From Cardiac Cells to Genetic Regulatory Networks

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Joint work with

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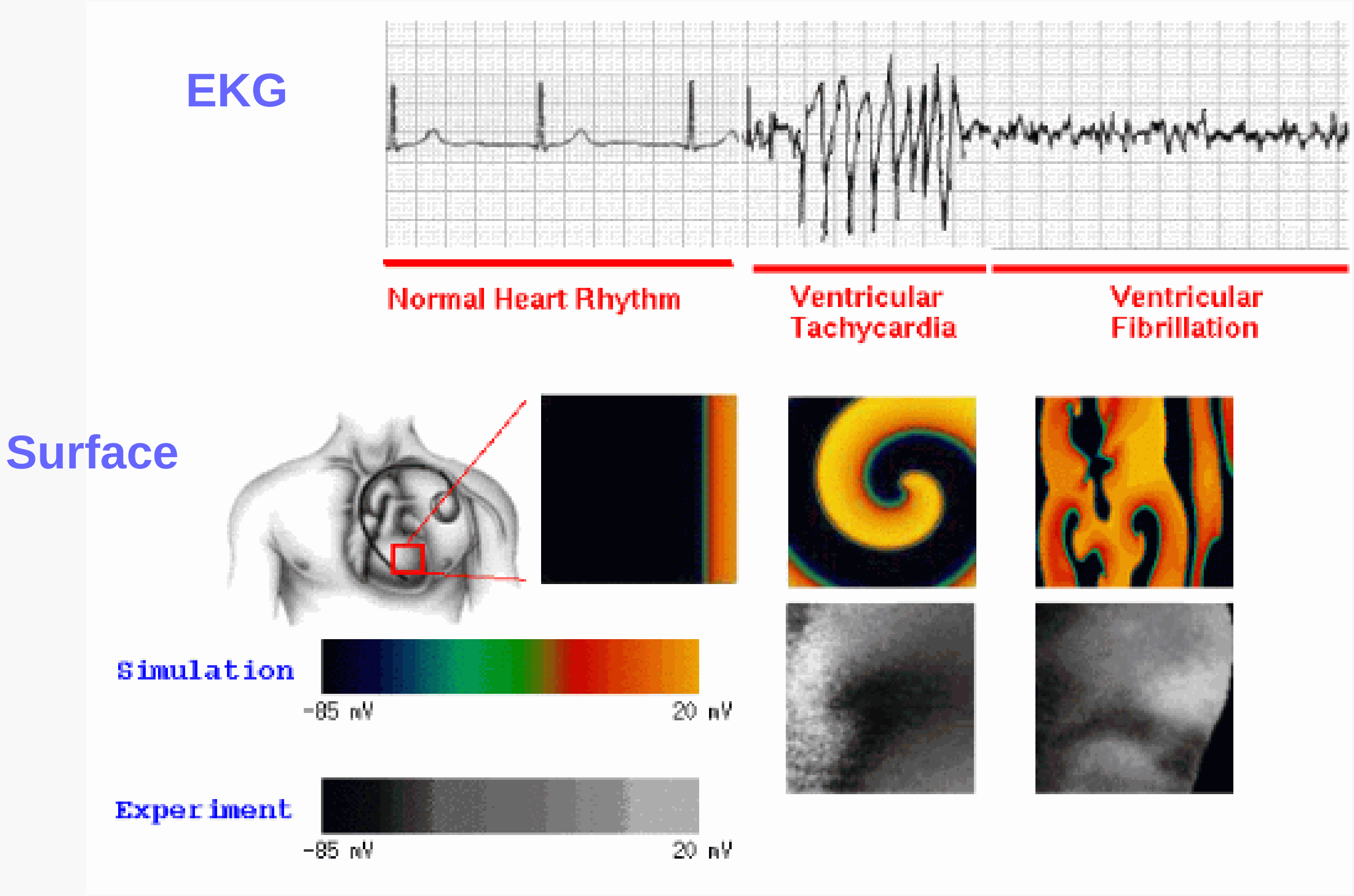
Overview

- **Background**
  - Cardiac Cells, Action Potential, Restitution
- **Biological Switching**
- **Minimal Model**
  - Resistor Model
  - Sigmoid Closure and Conductance Model
- **Piecewise Multi Affine Minimal Model**
  - Optimal Polygonal Approximation
  - Model Comparison
- **Parameter Identification**
  - RoverGene
- **Conclusion**

Background

Emergent Behavior in Heart Cells

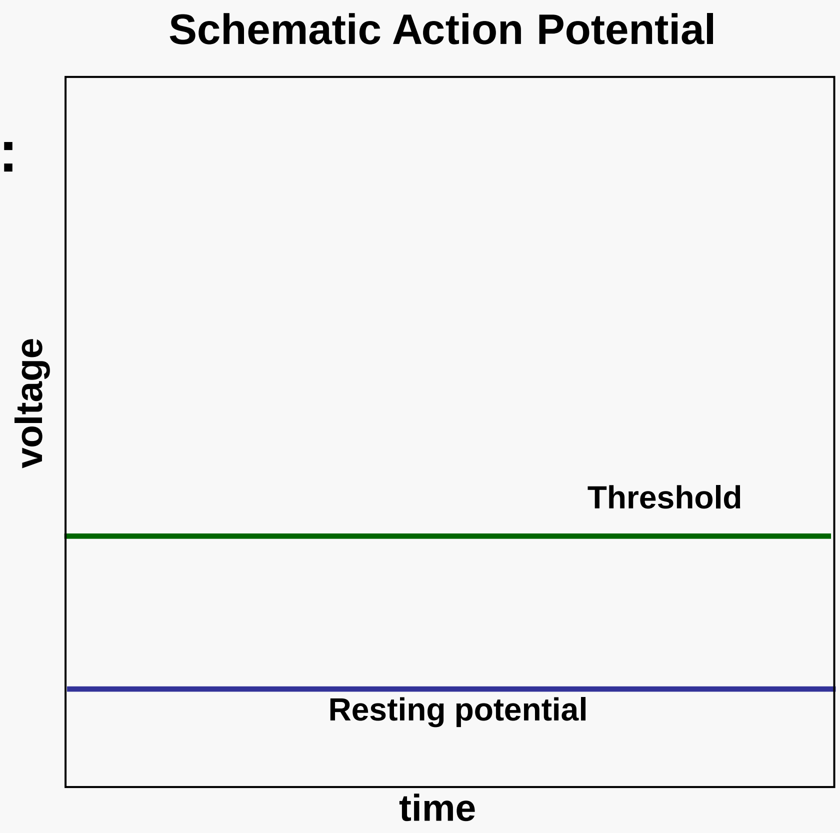


Arrhythmia afflicts **more than** **3 million Americans** **alone**

Single Cell Reaction: Action Potential

Membrane's AP depends on:

- **Stimulus (voltage or current):**
  - External / Neighboring cells
- **Cell's state**



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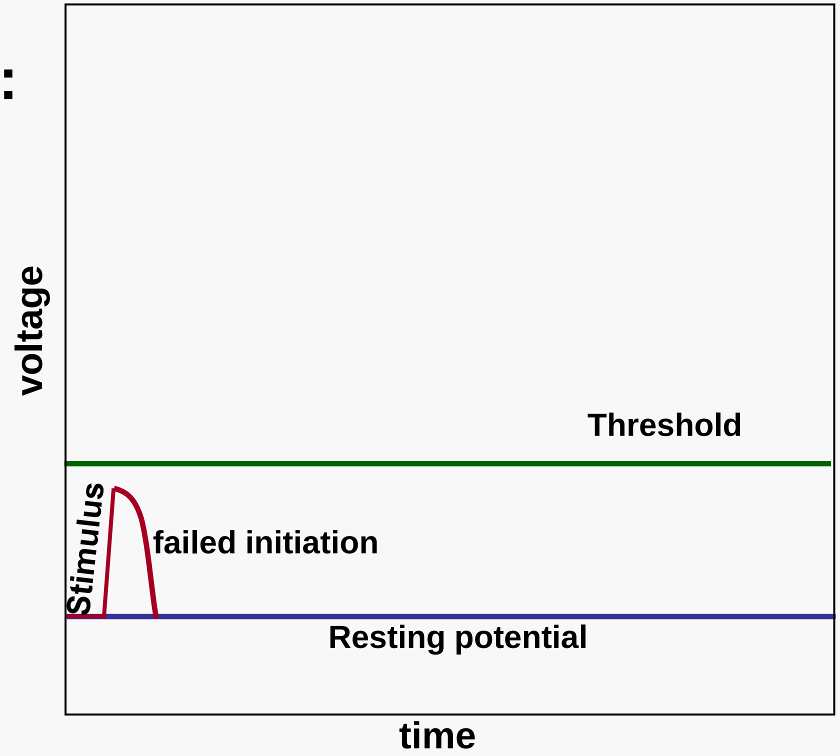
Schematic Action Potential



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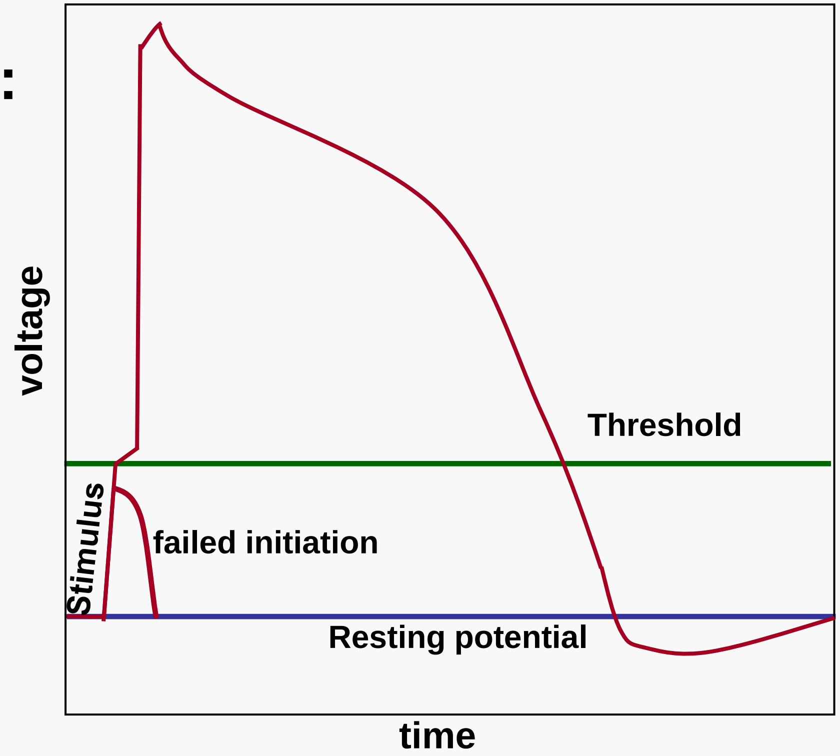

Single Cell Reaction: Action Potential

Membrane's AP depends on:

- Stimulus (voltage or current):
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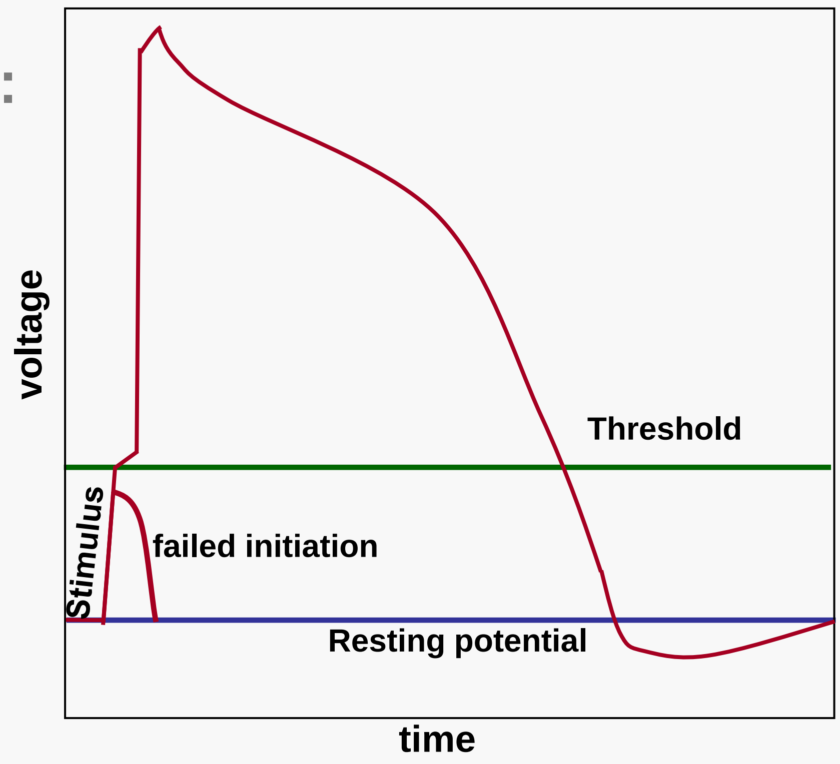
AP has nonlinear behavior!

