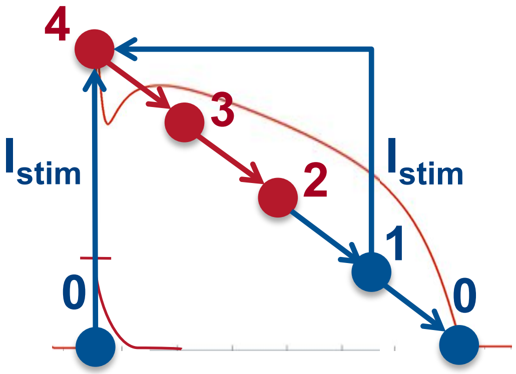


Square Wave

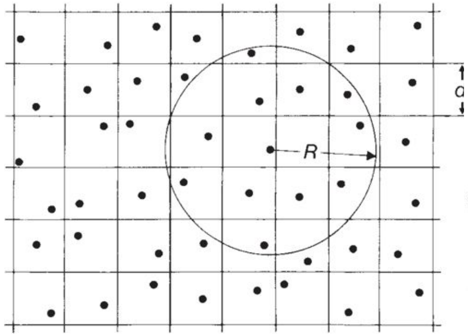


Hexagonal Wave

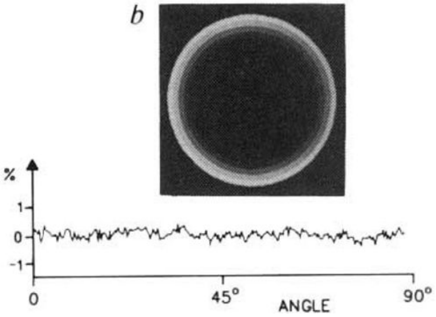
– **Recent approach:** Preserves most wave properties



