Automatic Parameter-Range Estimation for Cardiac Cells

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SUNY at Stony Brook

Joint work with

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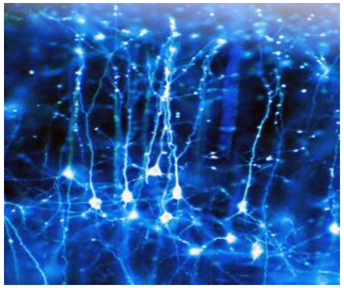
James Glimm, Colas Le Guernic, and Scott A. Smolka

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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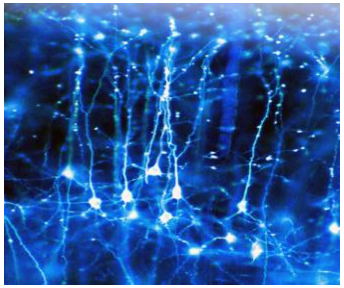
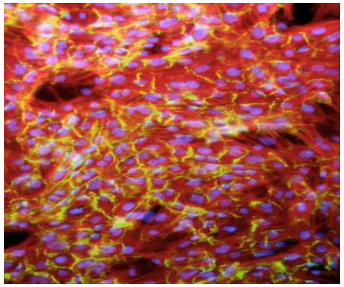


Neurons of a squirrel
University College London



Artificial cardiac tissue
University of Washington

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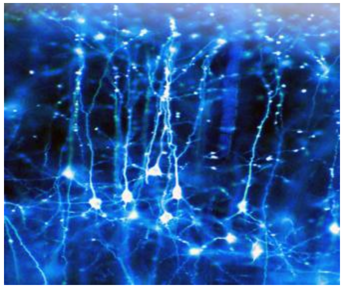

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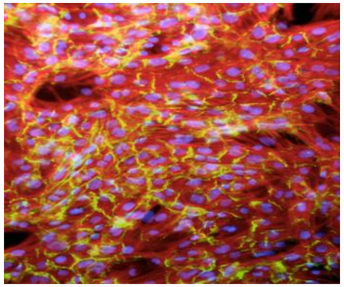

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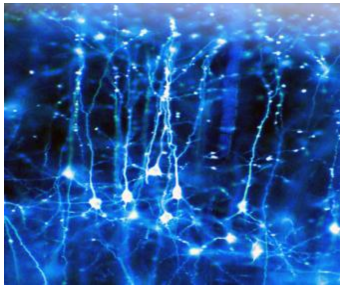

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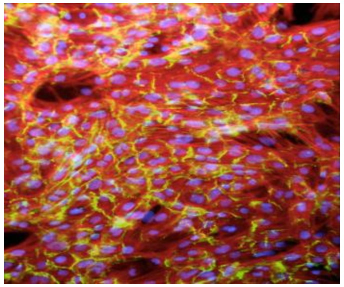

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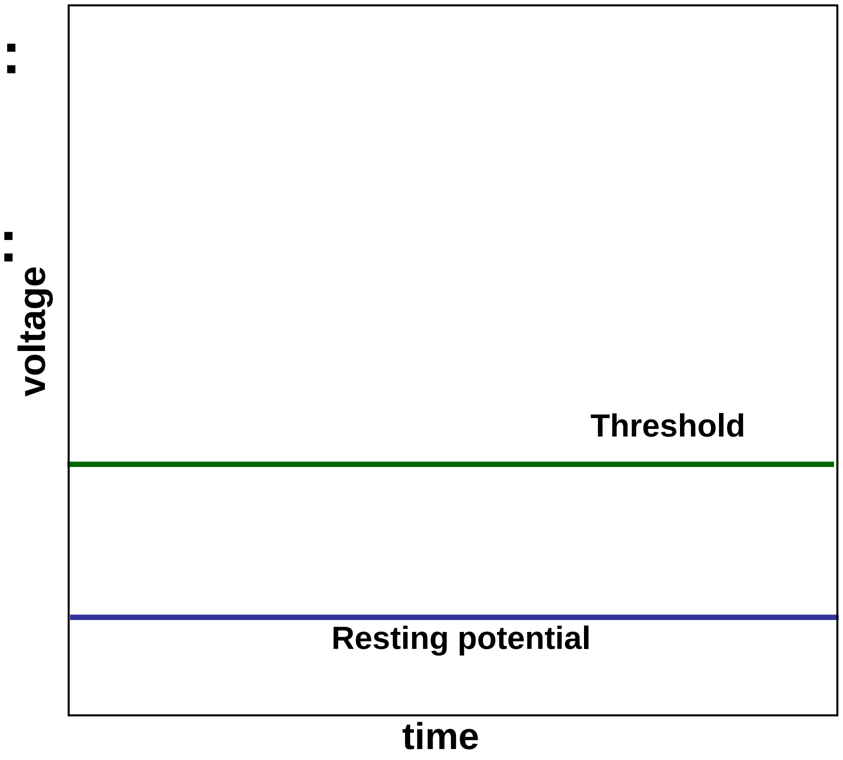
Single Cell Reaction: Action Potential

Membrane's AP depends on:

- **Stimulus** (voltage or current):
  - External / Neighboring cells
- **Cell's state** (excitable or not):
  - Parameters value

Schematic Action Potential



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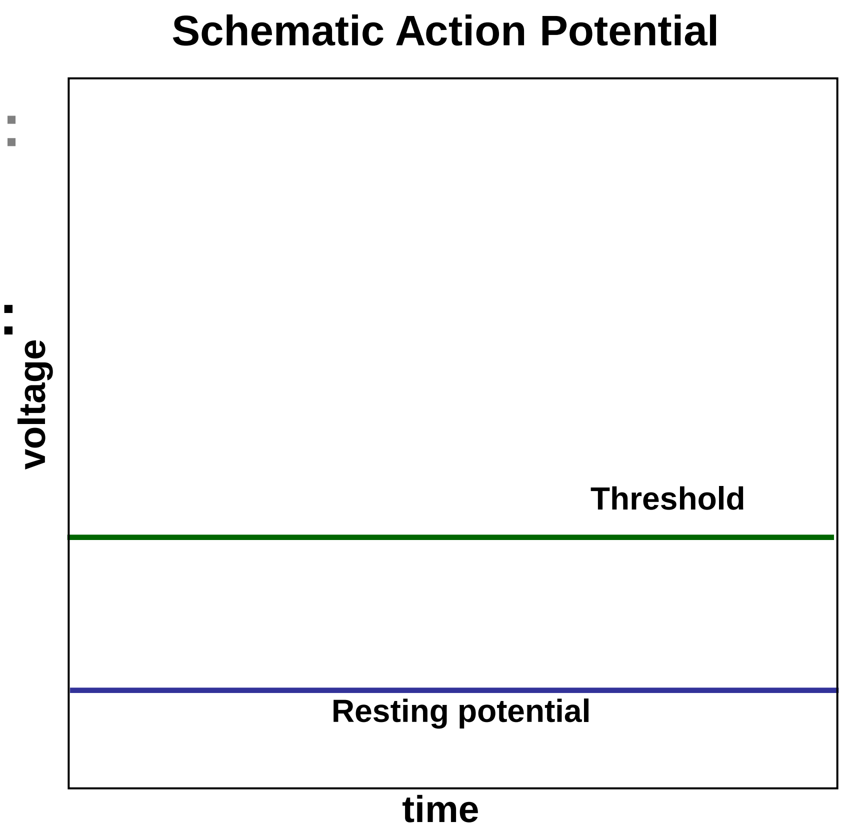

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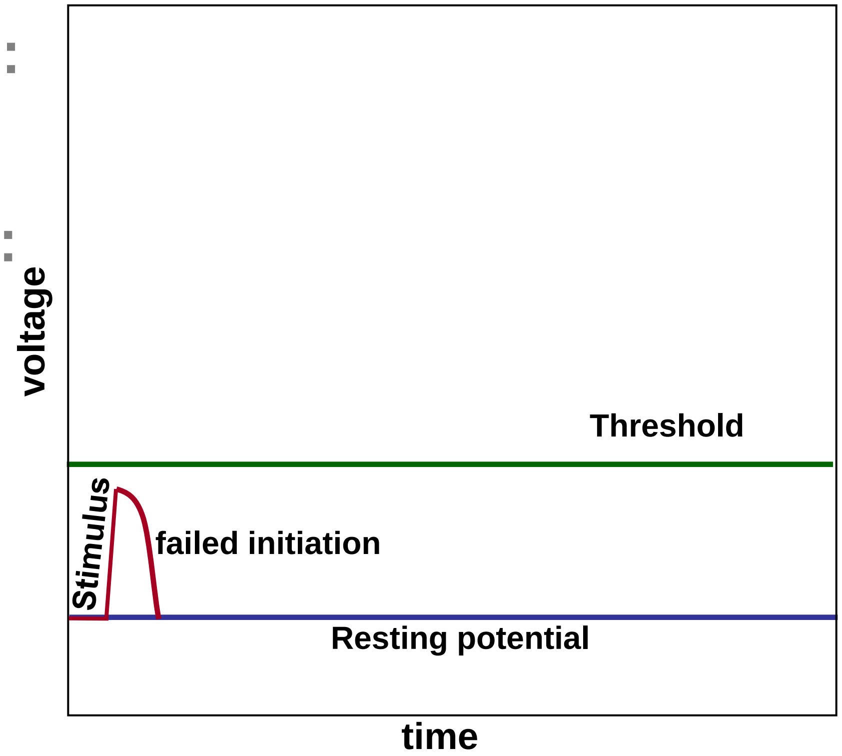

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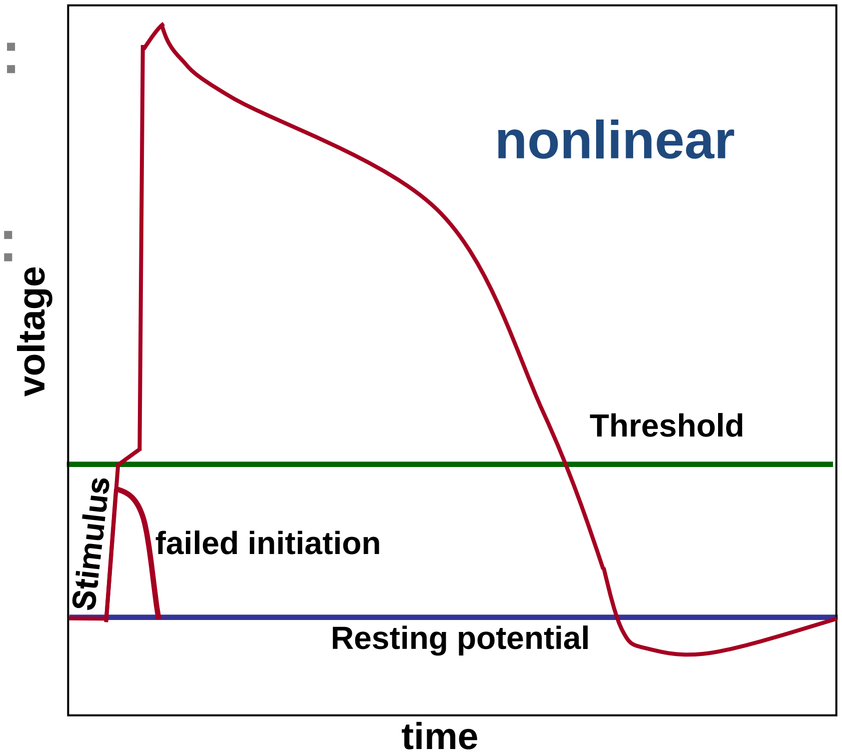

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$$\frac{\partial \mathbf{u}}{\partial t} = R(\mathbf{u}) + \nabla(D\nabla \mathbf{u})$$

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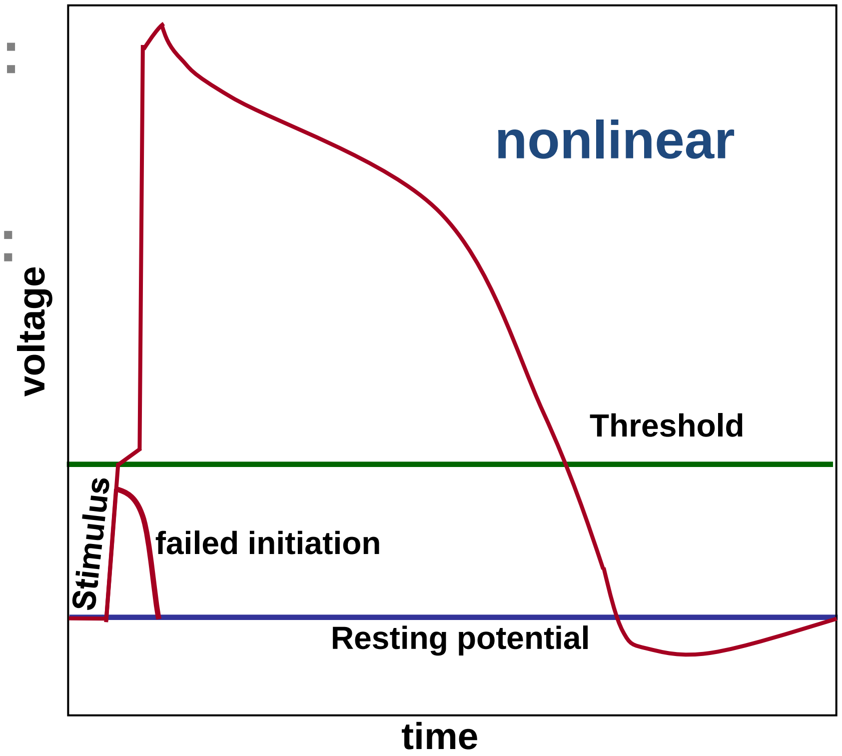

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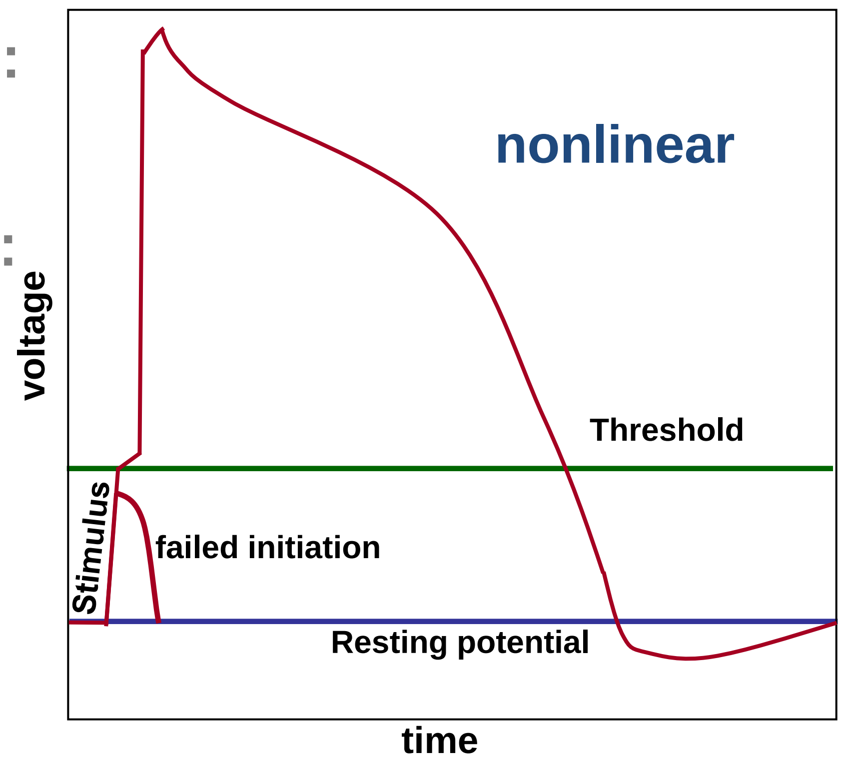

