Predicting Emergent Behavior in Cardiac Tissue: A Grand Challenge

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SUNY at Stony Brook

Joint work with

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James Glimm, Colas Le Guernic, and Scott A. Smolka

Excitable Cells

- Generate action potentials (elec. pulses) in response to electrical stimulation
  - Examples: neurons, cardiac cells, etc.
- Local regeneration allows electric signal propagation without damping
- Building block for electrical signaling in brain, heart, and muscles

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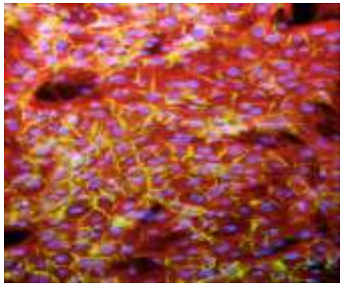
Neurons of a squirrel
University College London



Artificial cardiac tissue
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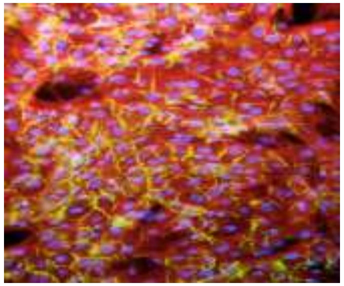

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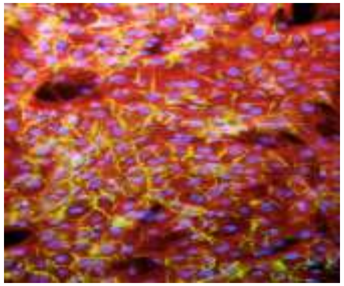

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Single Cell Reaction: Action Potential

Membrane's AP depends on:

- **Stimulus (voltage or current):**
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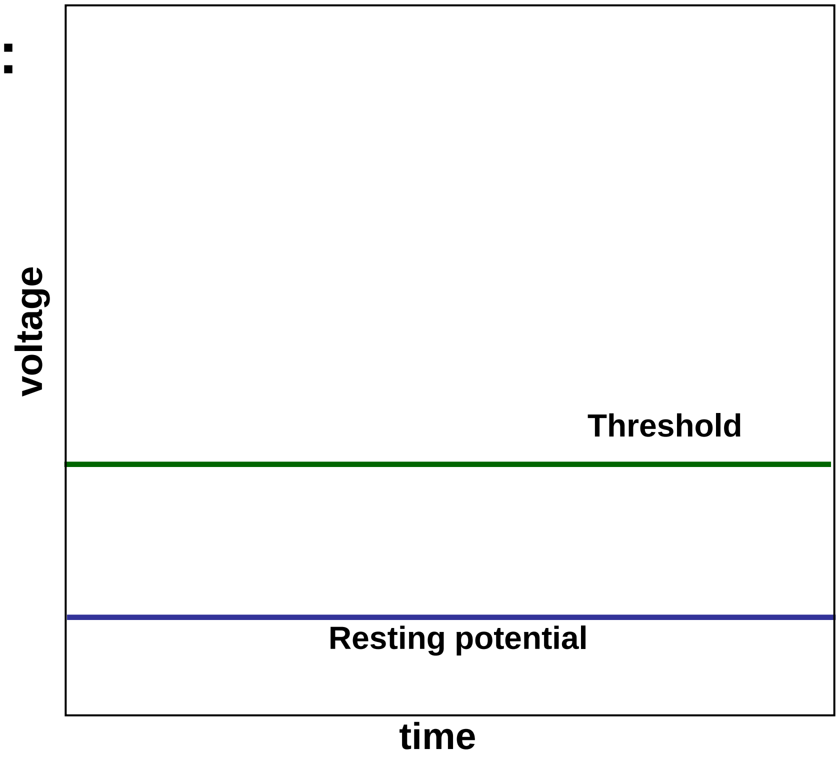
- **Cell itself (excitable or not):**
  - **State / Parameters value**

Schematic Action Potential



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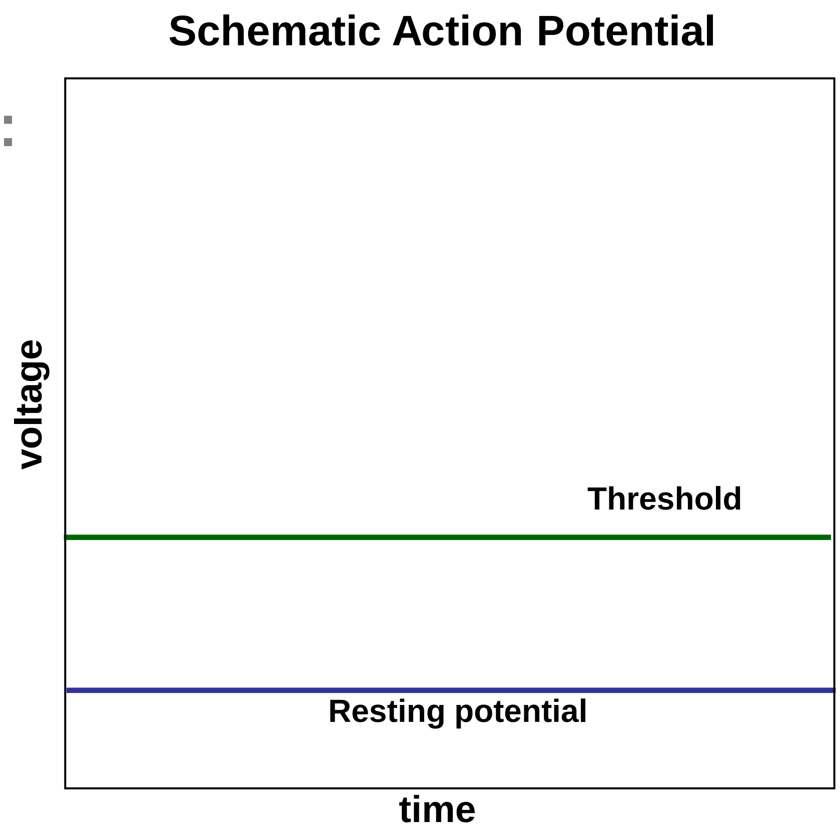

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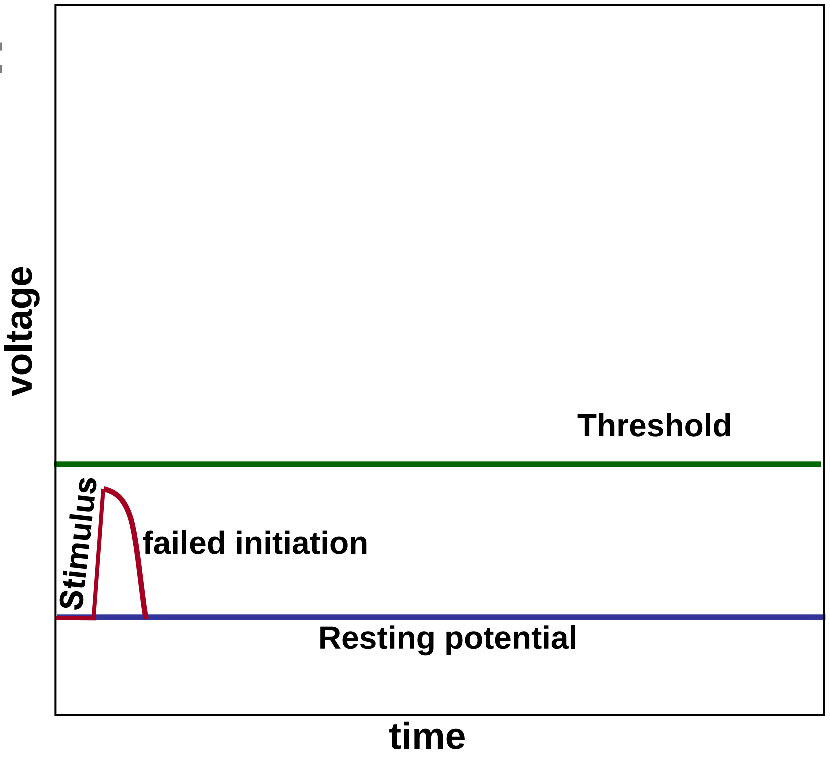

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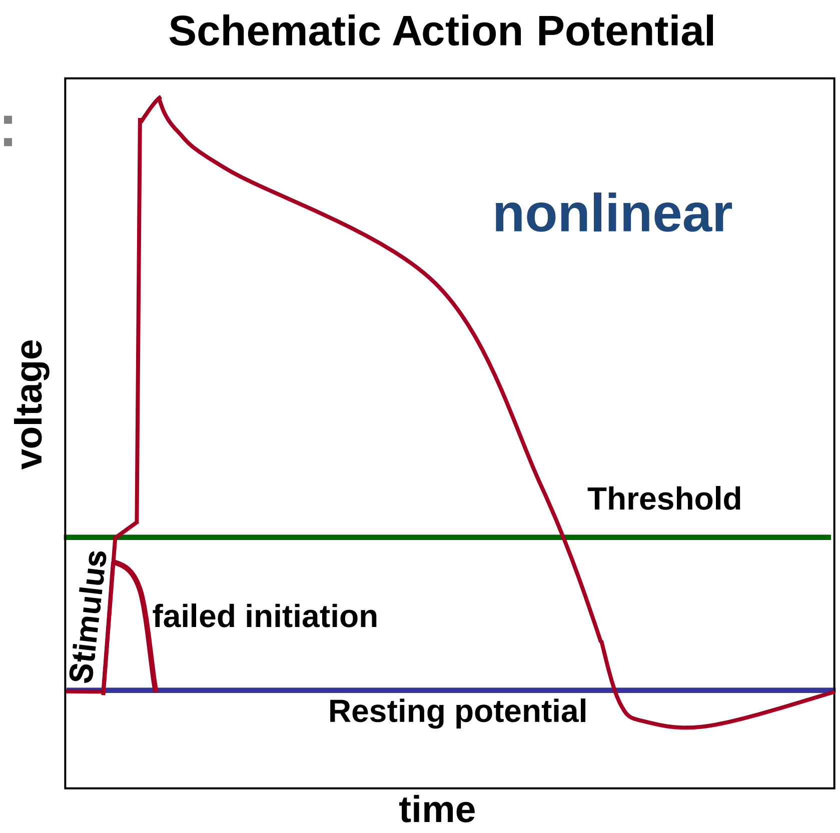

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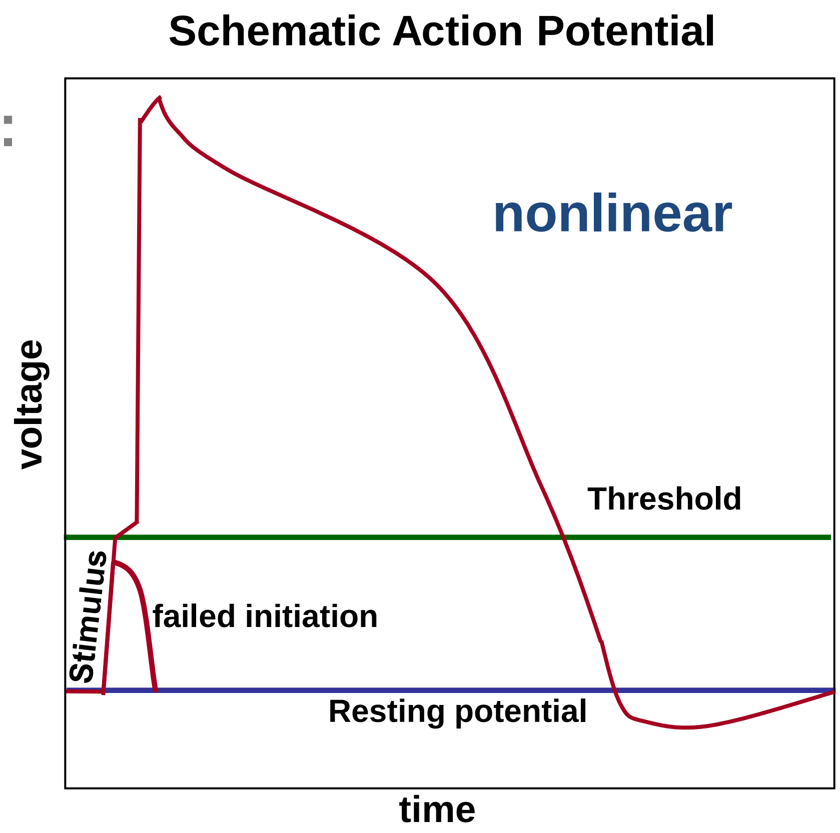
Tissue: Reaction / diffusion

$$\frac{\partial \mathbf{u}}{\partial t} = R(\mathbf{u}) + \nabla(D\nabla \mathbf{u})$$



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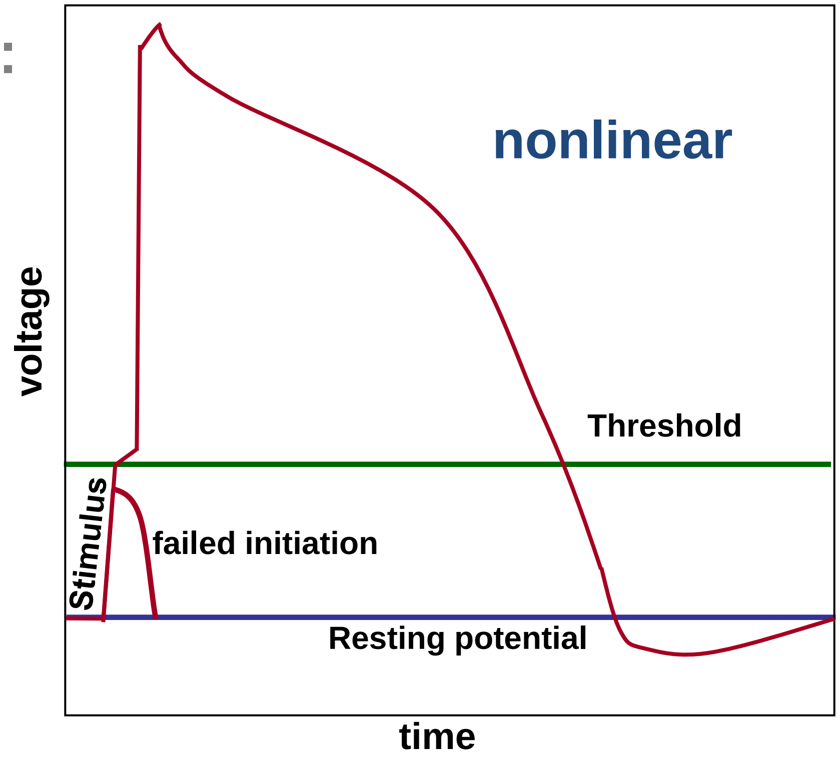
Behavior
In time

Schematic Action Potential



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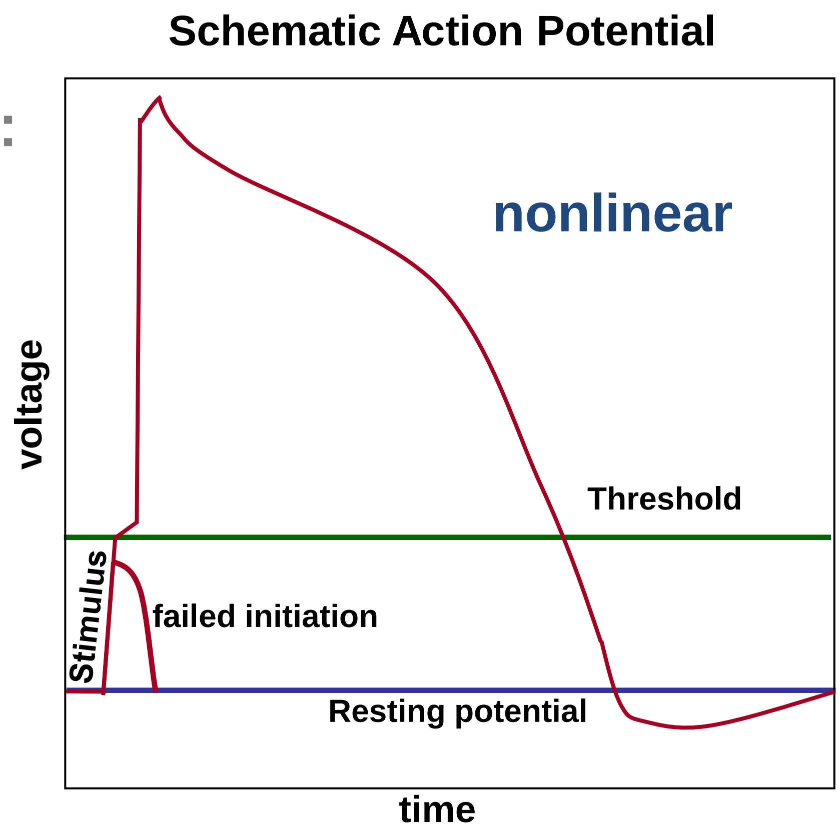