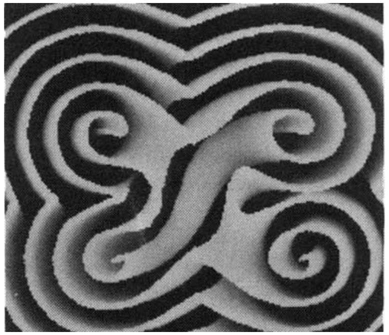
Action Potential



Random Grid

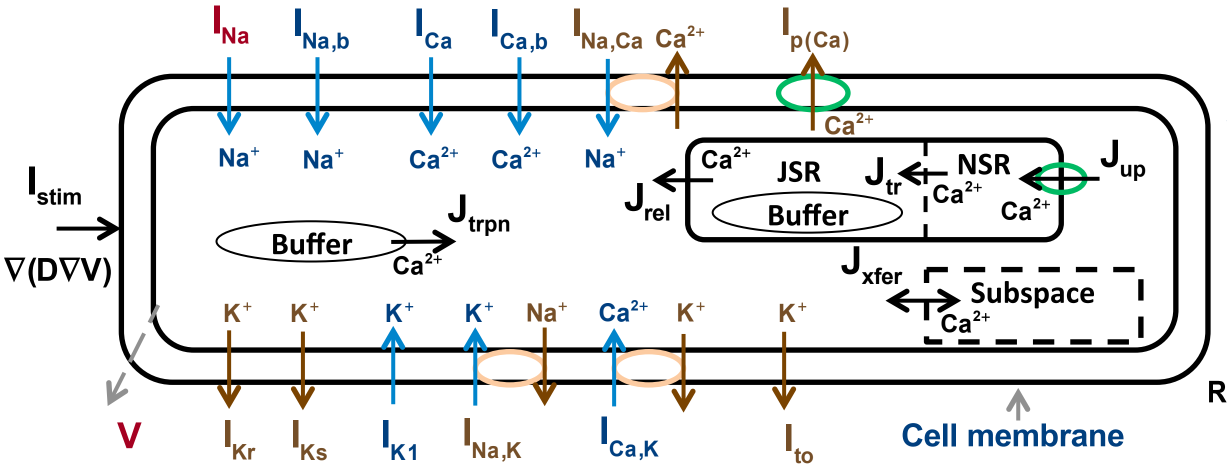


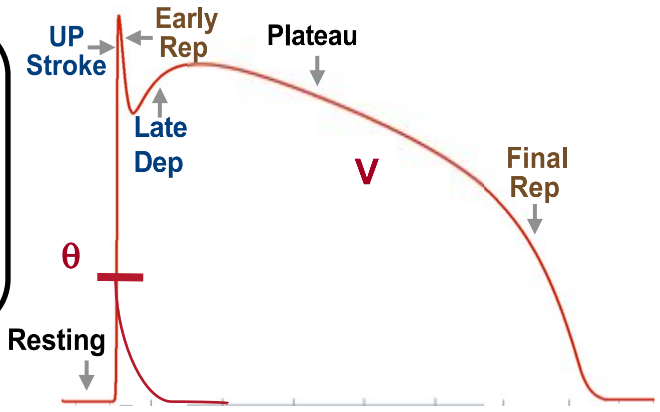
Isotropy



3D Wave

Cellular Approximation Challenge





The 67-variable IMW myocyte model **Myocyte Action Potential**

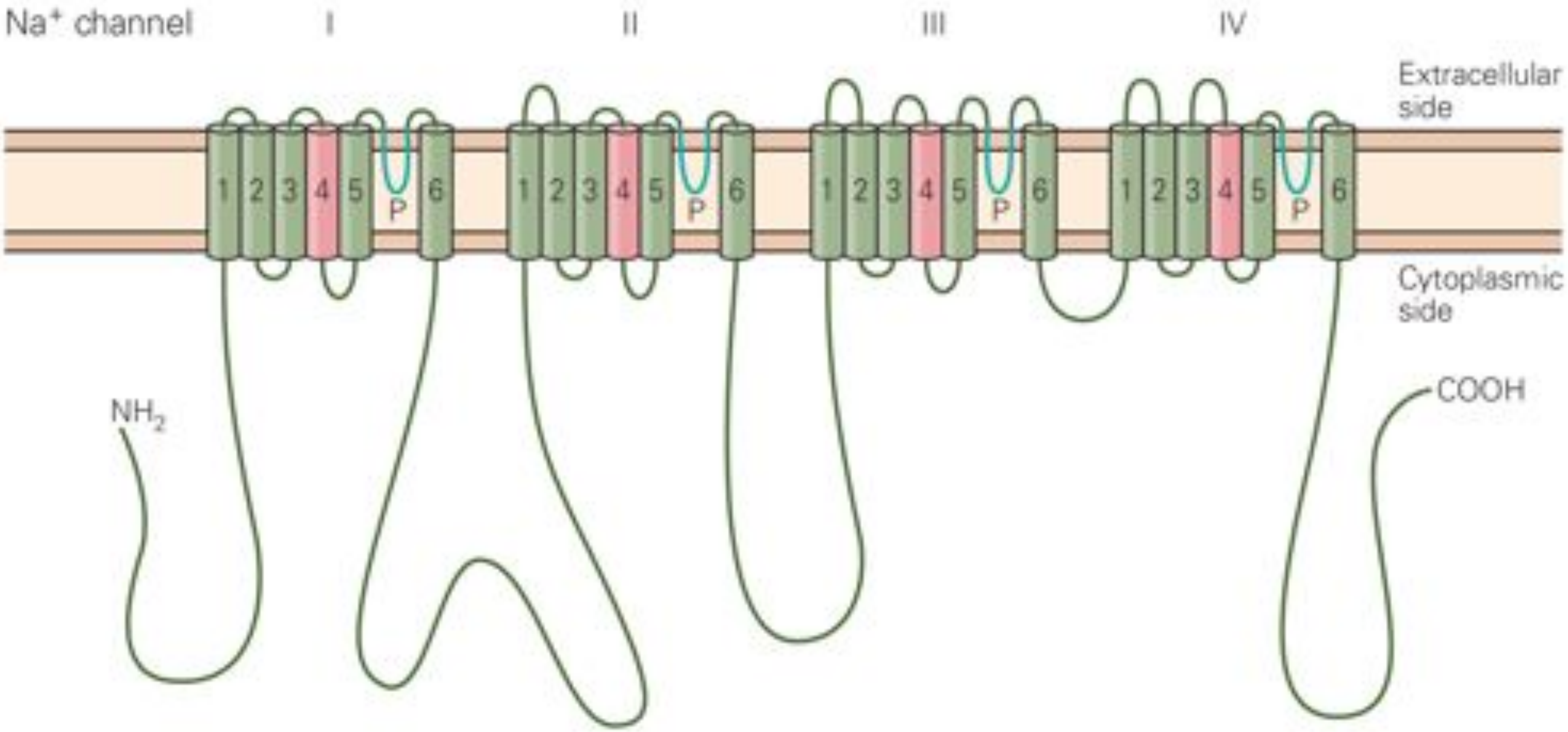