- Reaction diffusion system:

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

Schematic Action Potential



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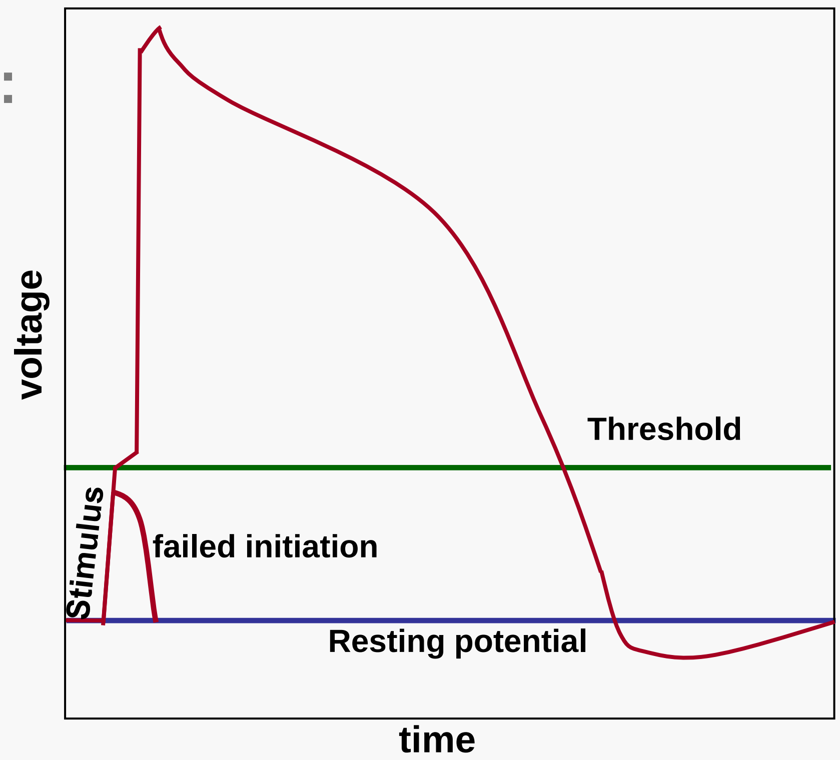
Behavior
In time

Schematic Action Potential



Single Cell Reaction: Action Potential

Membrane's AP depends on:

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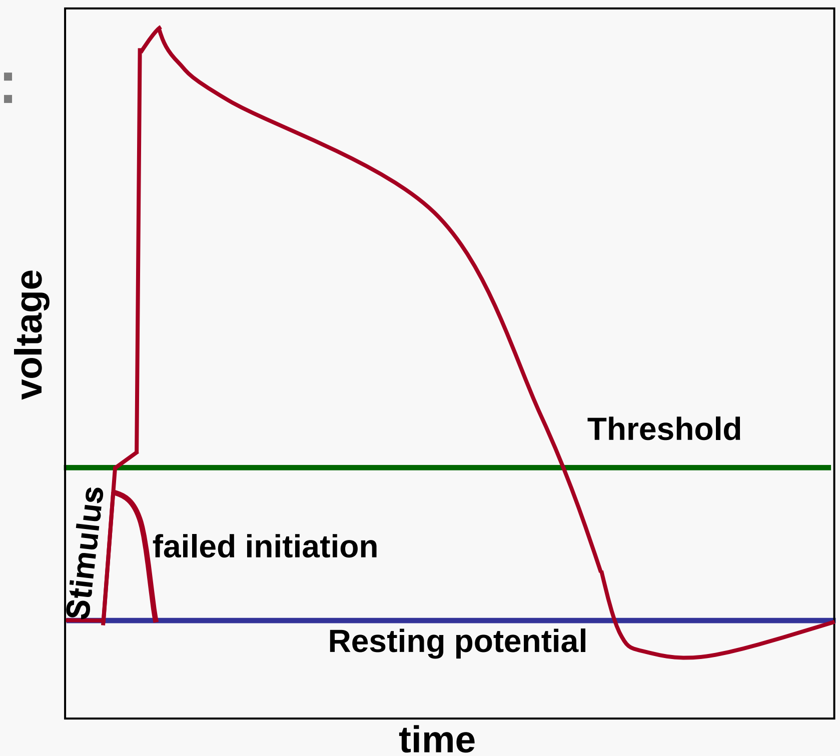
Reaction

Schematic Action Potential



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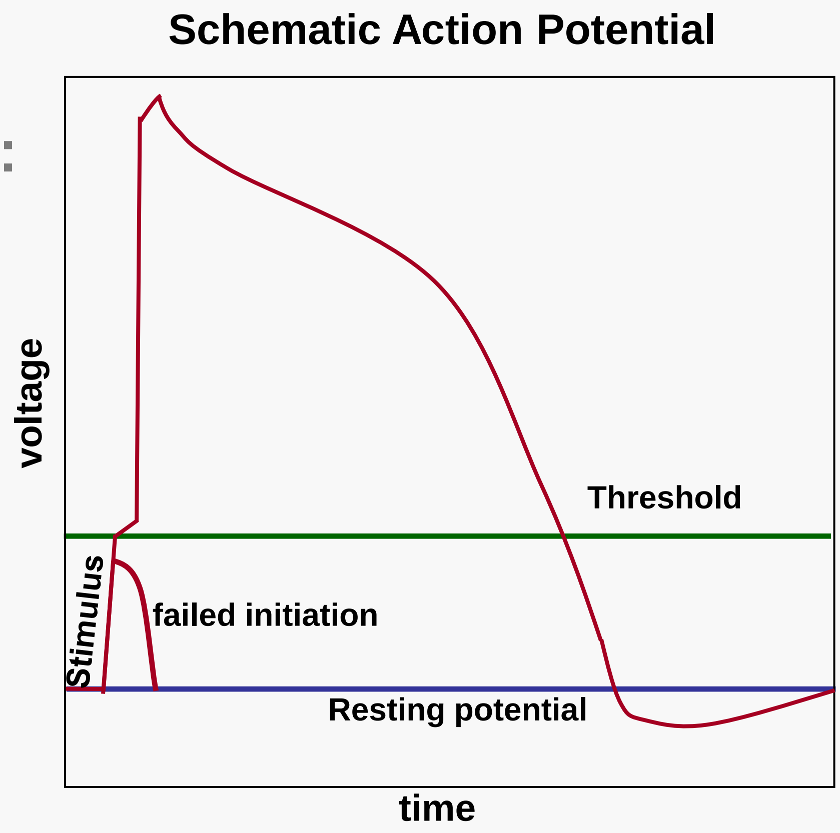
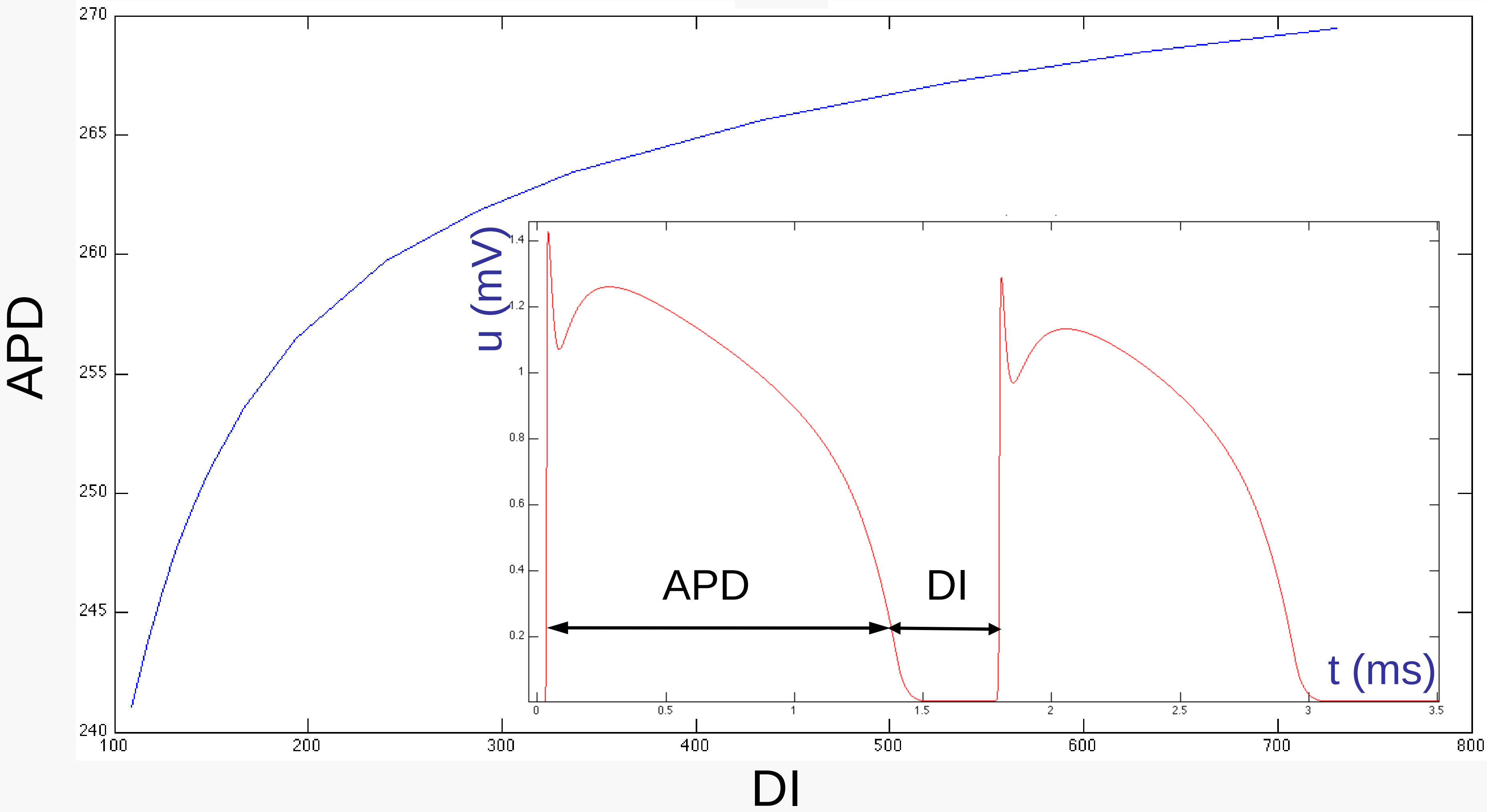
Diffusion



Frequency Response

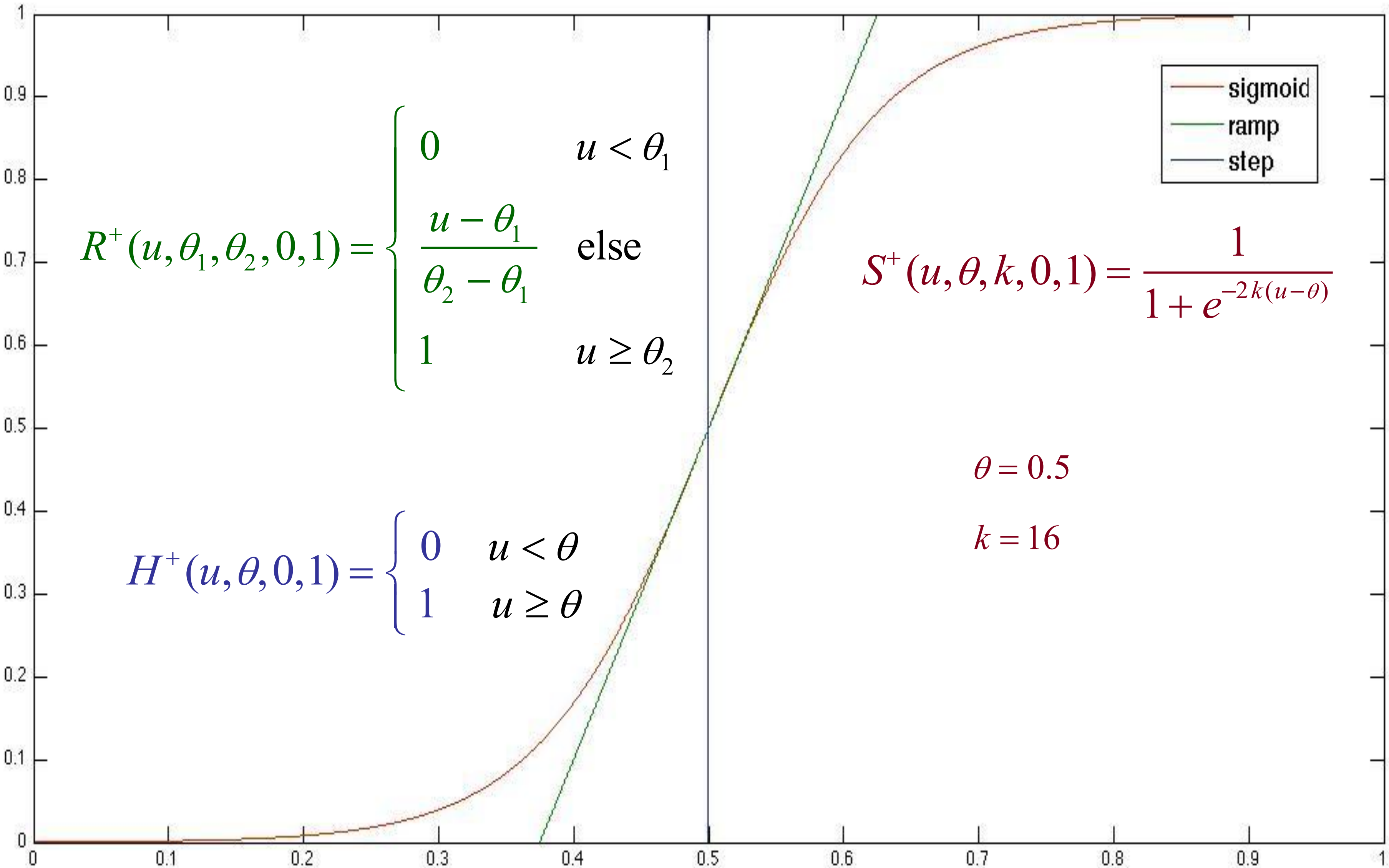


Existing Models

- **Detailed ionic models:**
  - **Luo and Rudi:** **14 variables**
  - **Tusher, Noble^2 and Panfilov:** **17 variables**
  - **Priebe and Beuckelman:** **22 variables**
  - **Iyer, Mazhari and Winslow:** **67 variables**
- **Approximate models:**
  - **Cornell:** **3 or 4 variables**
  - **SUNYSB: 2 or 3 variable**

Biological Switching

Biological Switching



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

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

$$\theta = 0.5$$

$$k = 16$$

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

Threshold-Based Switching Functions

- **Arithmetic Generalization of Boolean predicates $u \leq \theta$:**

  - Step: $H^+(u,\theta,0,1)$, $H^-(u,\theta,0,1) = 1 - H^+(u,\theta,0,1)$
  - Sigmoid: $S^+(u,\theta,k,0,1)$, $S^-(u,\theta,k,0,1) = 1 - S^+(u,\theta,k,0,1)$
  - Ramp: $R^+(u,\theta_1,\theta_2,0,1)$, $R^-(u,\theta_1,\theta_2,0,1) = 1 - R^+(u,\theta_1,\theta_2,0,1)$

- **Boolean algebra generalizes to probability algebra:**

  $\sim(u \leq \theta)$: $H^-(u,\theta,0,1) = 1 - H^+(u,\theta,0,1)$

  $(u \leq \theta_1)$ & $(v \leq \theta_2)$: $H^+(u,\theta_1,0,1) * H^+(v,\theta_2,0,1)$

  $(u \leq \theta_1)$ | $(u \leq \theta_2)$: $H^+(u,\theta_1,0,1) + H^+(v,\theta_2,0,1) - H^+(u,\theta_1,0,1) * H^+(v,\theta_2,0,1)$

- **Generalization:** $H^\pm(u,\theta,u_m,u_M)$, $S^\pm(u,\theta,k,u_m,u_M)$, $R^\pm(u,\theta_1,\theta_2,u_m,u_M)$

$$S^\pm(u,\theta,k,u_m,u_M) = u_m + (u_M - u_m) S^+(u,k,\theta)$$

Gene Regulatory Networks (GRN)