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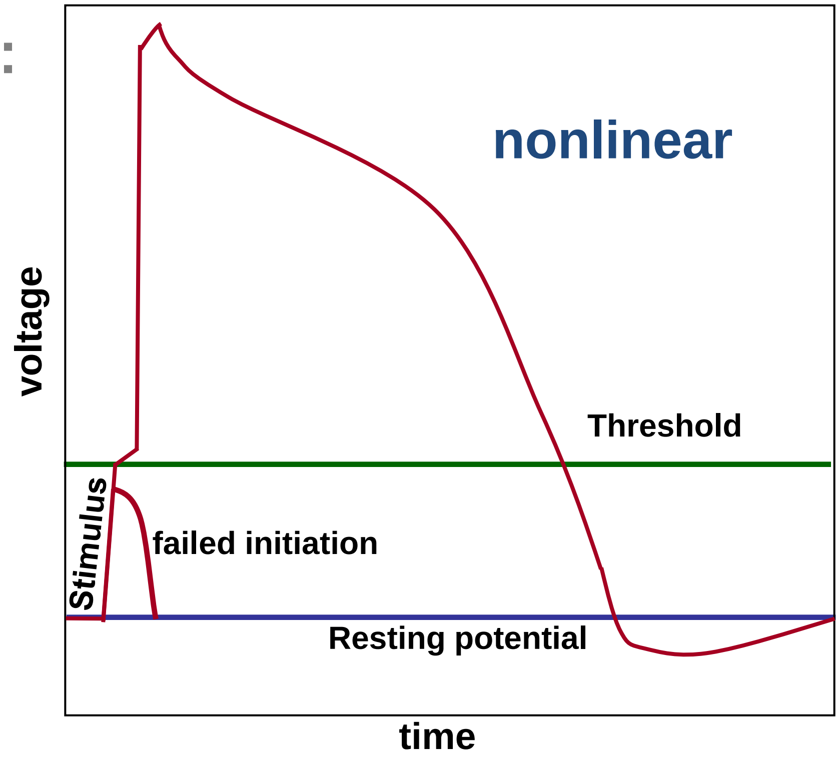
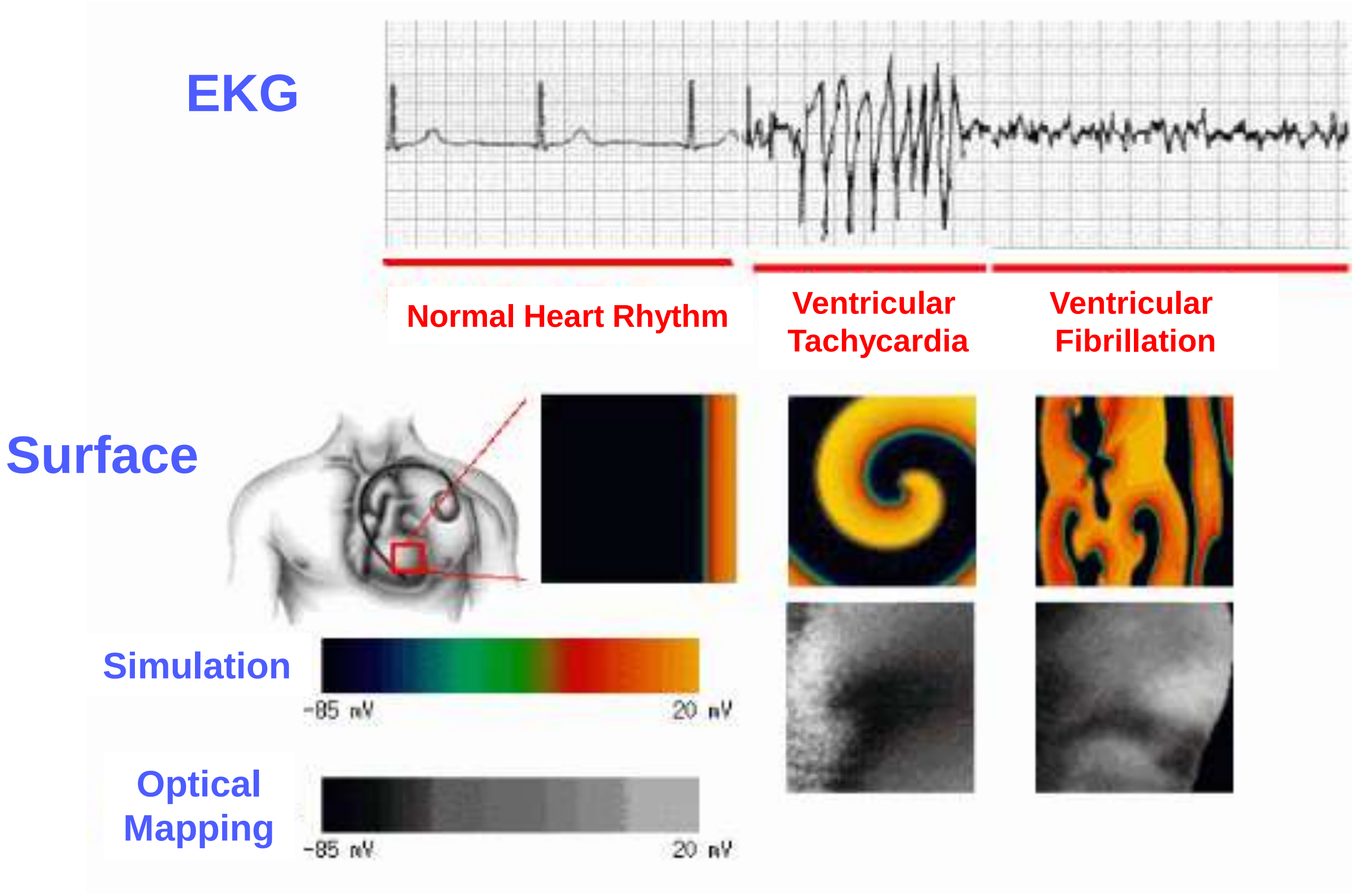
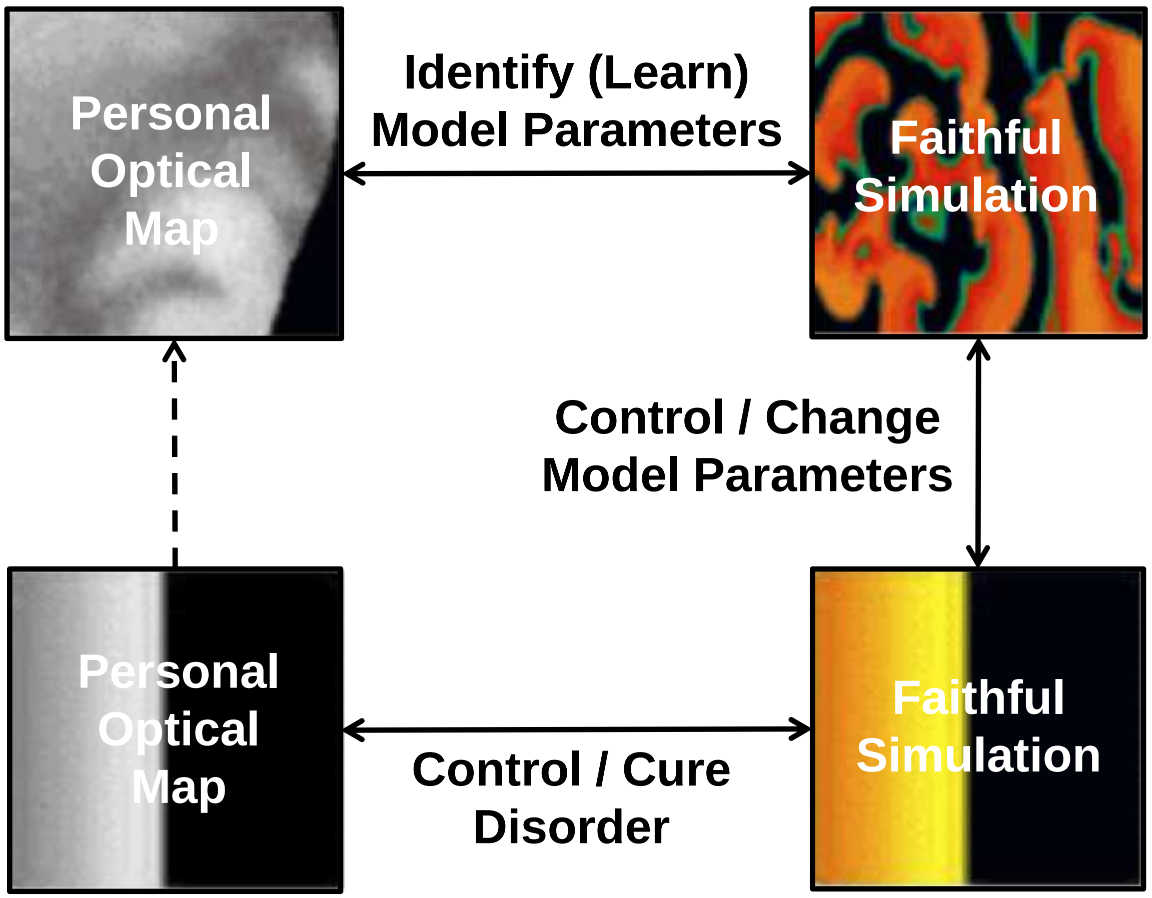


Emergent Behavior in Cardiac Cells



Arrhythmia afflicts more than 3 million Americans alone

The Grand SB-Challenge



Human Cardiac-Cell Models

Iyer-Mazhari-Winslow-04

Variables: 67
Parameters: 94

Most Detailed Ionic Model

- **Latest experimental data**
- **Multi-affine ODE (MA law)**

Human Cardiac-Cell Models

Tusscher-Noble²-Panfilov-03

Variables: 17
Parameters: 44

Less Detailed Ionic Model

- **Recent experimental data**
- **Sigmoidal ODE (Luo-Rudi)**

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- Maesoscopic behavior
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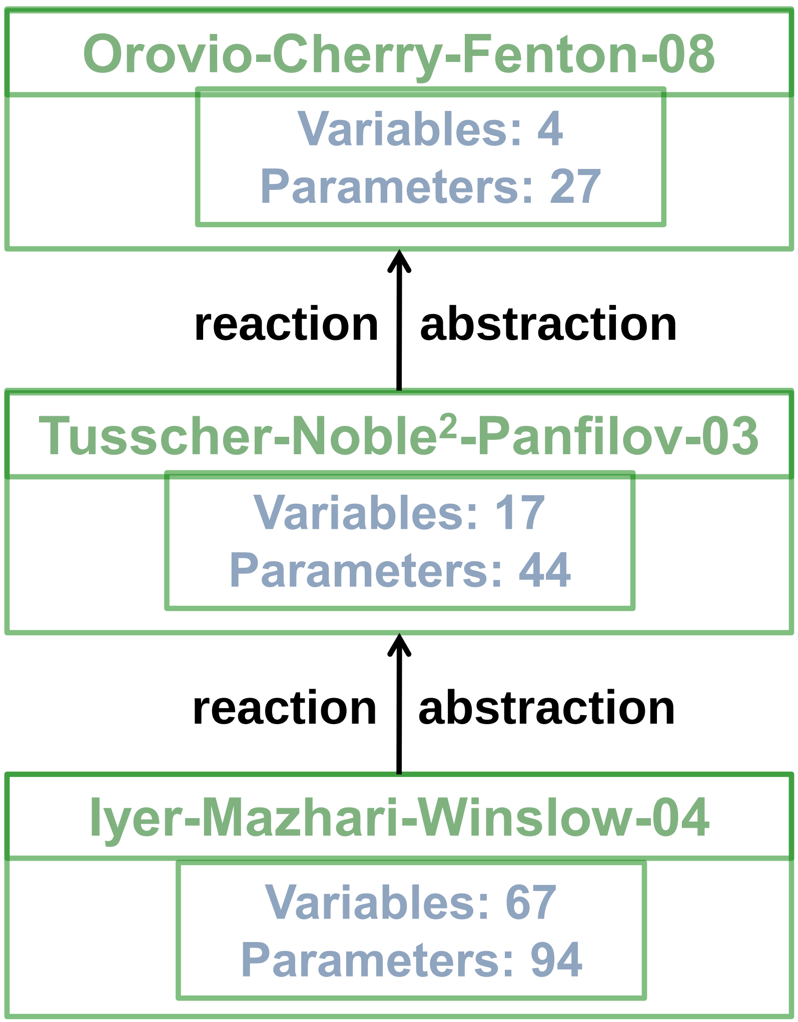

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Enzymatic Reactions (QSSA)

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + P$$

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$$d[C]/dt = k_1[E][S] - (k_{-1} + k_2)[C]$$

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Assume $E = S$ **and express** E :

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$$[E] = [E_t] - [C]$$

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Michaelis-Menten Relation (Sigmoidal):

$$d[P]/dt = a/(1 + e^{-(u-\theta)}) = a\,\mathbf{S}^{+}(u,\theta,1)$$

$$u = \ln[S],\;\; a = k_2 E_t,\;\; \theta = \ln(k_{-1} + k_2)/k_1$$

Simulation: Hardware and Dimension

Orovio-Cherry-Fenton-08
Variables: 4
Parameters: 27

↑ reaction abstraction

Tusscher-Noble²-Panfilov-03
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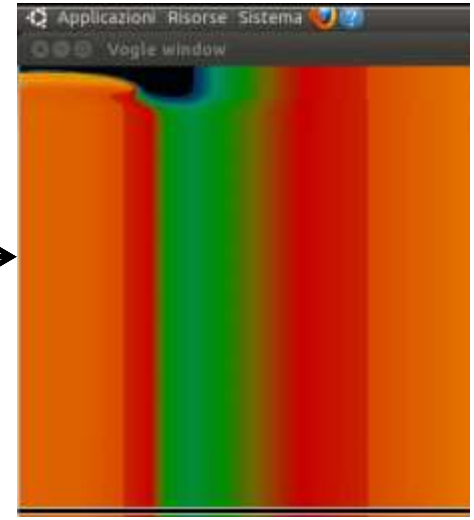
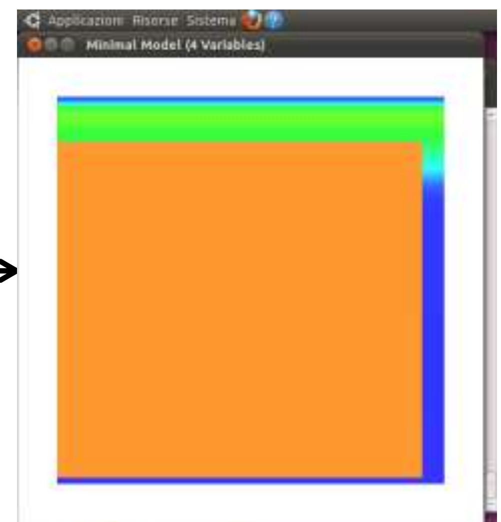
Multi-Core



1s – ?s

NVIDIA GPU



1s – 1s

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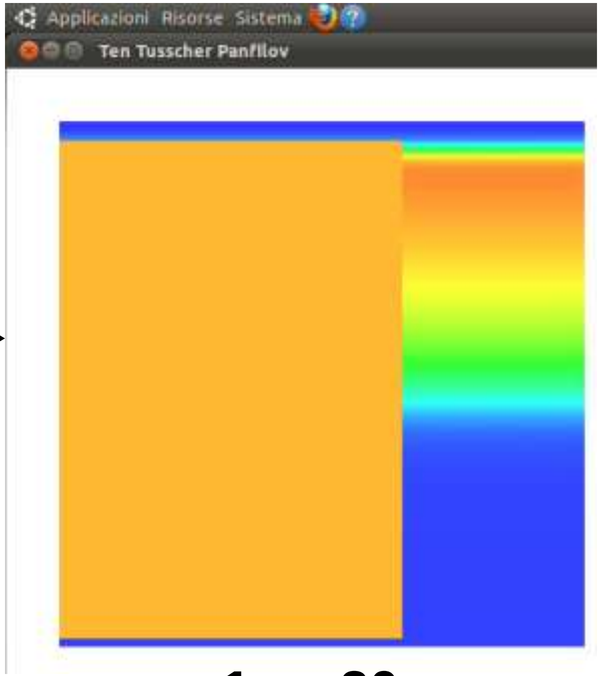

1s – 20s

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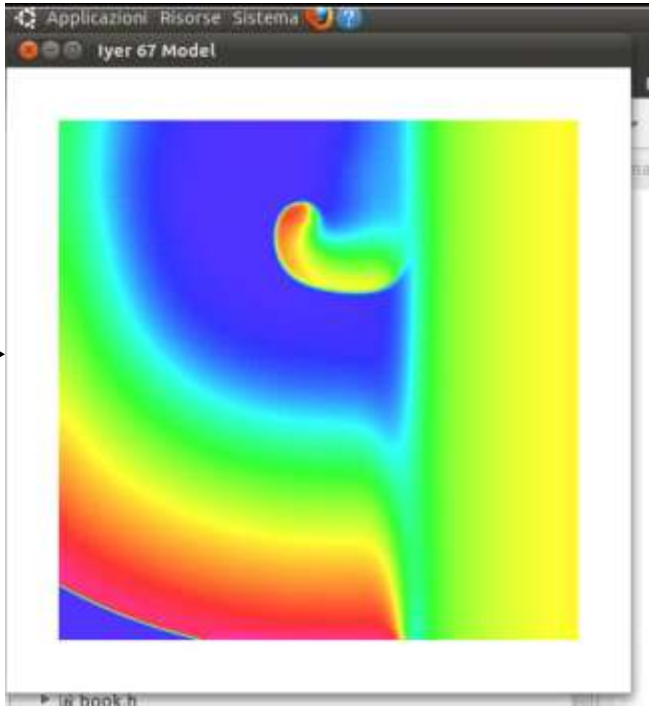
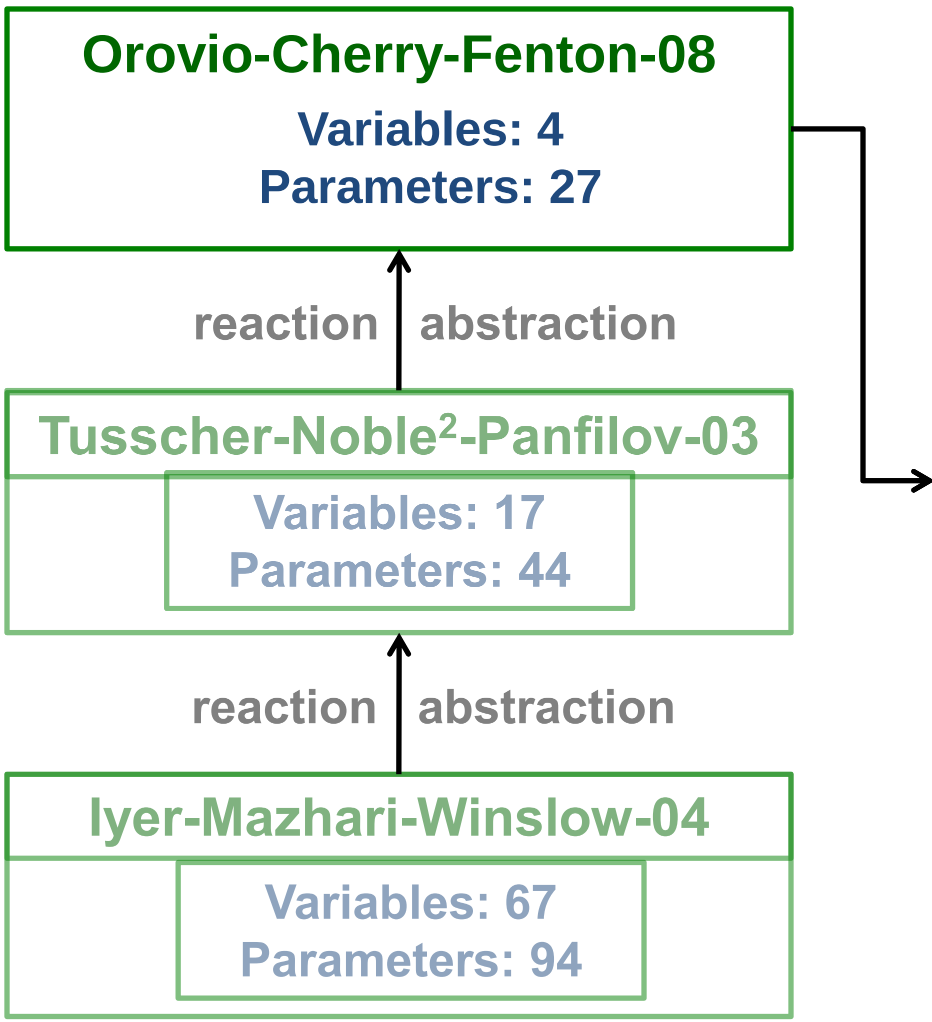


1s – 40s

Wrong Behavior!