$$\frac{\partial V}{\partial t} = -(\nabla(D\nabla V) + I_{Na} + I_{Ca} + I_{Ca,K} + I_{Kr} + I_{Ks} + I_{K1} + I_{Na,Ca} + I_{Na,K} + I_{to} + I_{p(Ca)} + I_{Cab} + I_{Nab})$$

Assumption: V is the only variable of interest

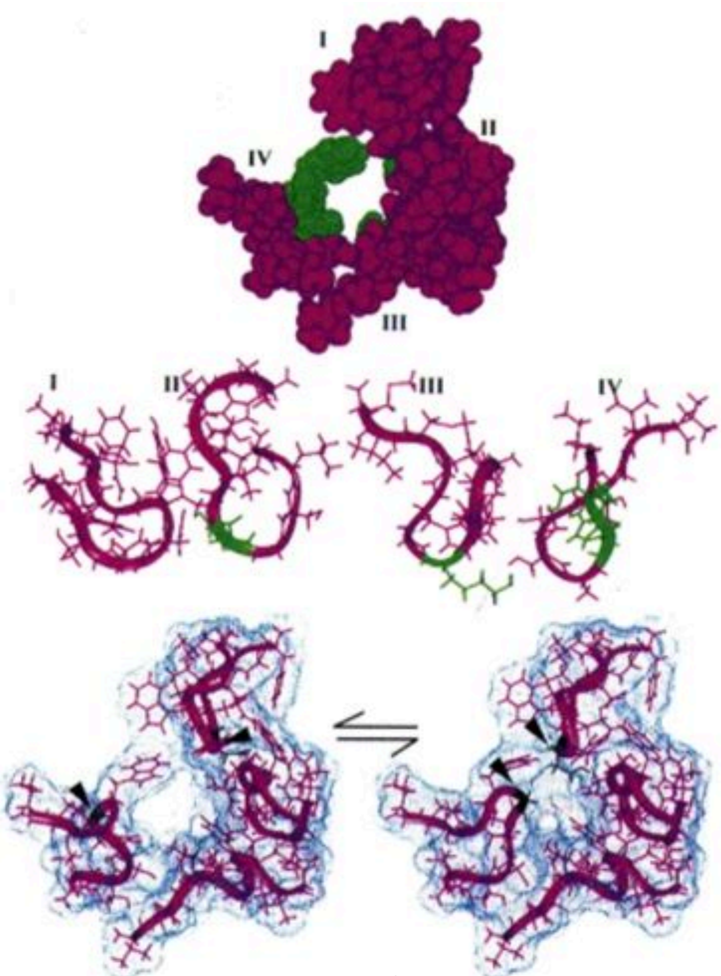
Question: Is there a systematic way to approximate the model?