- GRNs have the following general form:

$$\dot{x}_i = \sum_{m=1}^{m_i} \prod_{n=1}^{n_m} a_{mn} s^{\pm}(x_{mn,}, \theta_{mn}, k_{mn}, u_{mn}, v_{mn}) - b_i x_i$$

where:

a_{mn} : are activation / inhibition constants

b_i : are decay constants

$s^{\pm}(..)$: are possibly complemented sigmoidal functions

- **Note:** steps and ramps are sigmoid approximations

Minimal Model

Cornell's Minimal Resistor Model

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

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

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

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

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

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

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

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v/\tau_{fi}$$

Cornell's Minimal Resistor Model

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

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

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

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

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

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u-u)v/\tau_{fi}$$

voltage

Cornell's Minimal Resistor Model

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

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

$$J_{si} = - \ldots ,1)\; ws/\tau_{si}$$

Diffusion
Laplacia
n

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

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

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

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

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u-u)v/\tau_{fi}$$

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Cornell's Minimal Resistor Model

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

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

$$J_{si} = -H^{+}(u, \ldots$$

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

Fast input current

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

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

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Cornell's Minimal Resistor Model

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

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

$$J_{si} = -H^{+}(u,\theta_w,0 \ldots$$

$$J_{so} = H^{-}(u,\theta_w,0,1)\ u/\tau_0 + H^{+}(u,\theta_w,0,1)/\tau_{so}$$

Slow input current

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

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

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

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v / \tau_{fi}$$

Cornell's Minimal Resistor Model

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

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

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v/\tau_{fi}$$

Slow output current

Cornell's Minimal Resistor Model

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

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$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v/\tau_{fi}$$

Cornell's Minimal Resistor Model

$$\dot{u} = \nabla(D\nabla u) - (J_{fi} + J_{s}$$

Activation Threshold

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

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

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

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Cornell's Minimal Resistor Model

Heaviside (step)

$$\dot{u} = \nabla(D\nabla u) - (J_{fi} \ldots$$

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

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

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$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u-u)v/\tau_{fi}$$

Cornell's Minimal Resistor Model

Fast input Gate

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

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$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v/\tau_{fi}$$

Cornell's Minimal Resistor Model

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

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

Resistance
Time Cst

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

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

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

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$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v/\tau_{fi}$$

Piecewise
Nonlinear

Cornell's Minimal Resistor Model

$$\dot{u} = \nabla(D\nabla u \ldots)$$

Slow Input Gate

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

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

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

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Cornell's Minimal Resistor Model

$$\dot{u} = \nabla(D\nabla u) - (J_{fi} + J_{si} + \dots$$

Slow Output Gate

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

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Cornell's Minimal Resistor Model

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

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

Piecewise Bilinear

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

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

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

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

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

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v/\tau_{fi}$$

Cornell's Minimal Resistor Model

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Piecewise
Nonlinear

Cornell's Minimal Resistor Model

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

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

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

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

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

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

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

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v / \tau_{fi}$$

Cornell's Minimal Resistor Model

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

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

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

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

Piecewise Linear

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v/\tau_{fi}$$

Cornell's Minimal Resistor Model

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

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

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

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

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

$$\dot w = H^{-}(\ldots_\infty - w)/\tau_w^{-} \ldots /\tau_w^{+}$$

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

Sigmoid (s-step)

Nonlinear

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u-u)v/\tau_{fi}$$

Cornell's Minimal Resistor Model

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

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

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

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

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

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

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

$$J_{fi} = -H(u-\theta_v)(u-\theta_v)(u_u - u)v/\tau_{fi}$$

Voltage-controlled resistances

Piecewise Constant

$$\tau_v^- = H^+(u, \theta_v^-, \tau_{v1}^-, \tau_{v2}^-)$$

$$\tau_o = H^-(u, \theta_v^-, \tau_{o2}, \tau_{o1})$$

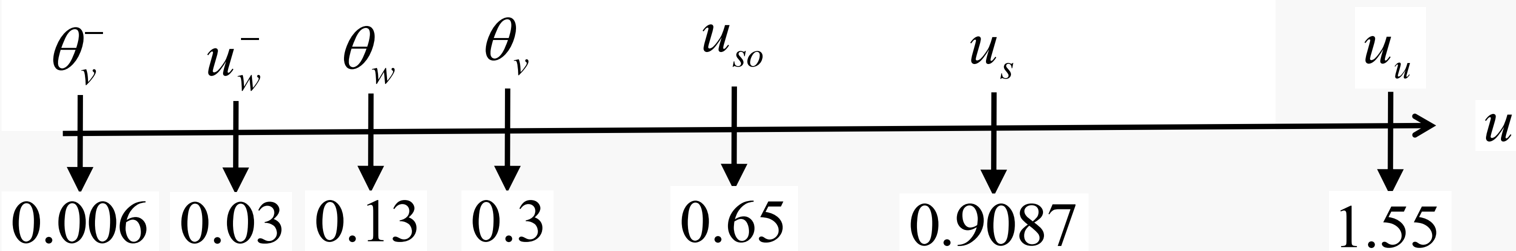
$$\tau_s = H^+(u, \theta_w, \tau_{s1}, \tau_{s2})$$

$$\tau_w^- = S^+(u, k_w^-, u_w^-, \tau_{w1}^-, \tau_{w2}^-)$$

$$\tau_{so} = S^+(u, k_{so}^-, u_{so}^-, \tau_{so1}^-, \tau_{so2}^-)$$

$$v_\infty = h^-(u, \theta_v^-, 0, 1)$$

$$w_\infty = h^-(u, \theta_v^-, 0, 1)\,(1 - u / \tau_{w\infty}) + h^+(u, \theta_v^-, 0, \mathrm{w}_\infty^*)$$



Voltage-controlled resistances

$$\tau_v^- = H^+(u, \theta_v^-, \tau_{v1}^-, \tau_{v2}^-)$$

$$\tau_o = H^-(u, \theta_v^-, \tau_{o2}, \tau_{o1})$$

$$\tau_s = H^+(u, \theta_w, \tau_{s1}, \tau_{s2})$$

Piecewise Constant

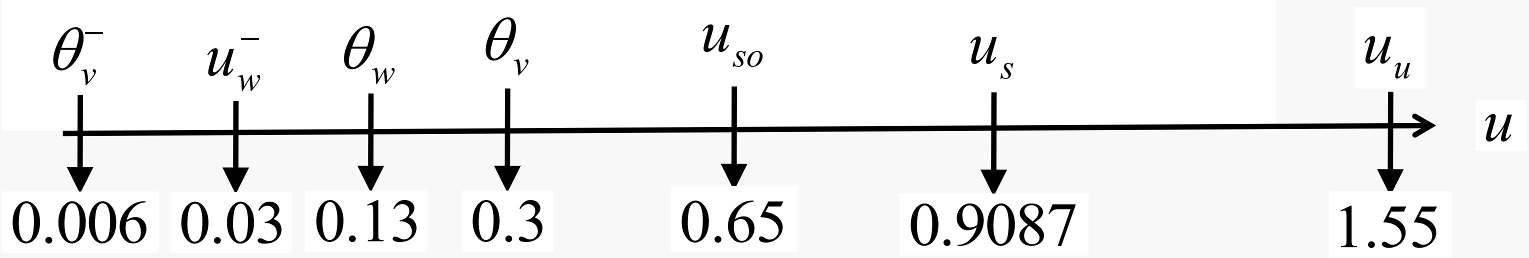
$$\tau_w^- = S^+(u, k_w^-, u_w^-, \tau_{w1}^-, \tau_{w2}^-)$$

$$\tau_{so} = S^+(u, k_{so}^-, u_{so}^-, \tau_{so1}^-, \tau_{so2}^-)$$

Sigmoidal

$$v_\infty = h^-(u, \theta_v^-, 0, 1)$$

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



Voltage-controlled resistances

$$\tau_v^- = H^+(u, \theta_v^-, \tau_{v1}^-, \tau_{v2}^-)$$
$$\tau_o = H^-(u, \theta_v^-, \tau_{o2}, \tau_{o1})$$
$$\tau_s = H^+(u, \theta_w, \tau_{s1}, \tau_{s2})$$

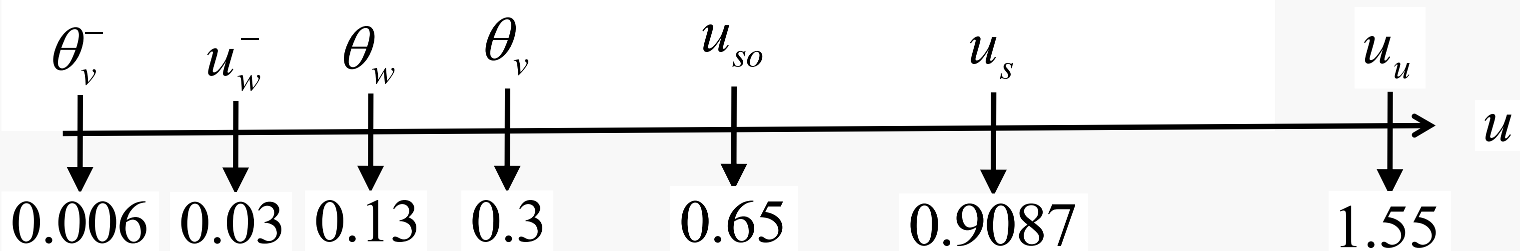
Piecewise Constant

$$\tau_w^- = S^+(u, k_w^-, u_w^-, \tau_{w1}^-, \tau_{w2}^-)$$
$$\tau_{so} = S^+(u, k_{so}^-, u_{so}^-, \tau_{so1}^-, \tau_{so2}^-)$$