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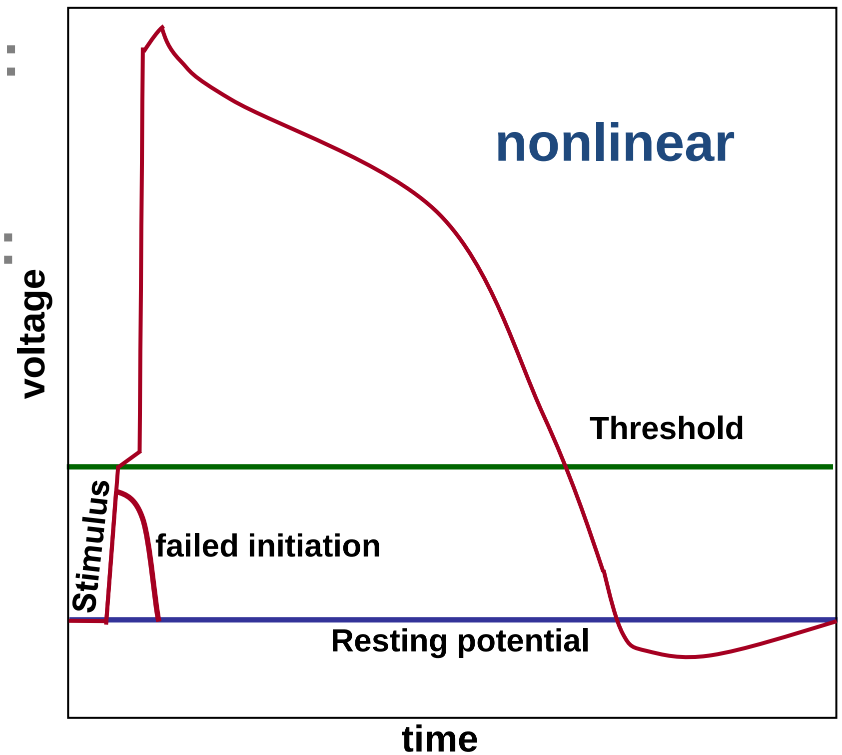

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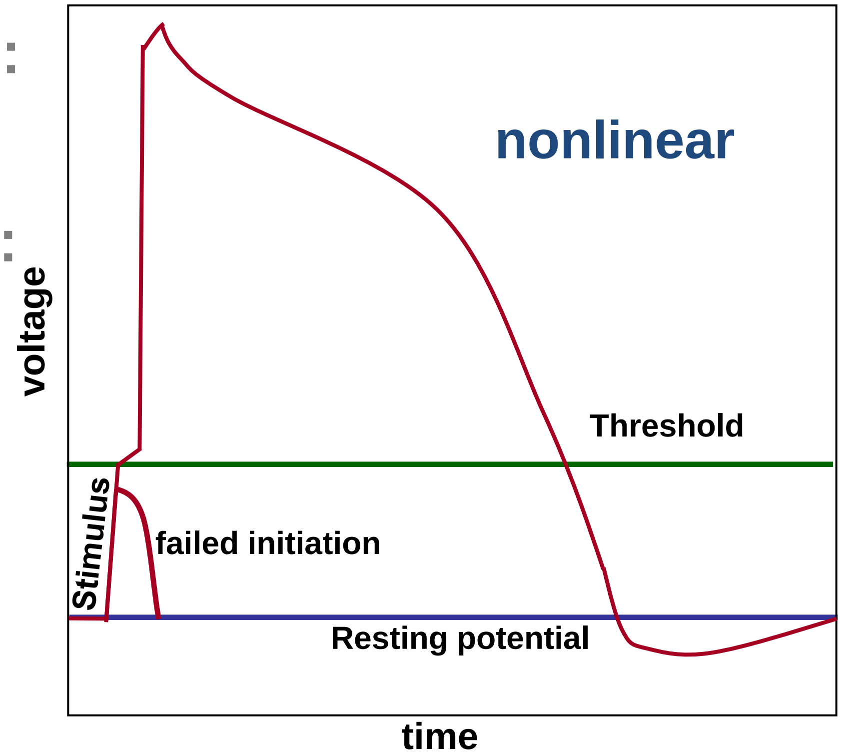
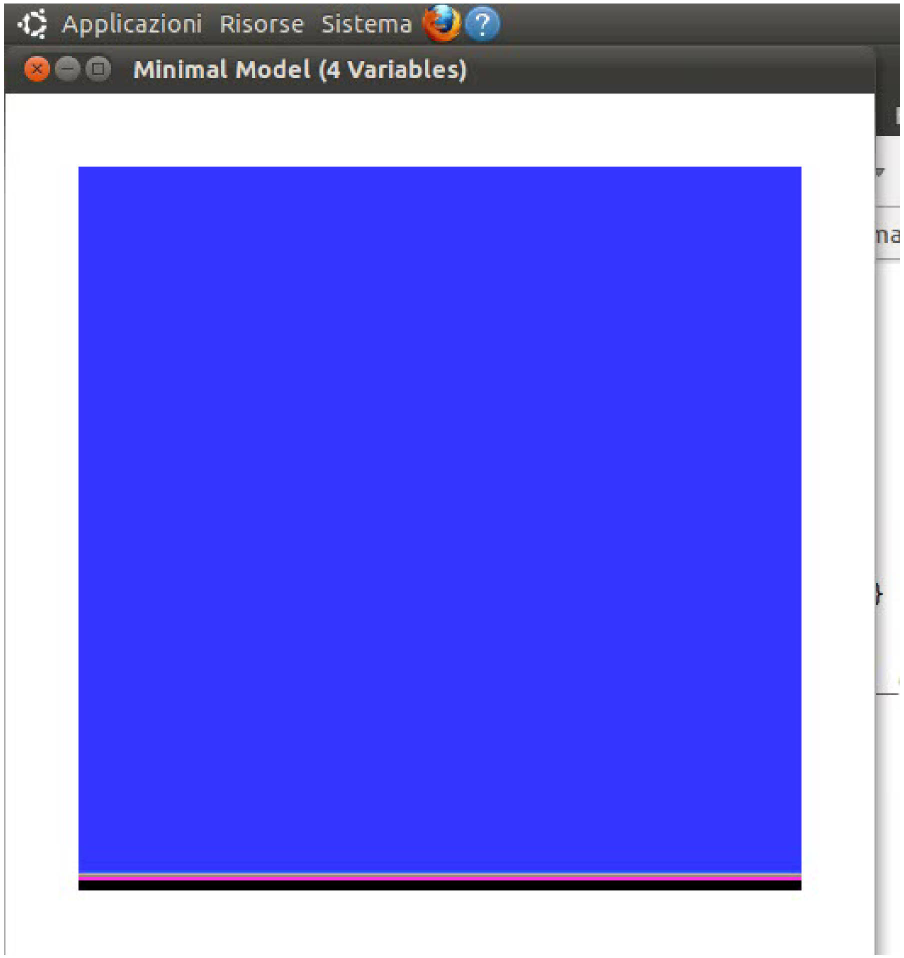
Diffusion

Schematic Action Potential

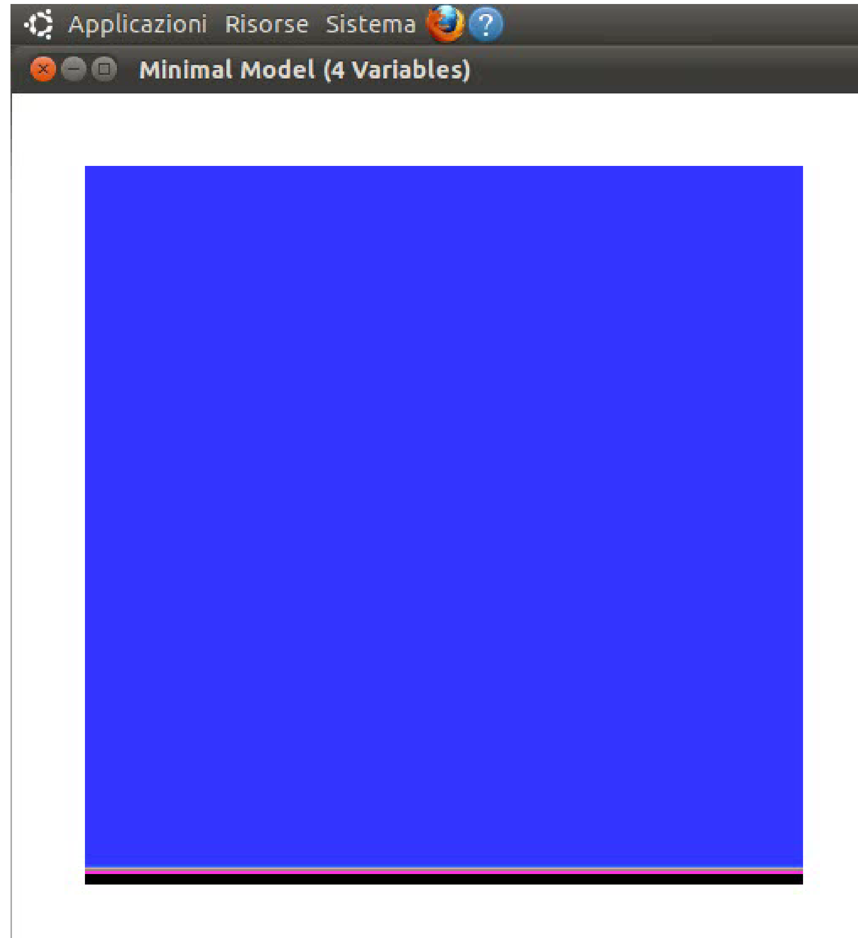


Lack of Excitability: Implications

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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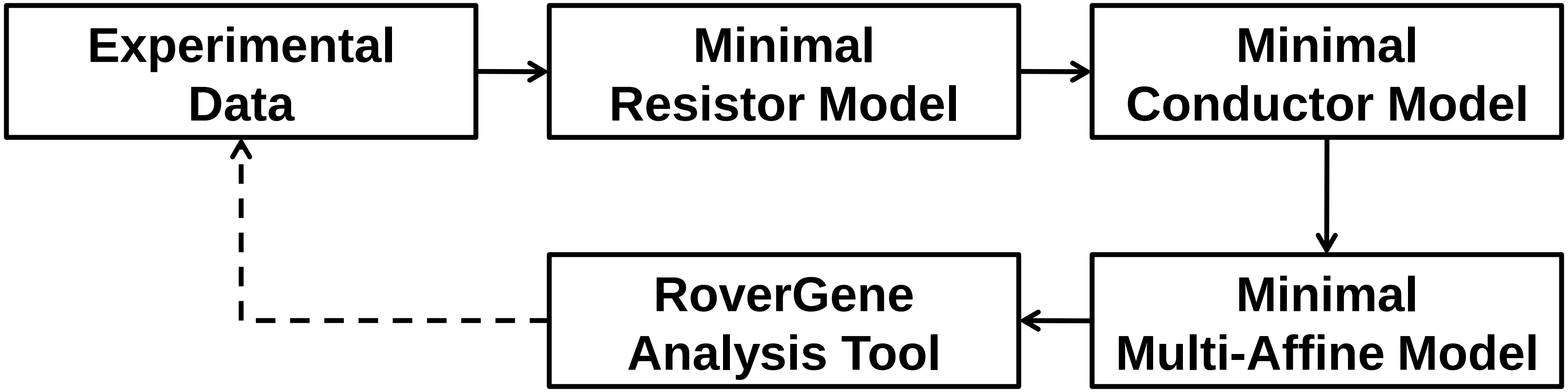
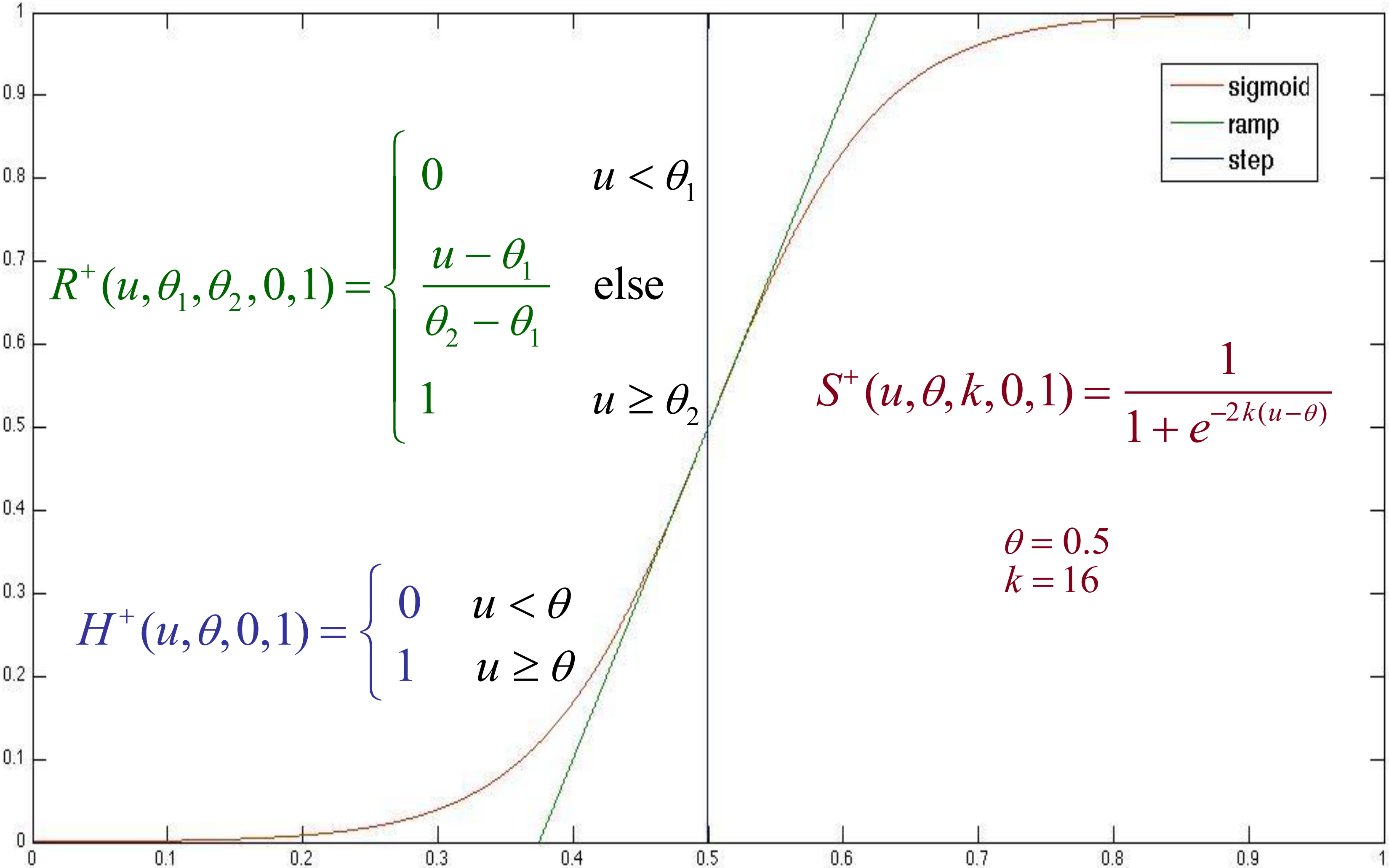


Biological Switching



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

$$S^{+}(u,\theta,k,0,1)=\frac{1}{1+e^{-2k(u-\theta)}}$$

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

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

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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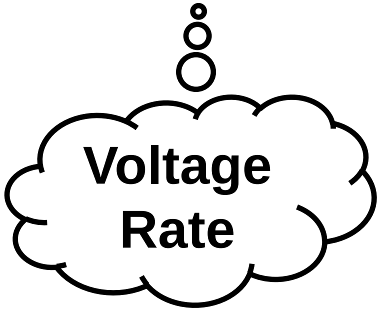