Idea: Approximate each channel at a time

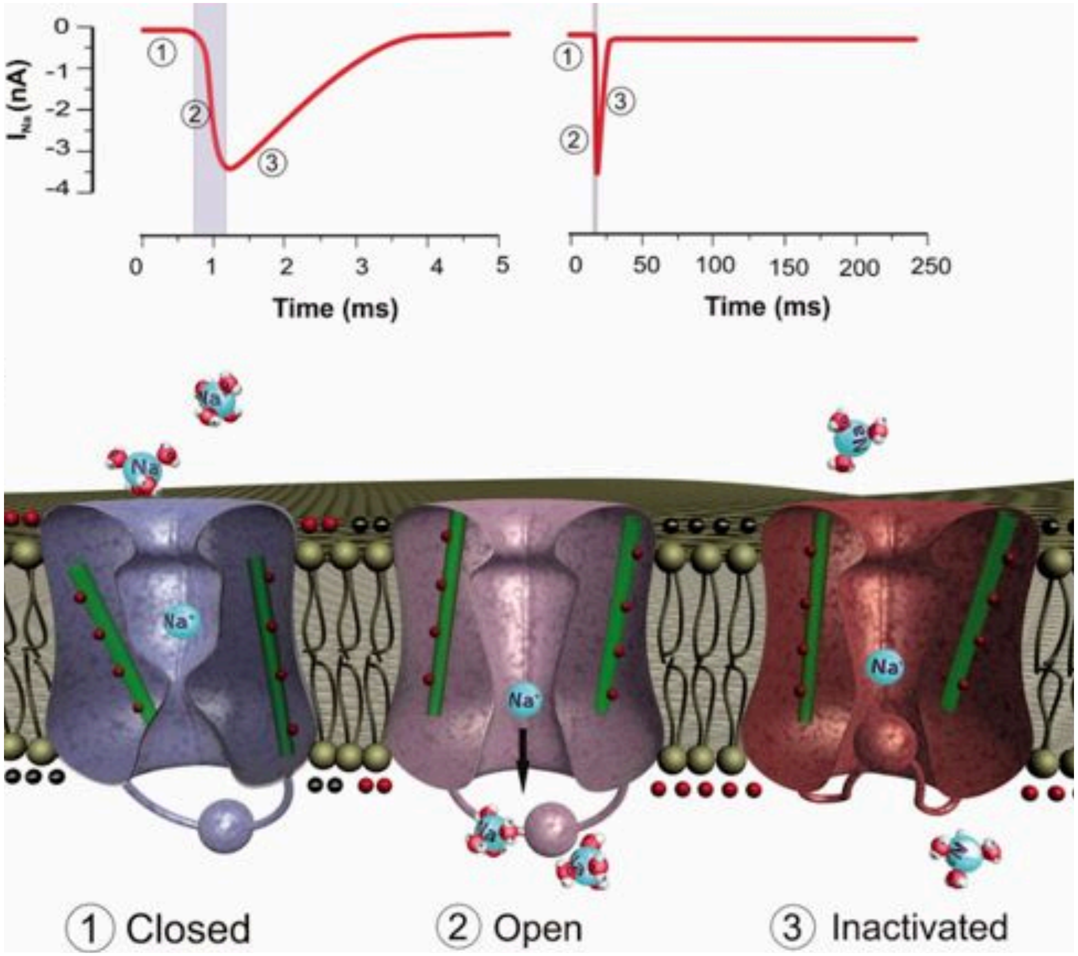
Channel Approximation: Na$^+$ Channel



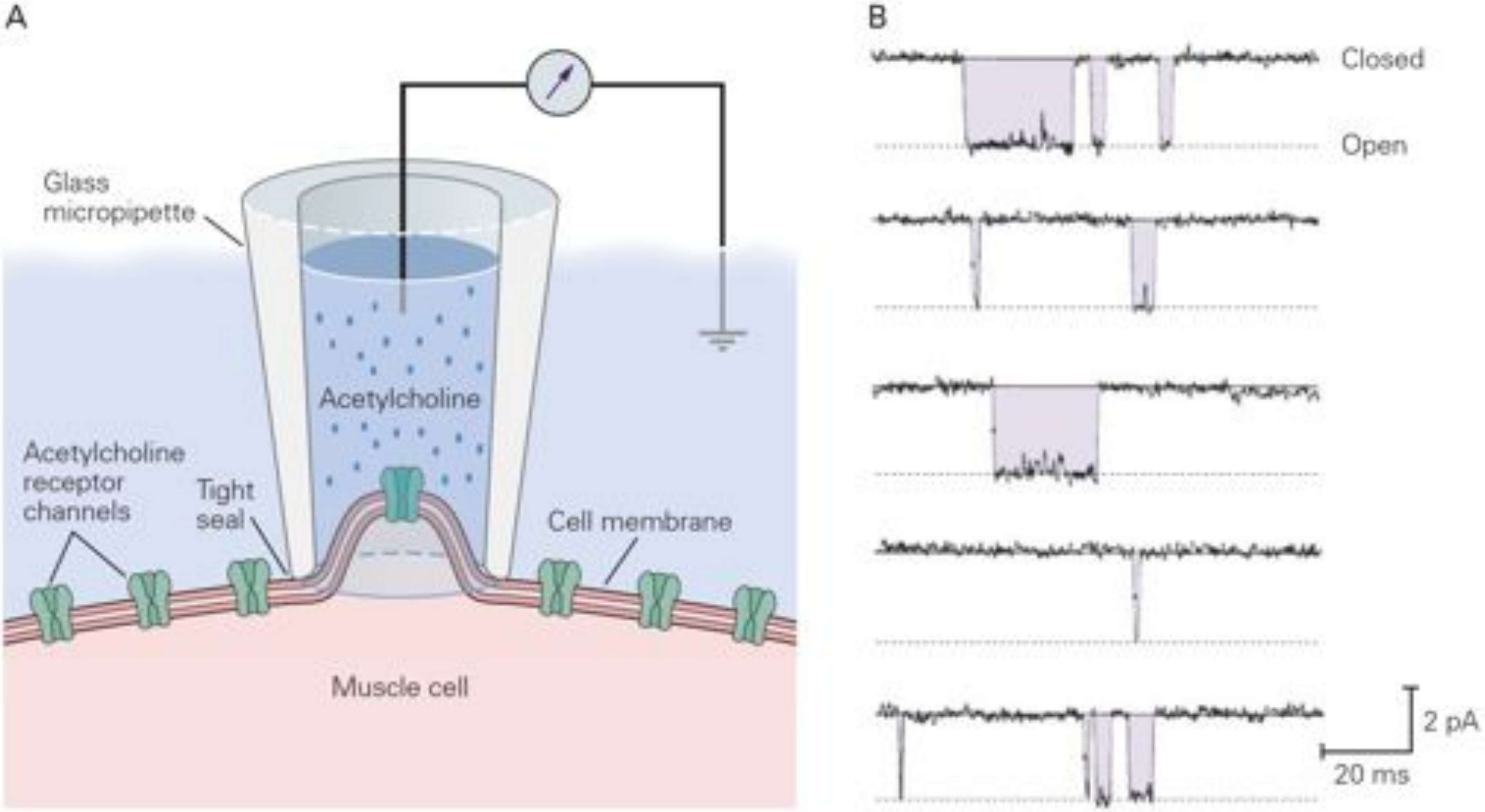
Channel Approximation: Na⁺ Channel



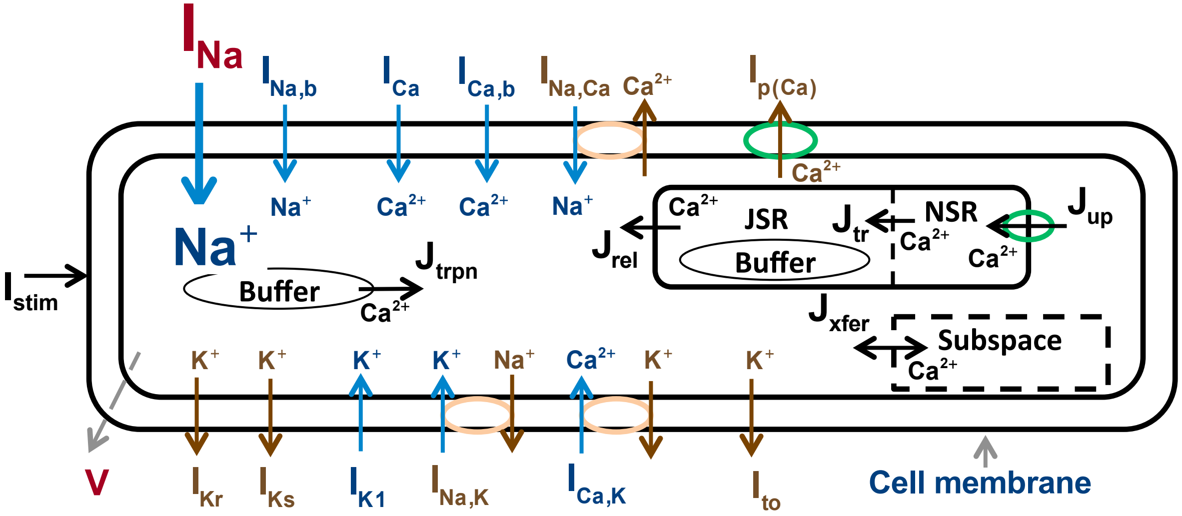
Top view



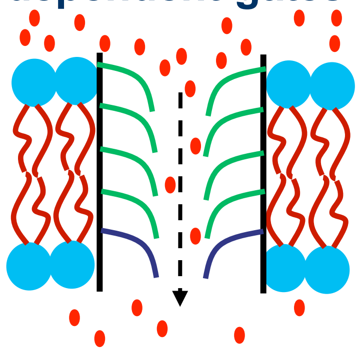