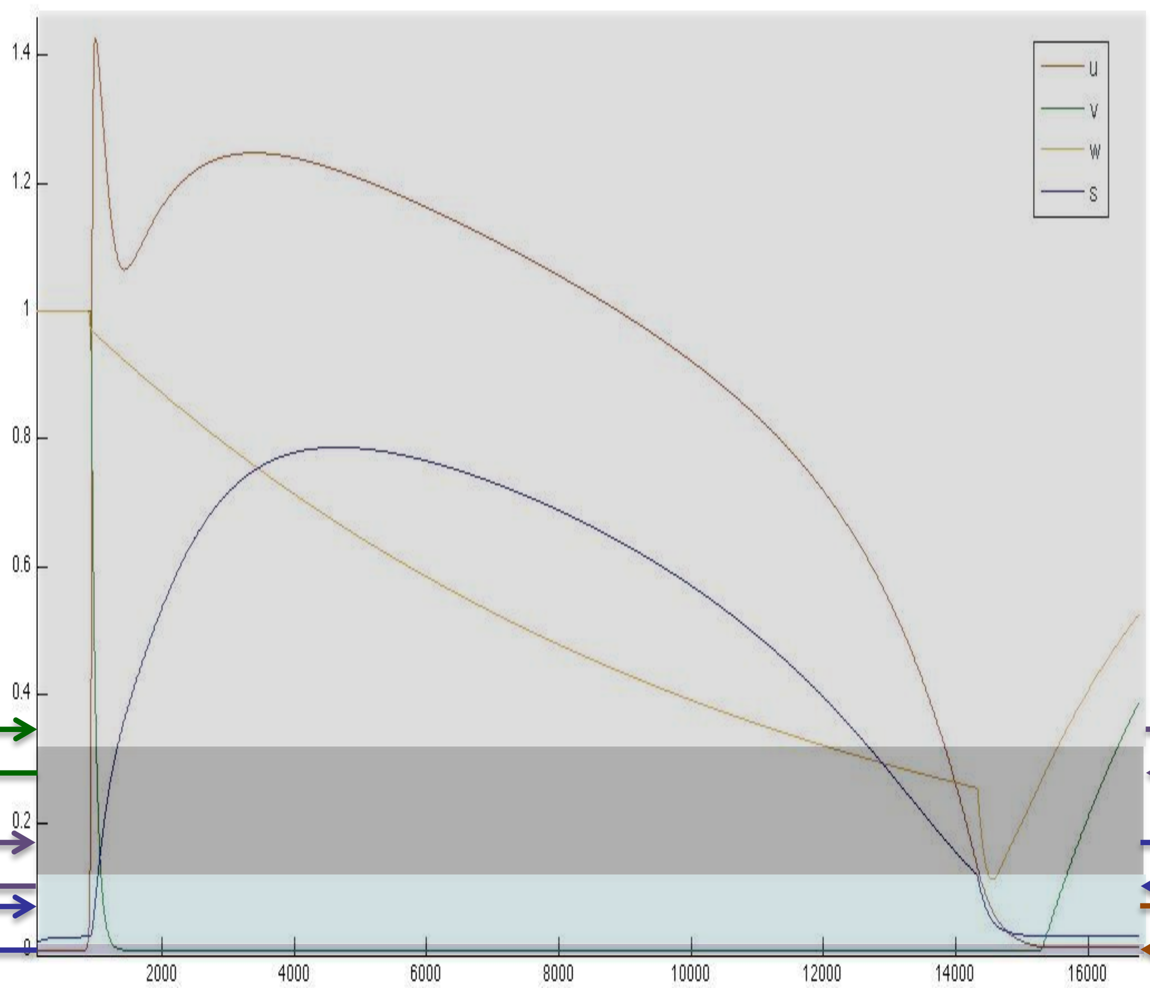
Sigmoidal

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

Piecewise Linear



Cornell's Minimal Resistance Model



$u \geq \theta_v$

$u \geq \theta_w$

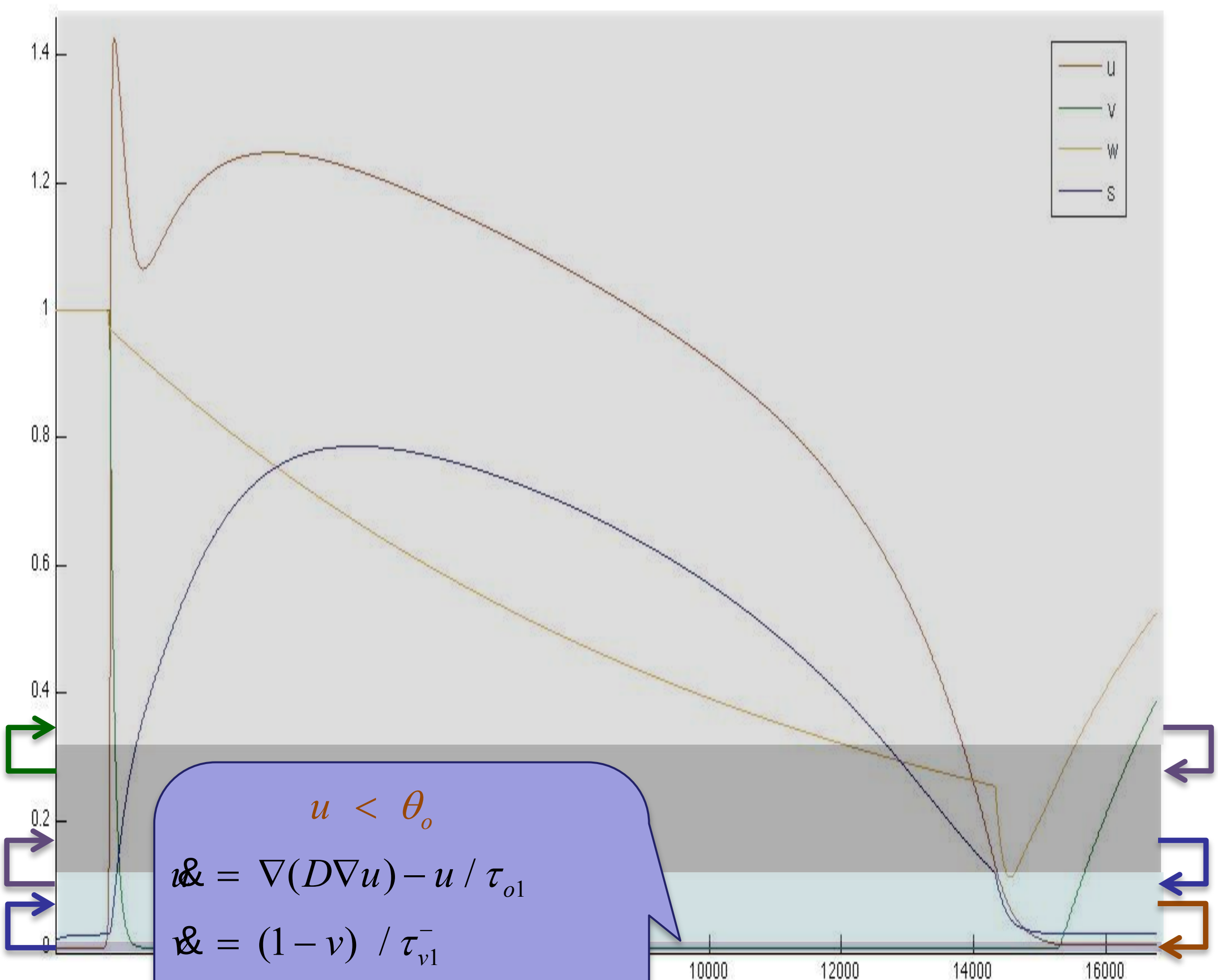
$u \geq \theta_o$

$u < \theta_v = 0.3$

$u < \theta_w = 0.13$

$u < \theta_o = \theta_v^- = 0.006$

Cornell's Minimal Resistance Model



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$u < \theta_o = \theta_v^- = 0.006$

$u < \theta_o$

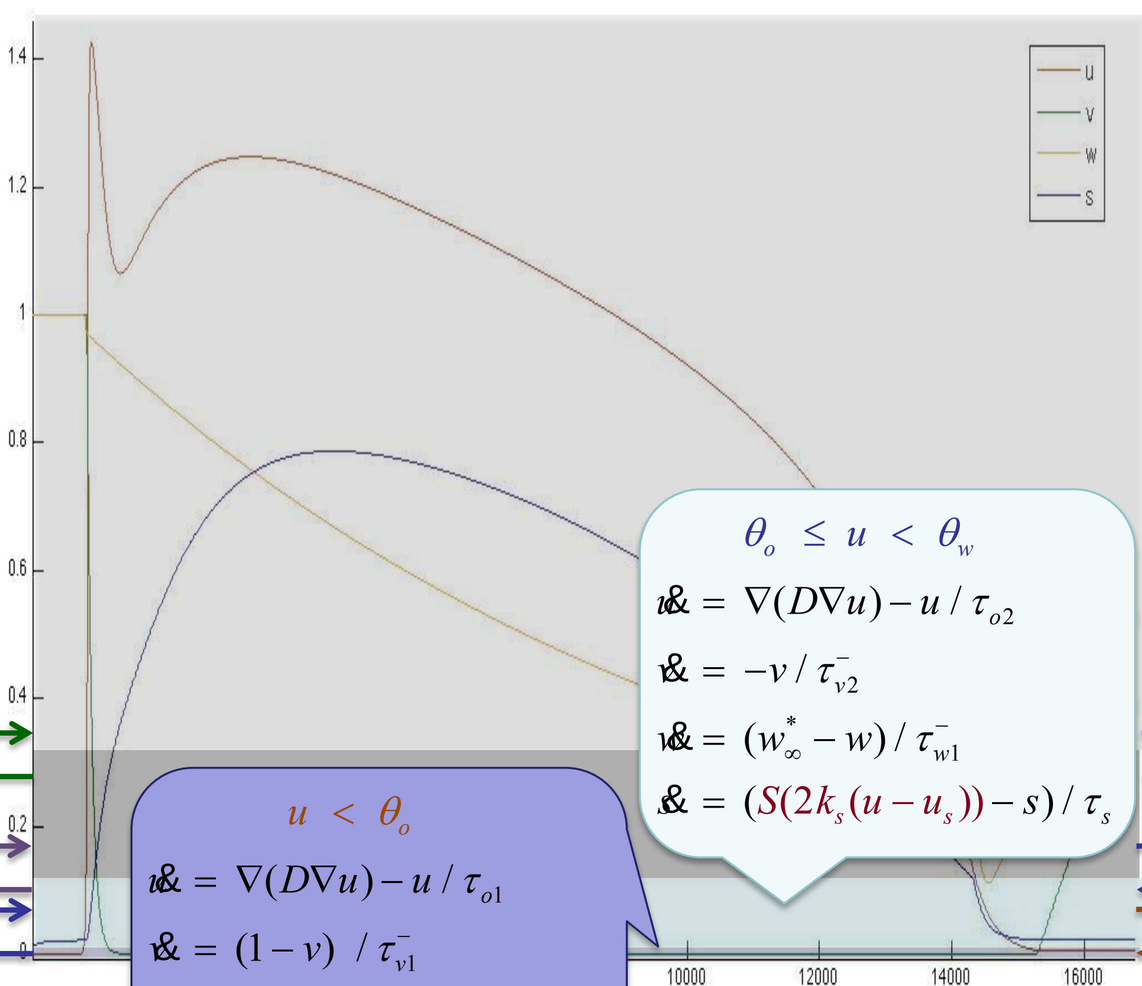
$$\dot{u} = \nabla(D\nabla u) - u / \tau_{o1}$$

$$\dot{v} = (1 - v) \;/\; \tau_{v1}^-$$

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

$$\dot{s} = (S(2k_s(u - u_s)) - s) / \tau_s$$

Cornell's Minimal Resistance Model



$u \geq \theta_v$

$u \geq \theta_w$

$u \geq \theta_o$

$u < \theta_o$

$$\dot{u} = \nabla(D\nabla u) - u / \tau_{o1}$$

$$\dot{v} = (1 - v) \ / \tau_{v1}^{-}$$

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

$$\dot{s} = (S(2k_s(u - u_s)) - s) / \tau_s$$

$\theta_o \leq u < \theta_w$

$$\dot{u} = \nabla(D\nabla u) - u / \tau_{o2}$$

$$\dot{v} = -v / \tau_{v2}^{-}$$

$$\dot{w} = (w_\infty^{*} - w) / \tau_{w1}^{-}$$

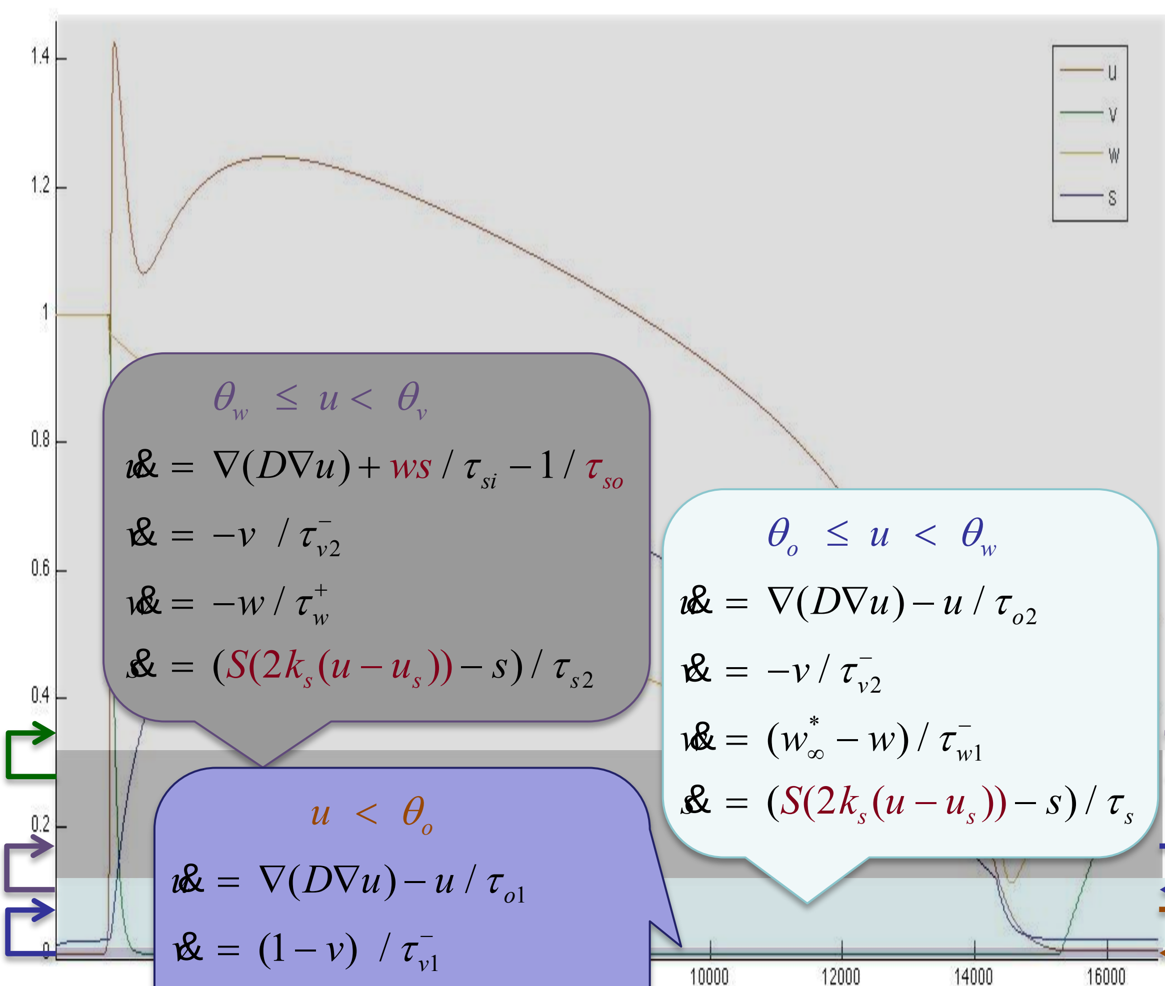
$$\dot{s} = (S(2k_s(u - u_s)) - s) / \tau_s$$

$u < \theta_v = 0.3$

$u < \theta_w = 0.13$

$u < \theta_o = \theta_v^{-} = 0.006$

Cornell's Minimal Resistance Model



$\theta_w \le u < \theta_v$

$$\dot{u} = \nabla(D\nabla u) + ws/\tau_{si} - 1/\tau_{so}$$
$$\dot{v} = -v/\tau_{v2}^{-}$$
$$\dot{w} = -w/\tau_{w}^{+}$$
$$\dot{s} = (S(2k_s(u-u_s)) - s)/\tau_{s2}$$

$\theta_o \le u < \theta_w$

$$\dot{u} = \nabla(D\nabla u) - u/\tau_{o2}$$
$$\dot{v} = -v/\tau_{v2}^{-}$$
$$\dot{w} = (w_{\infty}^{*} - w)/\tau_{w1}^{-}$$
$$\dot{s} = (S(2k_s(u-u_s)) - s)/\tau_{s}$$

$u < \theta_o$

$$\dot{u} = \nabla(D\nabla u) - u/\tau_{o1}$$
$$\dot{v} = (1-v)/\tau_{v1}^{-}$$
$$\dot{w} = (1 - u/\tau_{w\infty} - w)/\tau_{w}^{-}$$
$$\dot{s} = (S(2k_s(u-u_s)) - s)/\tau_{s}$$