Param. Estim: Hardware and Dimension



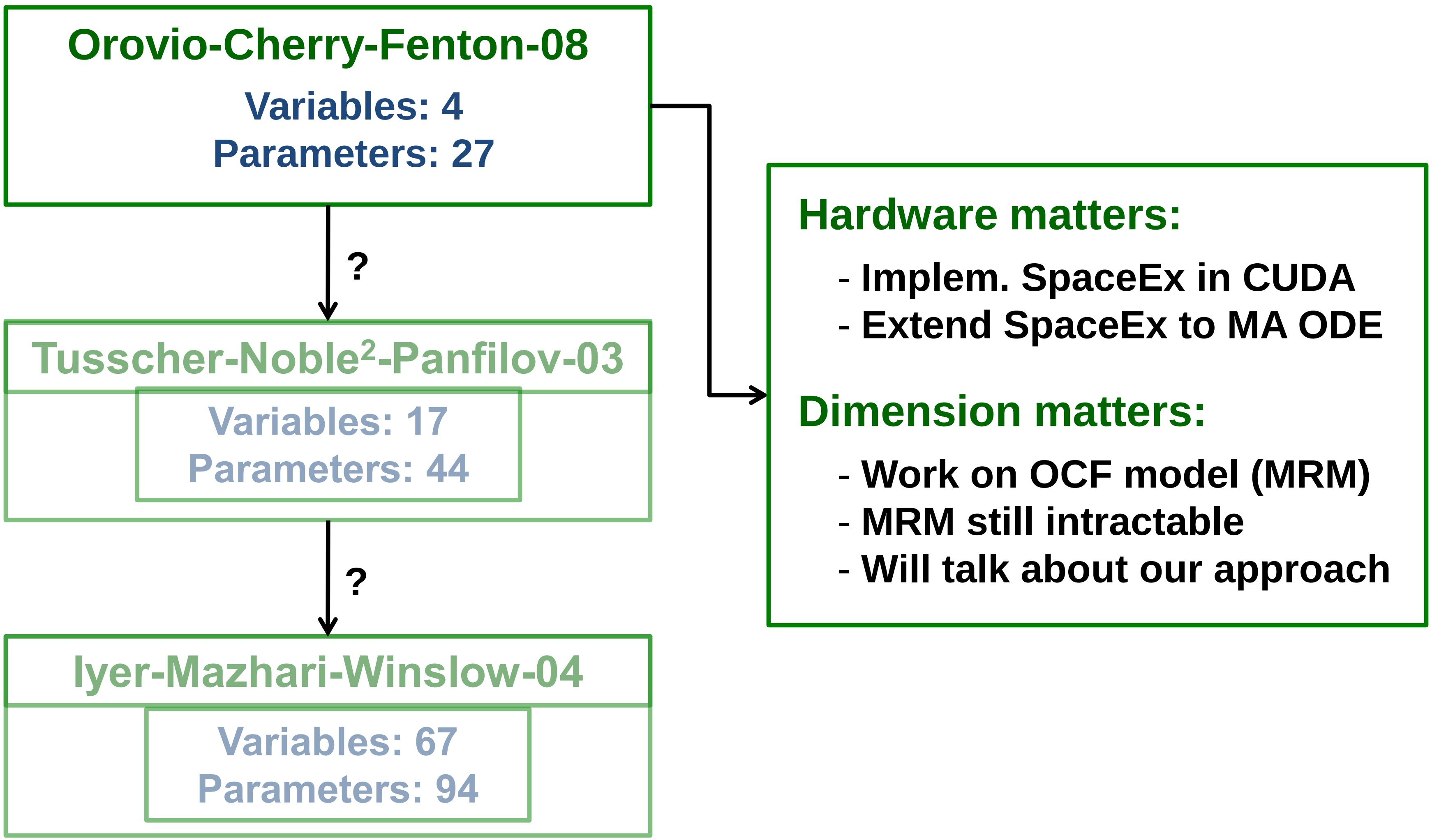
Hardware matters:

- Implem. SpaceEx in CUDA
- Extend SpaceEx to MA ODE

Dimension matters:

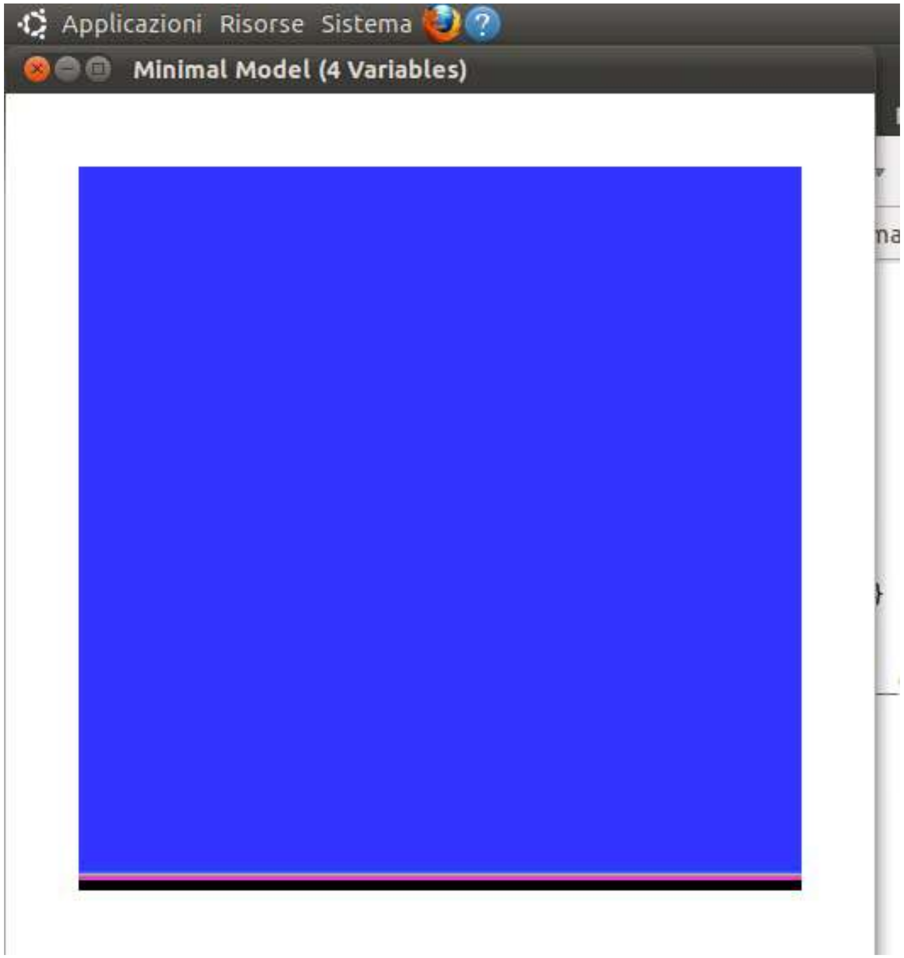
- Work on OCF model (MRM)
- MRM still intractable
- Will talk about our approach

Param. Estim: Hardware and Dimension

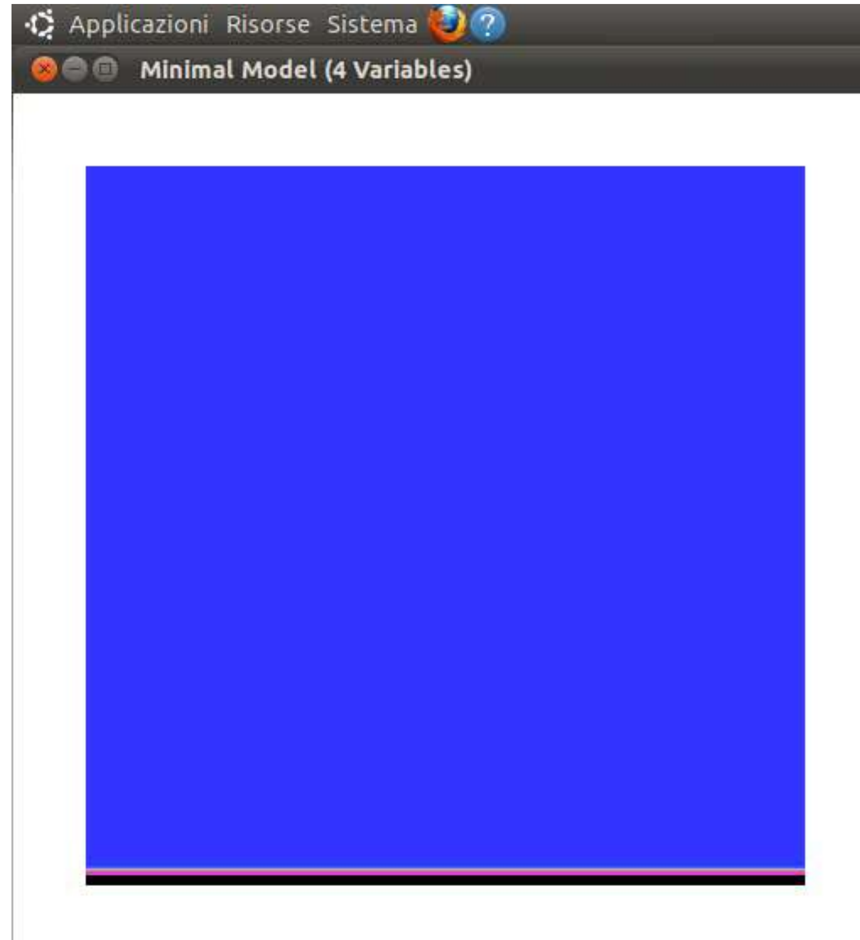


Lack of Excitability: Implications

Stimulus: bottom row, every 300ms



No Obstacle



Obstacle of UT

Problem to Solve

- What circumstances lead to a loss of excitability?
- What parameter ranges reproduce loss of excitability?

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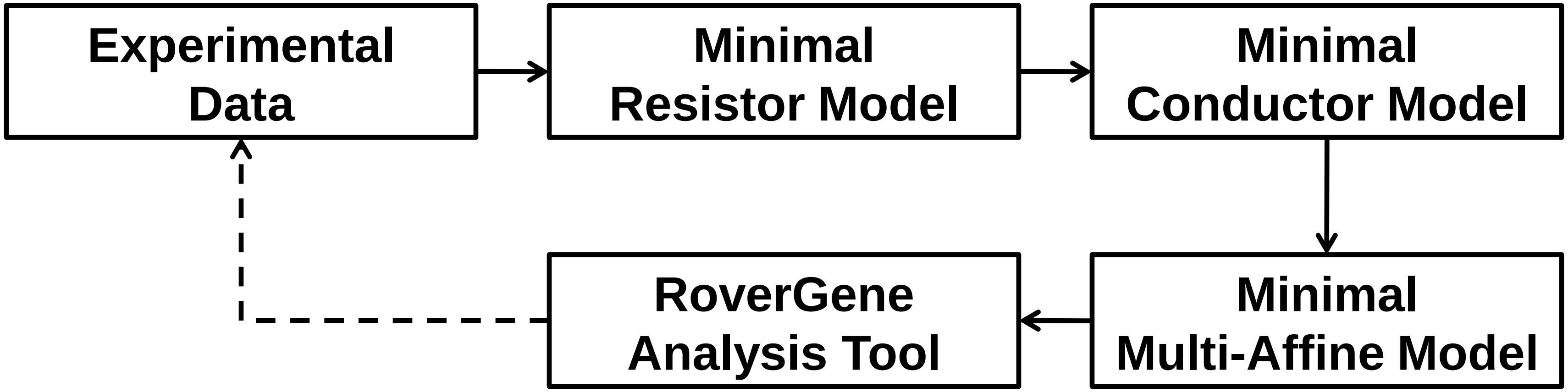
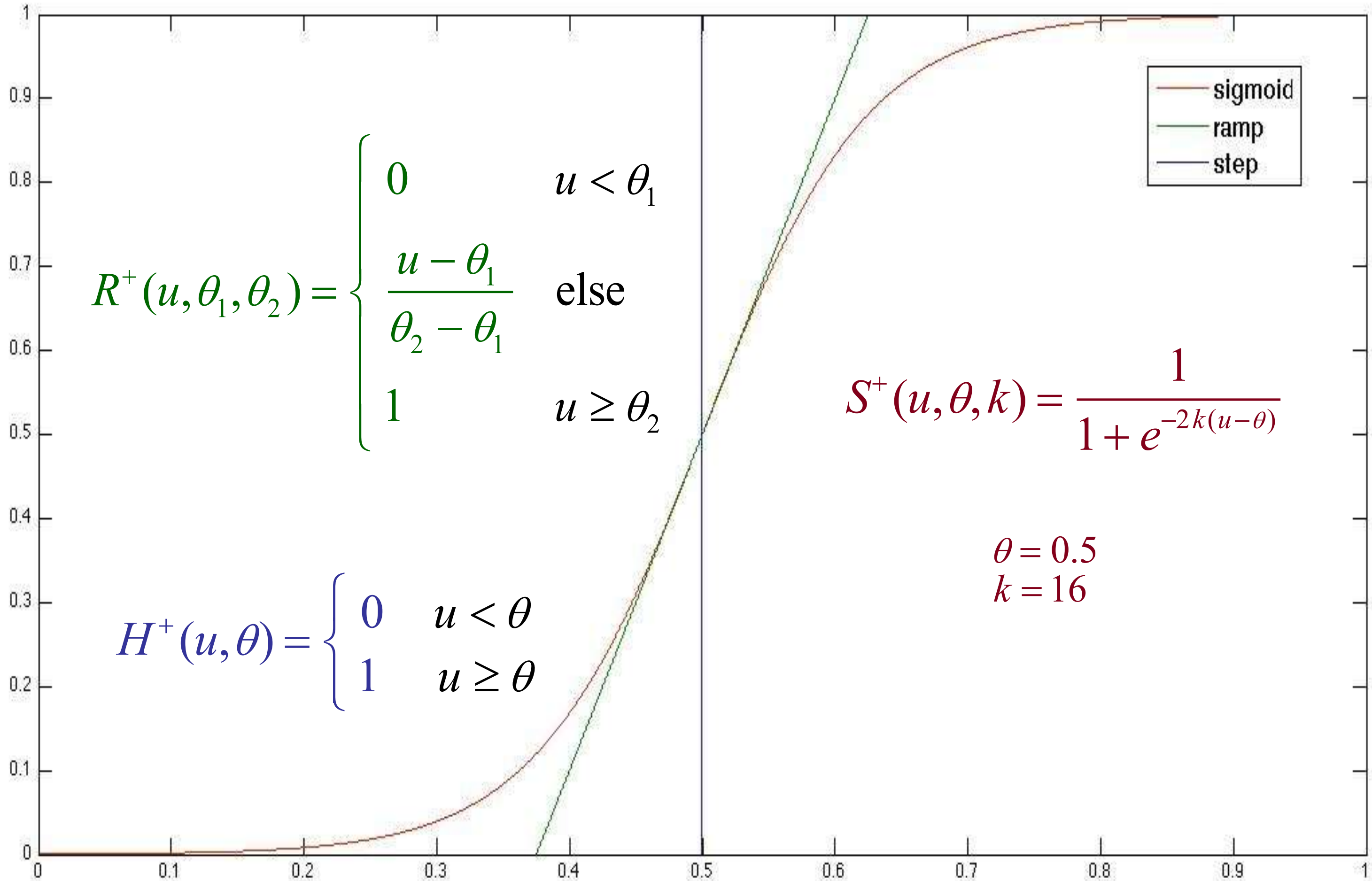


Biological Switching



$$R^{+}(u,\theta_1,\theta_2) = \begin{cases} 0 & u < \theta_1 \\ \dfrac{u-\theta_1}{\theta_2-\theta_1} & \text{else} \\ 1 & u \geq \theta_2 \end{cases}$$

$$S^{+}(u,\theta,k) = \frac{1}{1+e^{-2k(u-\theta)}}$$

$$\theta = 0.5$$
$$k = 16$$

$$H^{+}(u,\theta) = \begin{cases} 0 & u < \theta \\ 1 & u \geq \theta \end{cases}$$

Minimal Resistor Model: Voltage ODE

$$\dot{u}(u,v,w,s) = \nabla(D\nabla u) - (J_{fi}(u,v) + J_{si}(u,w,s) + J_{so}(u))$$

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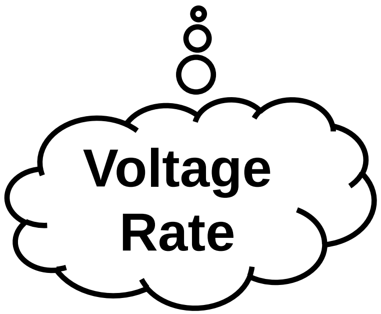

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Diffusion
Laplacian

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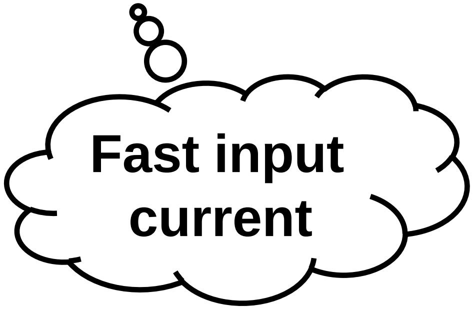

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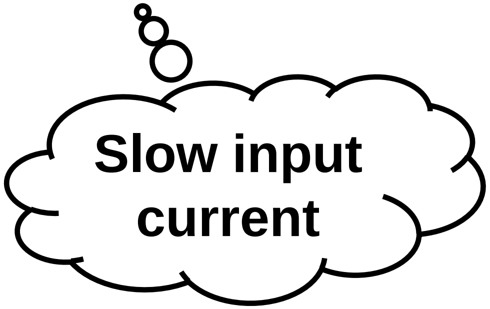

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Slow output current

MRM: Currents Equations

$$\dot{u}(u,v,w,s) = \nabla(D\nabla u) - (J_{fi}(u,v) + J_{si}(u,w,s) + J_{so}(u))$$

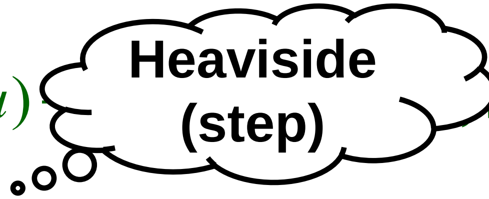
$$J_{fi}(u,v) = -H^{+}(u,\theta_{v})\ (u-\theta_{v})(u_{u}-u)v/\tau_{fi}$$

$$J_{si}(u,w,s) = -H^{+}(u,\theta_{w})\ ws/\tau_{si}$$

$$J_{so}(u) = H^{-}(u,\theta_{w})\ u/\tau_{o}(u) + H^{+}(u,\theta_{w})/\tau_{so}(u)$$

MRM: Currents Equations

$\dot{u}(u,v,w,s) = \nabla(D\nabla u)$ … $w,s) + J_{so}(u))$



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MRM: Currents Equations

Constant Resistance

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Piecewise Nonlinear

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Piecewise Resistance

Sigmoidal Resistance

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Piecewise
Nonlinear

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$$\dot{v}(u,v) = H^{-}(u,\theta_v)\ (v_\infty - v)\ / \tau_v^{-}(u) - H^{+}(u,\theta_v)v\ / \tau_v^{+}$$

$$\dot{w}(u,w) = H^{-}(u,\theta_w)(w_\infty - w) / \tau_w^{-}(u) - H^{+}(u,\theta_w)w / \tau_w^{+}$$

$$\dot{s}(u,s) = (S^{+}(u,u_s,k_s) - s) / \tau_s(u)$$

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$$J_{si}(u,w,s) = -H^{+}(u,\theta_w,0,1)\ ws / \tau_{si}$$

$$J_{so}(u) = H^{-}(u,\theta_w,0,1)\ u / \tau_o(u) \ldots {}_{so}(u)$$

Piecewise Resistance

$$\dot{v}(u,v) = H^{-}(u,\theta_v)\ (v_\infty - v)\ / \tau_v^{-}(u) - H^{+}(u,\theta_v)v\ / \tau_v^{+}$$

$$\dot{w}(u,w) = H^{-}(u,\theta_w)(w_\infty - w) / \tau_w^{-}(u) - H^{+}(u,\theta_w)w / \tau_w^{+}$$

$$\dot{s}(u,s) = (S^{+}(u,u_s,k_s) - s) / \tau_s(u)$$

Piecewise Resistance

MRM: Gates ODEs

$$\dot{u}(u,v,w,s) = \nabla(D\nabla u) - (J_{fi}(u,v) + J_{si}(u,w,s) + J_{so}(u))$$

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$$J_{so}(u) = H^{-}(u,\theta_w,0,1)\; u / \tau_o(u) + H^{+}(u,\theta_w,0,1) / \tau_{so}(u)$$

$$\dot{v}(u,v) = H^{-}(u,\theta_v)\,(v_\infty - v)\; / \tau_v^{-}(u) - H^{+}(u,\theta_v) v\; / \tau_v^{+}$$

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Sigmoidal Resistance

Sigmoid

MRM: Voltage-Controlled Resistances/SSV

$$\tau_v^-(u) = H^-(u,\theta_o)\ \tau_{v_1}^- + H^+(u,\theta_o)\ \tau_{v_2}^-$$

$$\tau_s(u) = H^-(u,\theta_w)\ \tau_{s_1} + H^+(u,\theta_w)\ \tau_{s_2}$$

$$\tau_o(u) = H^-(u,\theta_o)\ \tau_{o_1} + H^+(u,\theta_o)\ \tau_{o_2}$$

**Piecewis
e
Constant**

MRM: Voltage-Controlled Resistances/SSV

$$\tau_v^-(u) = H^-(u,\theta_o)\ \tau_{v_1}^- + H^+(u,\theta_o)\ \tau_{v_2}^-$$

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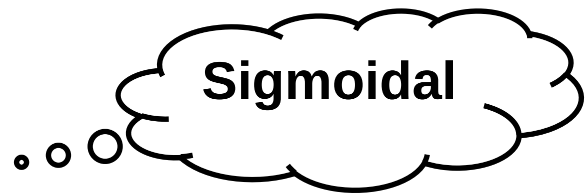
$$\tau_w^-(u) = \tau_{w_1}^- + (\tau_{w_2}^- - \tau_{w_1}^-)\ S^+(u,u_s,k_w^-)$$

$$\tau_{so}(u) = \tau_{so_1} + (\tau_{so_2} - \tau_{so_1})\ S^+(u,u_s,k_{so})$$



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Piecewise Constant

$$\tau_w^-(u) = \tau_{w_1}^- + (\tau_{w_2}^- - \tau_{w_1}^-)\ S^+(u,u_s,k_w^-)$$

$$\tau_{so}(u) = \tau_{so_1} + (\tau_{so_2} - \tau_{so_1})\ S^+$$

Sigmoidal

$$v_\infty(u) = H^-(u,\theta_o)$$

Piecewise Constant

$$w_\infty(u) = H^-(u,\theta_o)\ (1 - u/\tau_{w\infty}) + H^+(u,\theta_o)\ w_\infty^*$$