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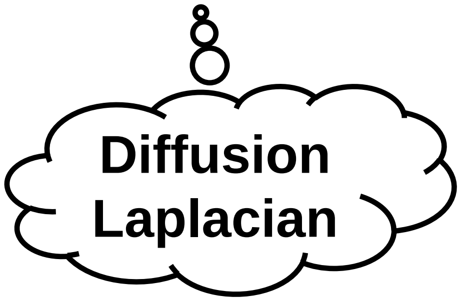

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Fast input current

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Slow input current

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Slow output current

MRM: Currents Equations

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

$$J_{fi}(u,v) = -H^{+}(u,\theta_v,0,1)\ (u-\theta_v)(u_u - u)v / \tau_{fi}$$

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

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

MRM: Currents Equations

Heaviside (step)

$$\dot{u}(u,v,w,s) = \nabla(D\nabla u) \ldots \text{[illegible]} \ldots w,s) + J_{so}(u))$$

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MRM: Currents Equations

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

Constant
Resistanc
e

$$J_{fi}(u,v) = -H^{+}(u,\theta_v,0,1)\ (u-\theta_v)(u_u - u)v / \tau_{fi}$$

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Piecewise Nonlinear

MRM: Currents Equations

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

Piecewise Bilinear

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**Piecewise
Resistanc
e**

**Sigmoidal
Resistanc
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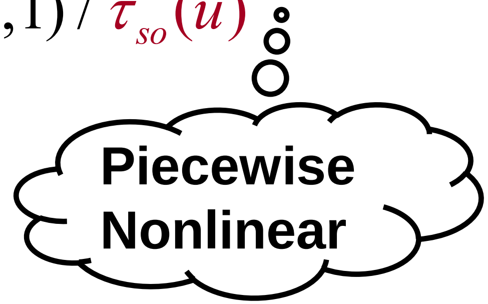

MRM: Gates ODEs

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

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

$$\dot{v}(u,v) = H^{-}(u,\theta_v,0,1)\ (v_\infty - v)\ / \tau_v^{-}(u) - H^{+}(u,\theta_v,0,1) v\ / \tau_v^{+}$$

$$\dot{w}(u,w) = H^{-}(u,\theta_w,0,1)(w_\infty - w) / \tau_w^{-}(u) - H^{+}(u,\theta_w,0,1) w / \tau_w^{+}$$

$$\dot{s}(u,s) = (S^{+}(u,u_s,k_s,0,1) - s) / \tau_s(u)$$

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

Piecewise Resistance

$$\dot{v}(u,v) = H^{-}(u,\theta_v,0,1)\ (v_\infty - v)\ /\tau_v^{-}(u) - H^{+}(u,\theta_v,0,1)v\ /\tau_v^{+}$$

$$\dot{w}(u,w) = H^{-}(u,\theta_w,0,1)(w_\infty - w)/\tau_w^{-}(u) - H^{+}(u,\theta_w,0,1)w/\tau_w^{+}$$

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$$\dot{s}(u,s) = (S^{+}(u,u_s,k_s,0,1) - s)/\tau_s(u)$$

Sigmoidal Resistance

Sigmoid

MRM: Voltage-Controlled Resistances/SSV

$$\tau_v^-(u) = H^-(u,\theta_o,0,1)\ \tau_{v_1}^- + H^+(u,\theta_o,0,1)\ \tau_{v_2}^-$$

$$\tau_s(u) = H^-(u,\theta_w,0,1)\ \tau_{s_1} + H^+(u,\theta_w,0,1)\ \tau_{s_2}$$

$$\tau_o(u) = H^-(u,\theta_o,0,1))\ \tau_{o_1} + H^+(u,\theta_o,0,1)\ \tau_{o_2}$$

Piecewis
e
Constant

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$$\tau_o(u) = H^-(u,\theta_o,0,1))\ \tau_{o_1} + H^+(u,\theta_o,0,1)\ \tau_{o_2}$$

Piecewis
e
Constant

$$\tau_w^-(u) = \tau_{w_1}^- + (\tau_{w_2}^- - \tau_{w_1}^-)\ S^+(u,u_s,k_w^-,0,1)$$

$$\tau_{so}(u) = \tau_{so_1} + (\tau_{so_2} - \tau_{so_1})\ S^+(u,u_s,k_{so},0,1)$$

Sigmoidal

MRM: Voltage-Controlled Resistances/SSV

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Piecewis
e
Constant

$$\tau_w^-(u) = \tau_{w_1}^- + (\tau_{w_2}^- - \tau_{w_1}^-)\ S^+(u,u_s,k_w^-,0,1)$$

Sigmoidal

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

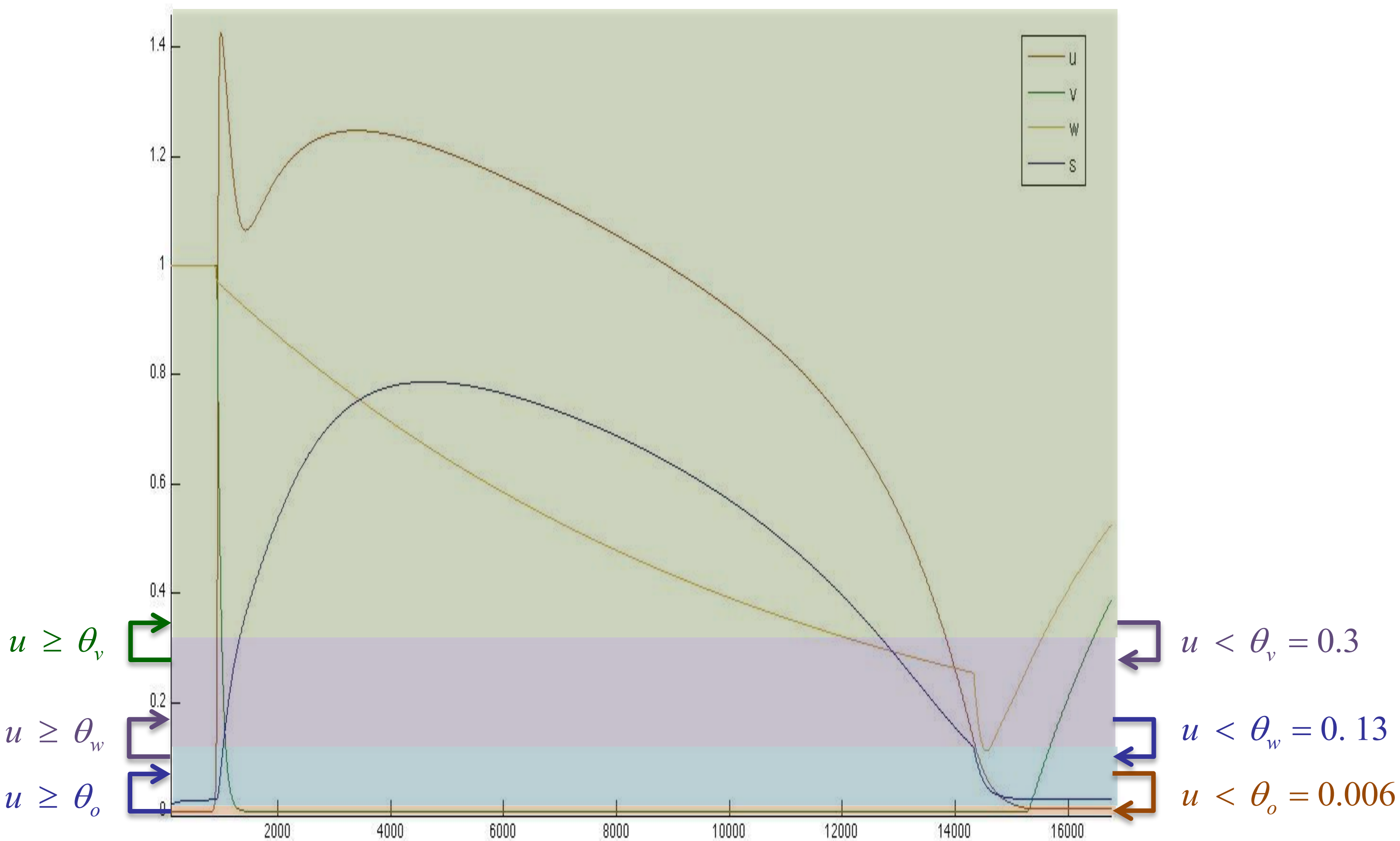
Piecewis
e
Constant

$$v_\infty(u) = H^-(u,\theta_o,0,1)$$

Piecewise
Linear

$$w_\infty(u) = H^-(u,\theta_o,0,1)\ (1 - u/\tau_{w\infty}) + H^+(u,\theta_o,0,1)\ w_\infty^*$$

Minimal Resistance Model (MRM)



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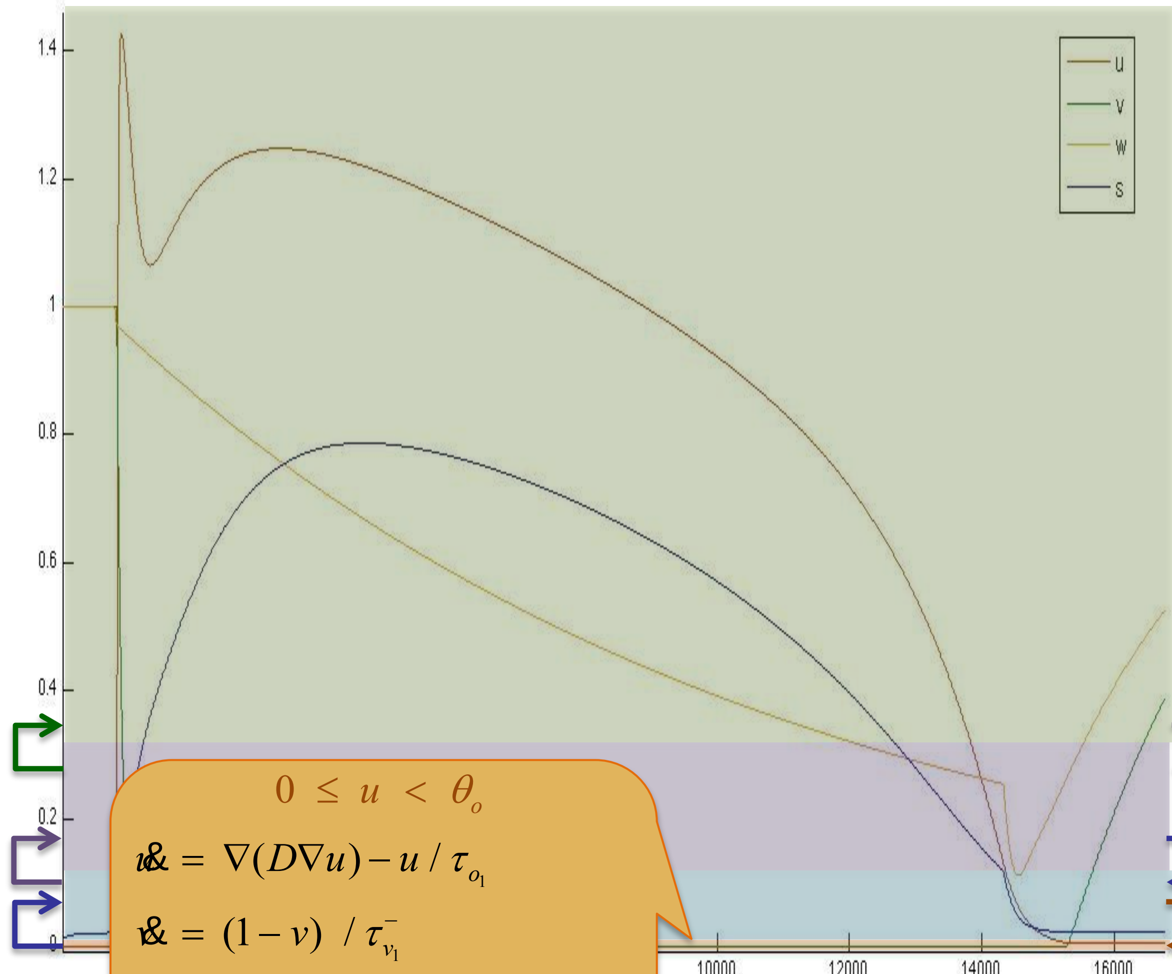

$u \geq \theta_v$ | $u < \theta_v = 0.3$

$u \geq \theta_w$ | $u < \theta_w = 0.13$

$u \geq \theta_o$ | $u < \theta_o = 0.006$

$$0 \leq u < \theta_o$$

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

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

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

$$\dot{s} = (S^{+}(u, u_s, k_s, 0, 1) - s) / \tau_{s_1}$$

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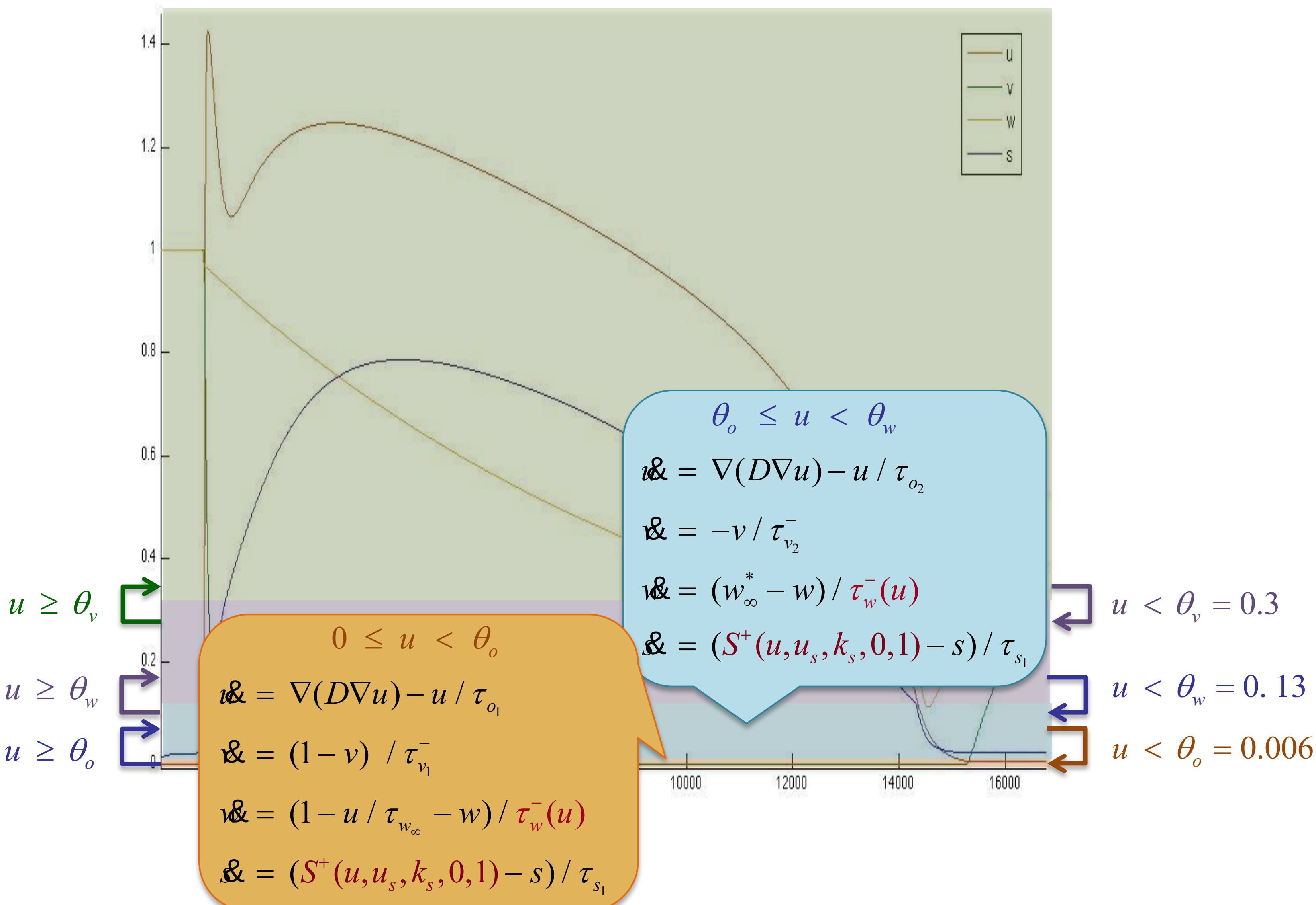