$u \ge \theta_v$

$u \ge \theta_w$

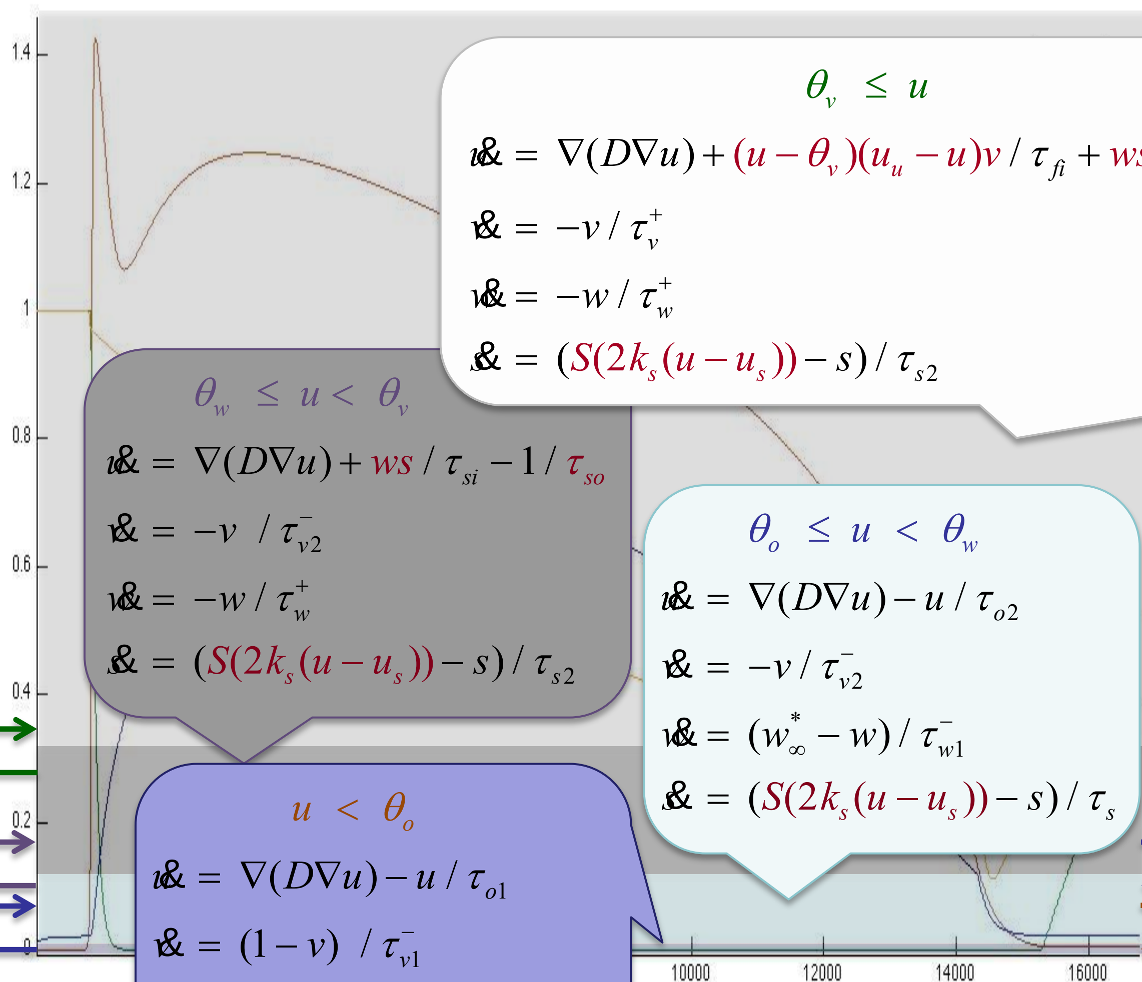
$u \ge \theta_o$

$u < \theta_v = 0.3$

$u < \theta_w = 0.13$

$u < \theta_o = \theta_v^{-} = 0.006$

Cornell's Minimal Resistance Model



$\theta_v \le u$

$$\dot{u} = \nabla(D\nabla u) + (u-\theta_v)(u_u-u)v/\tau_{fi} + ws/\tau_{fi} - 1/\tau_{so}$$
$$\dot{v} = -v/\tau_v^+$$
$$\dot{w} = -w/\tau_w^+$$
$$\dot{s} = (S(2k_s(u-u_s))-s)/\tau_{s2}$$

$\theta_w \le u < \theta_v$

$$\dot{u} = \nabla(D\nabla u) + ws/\tau_{si} - 1/\tau_{so}$$
$$\dot{v} = -v/\tau_{v2}^-$$
$$\dot{w} = -w/\tau_w^+$$
$$\dot{s} = (S(2k_s(u-u_s))-s)/\tau_{s2}$$

$\theta_o \le u < \theta_w$

$$\dot{u} = \nabla(D\nabla u) - u/\tau_{o2}$$
$$\dot{v} = -v/\tau_{v2}^-$$
$$\dot{w} = (w_\infty^* - w)/\tau_{w1}^-$$
$$\dot{s} = (S(2k_s(u-u_s))-s)/\tau_s$$

$u < \theta_o$

$$\dot{u} = \nabla(D\nabla u) - u/\tau_{o1}$$
$$\dot{v} = (1-v)/\tau_{v1}^-$$
$$\dot{w} = (1-u/\tau_{w\infty} - w)/\tau_w^-$$
$$\dot{s} = (S(2k_s(u-u_s))-s)/\tau_s$$

$u \ge \theta_v$

$u \ge \theta_w$

$u \ge \theta_o$

$u < \theta_v = 0.3$

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$u < \theta_o = \theta_v^- = 0.006$

Sigmoid Closure

For ab > 0, scaled sigmoids are closed under multiplicative inverses (division):

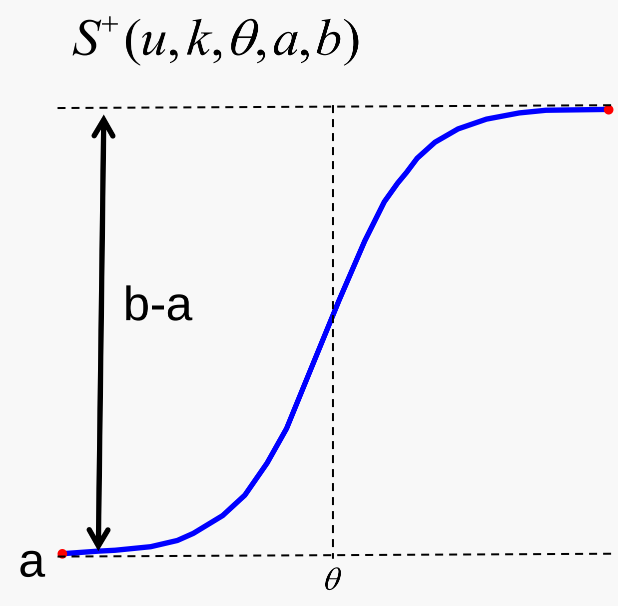
$$S^{+}(u,k,\theta,a,b)^{-1} = S^{-}(u,k,\theta+\ln(a/b)/2k,b^{-},a^{-})$$

Proof

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

$$= \frac{1}{a}\times\frac{a-b+b+ae^{-2k(u-\theta)}}{b+ae^{-2k(u-\theta)}} = \frac{1}{a}-\frac{\dfrac{1}{a}-\dfrac{1}{b}}{1+\dfrac{a}{b}e^{-2k(u-\theta)}} =$$

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



Sigmoid Closure

For ab > 0, scaled sigmoids are closed under multiplicative inverses (division):

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

Proof

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

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

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

Sigmoid Closure

For ab > 0, scaled sigmoids are closed under multiplicative inverses (division):

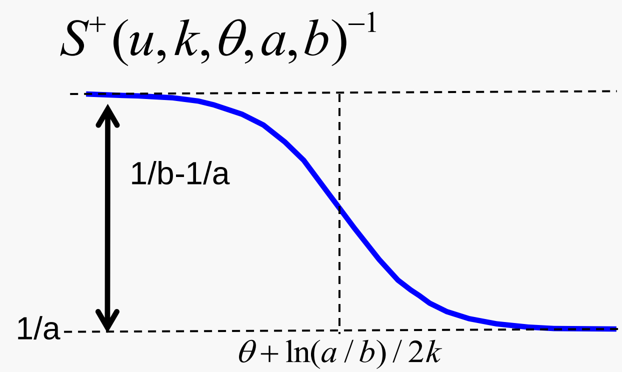
$$S^{+}(u,k,\theta,a,b)^{-1} = S^{-}(u,k,\theta+\ln(a/b)/2k,b^{-},a^{-})$$

Proof

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

$$= \frac{1}{a}\times\frac{a-b+b+ae^{-2k(u-\theta)}}{b+ae^{-2k(u-\theta)}} = \frac{1}{a}-\frac{\dfrac{1}{a}-\dfrac{1}{b}}{1+\dfrac{a}{b}e^{-2k(u-\theta)}} =$$

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



Resistances vs Conductances

Removing Divisions using Sigmoid Closure

$$\tau_w^- = S^-(u, k_w^-, u_w^-, \tau_{w1}^-, \tau_{w2}^-) \qquad g_w^- = 1/\tau_w^- = S^+(u, k_w^-, u'^-_w, g_{w1}^-, g_{w2}^-)$$

$$\tau_{so} = S^-(u, k_{so}, u_{so}, \tau_{so1}, \tau_{so2}) \qquad g_{so} = 1/\tau_{s0} = S^+(u, k_{so}, u'_{so}, g_{so1}, g_{so2})$$

Removing Divisions using $H^+(u,\theta,a,b)^{-1} = H^-(u,\theta,b^{-1},a^{-1})$

$$\tau_v^- = H^+(u, \theta_v^-, \tau_{v1}^-, \tau_{v2}^-)$$

$$\tau_o = H^-(u, \theta_v^-, \tau_{o1}, \tau_{o2})$$

$$\tau_s = H^+(u, \theta_w, \tau_{s1}, \tau_{s2})$$

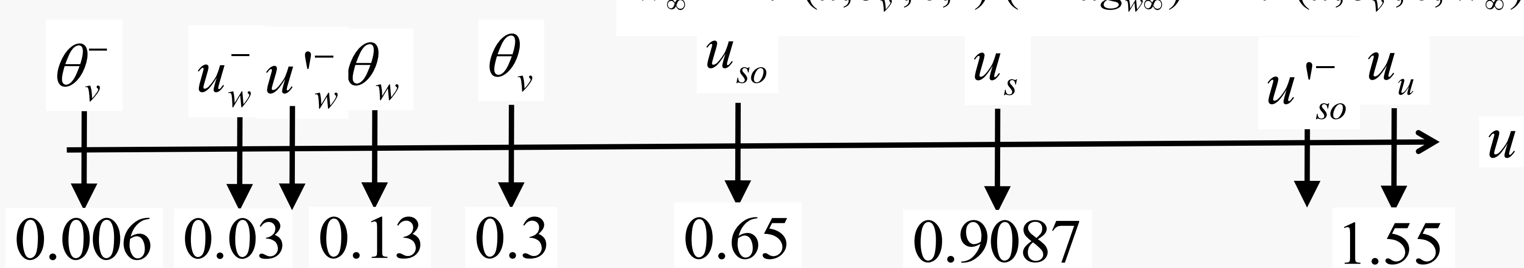
$$g_v^- = 1/\tau_v^- = H^-(u, \theta_v^-, g_{v1}^-, g_{v2}^-)$$

$$g_o = 1/\tau_o = H^+(u, \theta_v^-, g_{o1}, g_{o2})$$

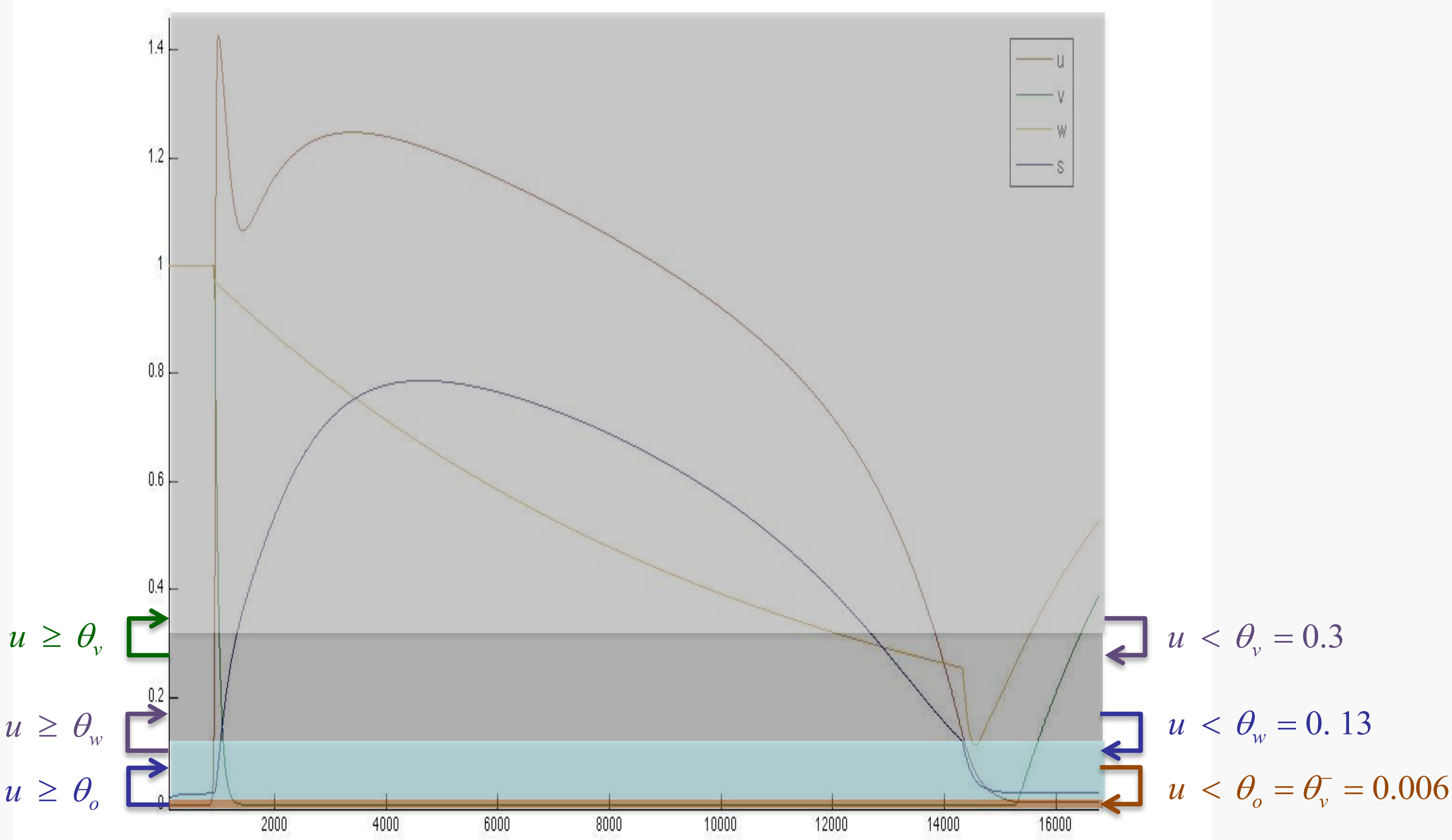
$$g_s = 1/\tau_s = H^-(u, \theta_w, g_{s1}, g_{s2})$$