Piecewise Linear

MRM: Scaled Steps and Sigmoids

$$\tau_v^-(u) = H^+(u, \theta_o, \tau_{v_1}^-, \tau_{v_2}^-)$$

$$\tau_s(u) = H^+(u, \theta_w, \tau_{s_1}, \tau_{s_2})$$

$$\tau_o(u) = H^+(u, \theta_o, \tau_{o_1}, \tau_{o_2})$$

**Piecewis
e
Constant**

MRM: Scaled Steps and Sigmoids

$$
\begin{aligned}
\tau_v^-(u) &= H^+(u, \theta_o, \tau_{v_1}^-, \tau_{v_2}^-) \\
\tau_s(u) &= H^+(u, \theta_w, \tau_{s_1}, \tau_{s_2}) \\
\tau_o(u) &= H^+(u, \theta_o, \tau_{o_1}, \tau_{o_2})
\end{aligned}
$$

Piecewis
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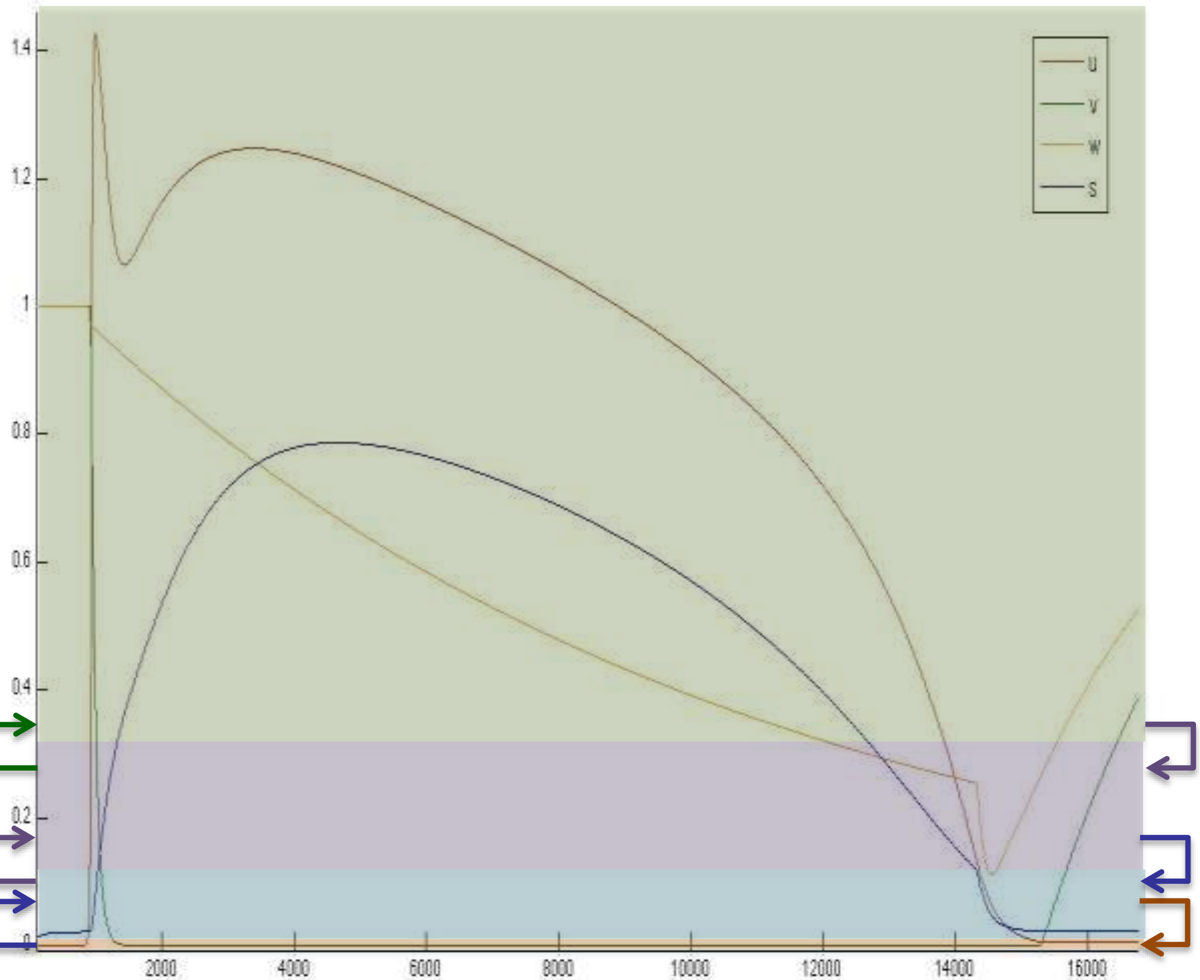
\end{aligned}
$$

Sigmoidal

Minimal Resistance Model (MRM)



$u \geq \theta_v$

$u \geq \theta_w$

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$u < \theta_v = 0.3$

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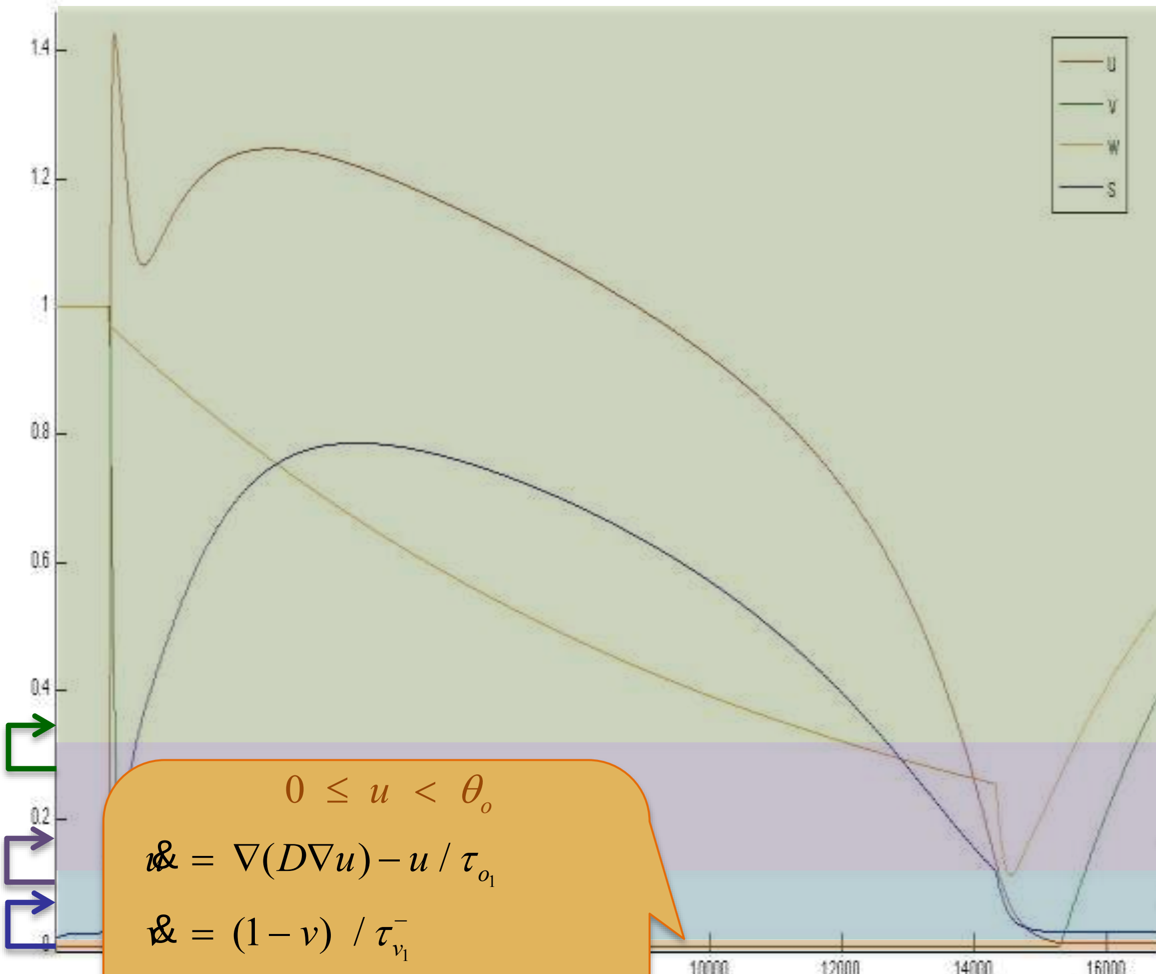

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$$0 \leq u < \theta_o$$

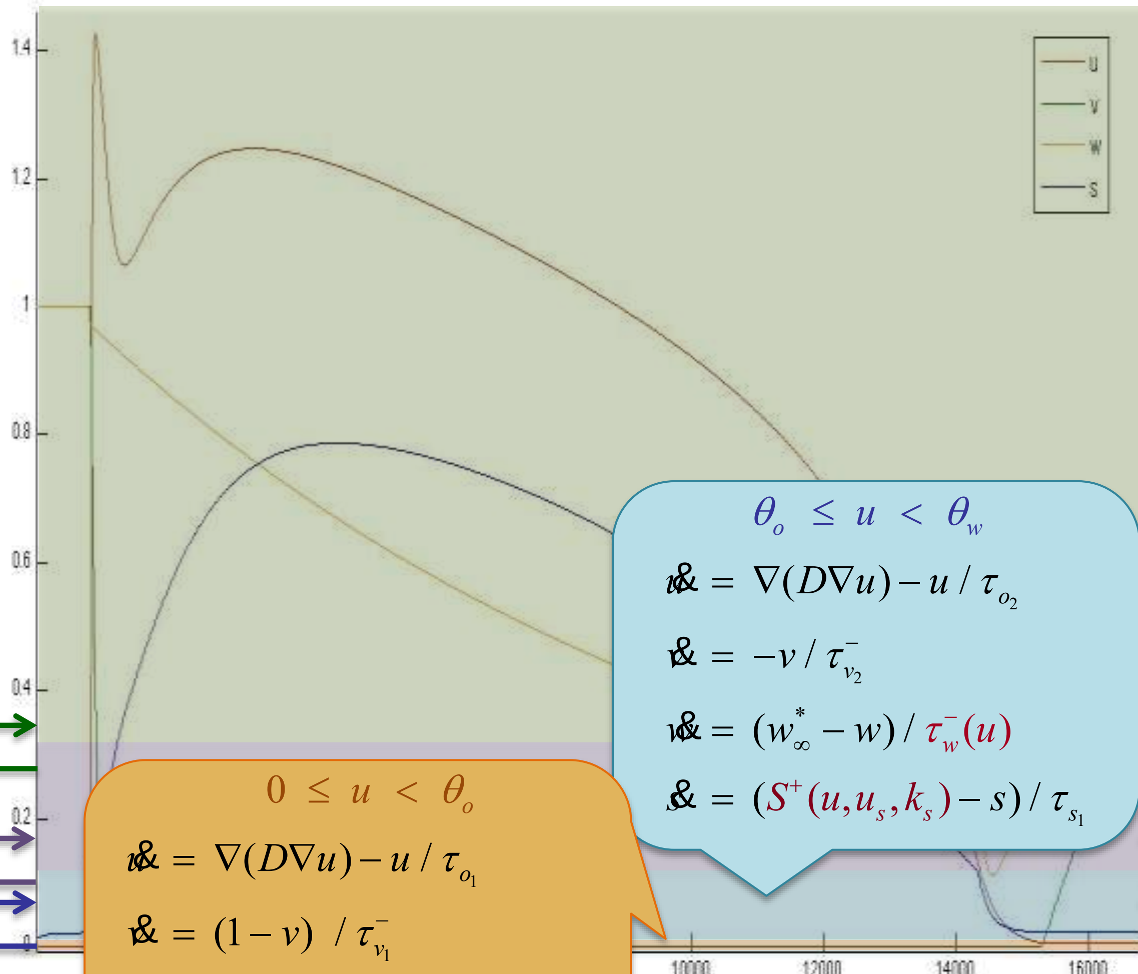
$$\dot{u} = \nabla(D\nabla u) - u / \tau_{o_1}$$

$$\dot{v} = (1 - v) / \tau_{v_1}^{-}$$

$$\dot{w} = (1 - u / \tau_{w_\infty} - w) / \tau_w^{-}(u)$$

$$\dot{s} = (S^{+}(u, u_s, k_s) - s) / \tau_{s_1}$$

Minimal Resistance Model (MRM)



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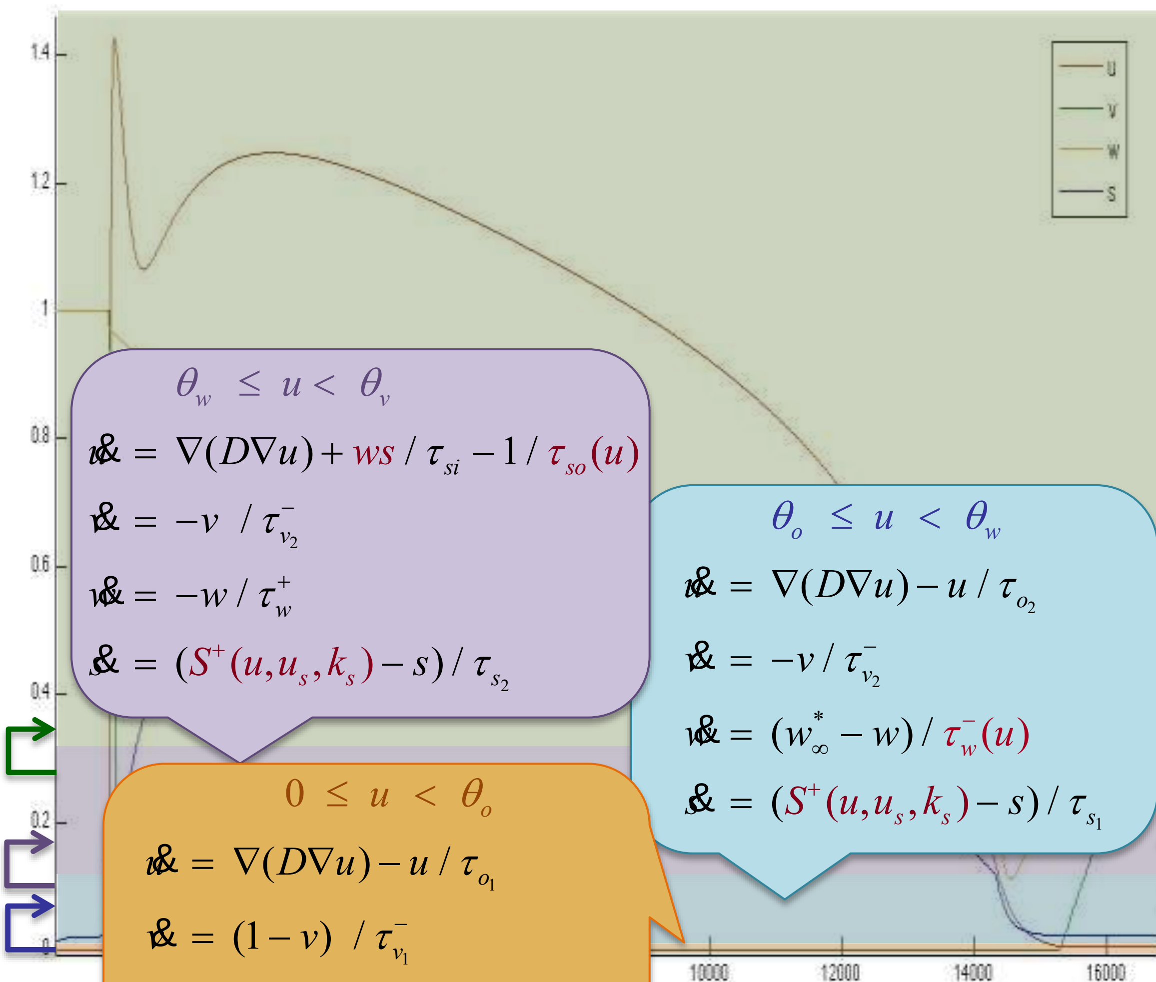

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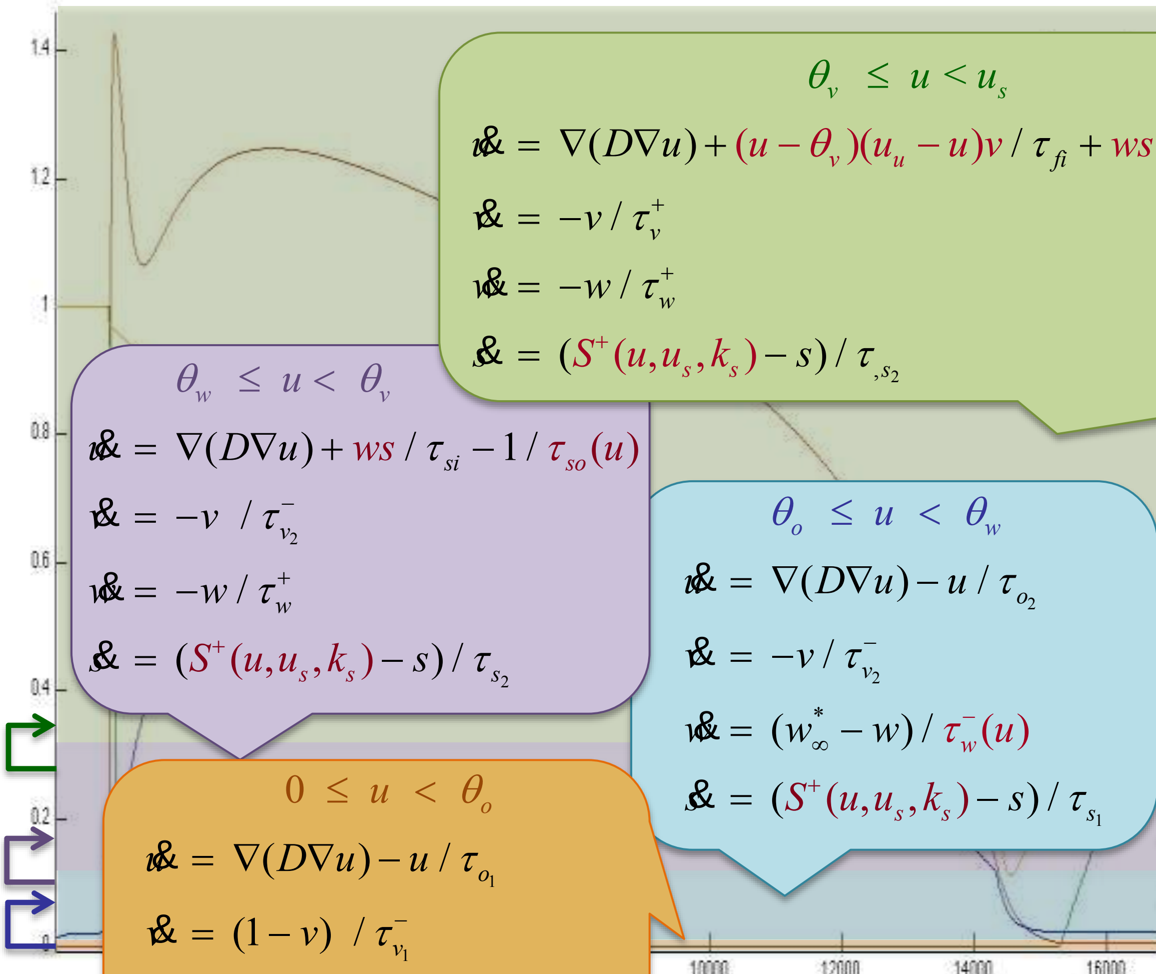

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Sigmoid Closure Property

Theorem: **For ab > 0, scaled sigmoids are closed under the reciprocal operation:**

$$S^{+}(u,k,\theta,a,b)^{-1} = S^{-}(u,k,\theta + \frac{\ln(\frac{a}{b})}{2k}, \frac{1}{b}, \frac{1}{a})$$