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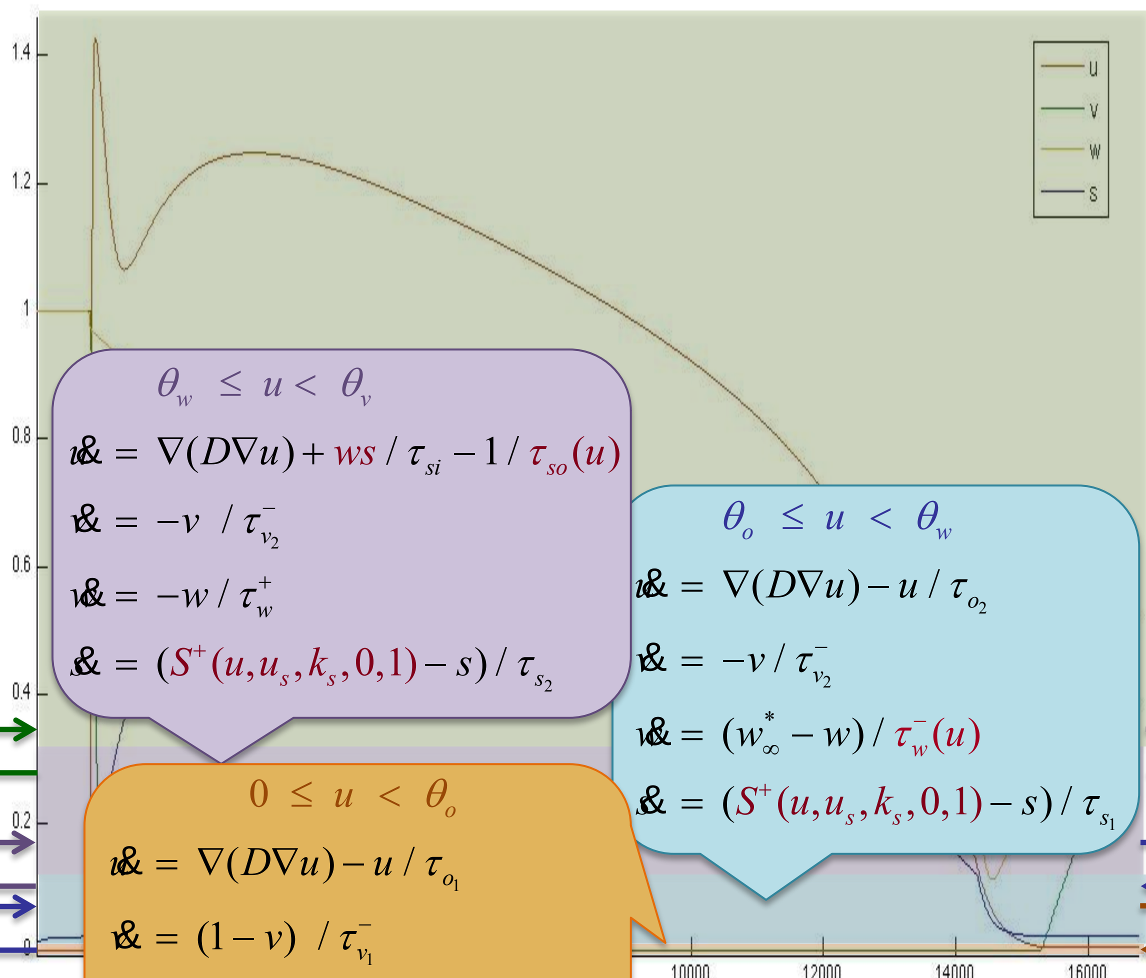

$\theta_w \le u < \theta_v$

$$\dot{u} = \nabla(D\nabla u) + ws/\tau_{si} - 1/\tau_{so}(u)$$

$$\dot{v} = -v/\tau_{v_2}^-$$

$$\dot{w} = -w/\tau_w^+$$

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$u \ge \theta_v$

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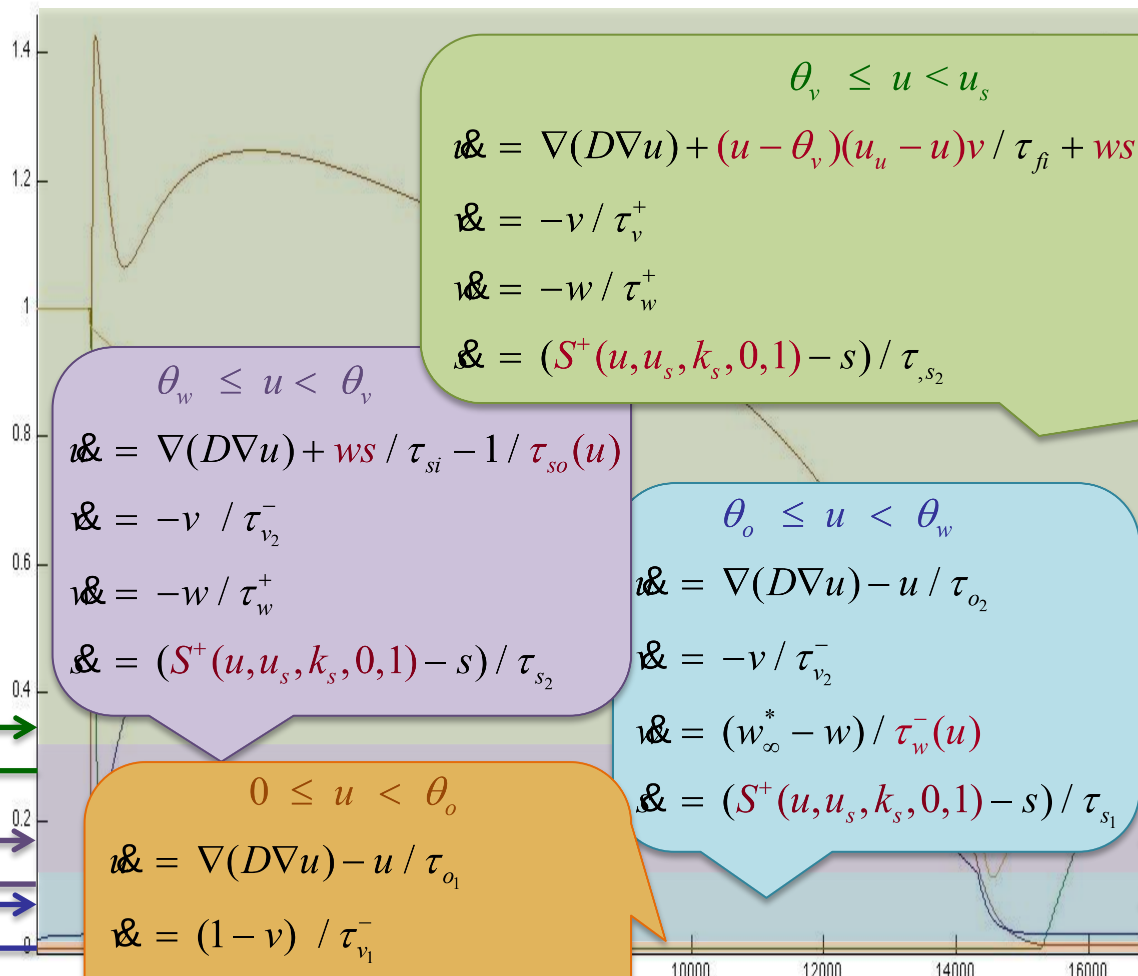
Minimal Resistance Model (MRM)



$$\theta_v \leq u < u_s$$

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$$0 \leq u < \theta_o$$

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

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

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Sigmoid Closure Property

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

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

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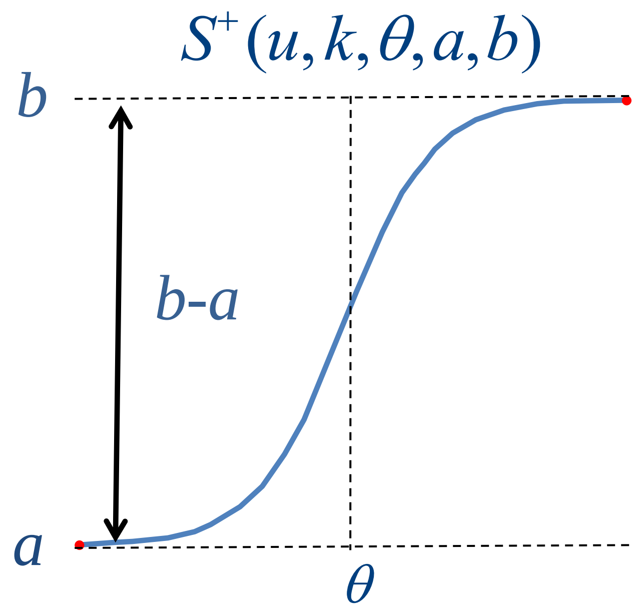
Proof:

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



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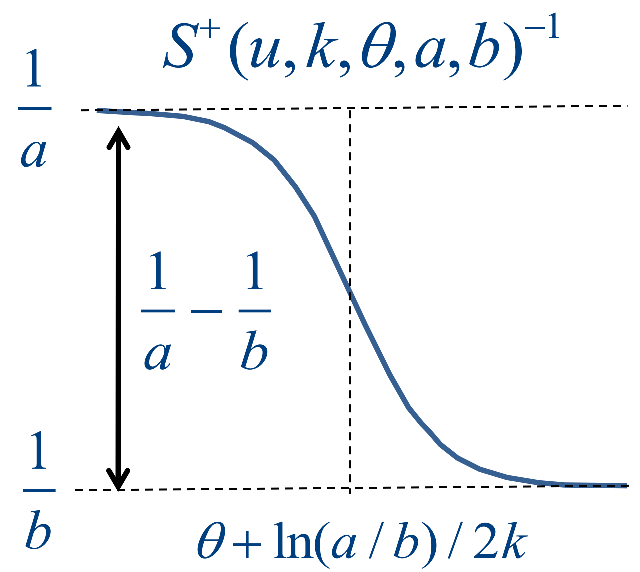
Proof:

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



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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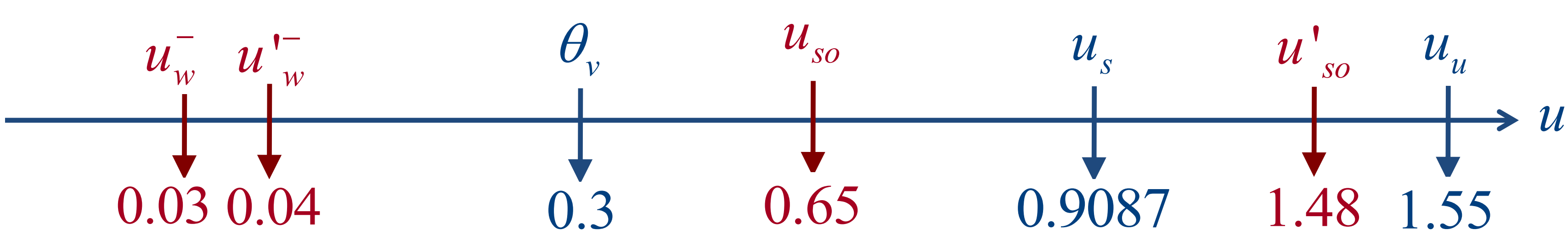

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Removing Divisions using Step Reciprocal:

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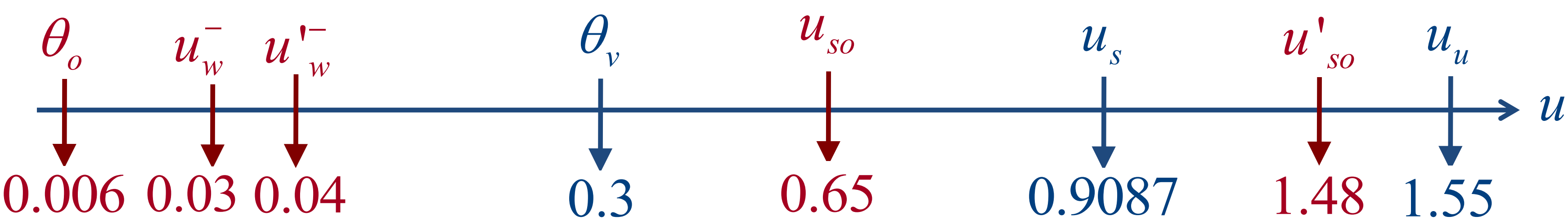

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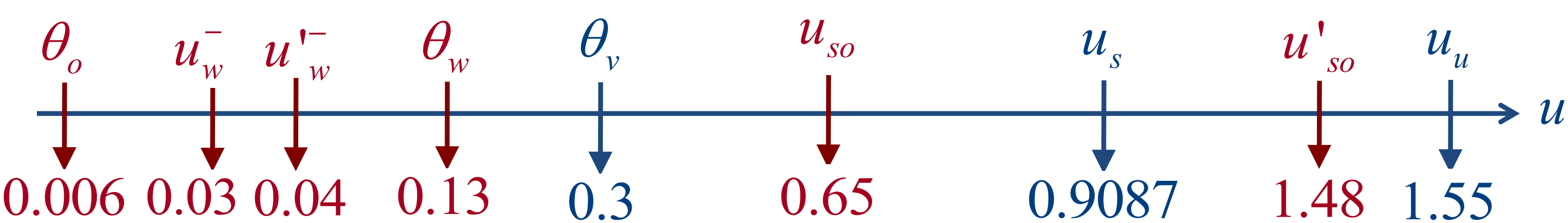