$$v_\infty = h^-(u, \theta_v^-, 0, 1)$$

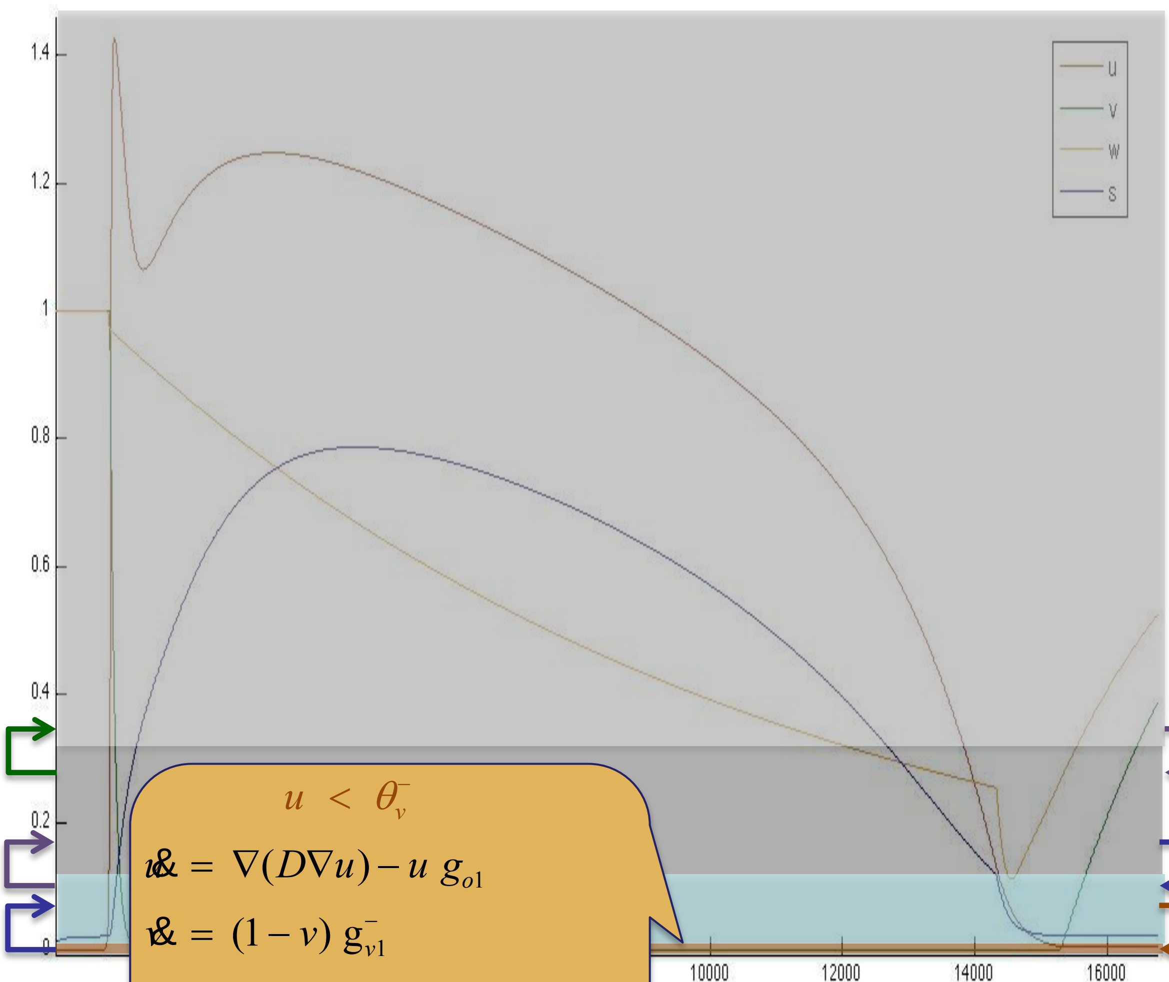
$$w_\infty = h^-(u, \theta_v^-, 0, 1)\,(1 - u g_{w\infty}) + h^+(u, \theta_v^-, 0, \mathrm{w}_\infty^*)$$



Conductances Minimal Model



Conductances Minimal Model



$u \geq \theta_v$

$u \geq \theta_w$

$u \geq \theta_o$

$u < \theta_v = 0.3$

$u < \theta_w = 0.13$

$u < \theta_o = \theta_v^- = 0.006$

$u < \theta_v^-$

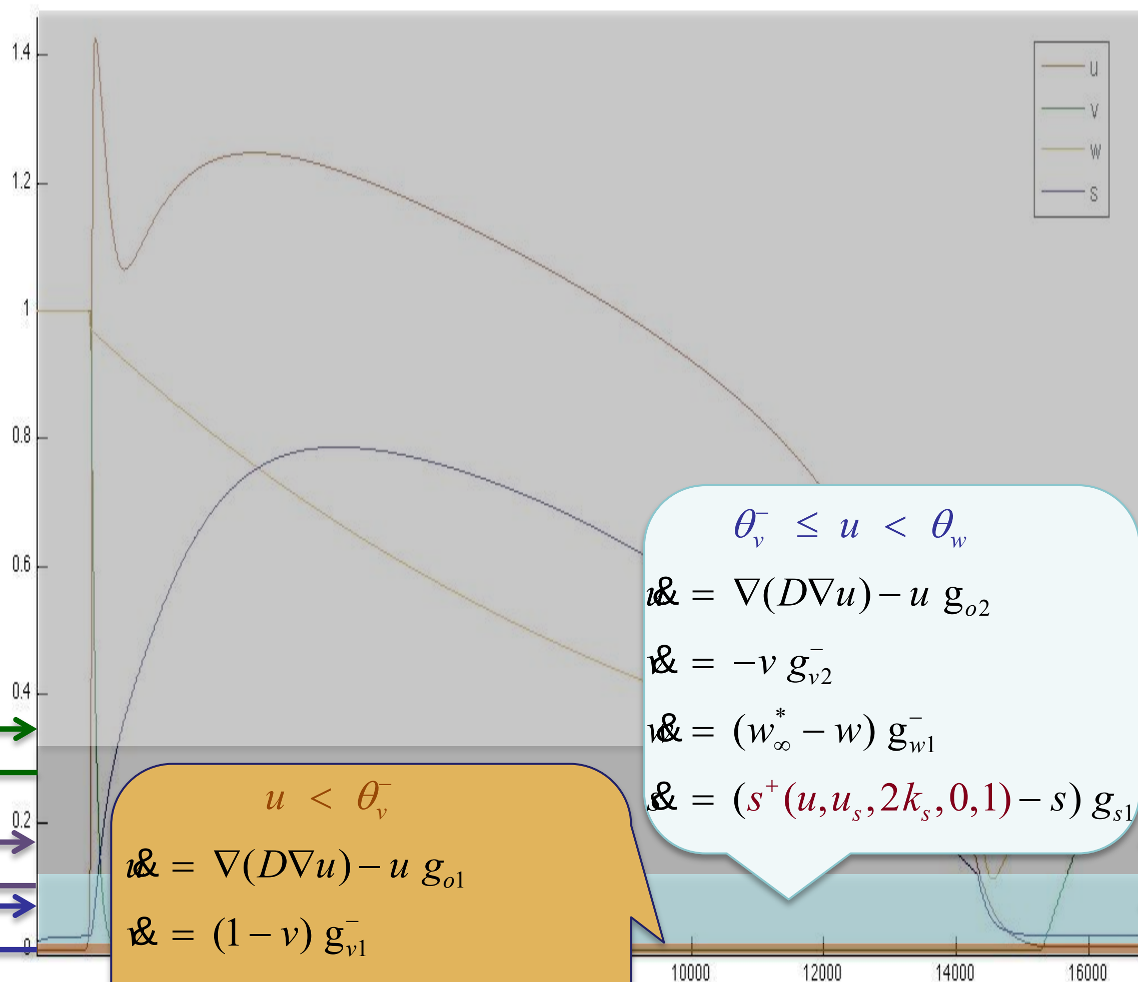
$$\dot{u} = \nabla(D\nabla u) - u\, g_{o1}$$

$$\dot{v} = (1 - v)\, g_{v1}^-$$

$$\dot{w} = (1 - u\, g_{w\infty} - w)\, g_w^-$$

$$\dot{s} = (s^+(u, u_s, 2k_s, 0, 1) - s)\, g_{s1}$$

Conductances Minimal Model



$u \ge \theta_v$

$u \ge \theta_w$

$u \ge \theta_o$

$u < \theta_v^-$

$$\dot{u} = \nabla(D\nabla u) - u\, g_{o1}$$

$$\dot{v} = (1 - v)\, g_{v1}^-$$

$$\dot{w} = (1 - u\, g_{w\infty} - w)\, g_w^-$$

$$\dot{s} = (s^+(u, u_s, 2k_s, 0, 1) - s)\, g_{s1}$$

$\theta_v^- \le u < \theta_w$

$$\dot{u} = \nabla(D\nabla u) - u\, g_{o2}$$

$$\dot{v} = -v\, g_{v2}^-$$

$$\dot{w} = (w_\infty^* - w)\, g_{w1}^-$$

$$\dot{s} = (s^+(u, u_s, 2k_s, 0, 1) - s)\, g_{s1}$$

$u < \theta_v = 0.3$

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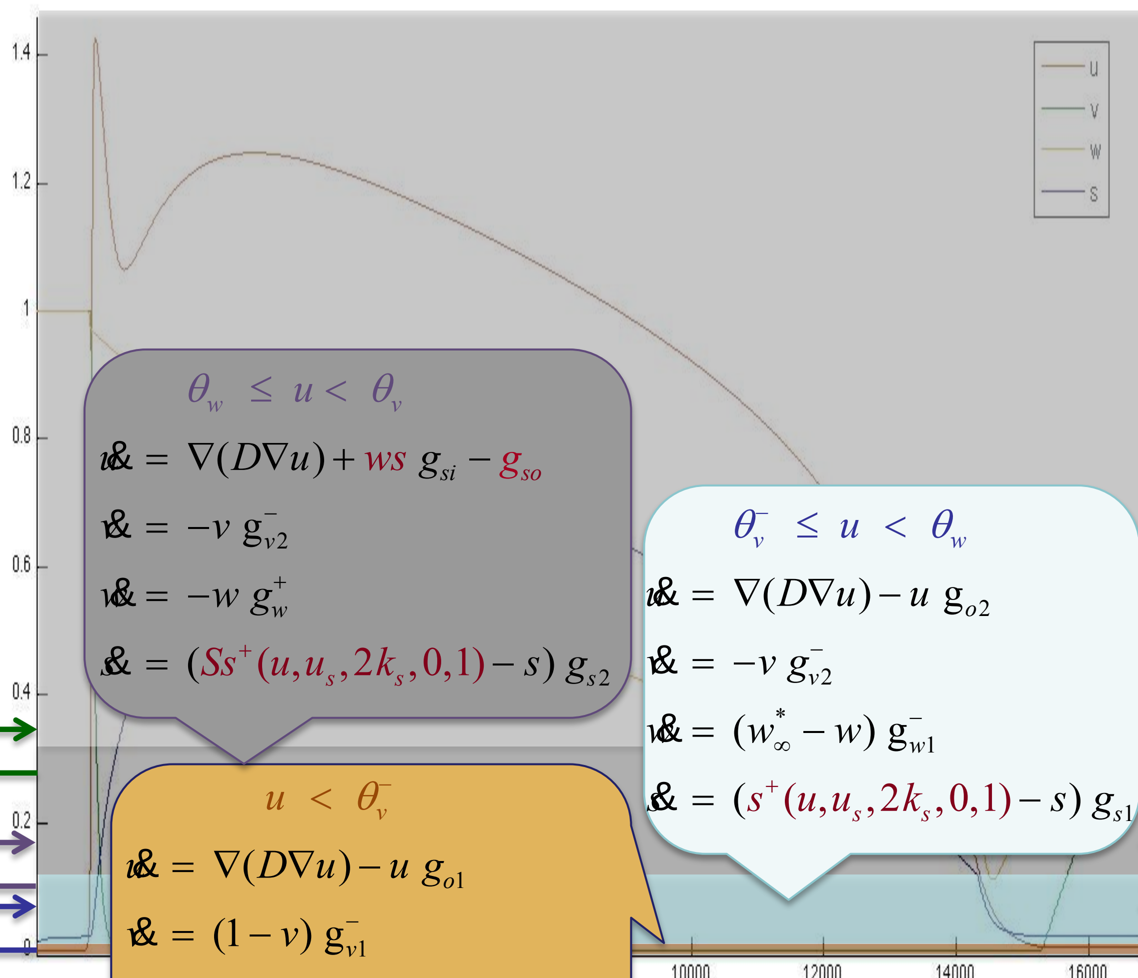
Conductances Minimal Model



$\theta_w \le u < \theta_v$

$$\dot{u} = \nabla(D\nabla u) + ws\, g_{si} - g_{so}$$
$$\dot{v} = -v\, g_{v2}^{-}$$
$$\dot{w} = -w\, g_{w}^{+}$$
$$\dot{s} = (Ss^{+}(u,u_s,2k_s,0,1) - s)\, g_{s2}$$

$\theta_v^{-} \le u < \theta_w$

$$\dot{u} = \nabla(D\nabla u) - u\, g_{o2}$$
$$\dot{v} = -v\, g_{v2}^{-}$$
$$\dot{w} = (w_{\infty}^{*} - w)\, g_{w1}^{-}$$
$$\dot{s} = (s^{+}(u,u_s,2k_s,0,1) - s)\, g_{s1}$$

$u < \theta_v^{-}$

$$\dot{u} = \nabla(D\nabla u) - u\, g_{o1}$$
$$\dot{v} = (1 - v)\, g_{v1}^{-}$$
$$\dot{w} = (1 - u\, g_{w\infty} - w)\, g_{w}^{-}$$
$$\dot{s} = (s^{+}(u,u_s,2k_s,0,1) - s)\, g_{s1}$$