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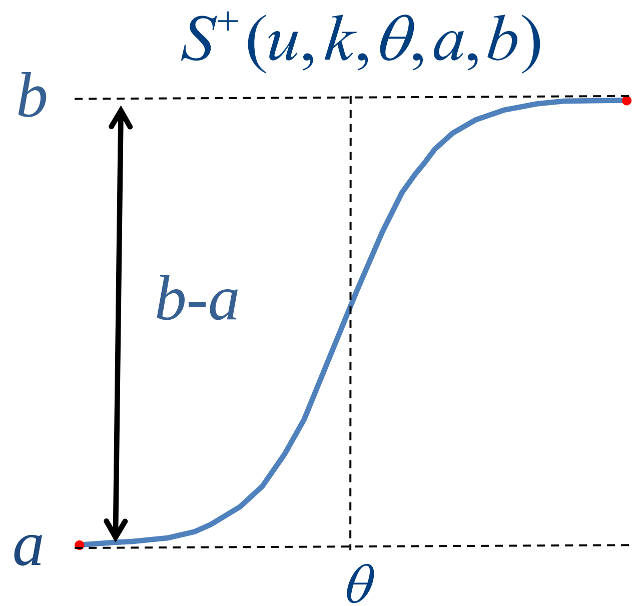
Proof:

$$S^{+}(u,k,\theta,a,b)^{-1} = (a + \frac{b-a}{1+e^{-2k(u-\theta)}})^{-1}$$



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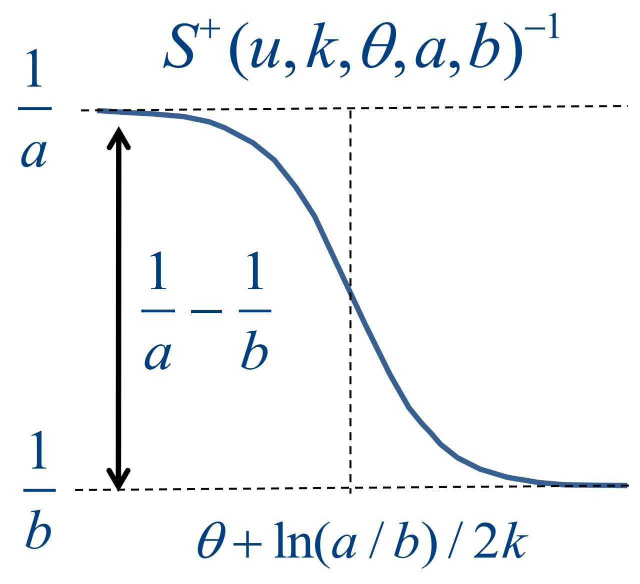
Proof:

$$S^{+}(u,k,\theta,a,b)^{-1} = \frac{1}{a} - \frac{\frac{1}{a} - \frac{1}{b}}{1 + e^{-2k(u-(\theta+\frac{\ln a - \ln b}{2k}))}}$$



From Resistances to Conductances

Removing Divisions using Sigmoid Reciprocal:

$$\tau_w^- = S^-(u, k_w^-, u_w^-, \tau_{w_1}^-, \tau_{w_2}^-) \qquad g_w^- = 1/\tau_w^- = S^+(u, k_w^-, u'^-_w, \tau_{w_1}^{-1}, \tau_{w_2}^{-1})$$

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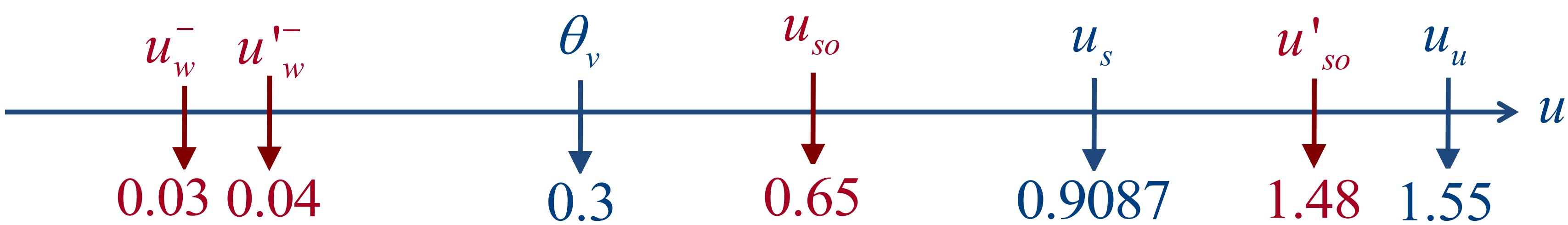
$$\tau_{so} = S^-(u, k_{so}, u_{so}, \tau_{so_1}, \tau_{so_2}) \qquad g_{so} = 1/\tau_{s0} = S^+(u, k_{so}, u'_{so}, \tau_{so_1}^{-1}, \tau_{so_2}^{-1})$$



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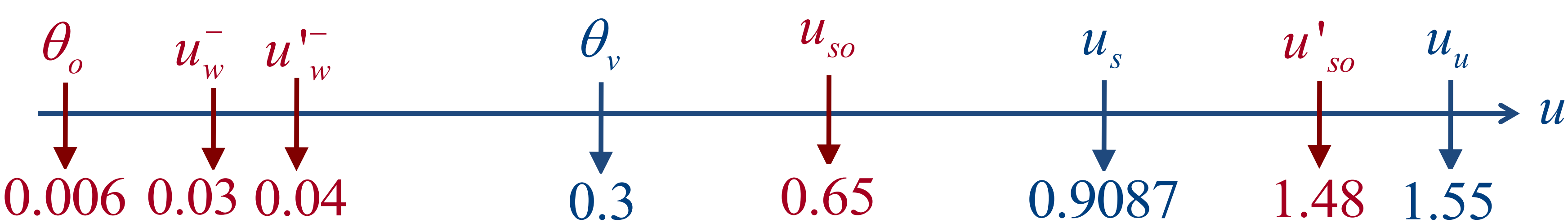
Removing Divisions using Step Reciprocal:

$$\tau_v^- = H^+(u, \theta_o, \tau_{v_1}^-, \tau_{v_2}^-) \qquad g_v^- = 1/\tau_v^- = H^-(u, \theta_o, \tau_{v_1}^{-1}, \tau_{v_2}^{-1})$$

$$\tau_o = H^-(u, \theta_o, \tau_{o_1}, \tau_{o_2}) \qquad g_o = 1/\tau_o = H^+(u, \theta_o, \tau_{o_1}^{-1}, \tau_{o_2}^{-1})$$

$$v_\infty = H^-(u, \theta_o, 0, 1) \qquad w_\infty = H^-(u, \theta_o, 0, 1)\,(1 - u g_{w\infty}) + H^+(u, \theta_o, 0, \mathrm{w}^*_\infty)$$



From Resistances to Conductances

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$$\tau_w^- = S^-(u, k_w^-, u_w^-, \tau_{w_1}^-, \tau_{w_2}^-) \qquad g_w^- = 1/\tau_w^- = S^+(u, k_w^-, u'^-_w, \tau_{w_1}^{-1}, \tau_{w_2}^{-1})$$

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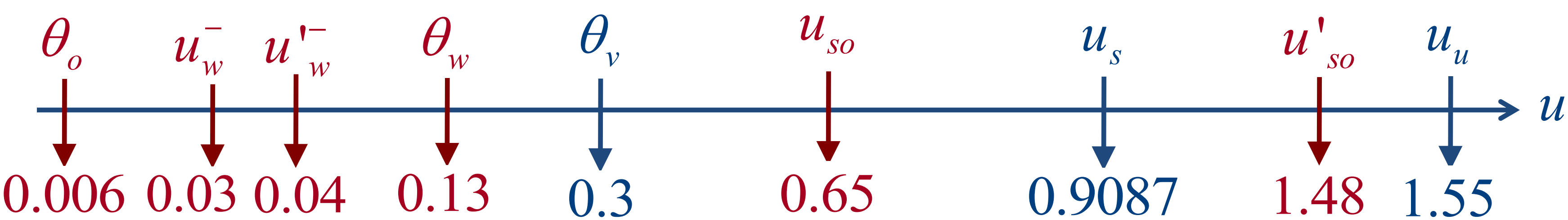
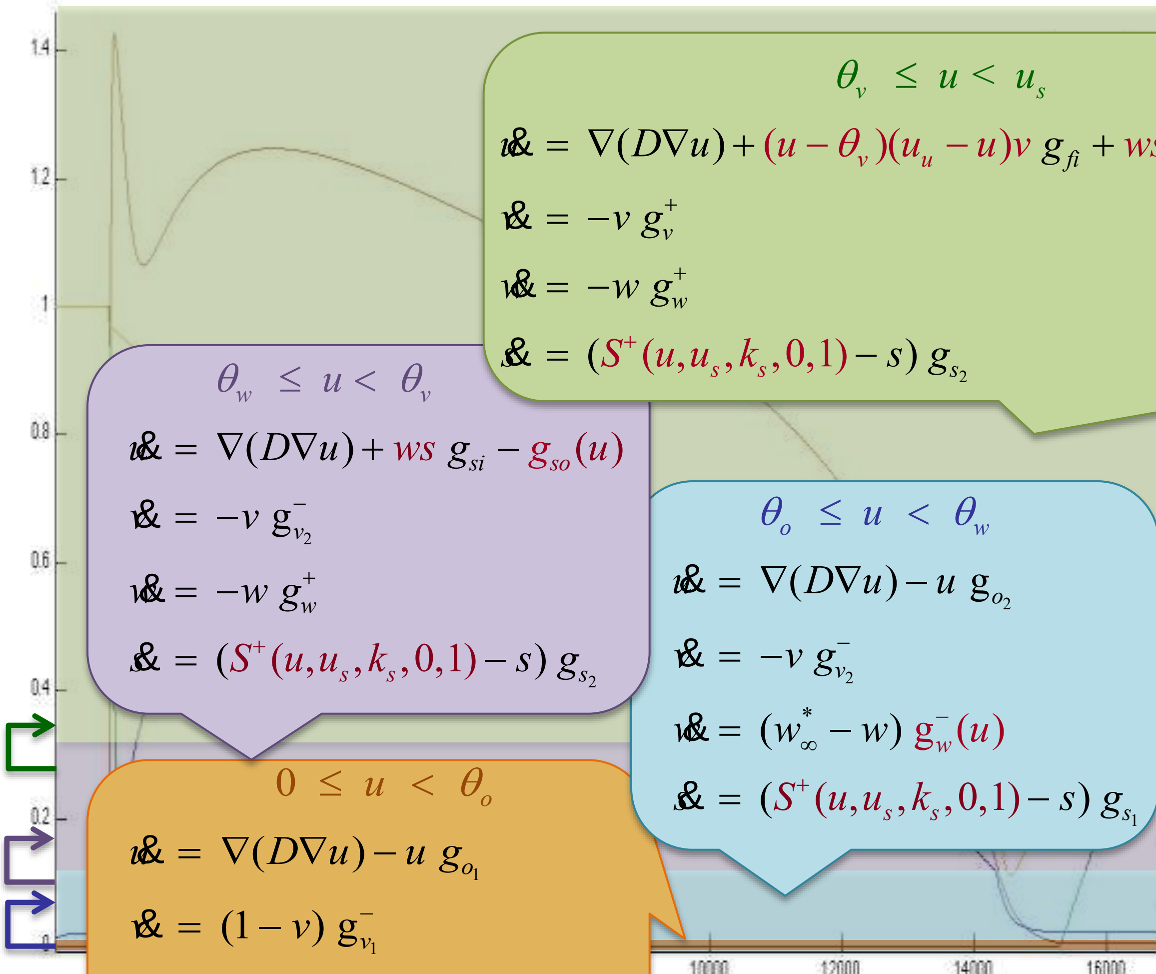


Minimal Conductance Model (MCM)



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$$\dot{v} = -v\, g_v^+$$
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$\theta_o \le u < \theta_w$

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$0 \le u < \theta_o$

$$\dot{u} = \nabla(D\nabla u) - u\, g_{o_1}$$
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Gene Regulatory Networks (GRN)

GRN canonical sigmoidal form:

$$\dot{u}_i = \sum_{j=1}^{m_i} a_{ij} \prod_{k=1}^{n_j} S^{\pm}(u_k, k_k, \theta_k, a_k, b_k) - b_i u_i$$

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Note: steps and ramps are sigmoid approximations

Optimal Polygonal Approximation

Given: One nonlinear curve and desired # segments

Find: Optimal polygonal approximation

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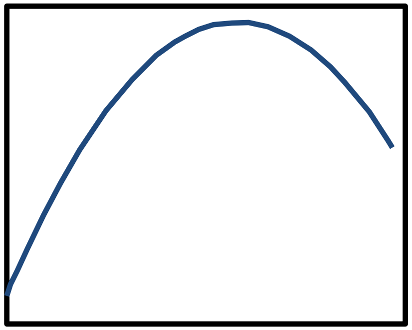
Example: What is the optimal polygonal approximation of the blue curve with 3 segments ?



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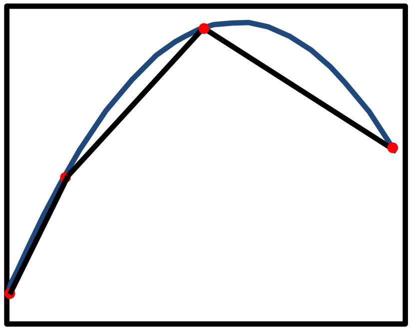

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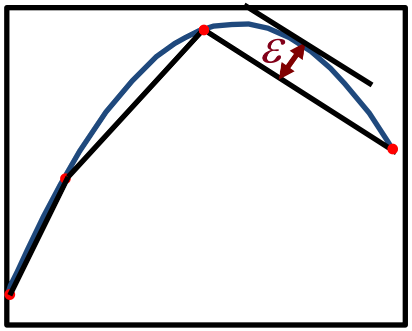

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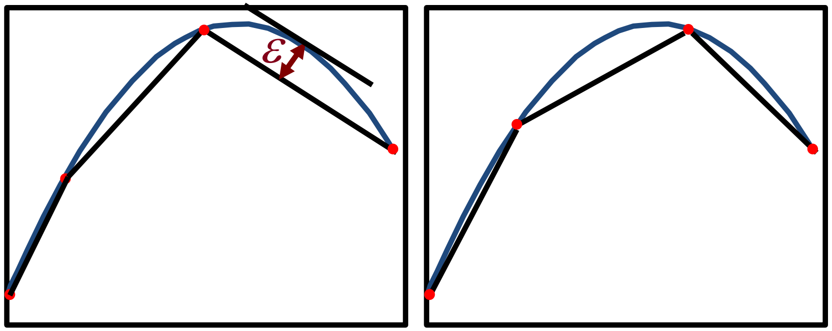

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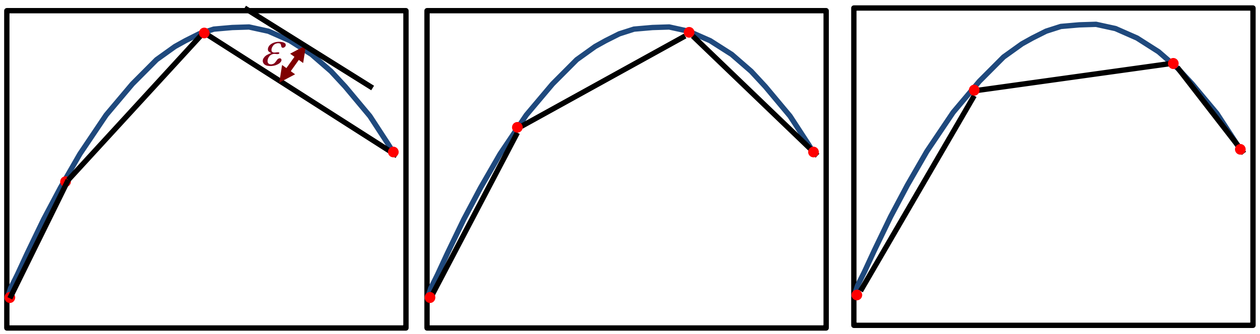

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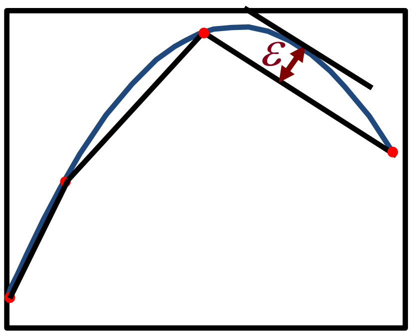

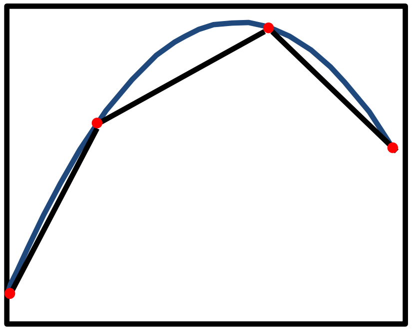

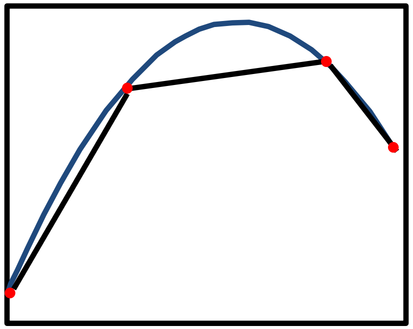

Dynamic Programming Algorithm

- **Complexity:** $O(P^2)$
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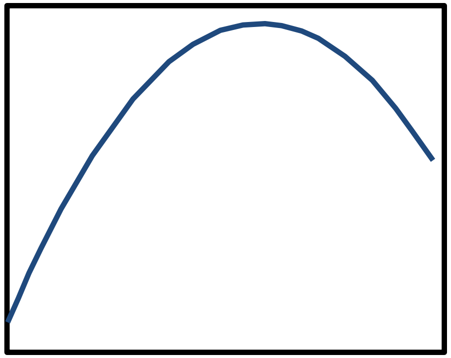

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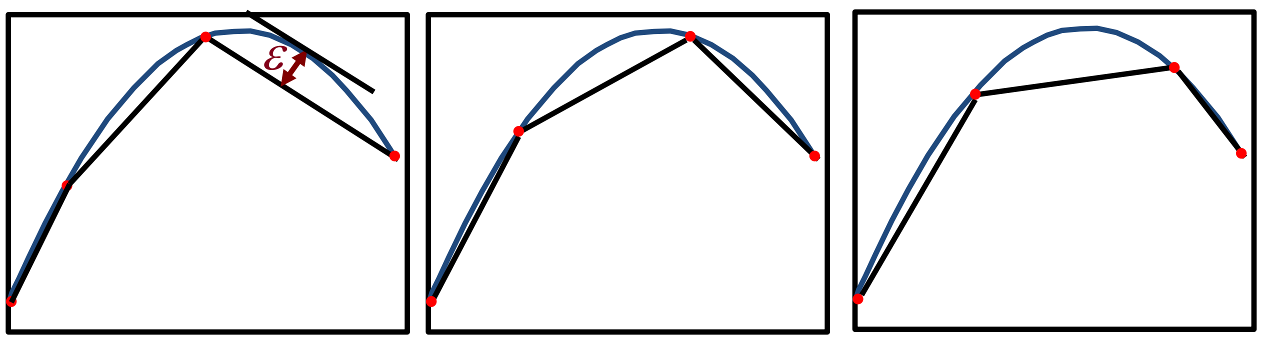

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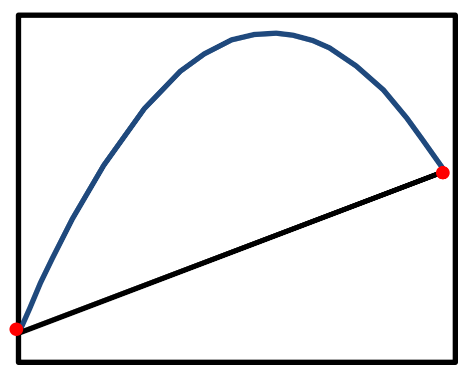

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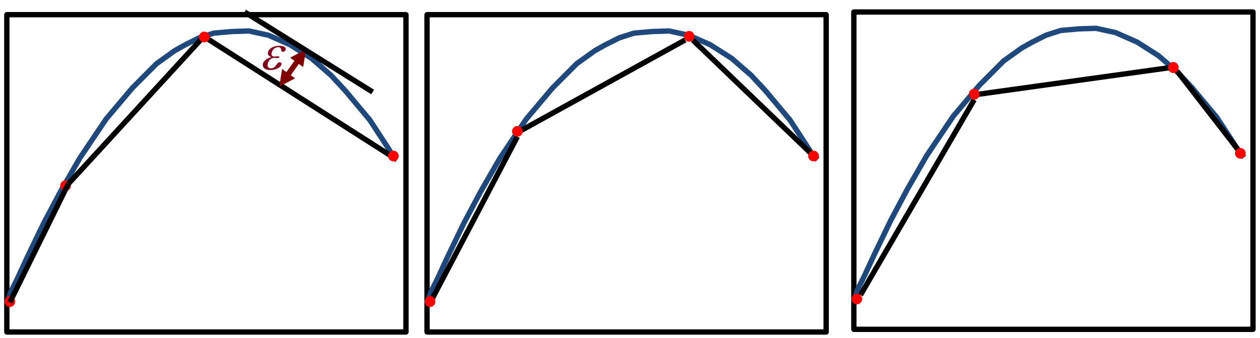