Channel Approximation: Patch-Clamp



Channel Approx: IMW Model

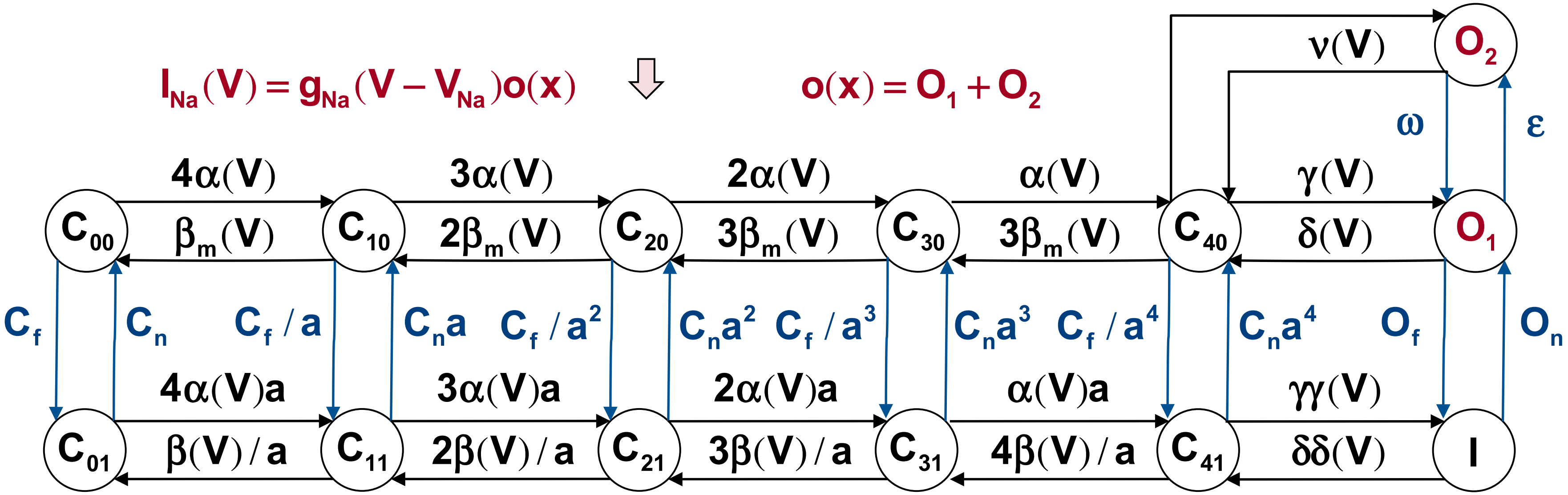


dependent gates



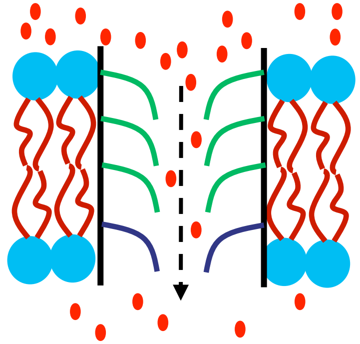
12-States CT-MDP

$$I_{Na}(V) = g_{Na}(V - V_{Na})o(x) \qquad o(x) = O_1 + O_2$$

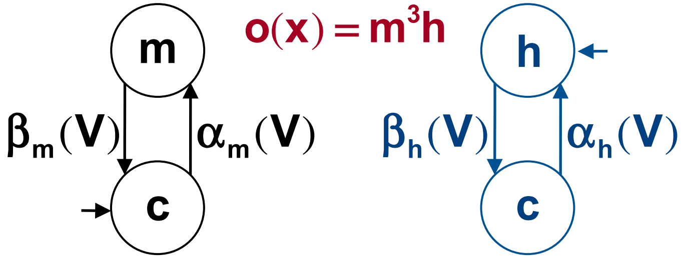