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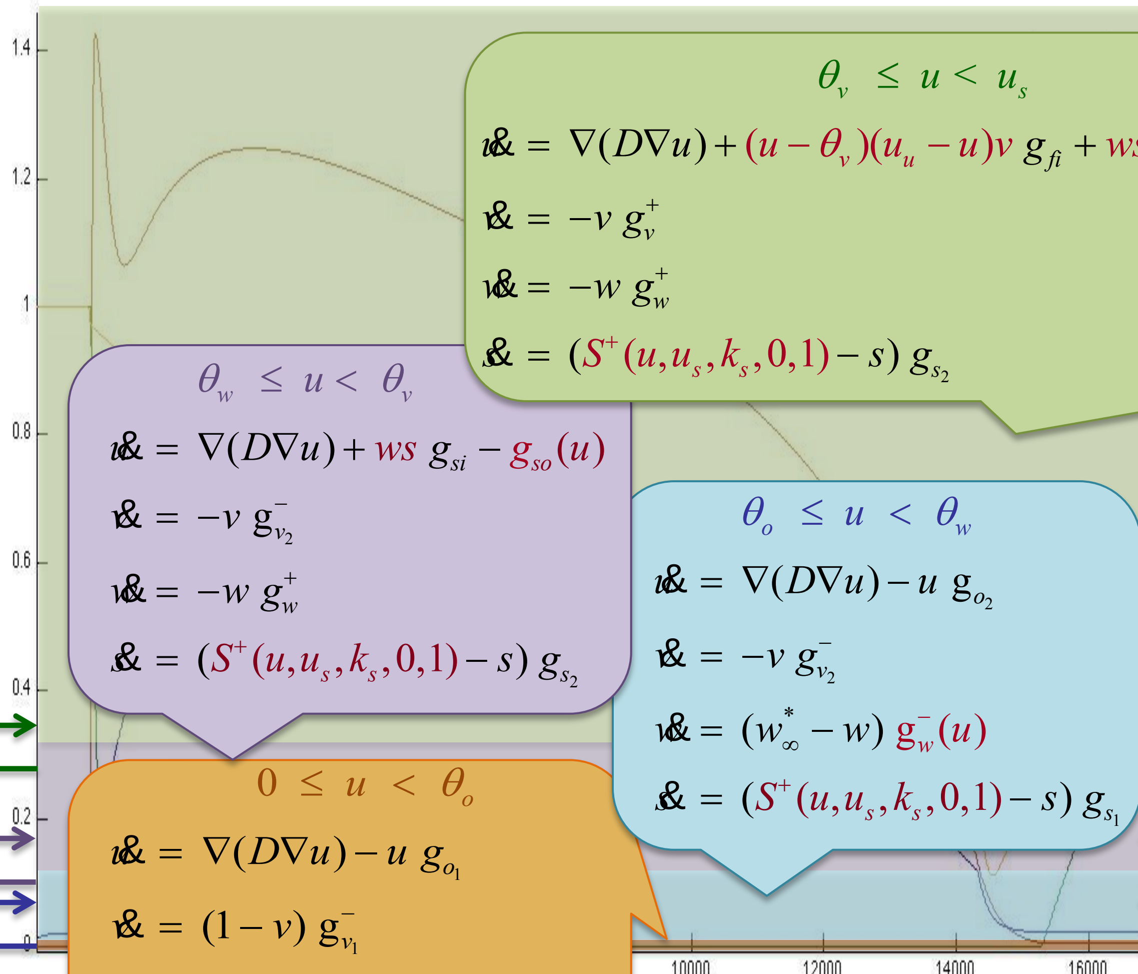

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Gene Regulatory Networks (GRN)

GRN canonical sigmoidal form:

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Note: steps and ramps are sigmoid approximations

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Given: **One nonlinear curve and desired # segments**

Find: **Optimal polygonal approximation**

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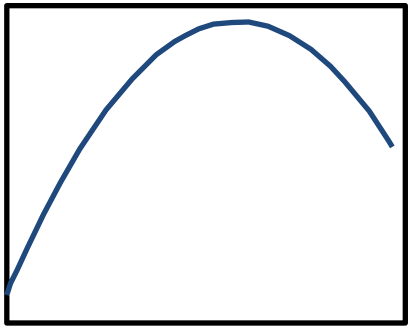
Example: What is the optimal polygonal approximation of the blue curve with 3 segments ?



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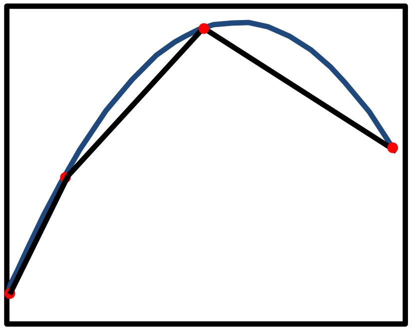

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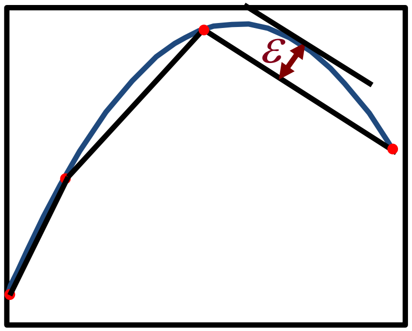

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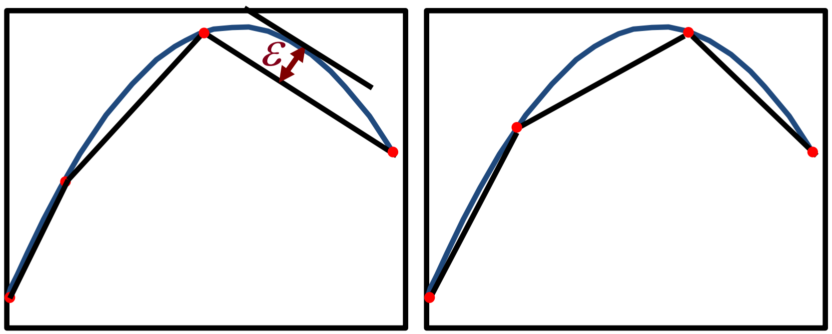

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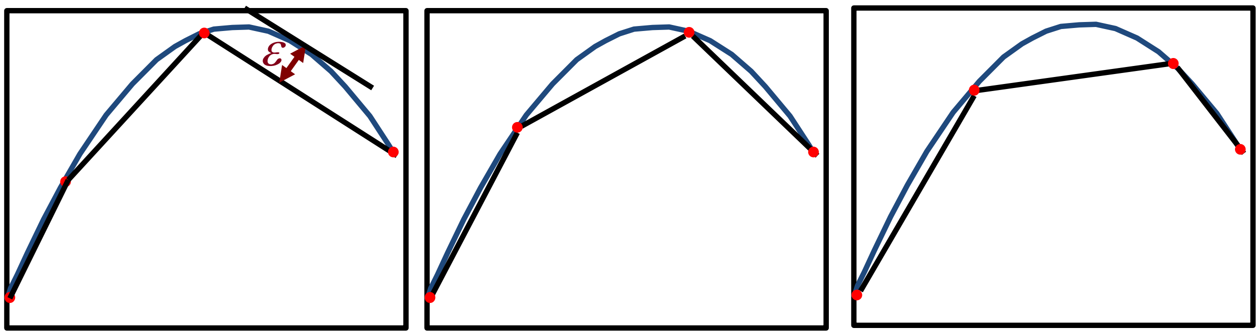

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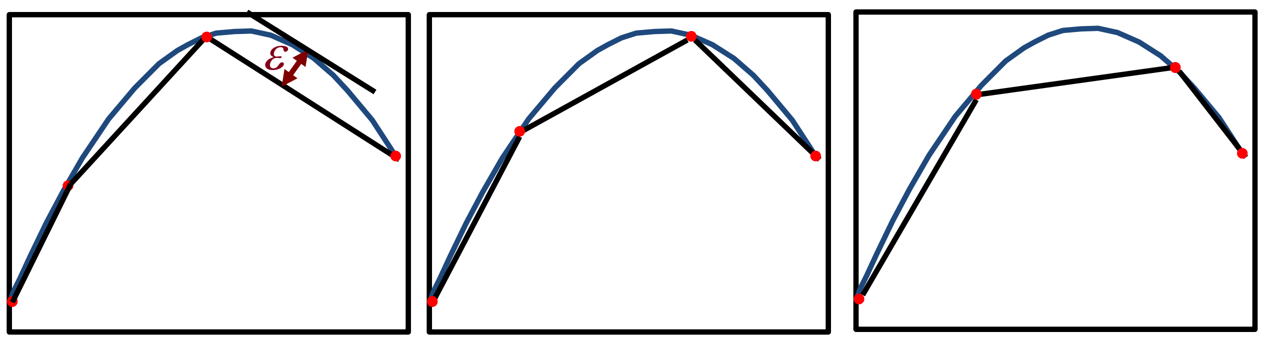
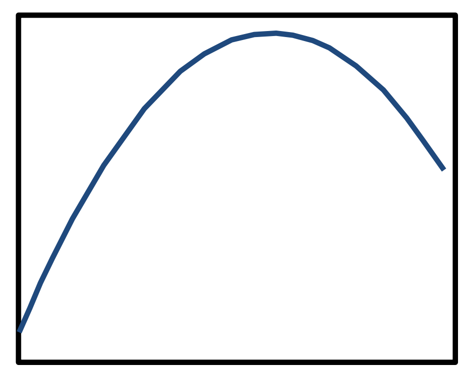


Dynamic Programming Algorithm

- **Complexity:** O(P^2S)
- **P:** # points of the curve
- **S:** # of segments



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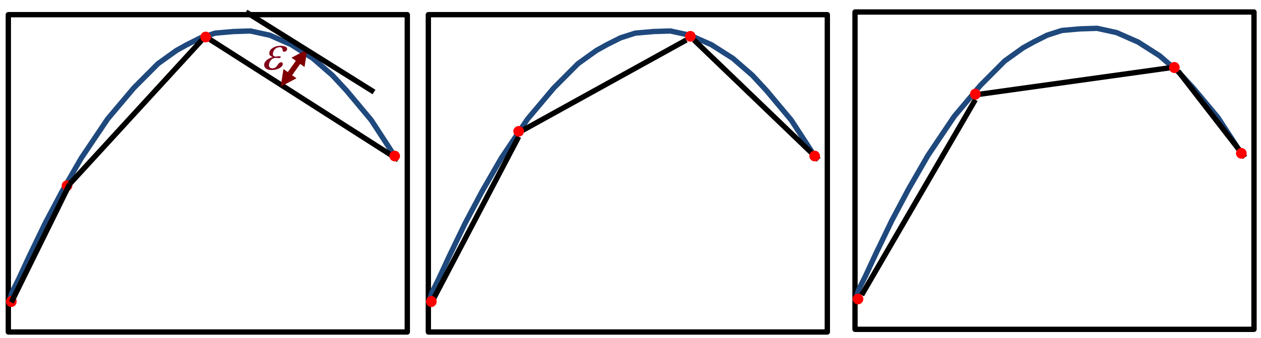

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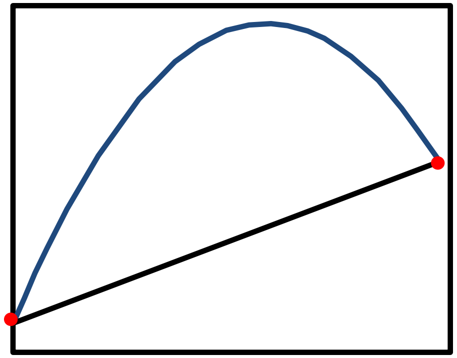

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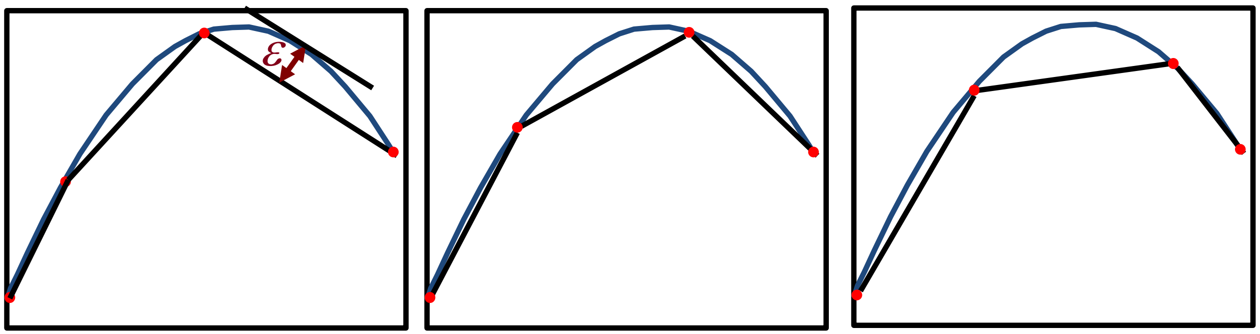

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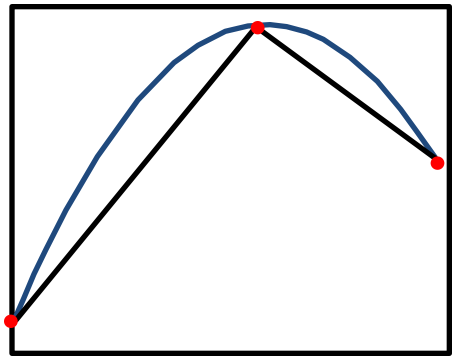

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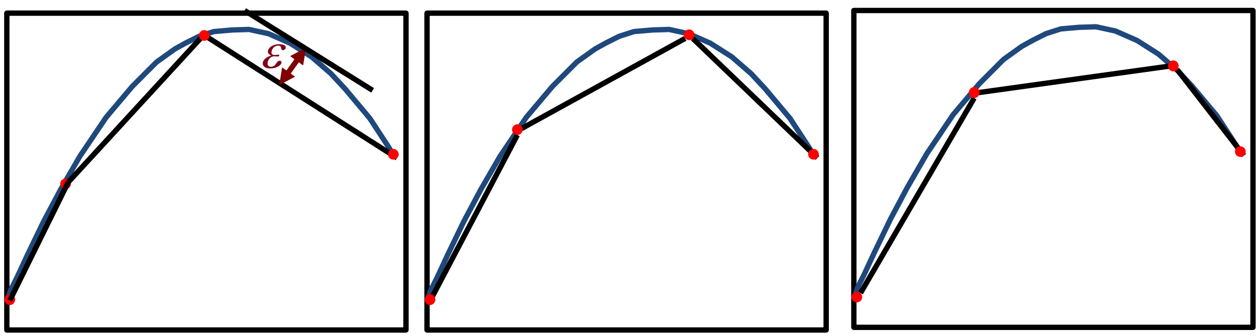

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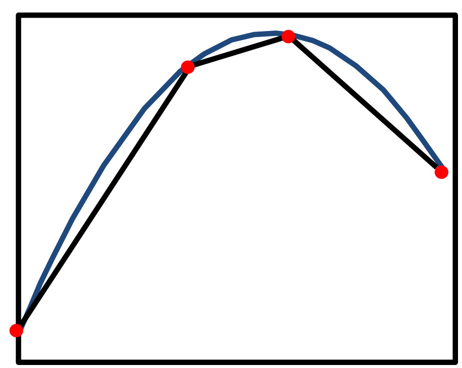

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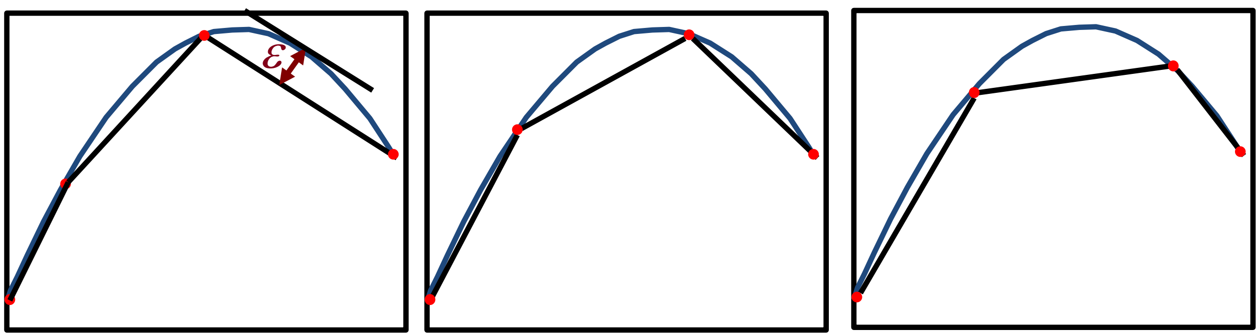

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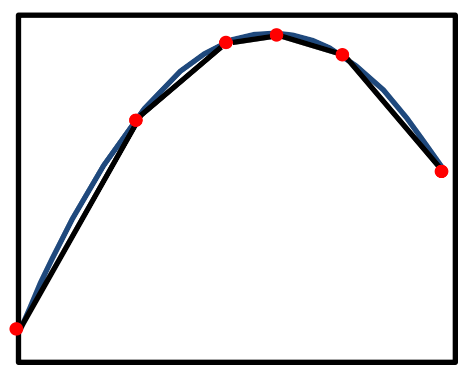

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Globally-Optimal Polygonal Approximation