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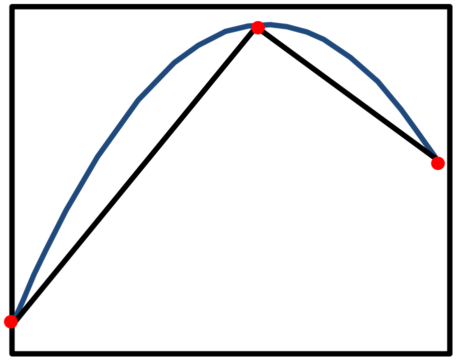

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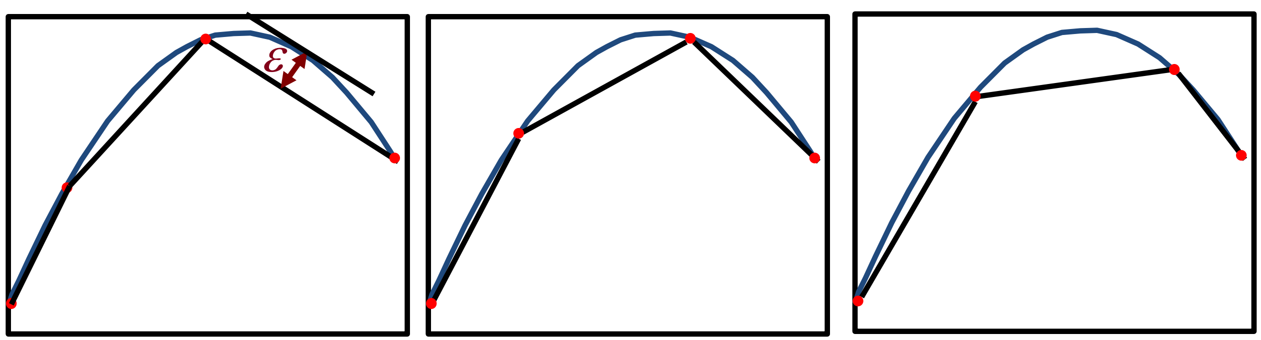

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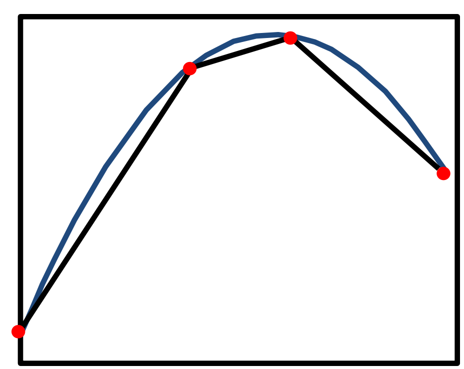

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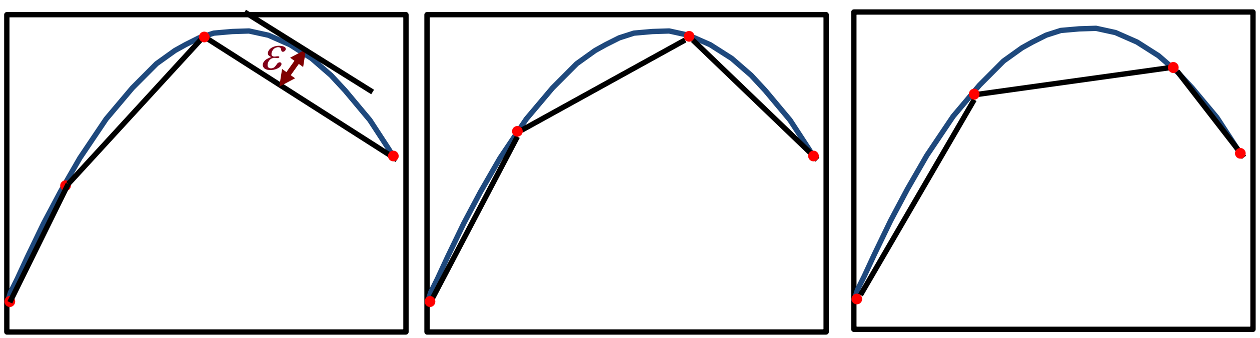

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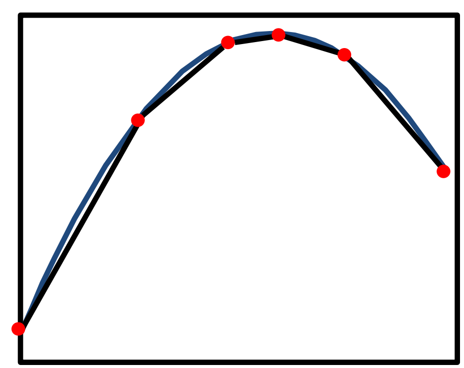

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Globally-Optimal Polygonal Approximation

Given: **Set of nonlinear curves and desired # of segments**

Find: **Globally optimal polygonal approximation**

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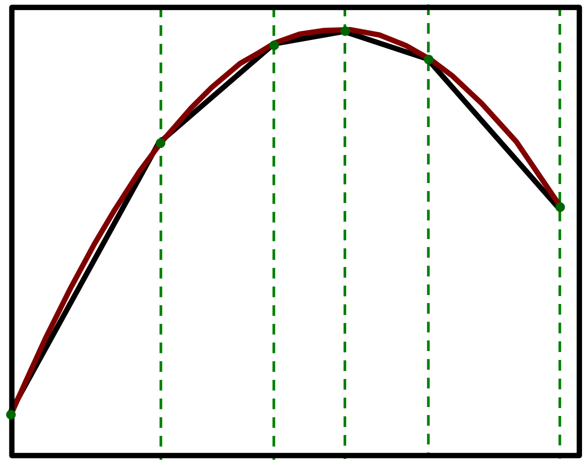

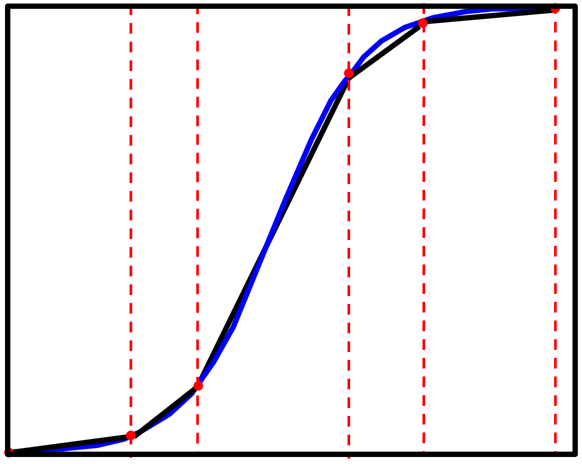

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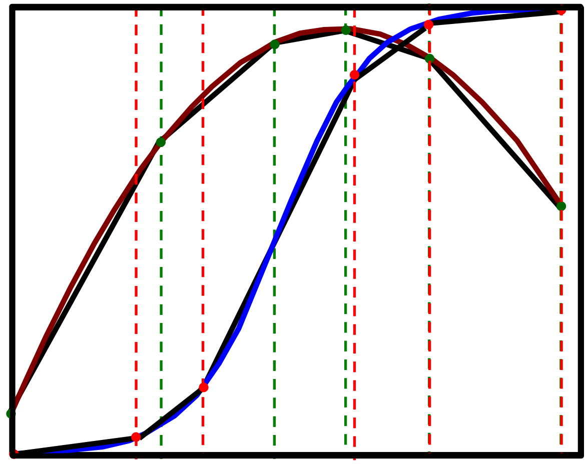

Combining the two we obtain 8 segments and not 5 segments

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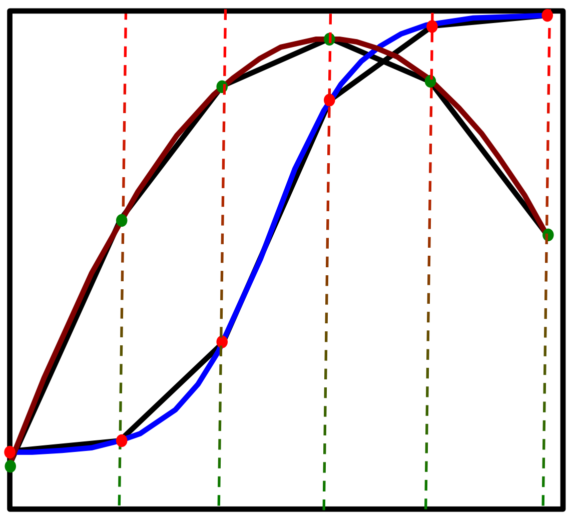

Solution: modify the OPAA to minimize the maximum error of a set of curves simultaneously.

Deriving the Piecewise Multi-Affine Model

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

$$\dot u = e + (u - \theta_v)(u_u - u)v\, g_{fi} + ws\, g_{si} - g_{so}(u)$$
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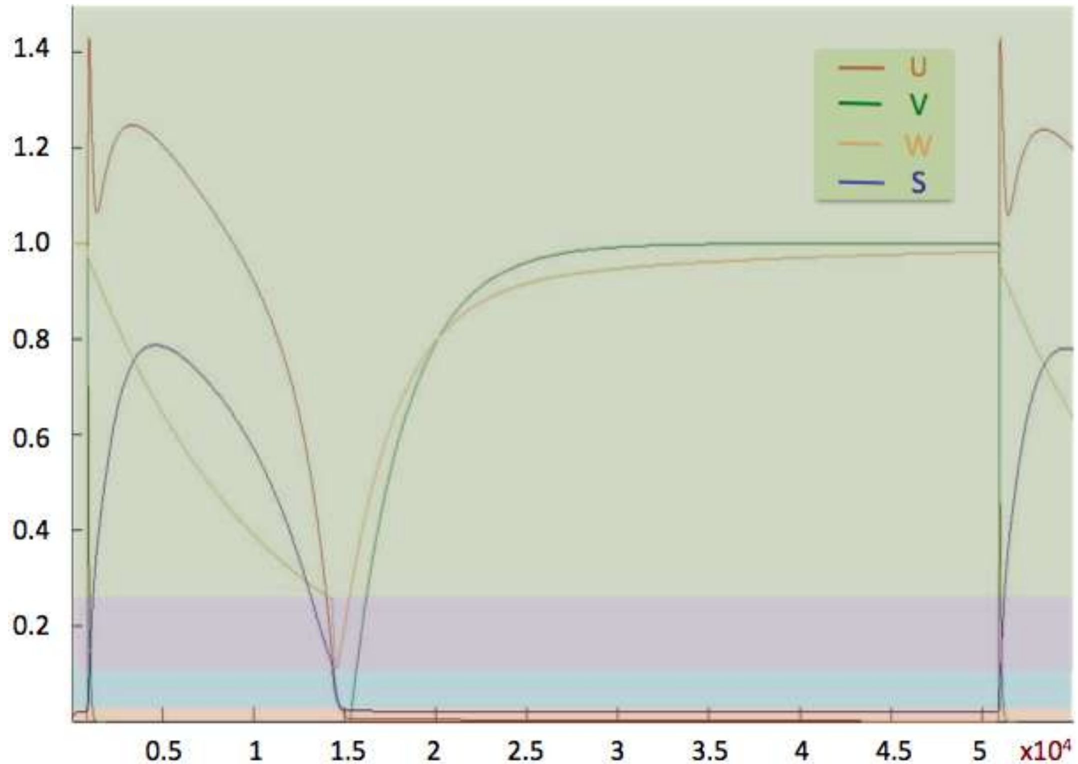

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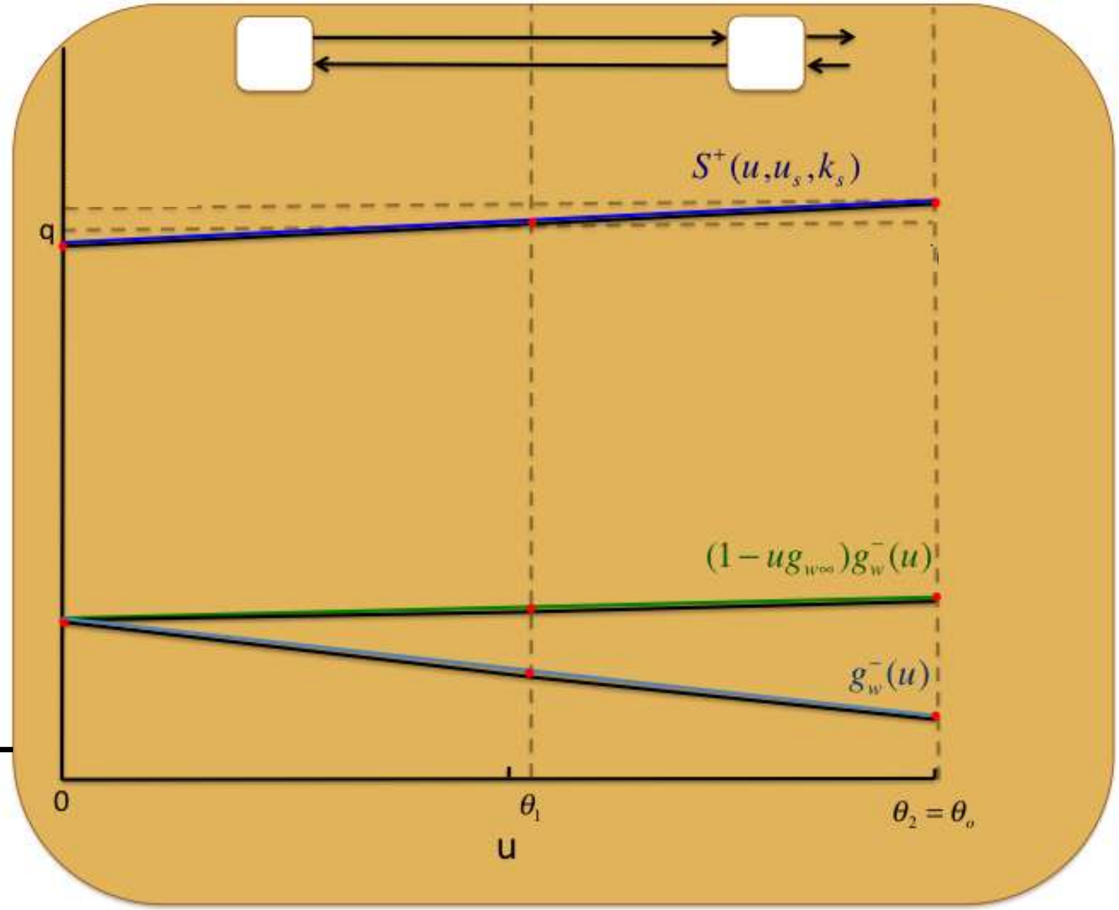

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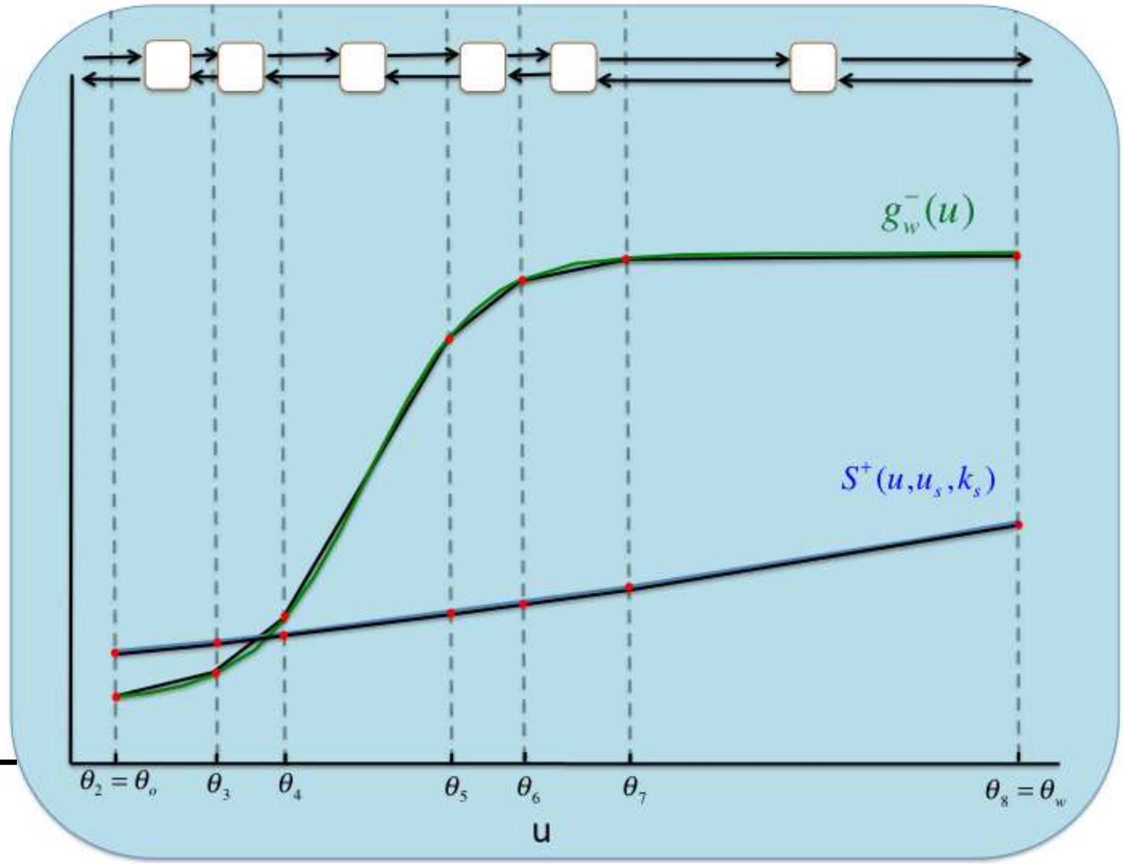

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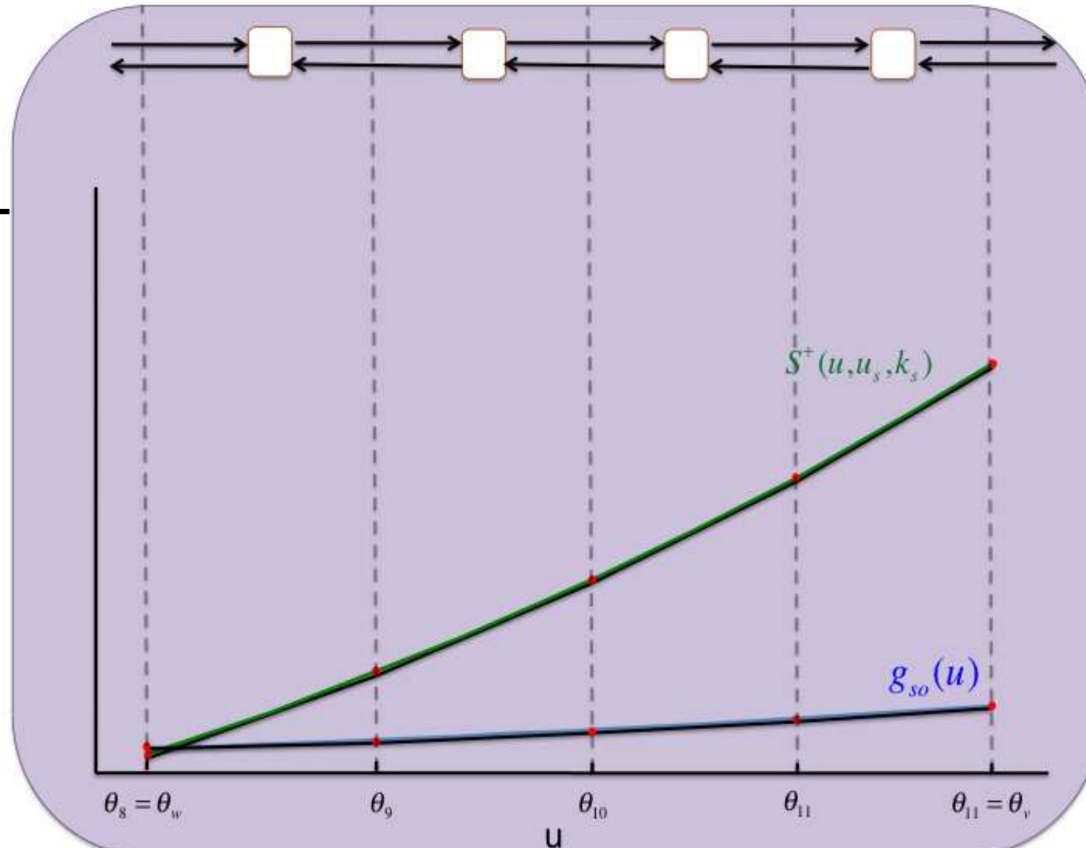