$$\dot{C}_{01} = C_f C_{00} + \beta(V) C_{11} / a - (C_n + 4\alpha(V)a) C_{01}$$

Channel Approx: HH-Na-Channel



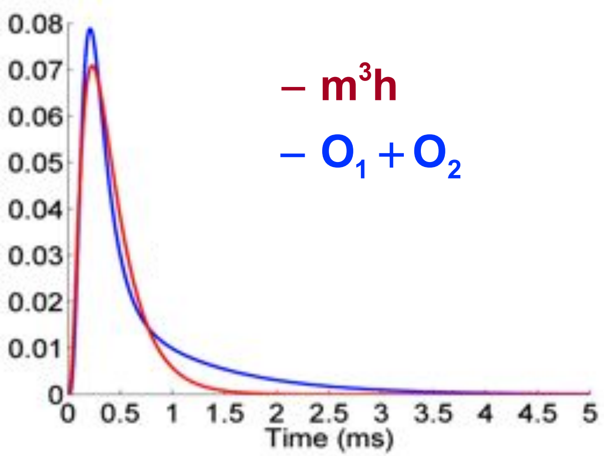
independent gates



$$o(x) = m^3h$$

$$\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m$$

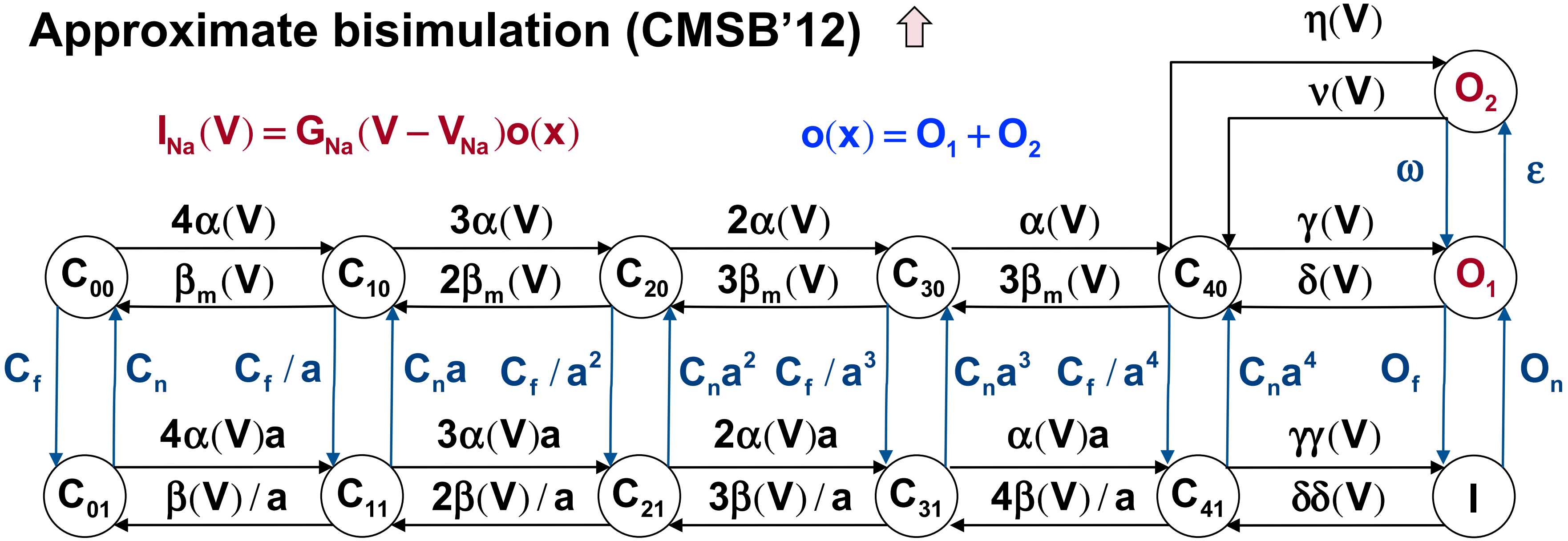
$$\dot{h} = \alpha_h(V)(1-h) - \beta_h(V)h$$