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

Find: **Globally optimal polygonal approximation**

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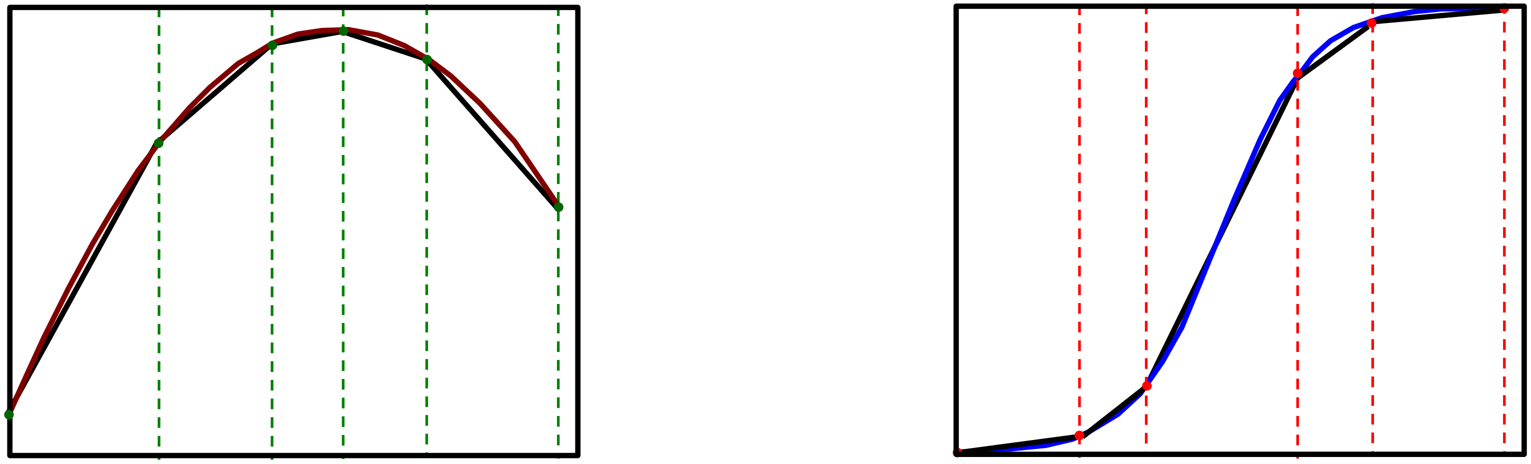
Example: **What is the optimal polygonal approximation of the curves below with 5 segments ?**



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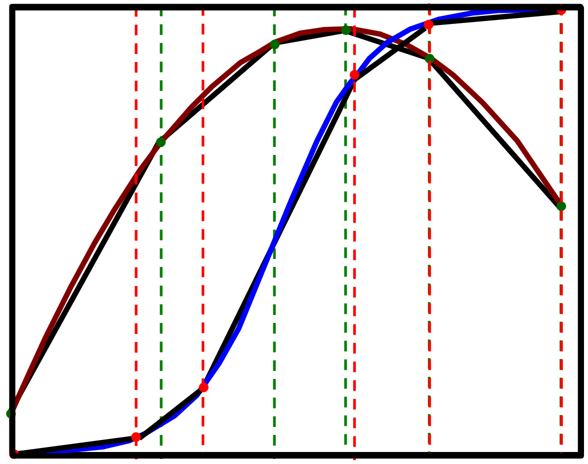

Combining the two we obtain 8 segments and not 5 segments

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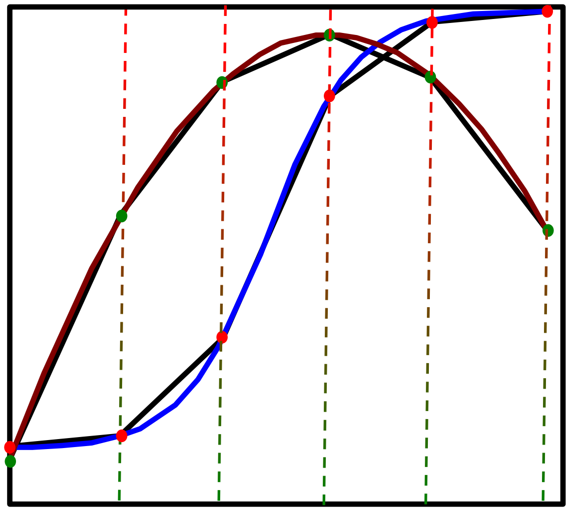

Solution: modify the OPAA to minimize the maximum error of a set of curves simultaneously.

Deriving the Piecewise Multi-Affine Model

$(\theta_v \le u < u_u)$

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

$u \ge \theta_v$

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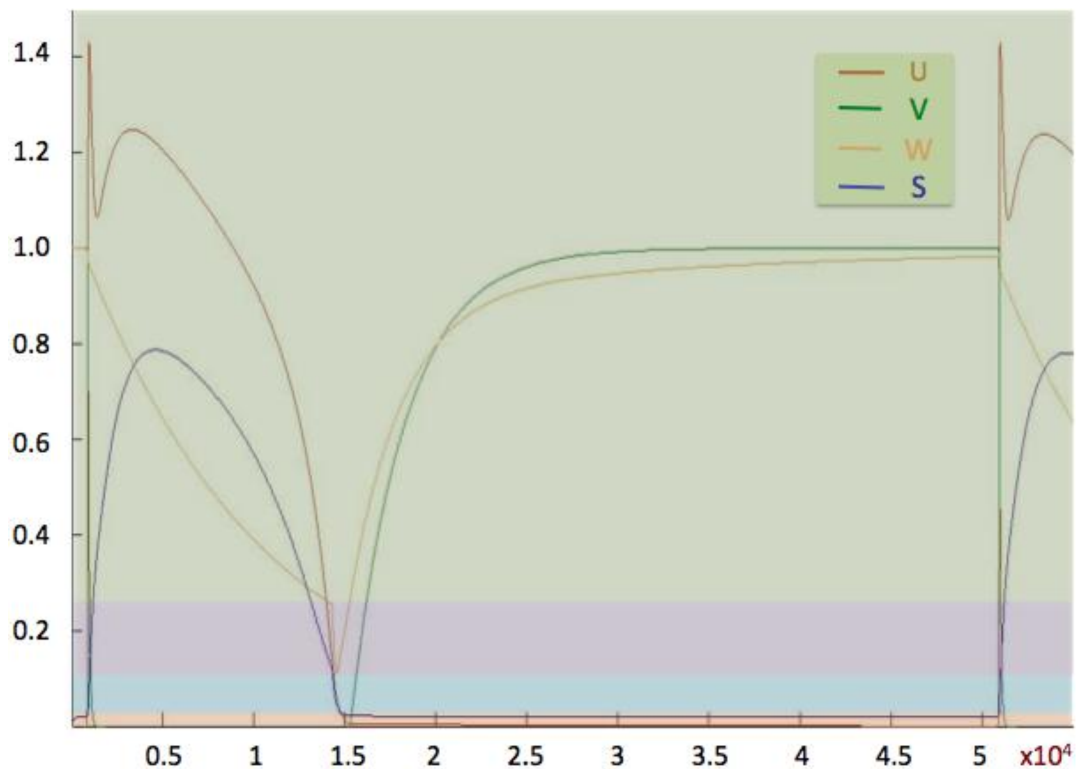

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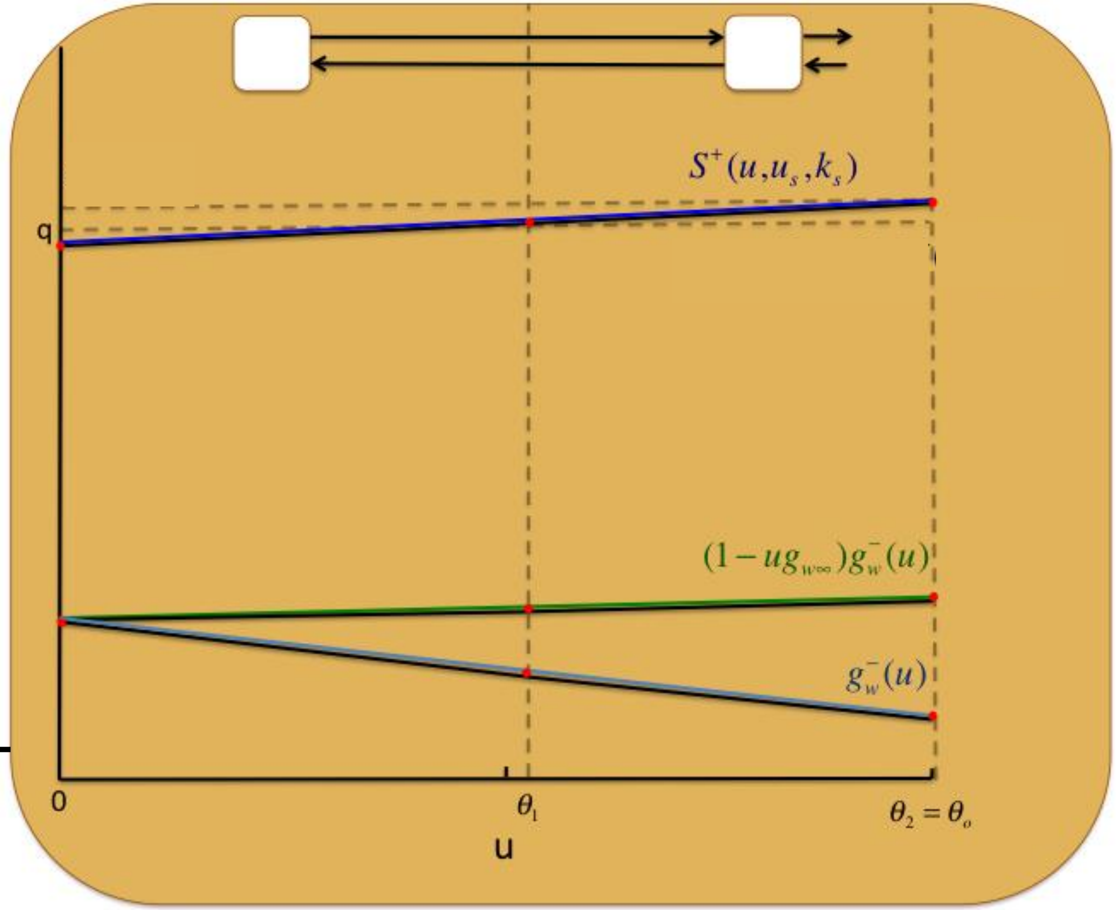

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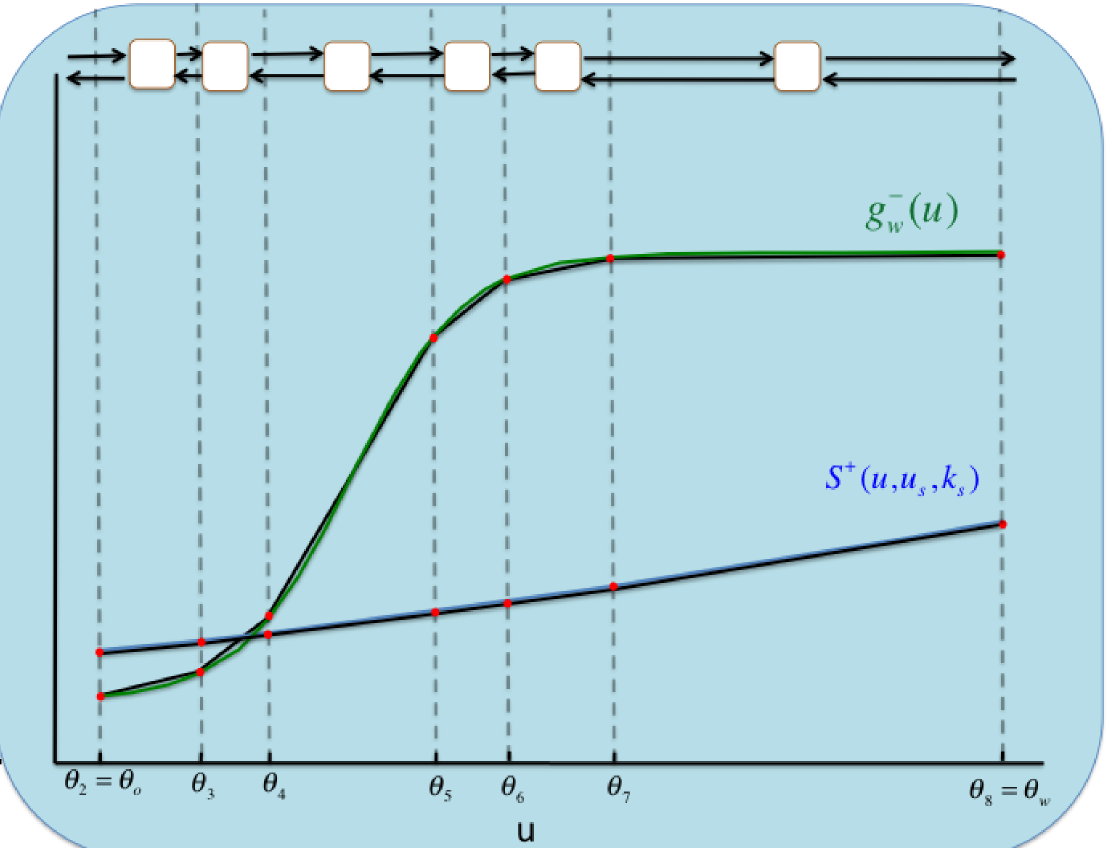

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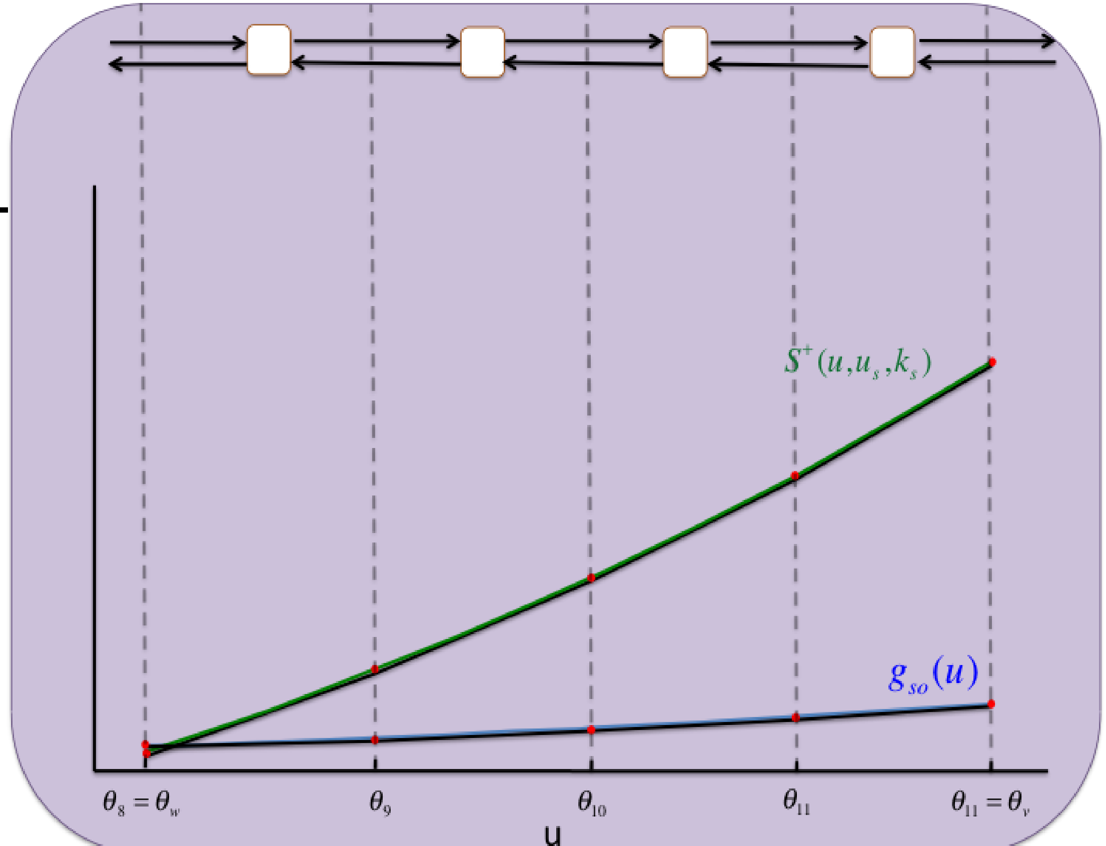