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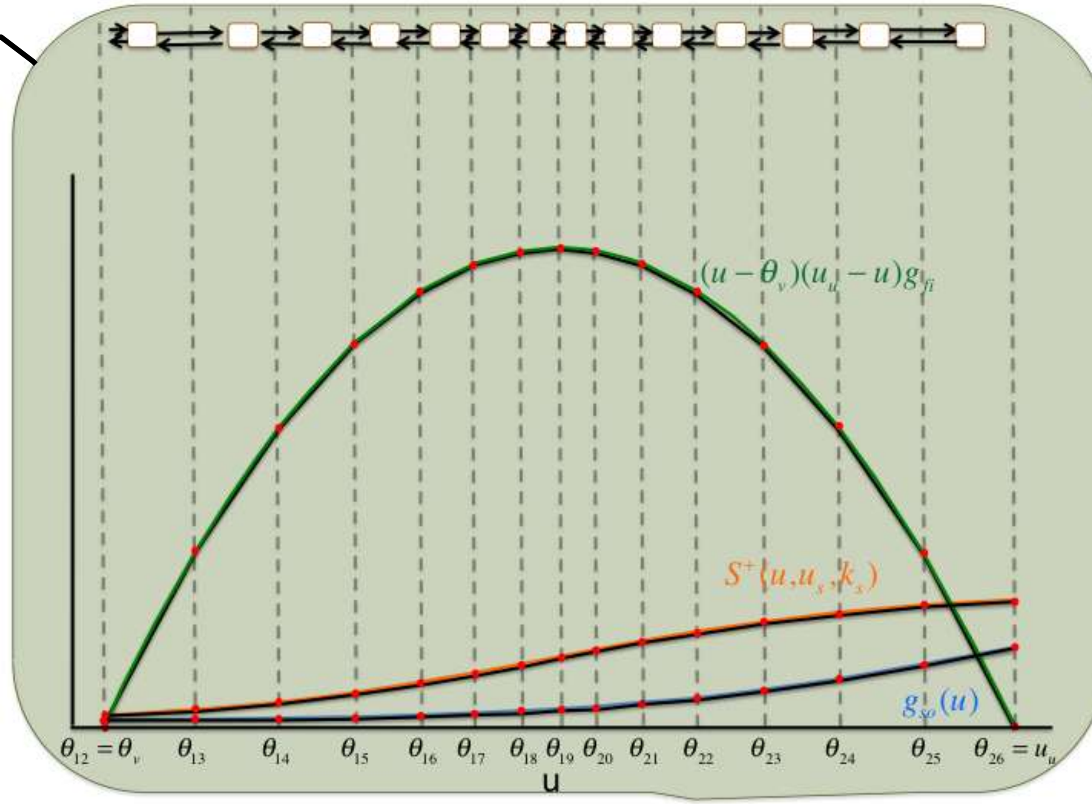

Deriving the Piecewise Multi-Affine Model

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

$$\dot{u} = e + \sum_{i=12}^{25} R(u,\theta_i,\theta_{i+1},u_{fi_i},u_{fi_{i+1}})\, v\, g_{fi} + ws\, g_{si} - \sum_{i=12}^{25} R(u,\theta_i,\theta_{i+1},u_{so_i},u_{so_{i+1}})\, g_{so}$$

$$\dot{v} = -v\, g_v^+$$

$$\dot{w} = -w\, g_w^+$$

$$\dot{s} = \left(\sum_{i=12}^{25} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s\right) g_{s_2}$$

$u < \theta_v$

$u \ge \theta_v$

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

$$\dot{u} = e + ws\, g_{si} - \sum_{i=8}^{11} R(u,\theta_i,\theta_{i+1},u_{so_i},u_{so_{i+1}})\, g_{so}$$

$$\dot{v} = -v\, g_{v_2}^-$$

$$\dot{w} = -w\, g_w^+$$

$$\dot{s} = \left(\sum_{i=8}^{11} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s\right) g_{s_2}$$

$u < \theta_w$

$u \ge \theta_w$

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

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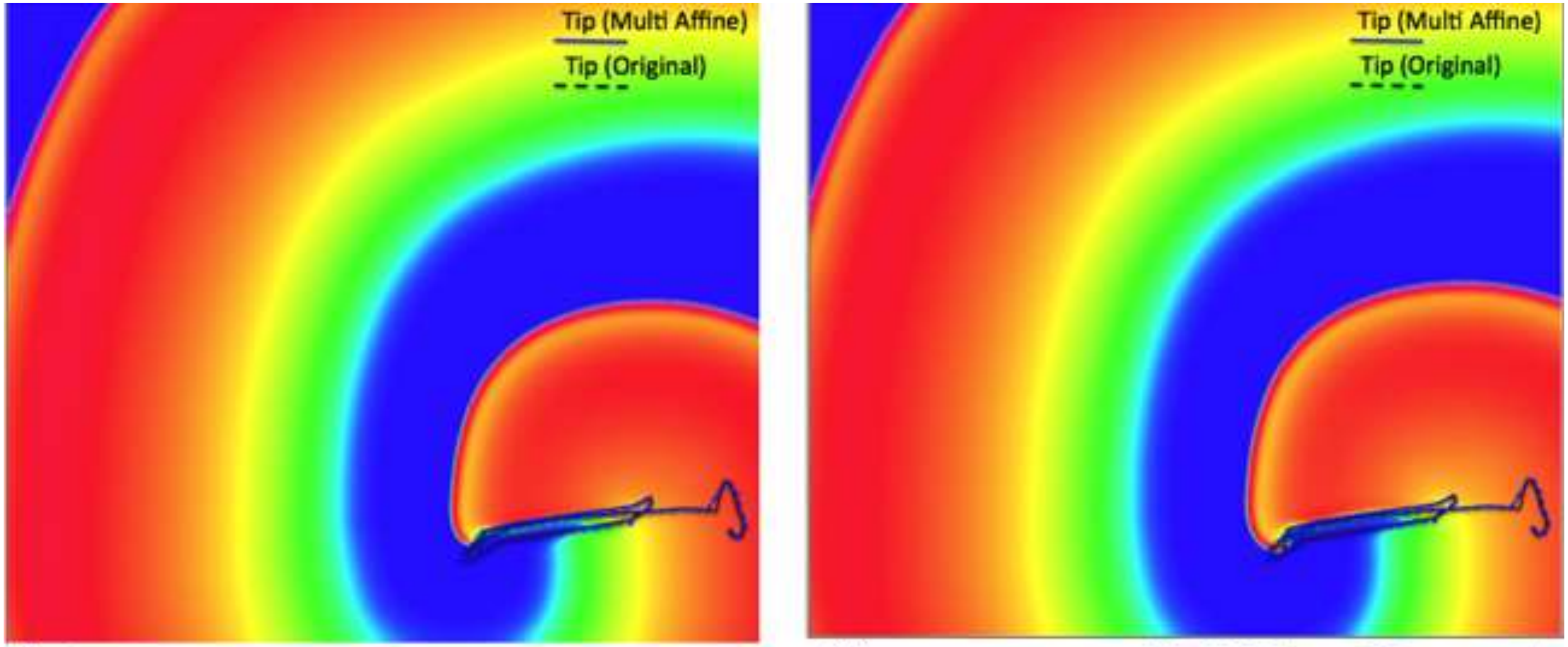
2D Comparison



(a) Original MRM

(b) Multi Affine (26 ramps)

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  - **Restated as an LTL formula:** $G\ (u < \theta_v)$

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$$g_{o_1} \in [1, 180] \quad g_{o_2} \in [0, 10] \quad g_{si} \in [0.1, 100] \quad g_{so} \in [0.9, 50]$$

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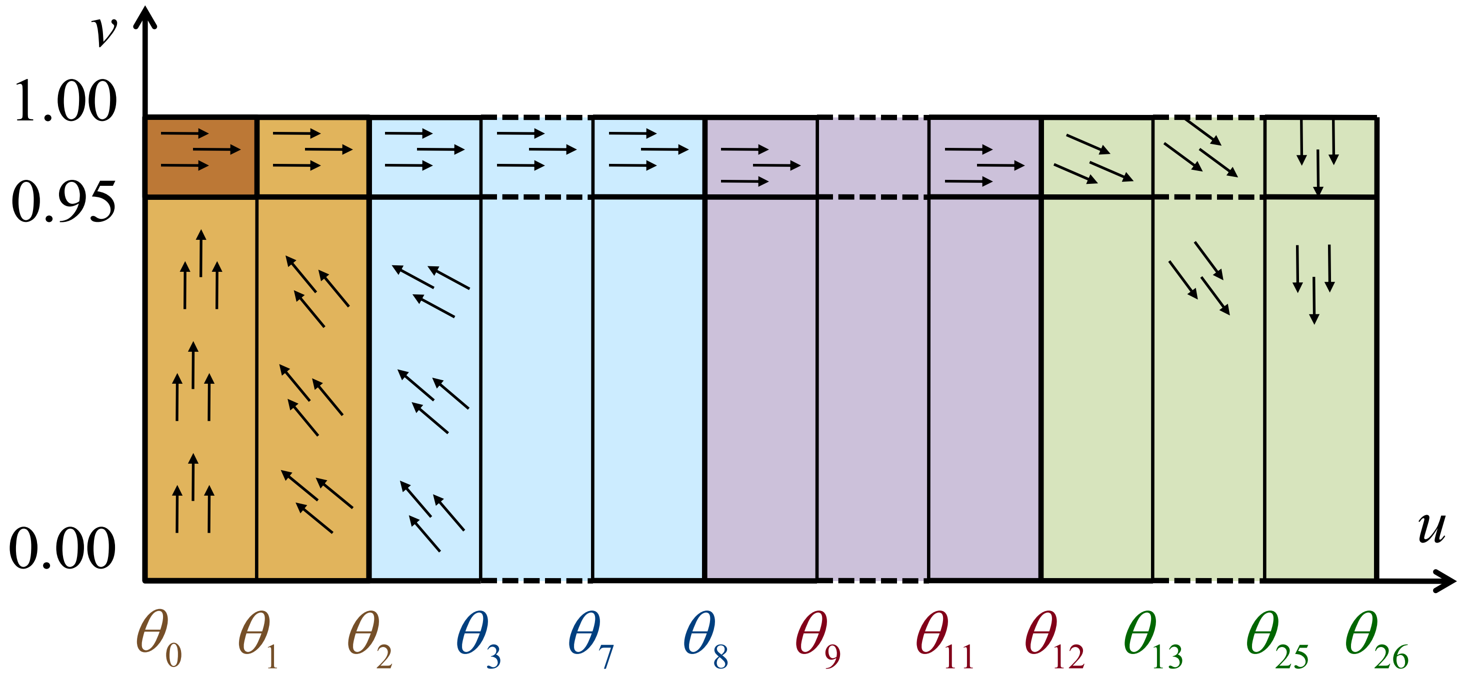
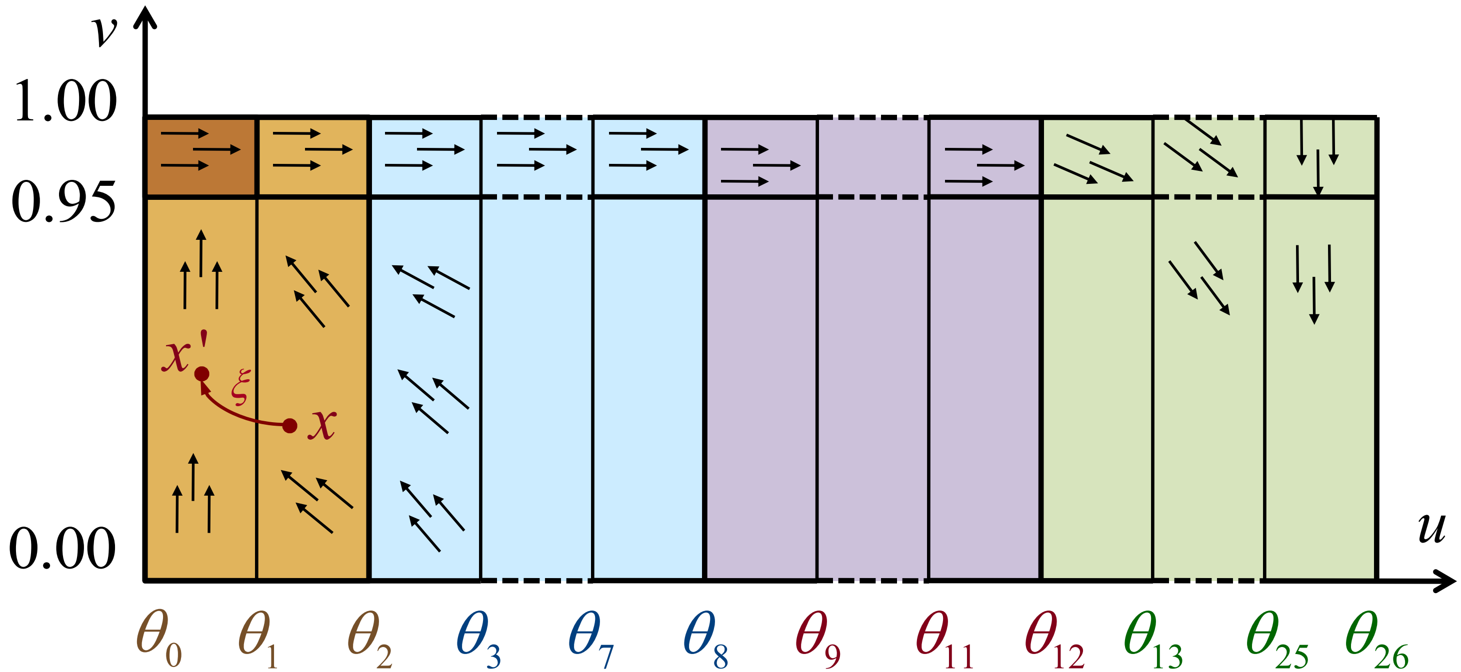
- **Stimulus:** $e = 1$

State Space Partition



- **Hyperrectangles: 4 dimensional (uv-projection)**
  - **Arrows: indicate the vector field**

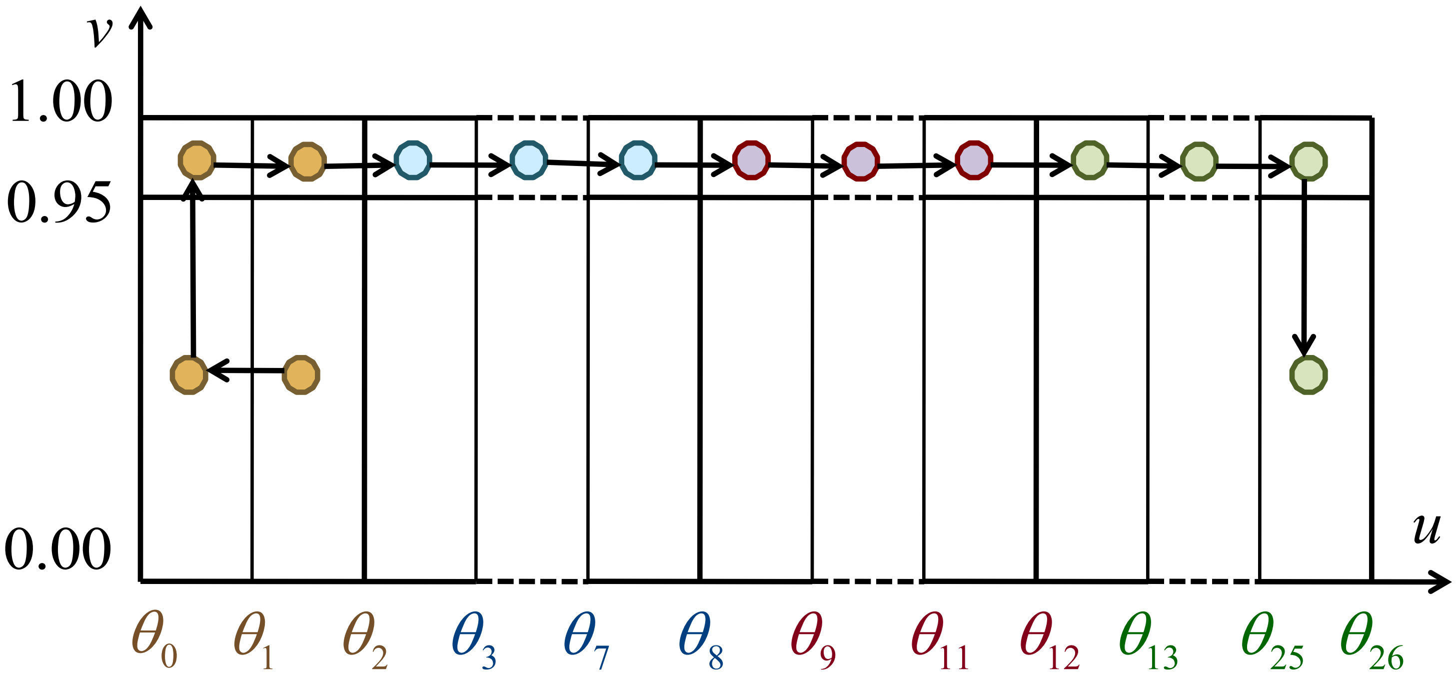
Embedding Transition System $T_X(p)$



$x \xrightarrow{T_X(p)} x'$ **iff** there is a **solution** ξ and **time** τ such that:

- $\xi(0) = x, \quad \xi(\tau) = x'$
- $\forall t \in [0, \tau].\ \xi(t) \in rect(x) \cup rect(x')$
- $rect(x)$ is adjacent to $rect(x')$

The Discrete Abstraction $T_R(p)$



$x \sim_{R(p)} x'$ **iff** $rect(x) = rect(x')$

$T_R(p)$ **is the quotient of** $T_X(p)$ **with respect to** $\sim_{R(p)}$

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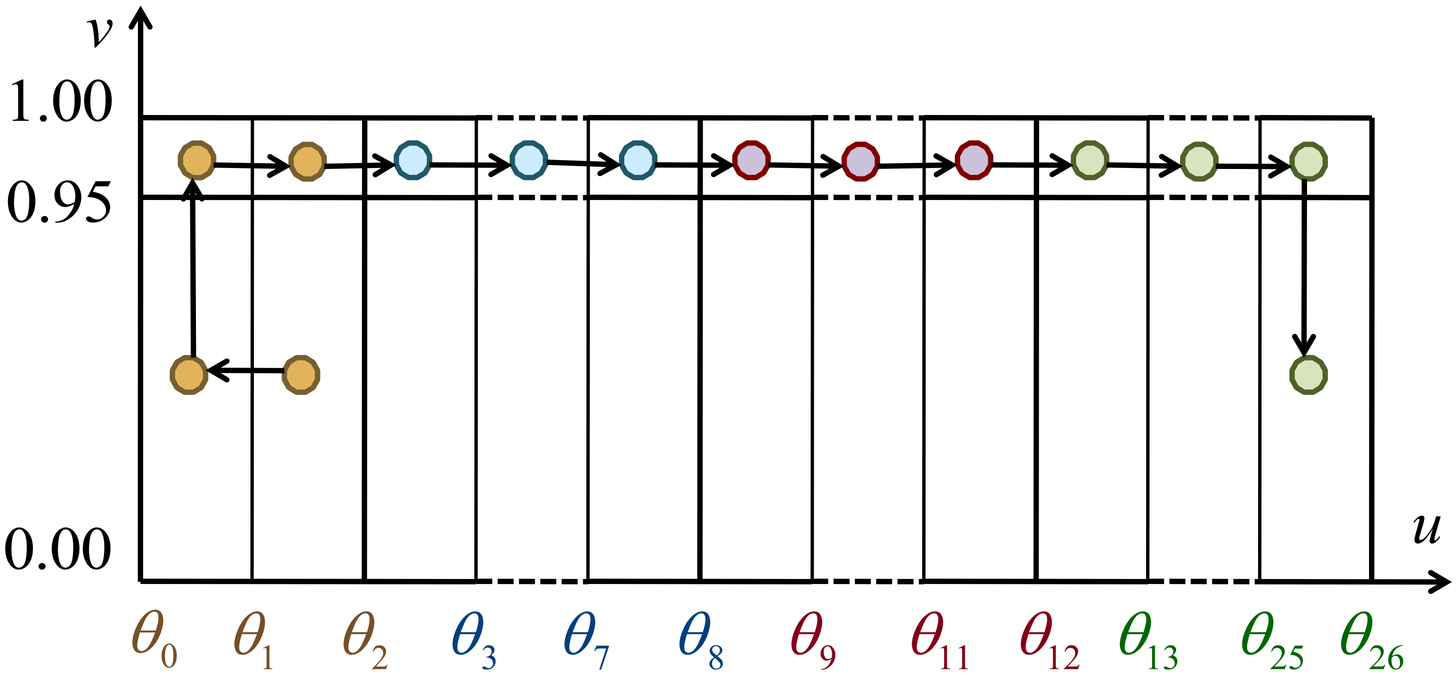