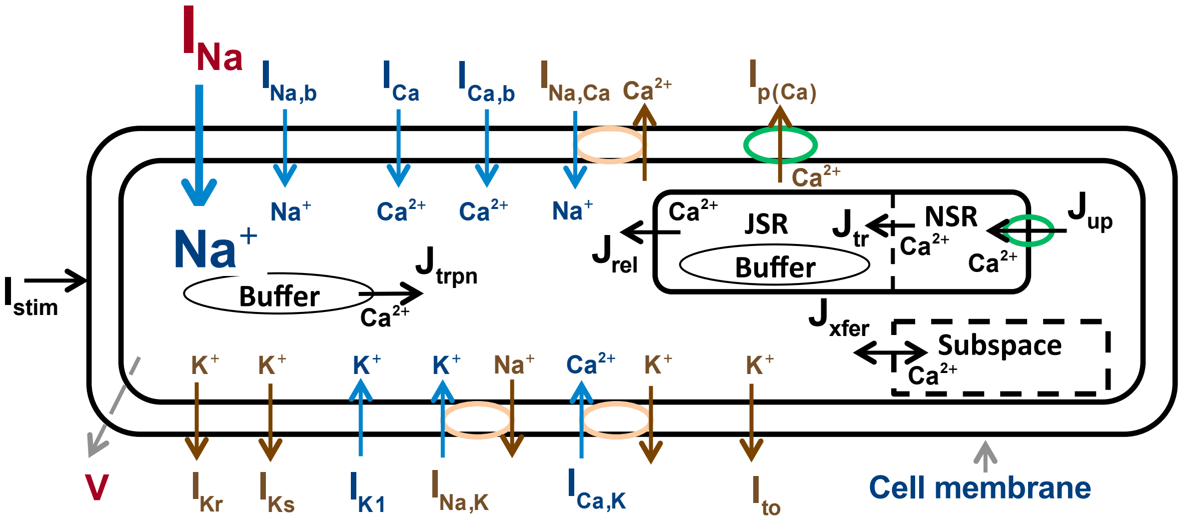
Approximate bisimulation (CMSB’12) ⇧

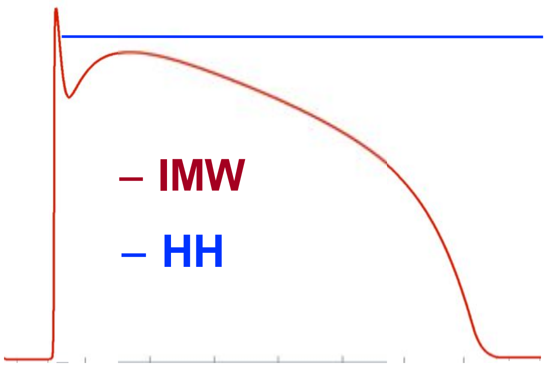
$$I_{Na}(V) = G_{Na}(V - V_{Na})o(x)$$

$$o(x) = O_1 + O_2$$



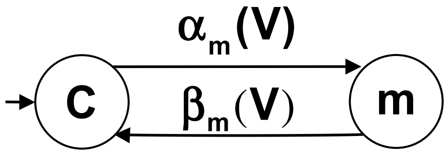
Compositionality Challenge: IMW with HH

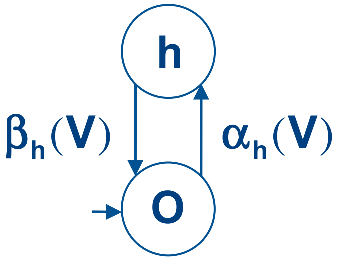




$$I_{Na}(V) = G_{Na}(V - V_{Na})o(V) \quad ⇩ \quad o(x) = m^3h$$

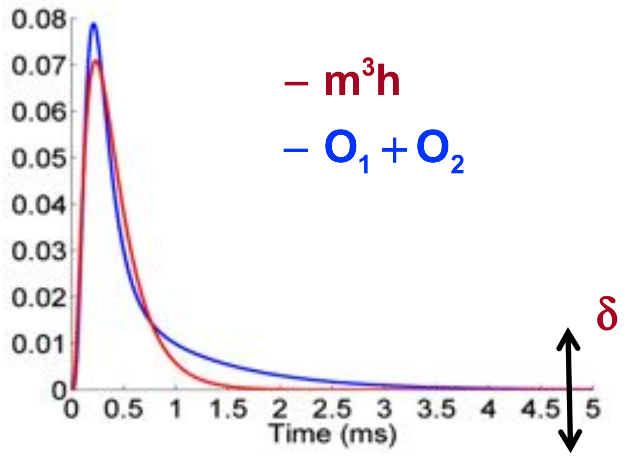
2-States CTMC
Rates depend on V





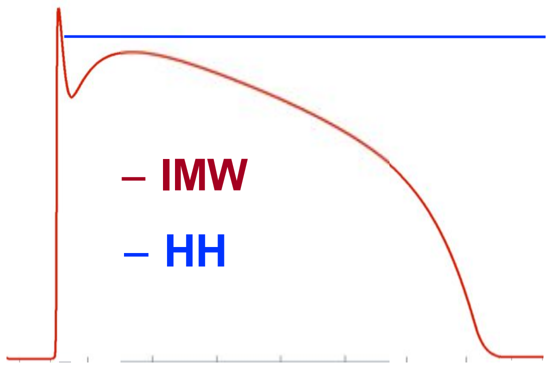
$$\dot{m} = \alpha_m(V)(1 - m) - \beta_m(V)m \qquad \dot{h} = \alpha_h(V)(1 - h) - \beta_h(V)h$$

Compositionality Challenge: IMW with HH



Problem: HH-Channel was not completely closing

Learned a better δ-bisimulation
A way to predict such problems?



Error δ was amplified
δ-bisim not compositional

$$\lightning \quad \frac{I_{Na}^{IMW} \cong^{\delta} I_{Na}^{HH}}{R \parallel I_{Na}^{IMW} \cong^{f(\delta)} R \parallel I_{Na}^{HH}}$$

Bisimulation Functions with SGC

Small-gain condition (SGC) for bisimulation function S:

1. S bounds output difference:

$$\| o(x_1) - o(x_2) \| \le S(x_1,x_2)$$

$x_1 = [m,h]$

$x_2 = [C_{00},\ldots,C_{41},I,O_1,O_2]$

2. S decays along trajectories:

$\forall u_1,u_2,x_1,x_2,\exists\lambda > 0,\gamma \ge 0$ st.

$$\dot{S} = \frac{\partial S}{\partial x_1}\underbrace{f_1(x_1,u_1)}_{\dot{x}_1} + \frac{\partial S}{\partial x_2}\underbrace{f_2(x_2,u_2)}_{\dot{x}_2} \le -\lambda S(x_1,x_2) + \gamma \| u_1 - u_2 \|$$

BFs compose linearly subject to SGC:

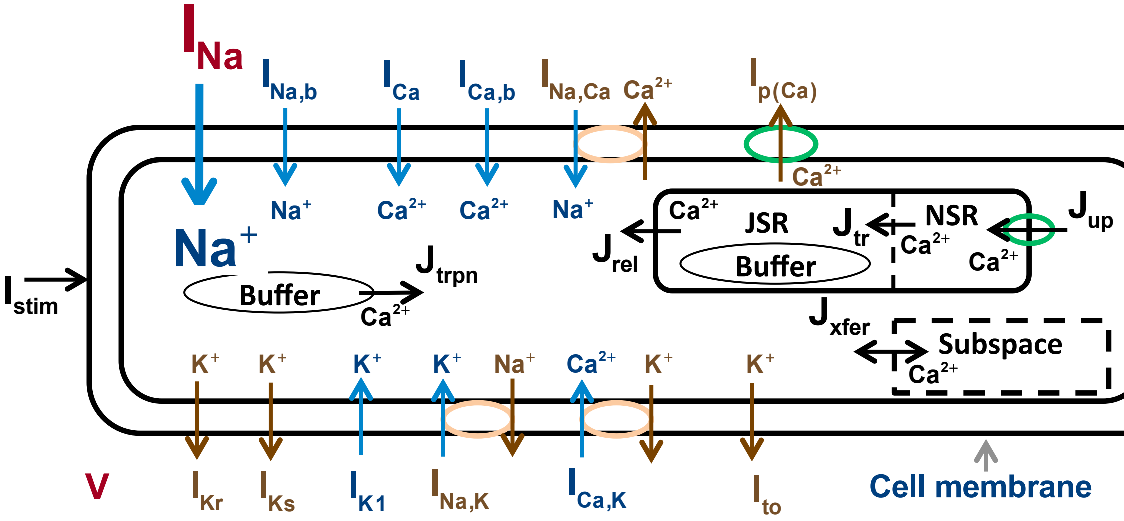
– BFs computed using SoS-TOOLS (HSCC’14-15)

$$\frac{R \cong^{S} R \qquad I_{Na}^{IMW} \cong^{T} I_{Na}^{HH}}{R \parallel I_{Na}^{IMW} \cong^{aS+bT} R \parallel I_{Na}^{HH}}$$