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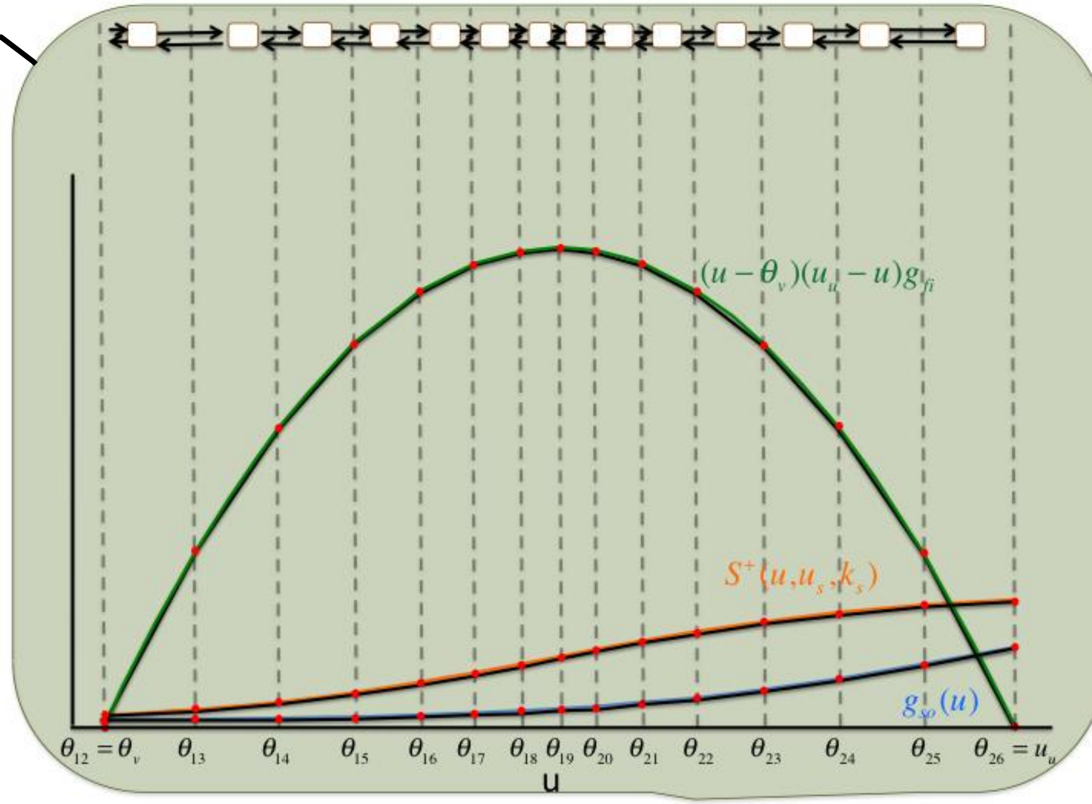

Deriving the Piecewise Multi-Affine Model

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

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

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

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

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

$u < \theta_v$

$u \geq \theta_v$

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

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

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

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

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$u < \theta_w$

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

$$\dot{u} = e - u\, g_{o_2}$$

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

$$\dot{w} = (w_\infty^* - w) \sum_{i=2}^{7} R(u,\theta_i,\theta_{i+1},u_{w_i},u_{w_{i+1}})\, g_{w_b}$$

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

$$\dot{u} = e - u\, g_{o_1}$$

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$$\dot{w} = \left(\sum_{i=0}^{1} \left(R(u,\theta_i,\theta_{i+1},u_{w_i}^+,u_{w_{i+1}}^+) - wR(u,\theta_i,\theta_{i+1},u_{w_i}^-,u_{w_{i+1}}^-)\right)\right) g_{w_a}$$

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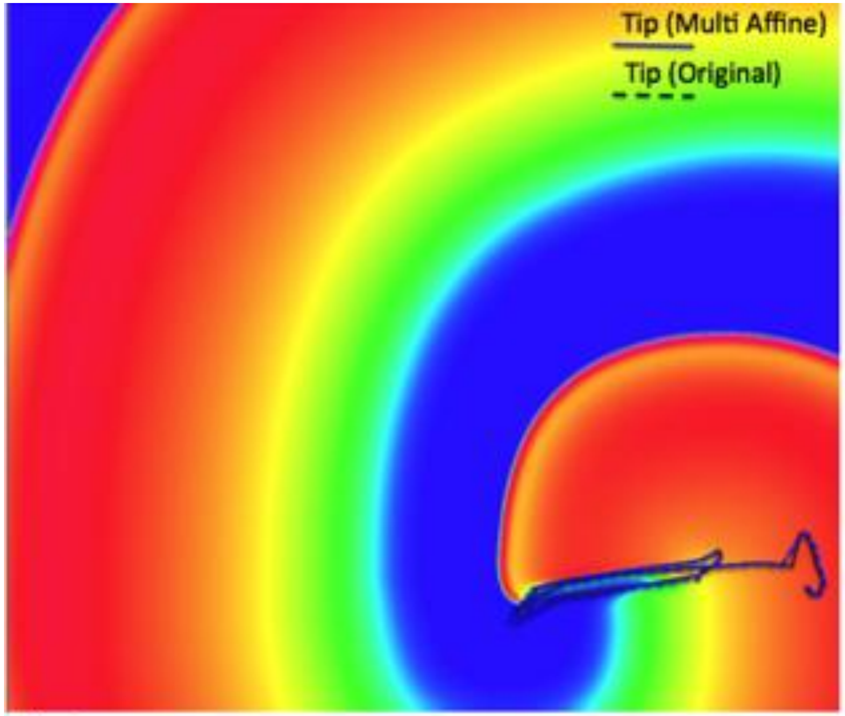
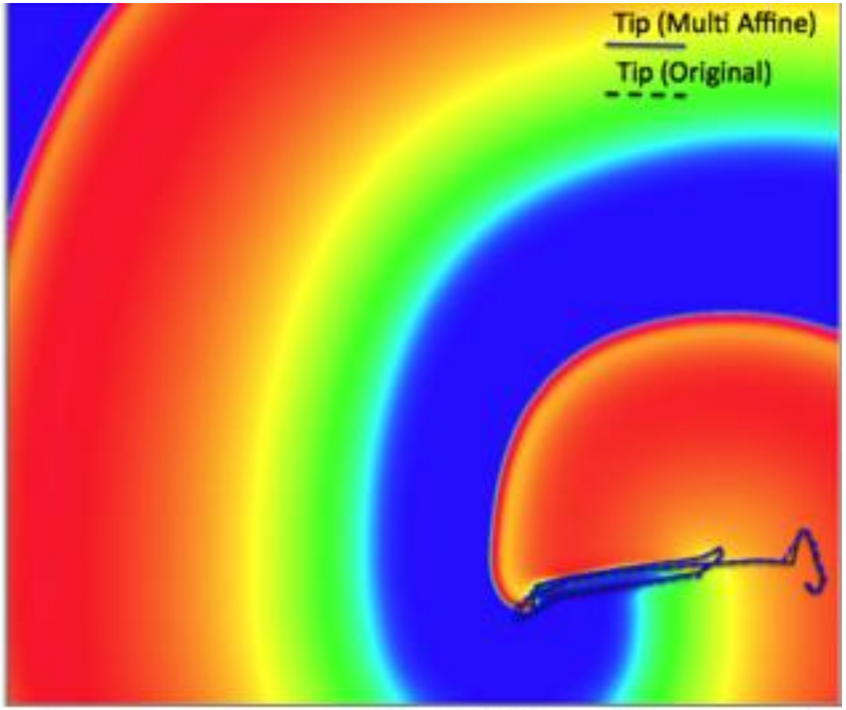
2D Comparison



(a) Original MRM



(b) Multi Affine (26 ramps)

Analysis Problem

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

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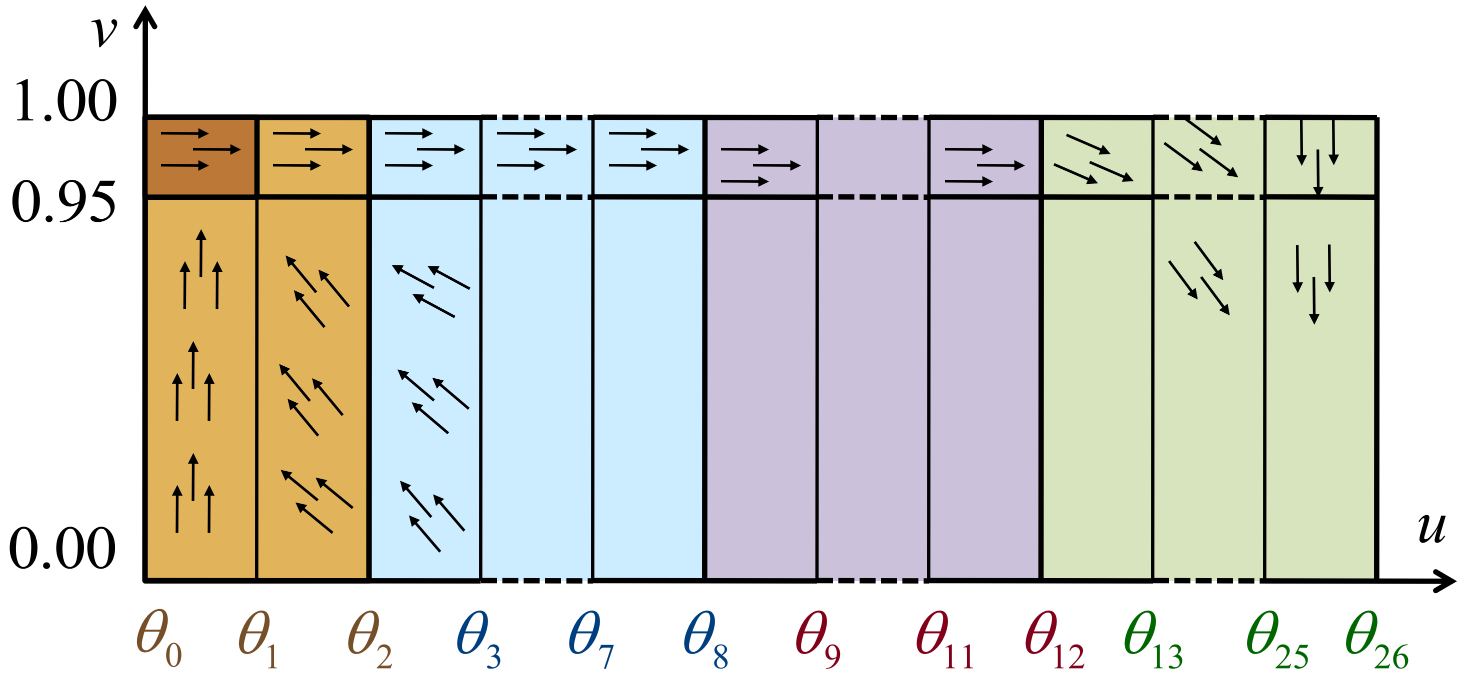
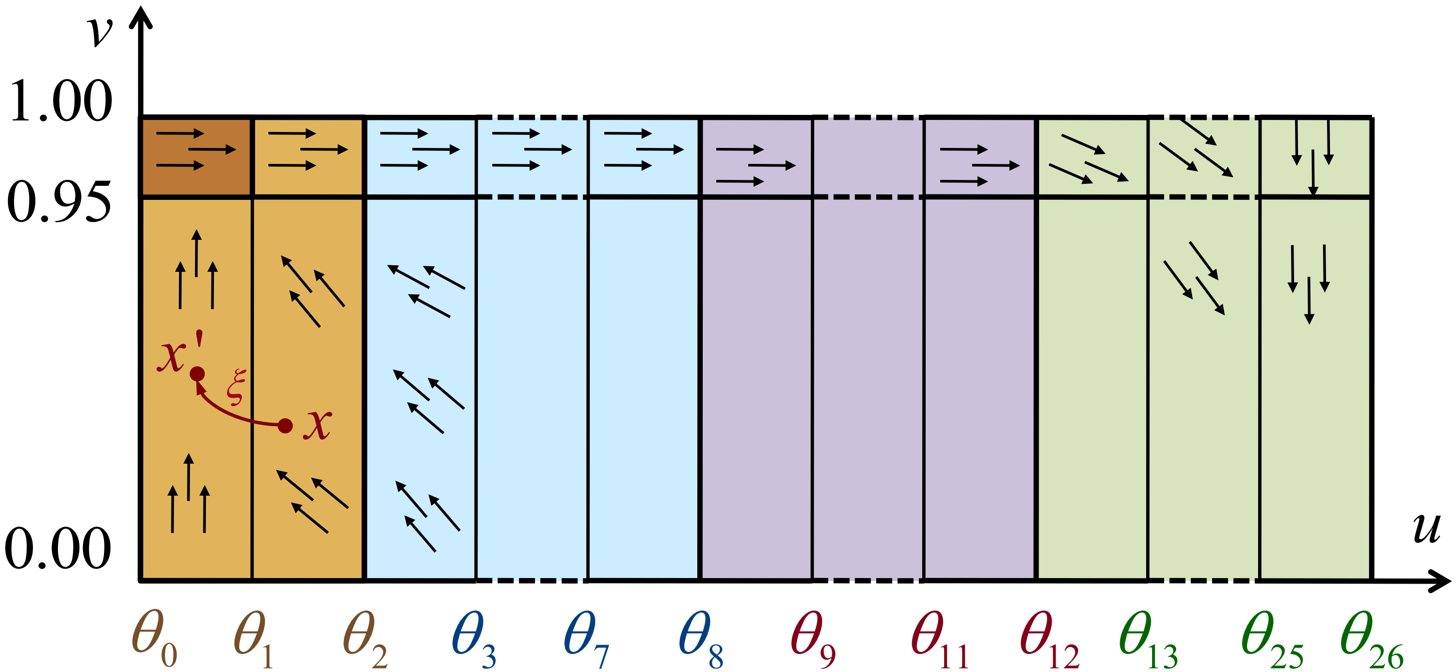
- **Stimulus:** $e = 1$