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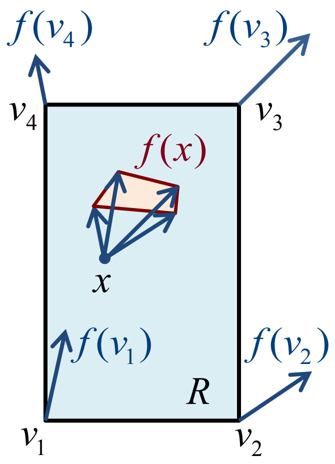
Theorem: $\forall p.\ T_X(p) \leq T_R(p)$

Computing $T_R(p)$



Theorem: If *f* is multi-affine then

$$\forall x \in R. f(x) \in cHull(\{f(v) \mid v \in V_R\})$$

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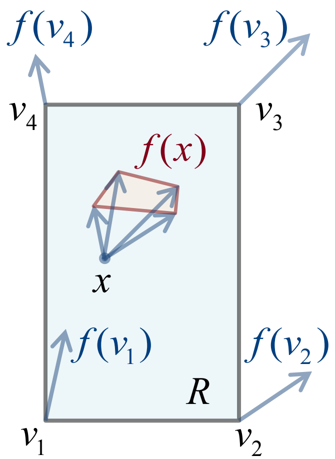

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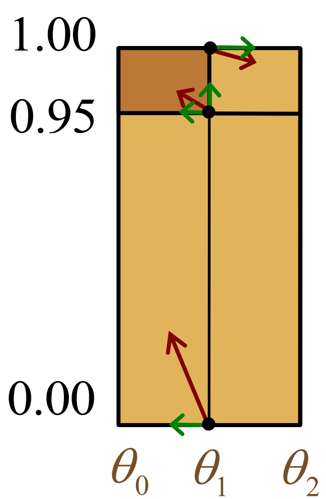
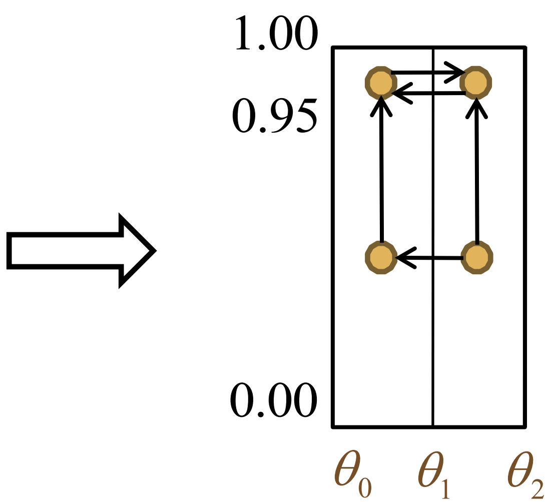
Corollary:

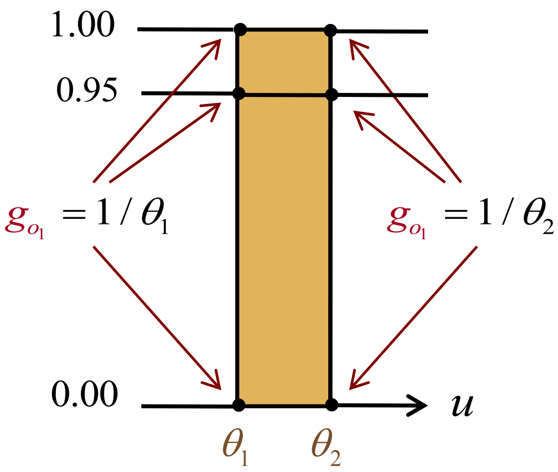




Partitioning the Parameter Space

- **In each vertex: affine equation in the parameters**

$$\dot{u} = 1 - u\, g_{o_1} = 0$$



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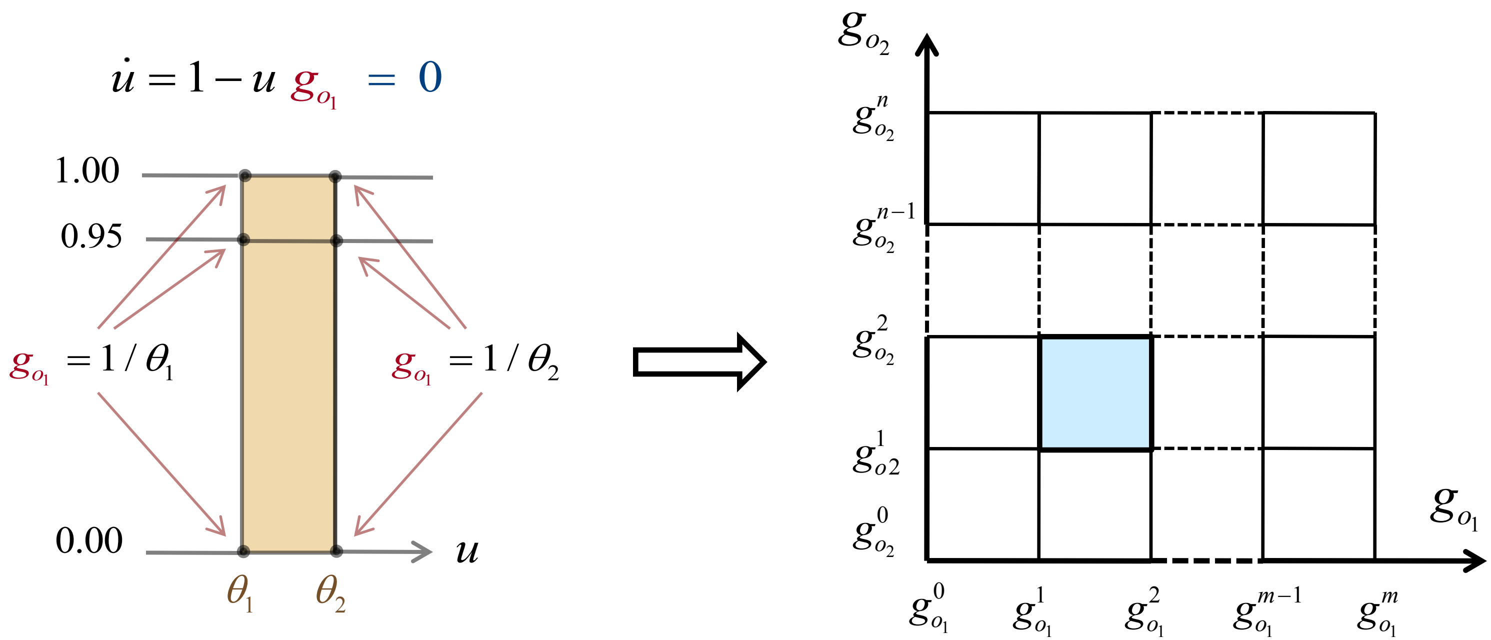
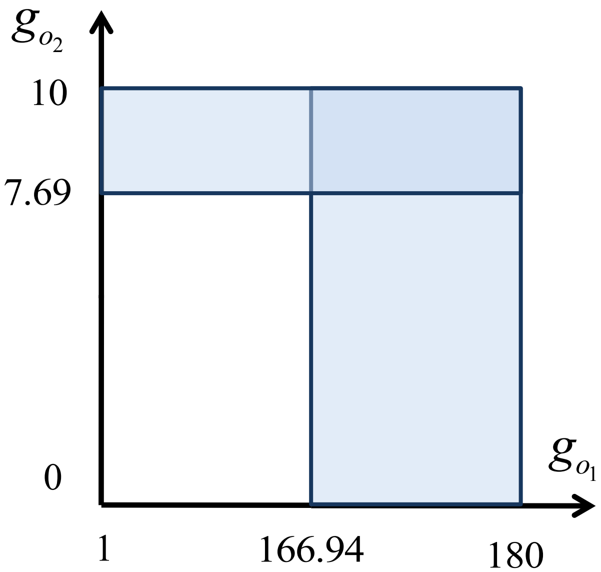
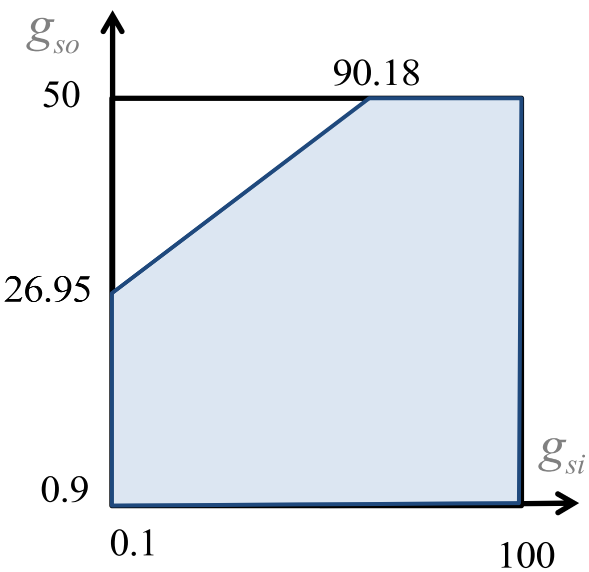


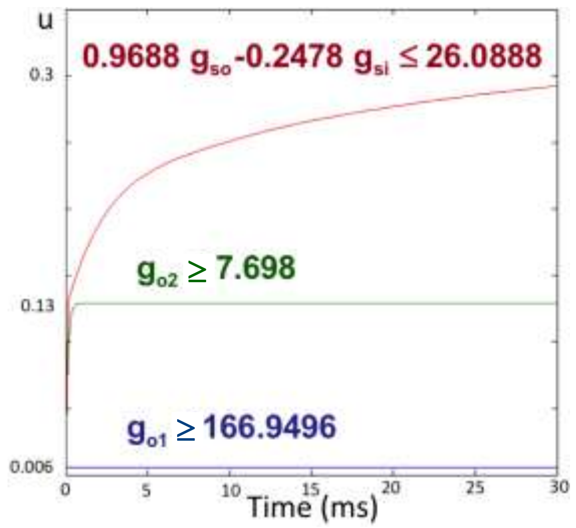
- **Parameter space:** 4 dimensional (g_{o_1}/g_{o_2} projection)
  - **Each rectangle:** a different transition system

Results

- **Rovergene:** **intelligently explores the PS rectangles**







independent **linearly dependent** **simulation**

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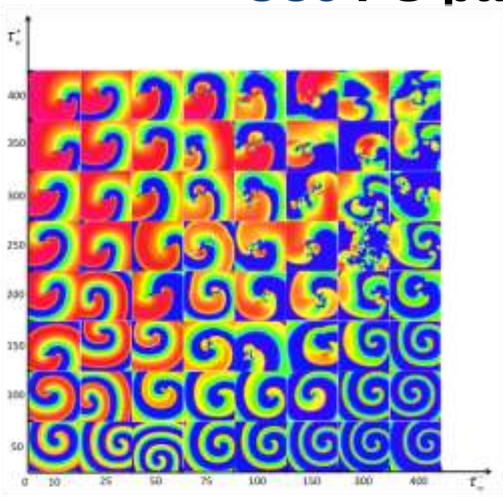

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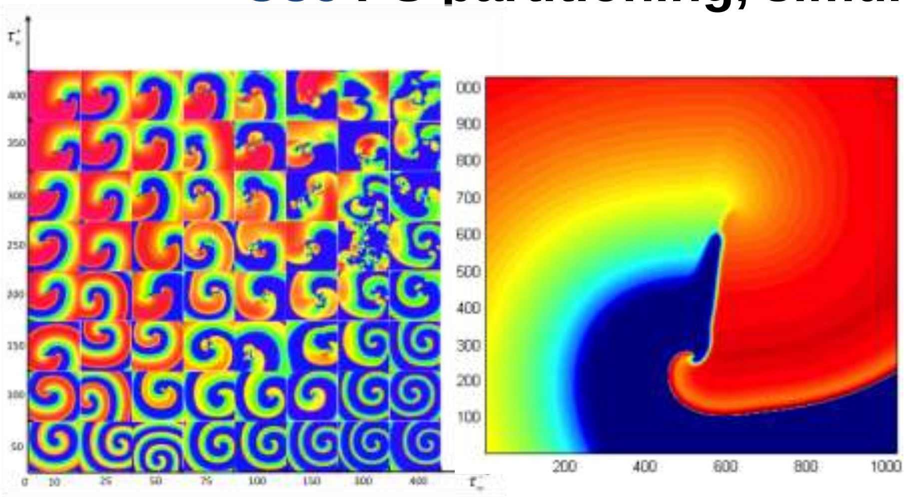

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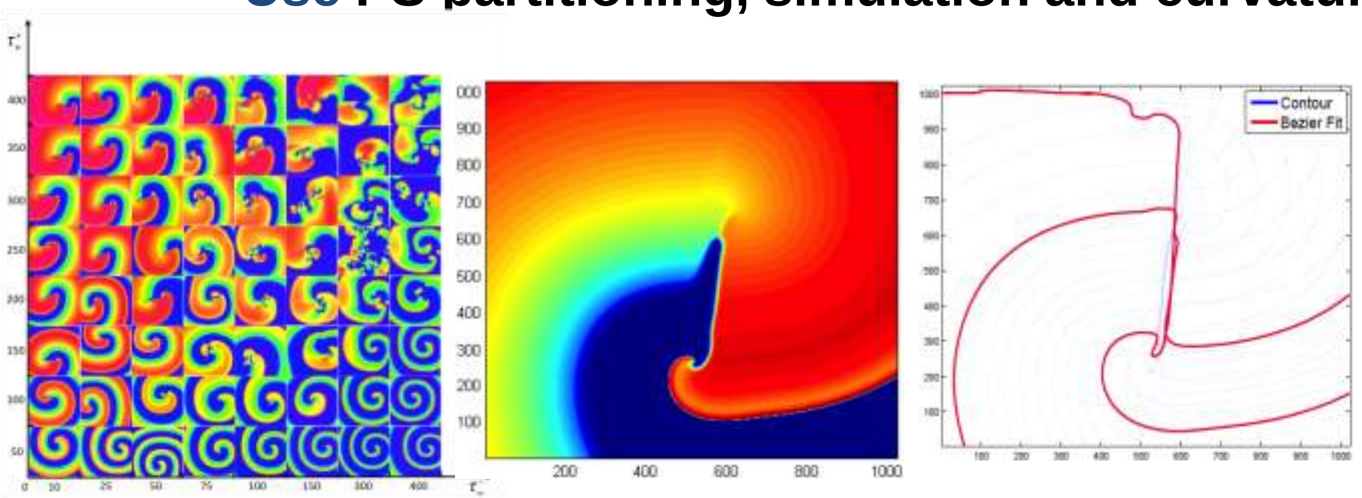

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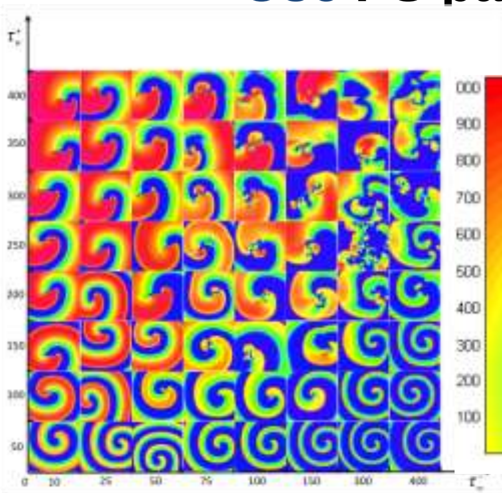

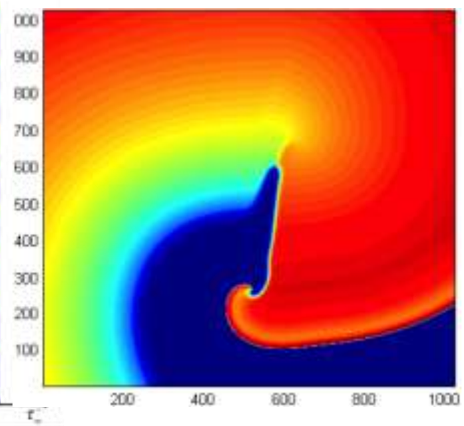

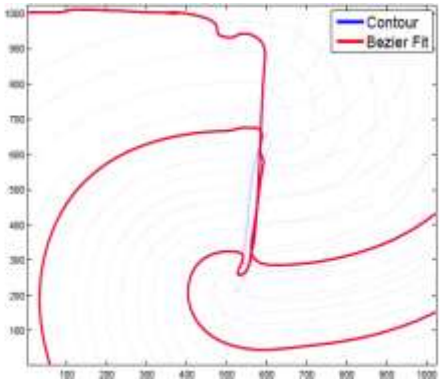

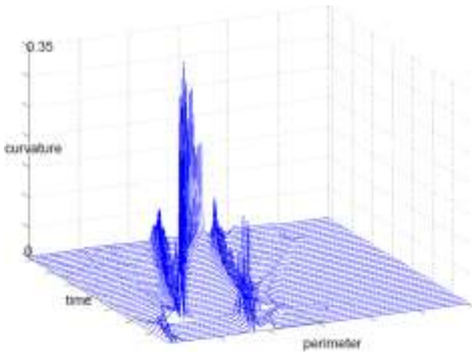

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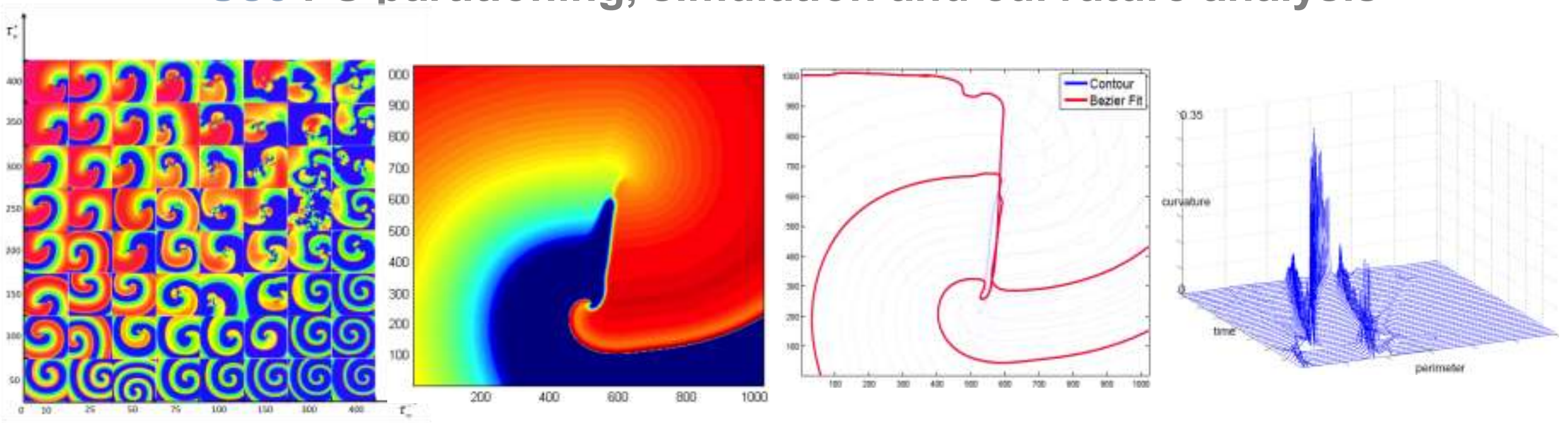

- Derive the MRM from Iyer model through TS abstraction