$u \ge \theta_v$

$u \ge \theta_w$

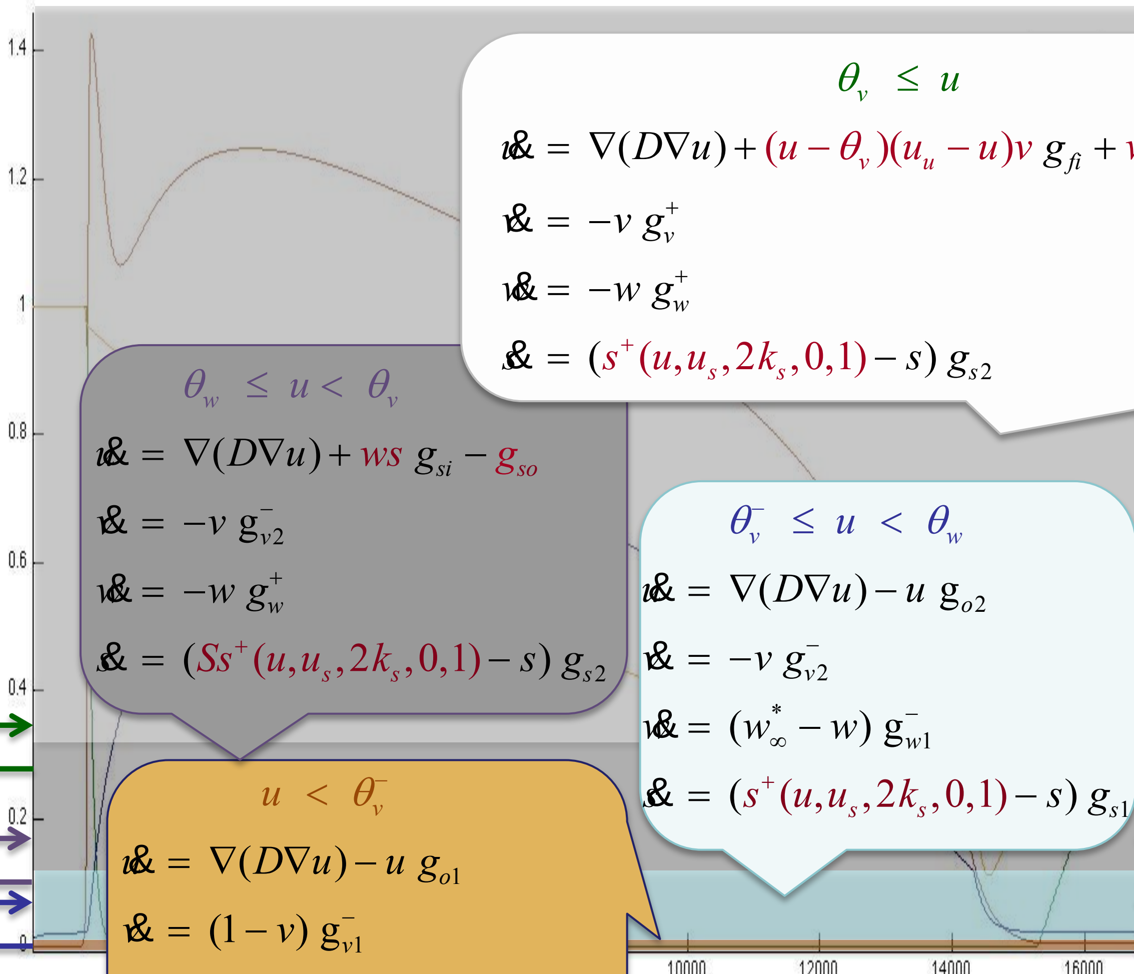
$u \ge \theta_o$

$u < \theta_v = 0.3$

$u < \theta_w = 0.13$

$u < \theta_o = \theta_v^{-} = 0.006$

Conductances Minimal Model



$\theta_v \leq u$

$$\dot{u} = \nabla(D\nabla u) + (u - \theta_v)(u_u - u)v\, g_{fi} + ws\, g_{si} - g_{so}$$
$$\dot{v} = -v\, g_v^+$$
$$\dot{w} = -w\, g_w^+$$
$$\dot{s} = (s^+(u,u_s,2k_s,0,1) - s)\, g_{s2}$$

$\theta_w \leq u < \theta_v$

$$\dot{u} = \nabla(D\nabla u) + ws\, g_{si} - g_{so}$$
$$\dot{v} = -v\, g_{v2}^-$$
$$\dot{w} = -w\, g_w^+$$
$$\dot{s} = (Ss^+(u,u_s,2k_s,0,1) - s)\, g_{s2}$$

$\theta_v^- \leq u < \theta_w$

$$\dot{u} = \nabla(D\nabla u) - u\, g_{o2}$$
$$\dot{v} = -v\, g_{v2}^-$$
$$\dot{w} = (w_\infty^* - w)\, g_{w1}^-$$
$$\dot{s} = (s^+(u,u_s,2k_s,0,1) - s)\, g_{s1}$$

$u < \theta_v^-$

$$\dot{u} = \nabla(D\nabla u) - u\, g_{o1}$$
$$\dot{v} = (1 - v)\, g_{v1}^-$$
$$\dot{w} = (1 - u\, g_{w\infty} - w)\, g_w^-$$
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$u \geq \theta_v$

$u \geq \theta_w$

$u \geq \theta_o$

$u < \theta_v = 0.3$

$u < \theta_w = 0.13$

$u < \theta_o = \theta_v^- = 0.006$

Piecewise Multi Affine Model

Our goals

- Derive a Piecewise Multi Affine model:
  - This should facilitate analysis
  - We want to improve the computational efficiency
- Identify the parameters based on:
  - Data generated by a detailed ionic model
  - Experimental, in-vivo data

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Optimal Polygonal Approximation

Problem to solve:

Given a nonlinear curve and the desired number of the segments return the optimal polygonal approximation:

Example:

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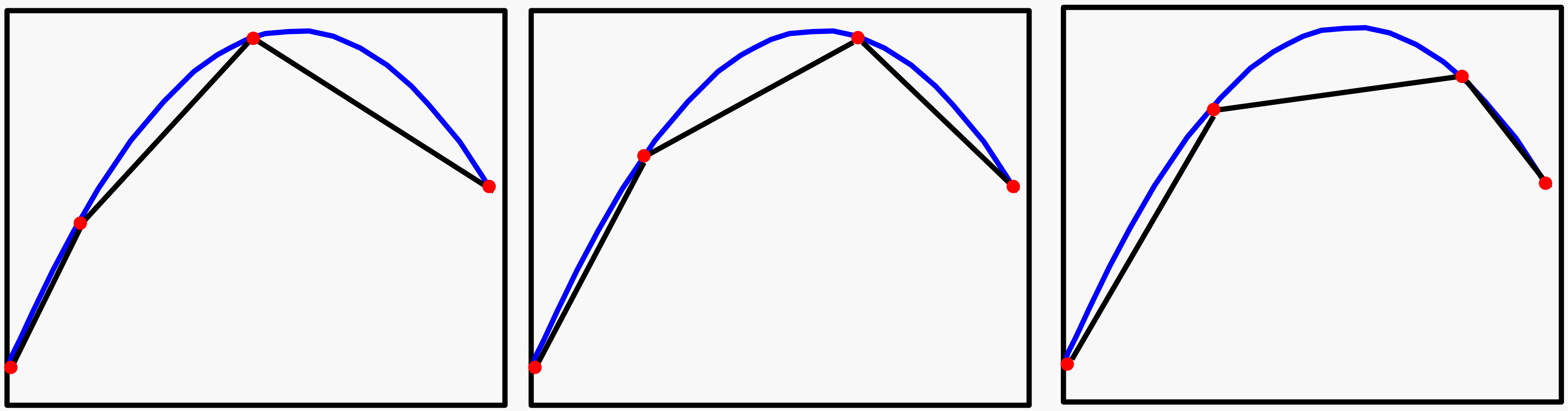
What is the optimal polygonal approximation of the blu curve with 3 segments ?



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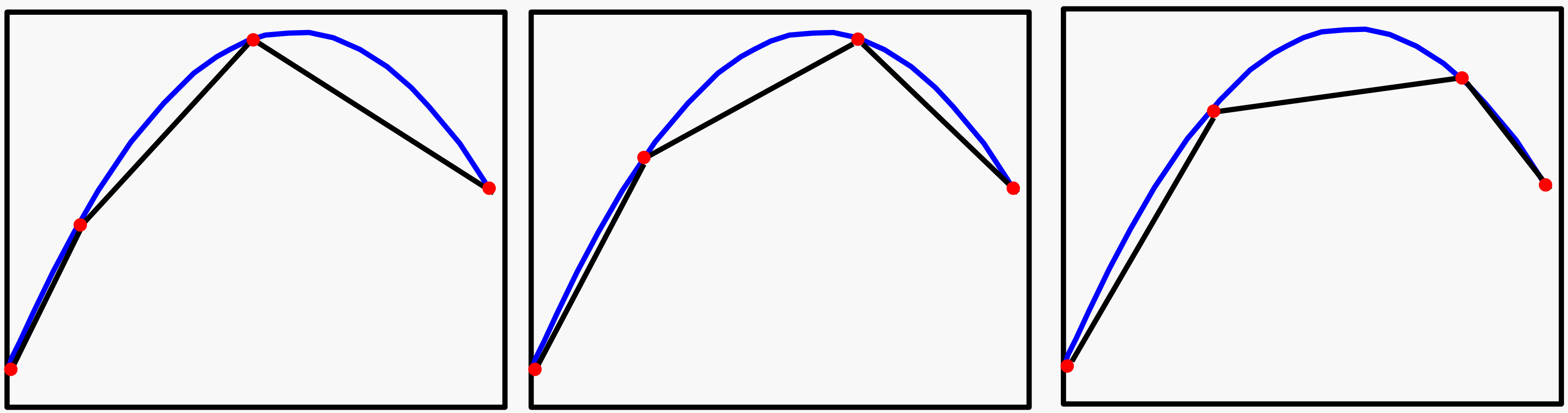
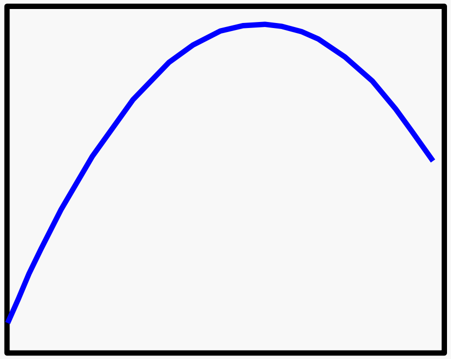


Dynamic Programming Algorithm
with Complexity $O(P^2S)$

P the number of points of the curve

S the number of segments

Marc Salotti, *An efficient algorithm for the optimal polygonal approximation of digitized curves*, Pattern Recognition Letters 22 (2001), Pag 215-221



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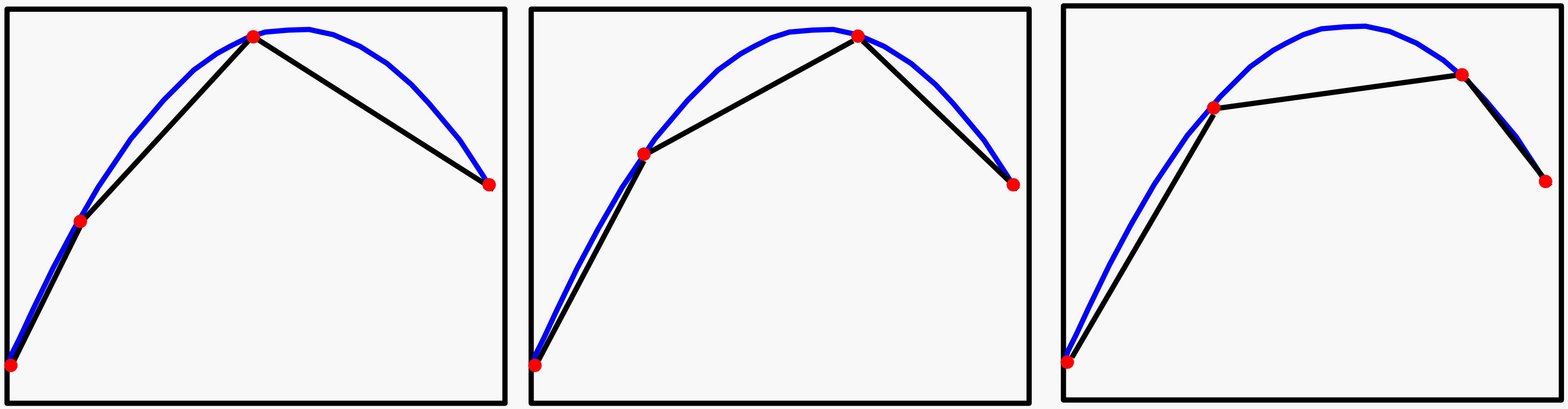

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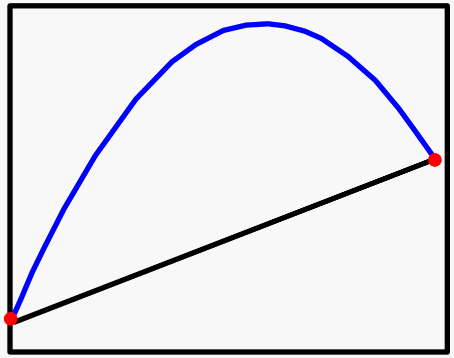

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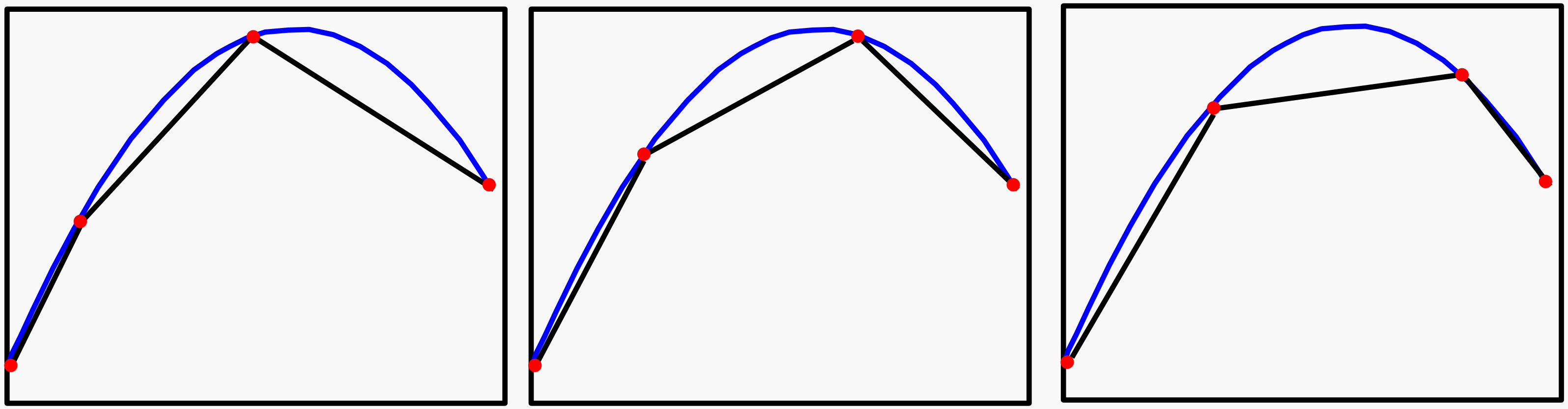

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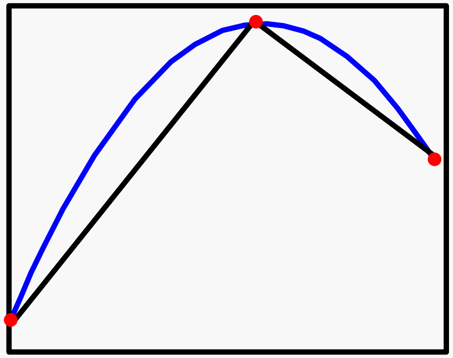