Conclusions

Models become increasingly sophisticated

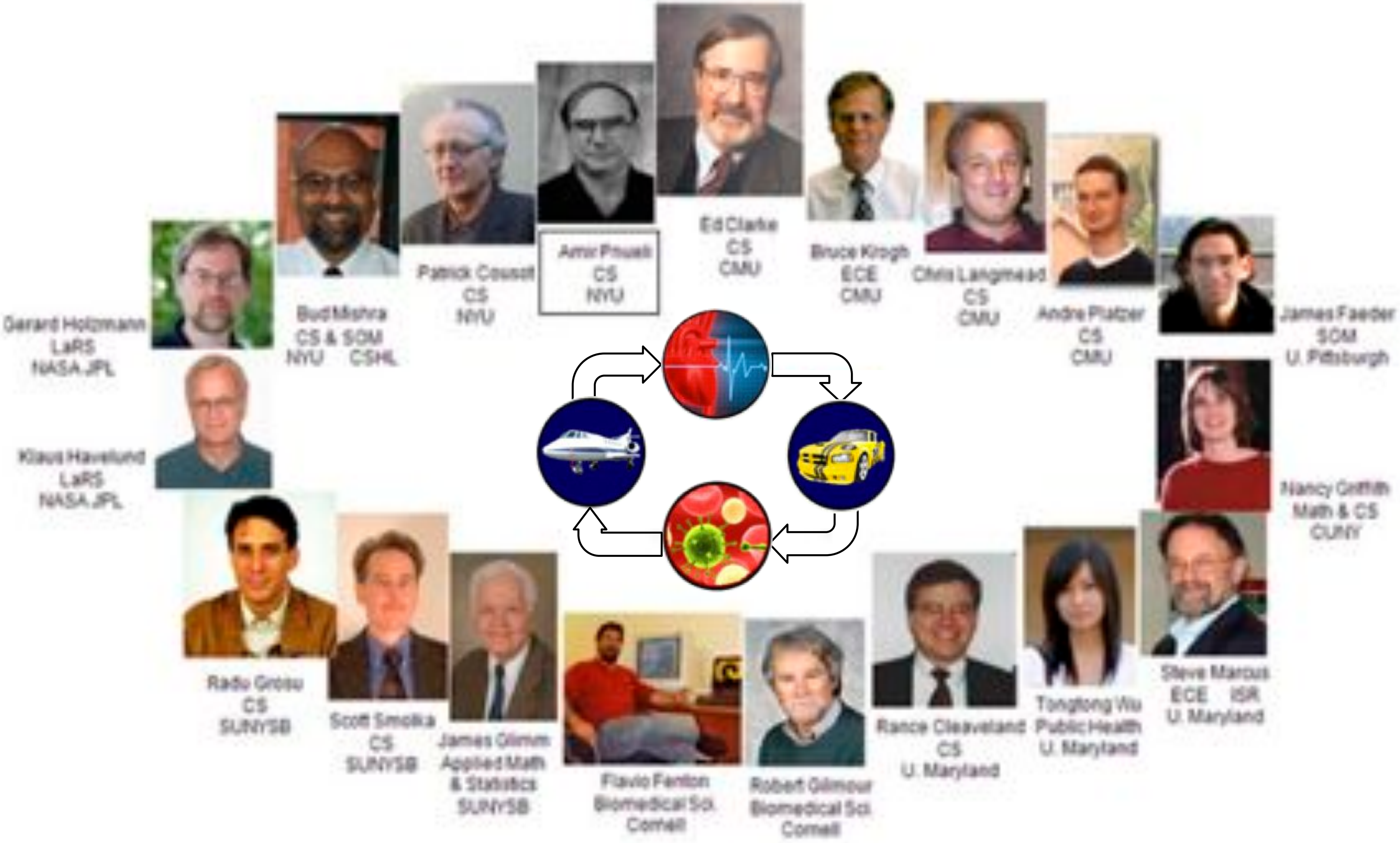
- Mollecular processes better understood
- Investigation of very specific treatments



However, simulation of whole organ infeasible

- No method to automatically learn a channel’s env
- Compositionality is a big obstacle

CMACS: Multi-Institutional, -Disciplinary Team



CyberHeart: Multi-Institutional, -Disciplinary Team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Stony Brook


Rance Cleaveland
UMD / Fraunhofer


Elizabeth Cherry
RIT


Ed Clarke
CMU


James Glimm
Stony Brook


Sean Gao
CMU


Radu Grosu
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Vienna


Arnab Ray
Fraunhofer


Rahul Mangharam
Penn


Flavio Fenton
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Sanjay Dixit
Director of Cardiac
Electrophysiology
Philadelphia VA Hospital