State Space Partition



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

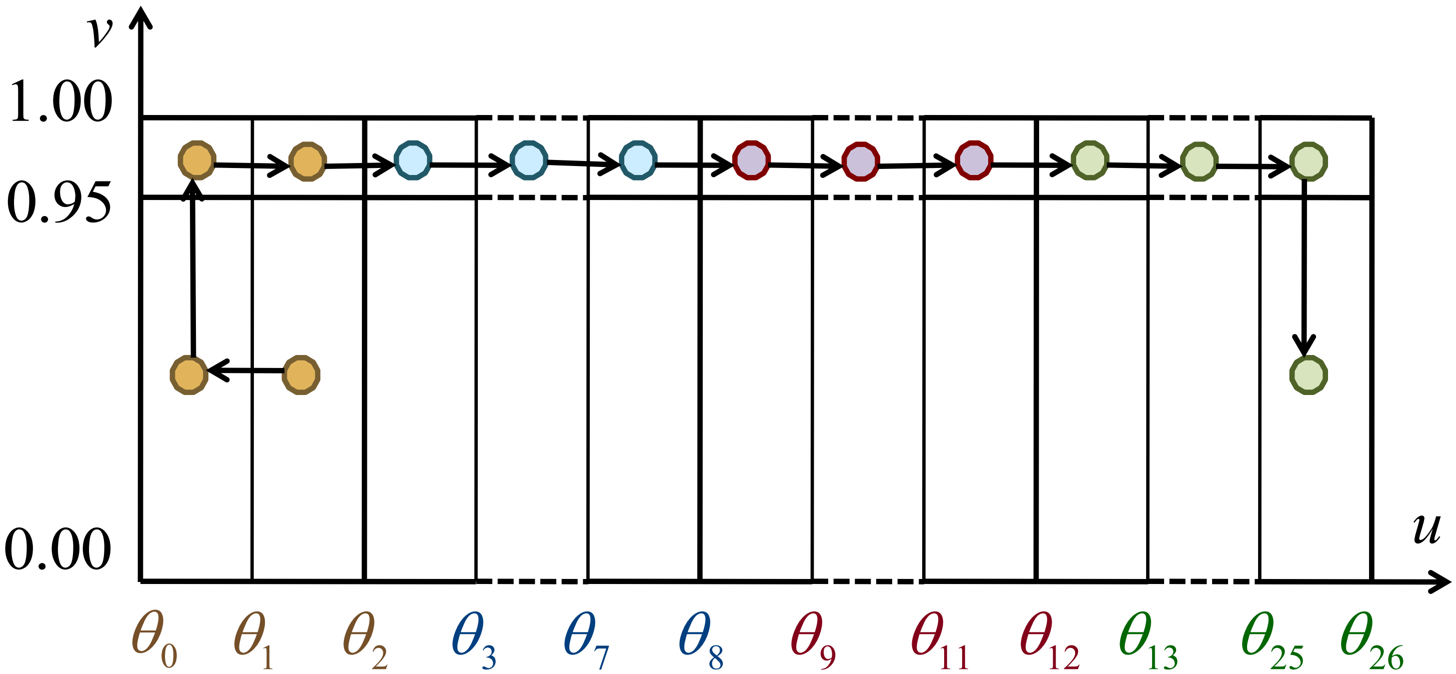
Embedding Transition System $T_X(p)$



$x \xrightarrow{T_X(p)} x'$ **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 $T_R(p)$



$x :_{R(p)} x'$ **iff** $rect(x) = rect(x')$

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

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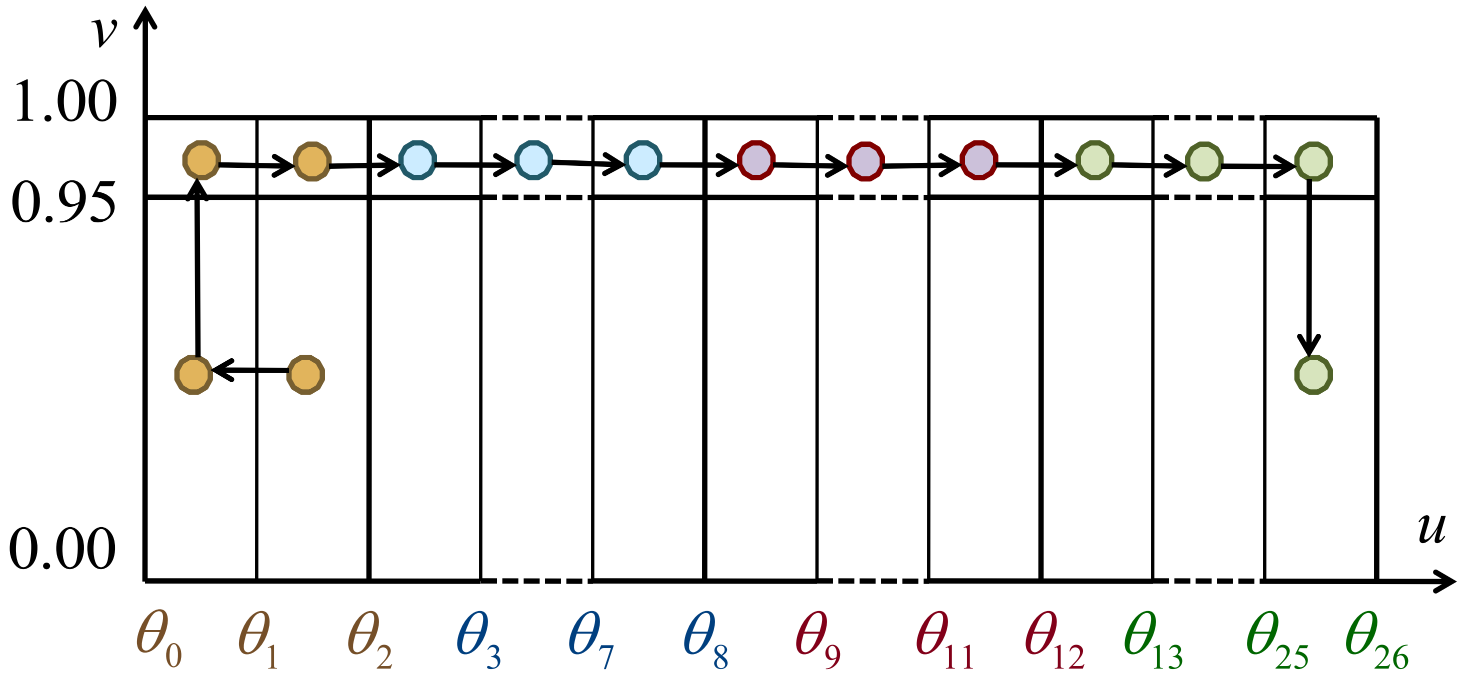

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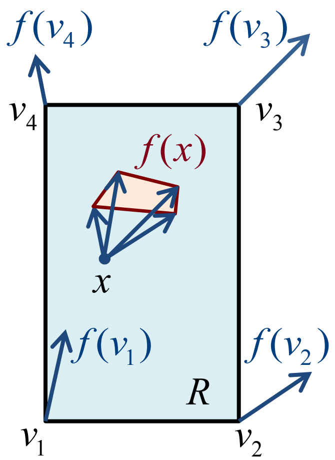
Theorem: $\forall p.\ T_X(p) \leq T_R(p)$

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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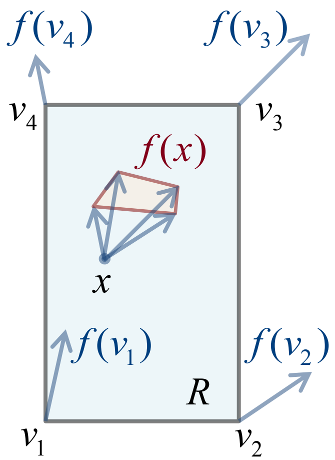

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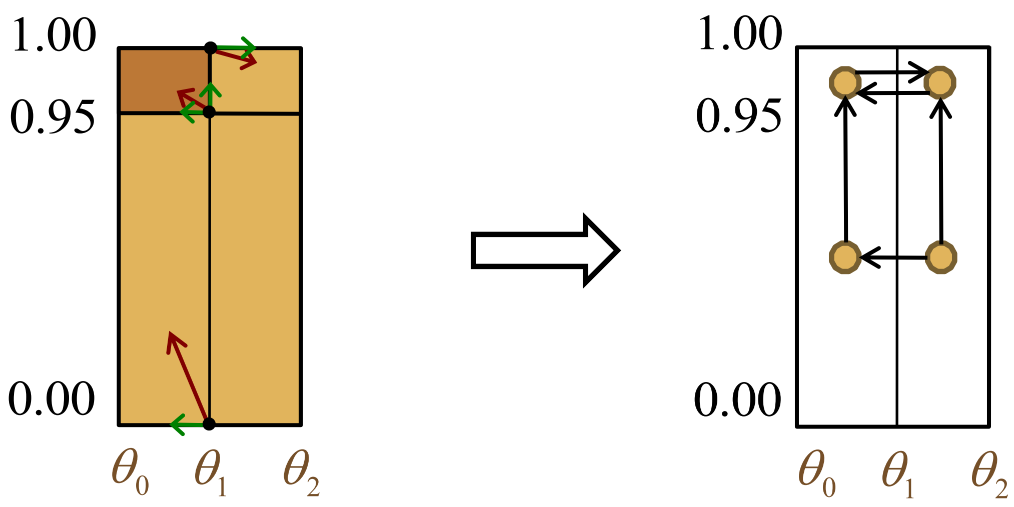
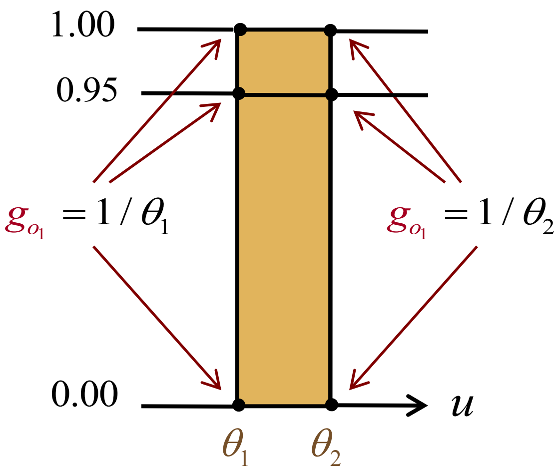
Corollary:



Partitioning the Parameter Space

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

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



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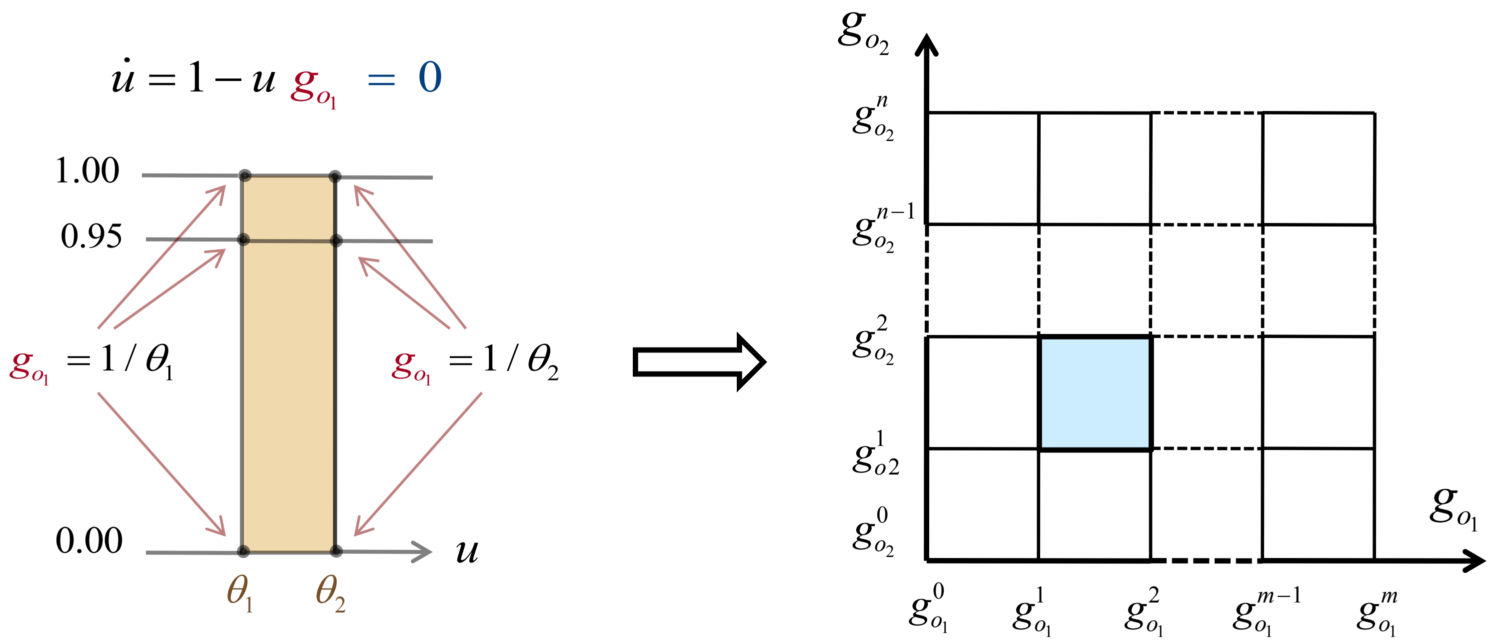
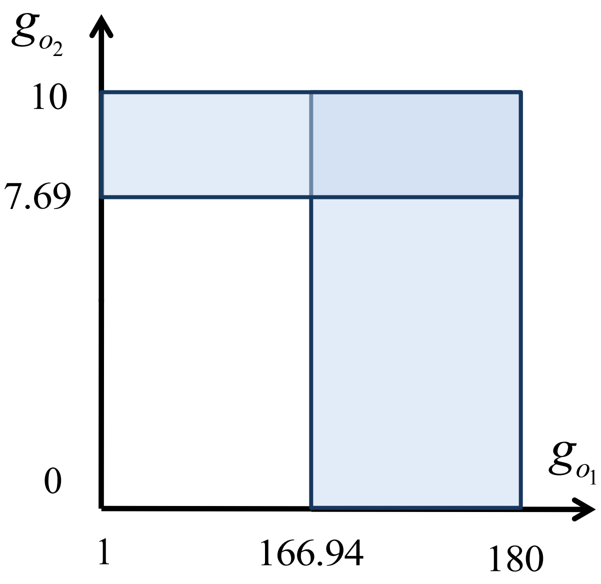
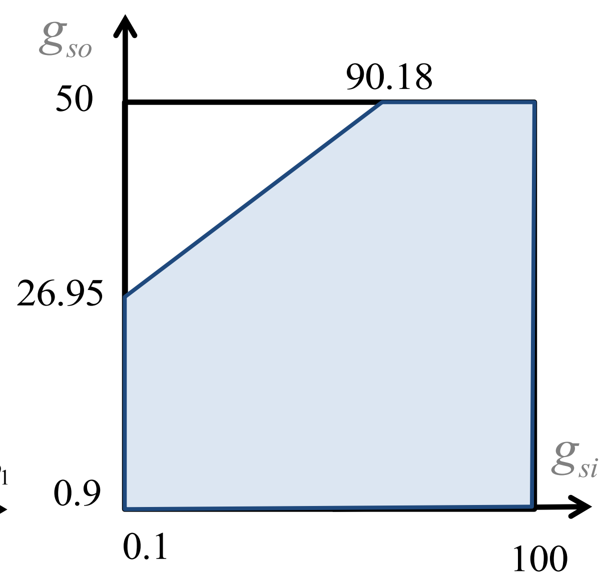


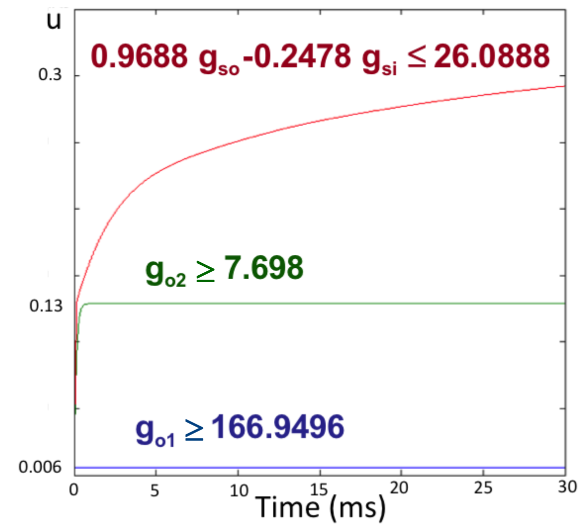
- **Parameter space:** **4 dimensional (g_{o_1}/g_{o_2} projection)**
  - **Each rectangle: a different transition system**

Results

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







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

Conclusions and Outlook

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  - **Validated both in MCM and MRM**
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