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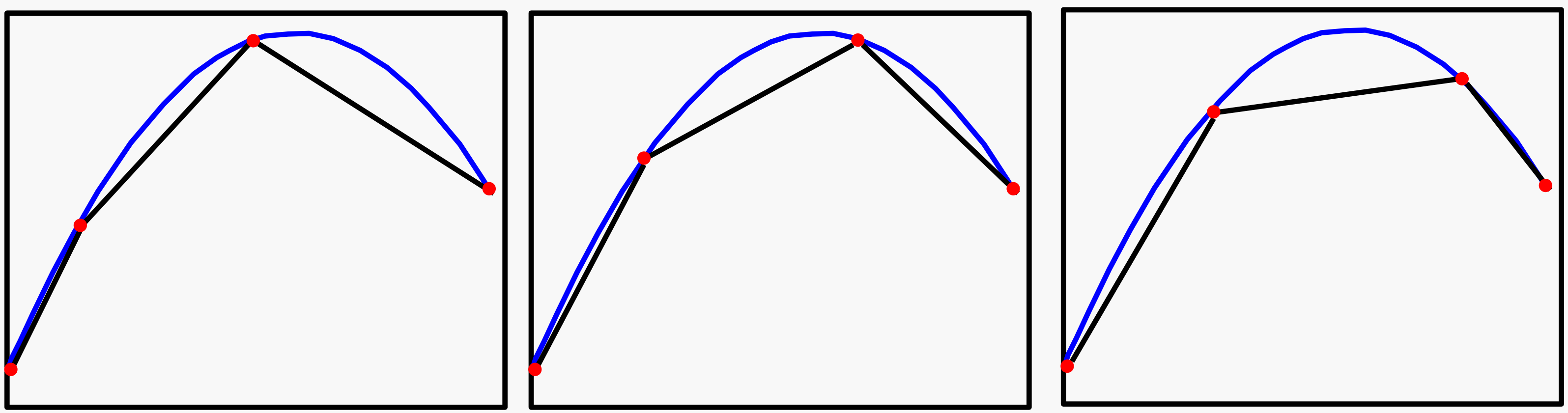

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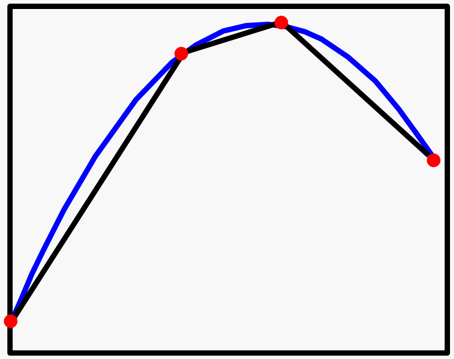

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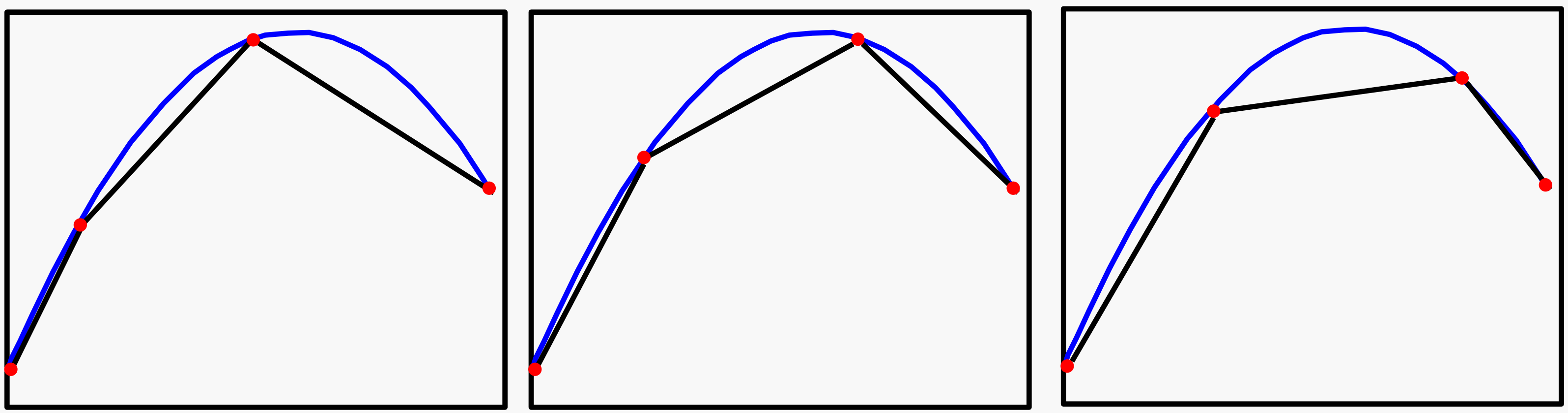

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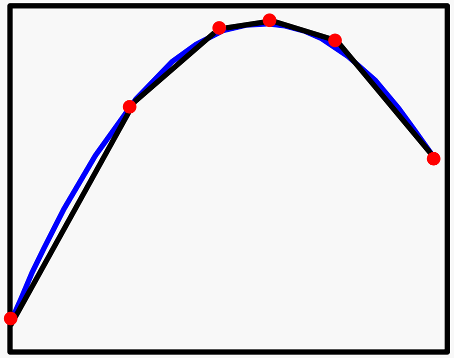

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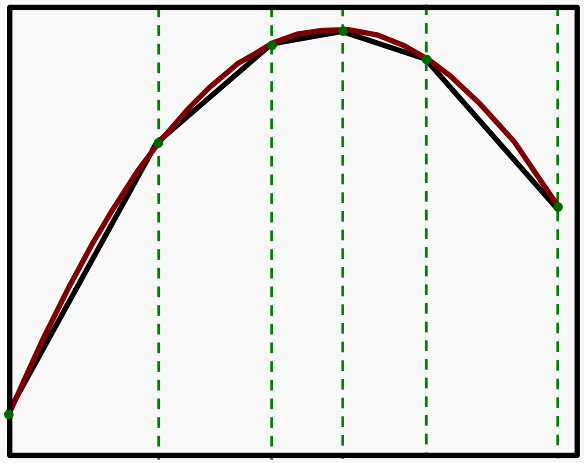
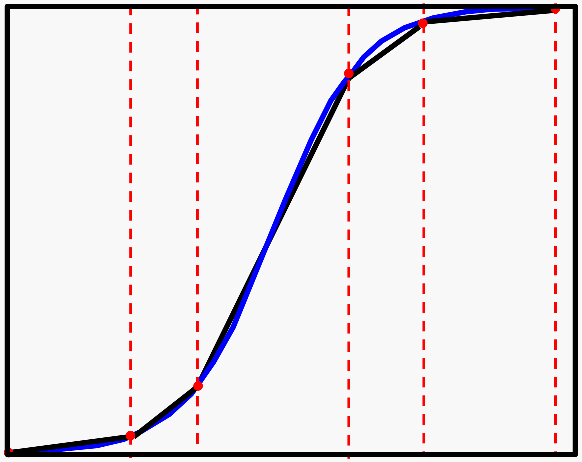
What is the optimal polygonal approximation of the blu and the red curve with 5 segments ?





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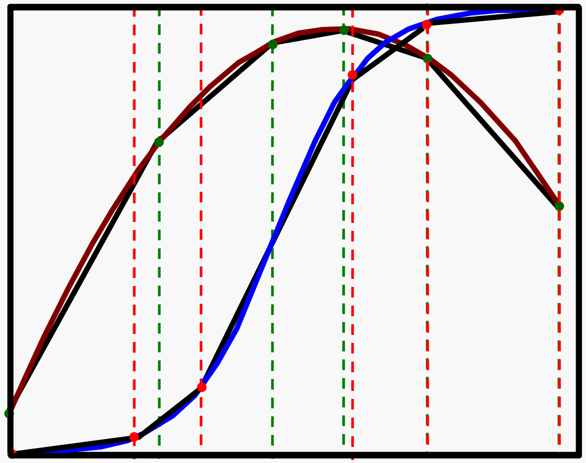

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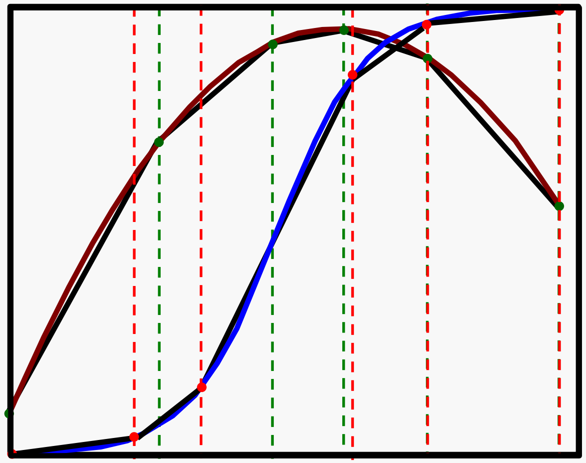

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Our solution: We modify the optimal polygonal approximation algorithm to perform the linearization on a set of curves trying to minimize the maximum error.

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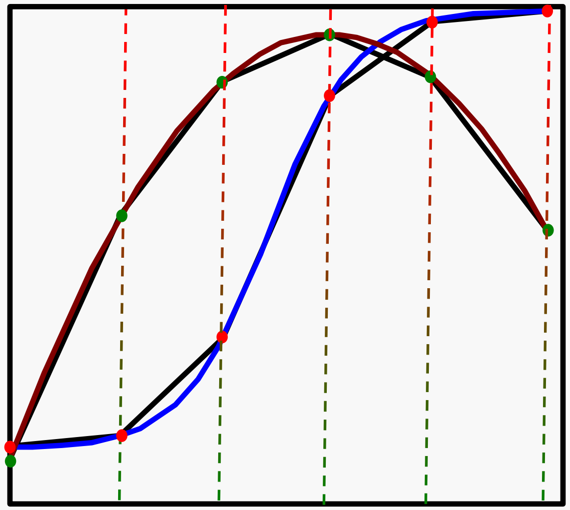

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Deriving the Piecewise Multi Affine Model

$(\theta_v < u \le u_u)$

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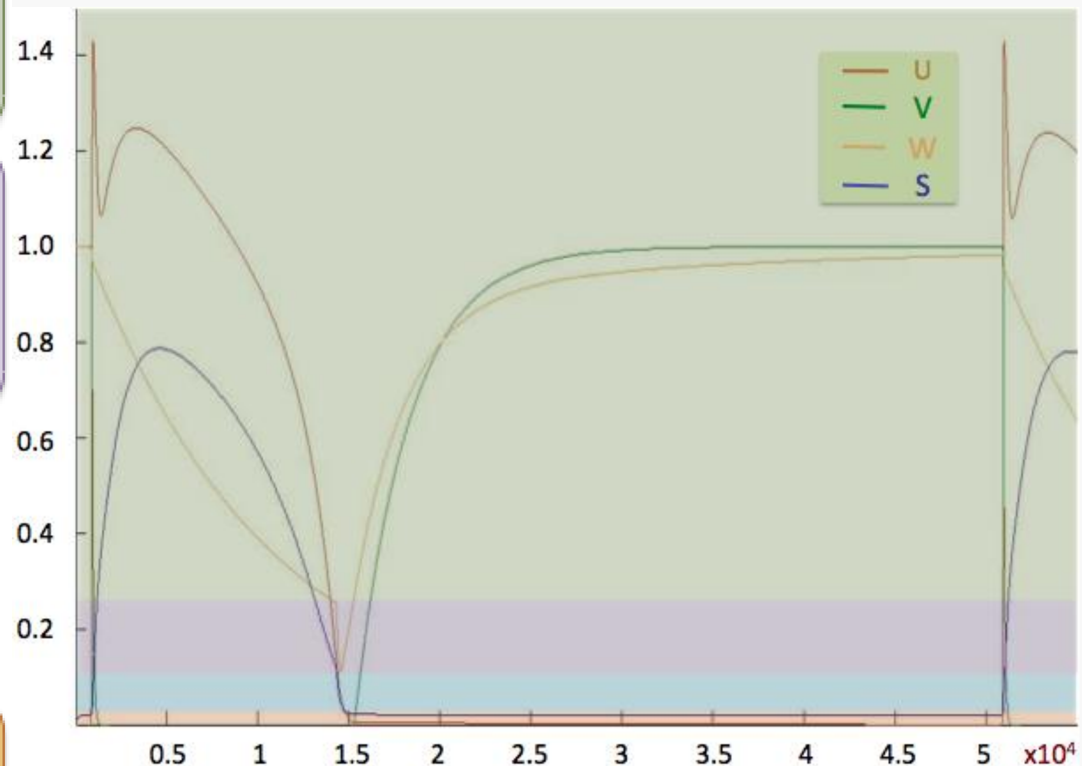

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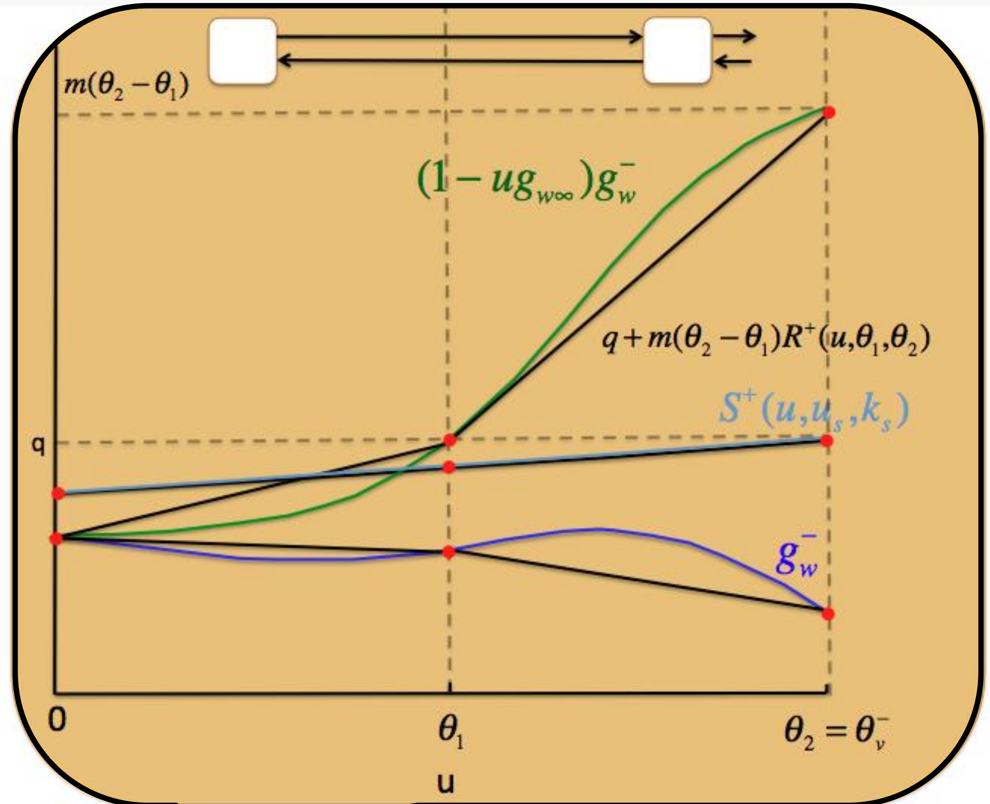

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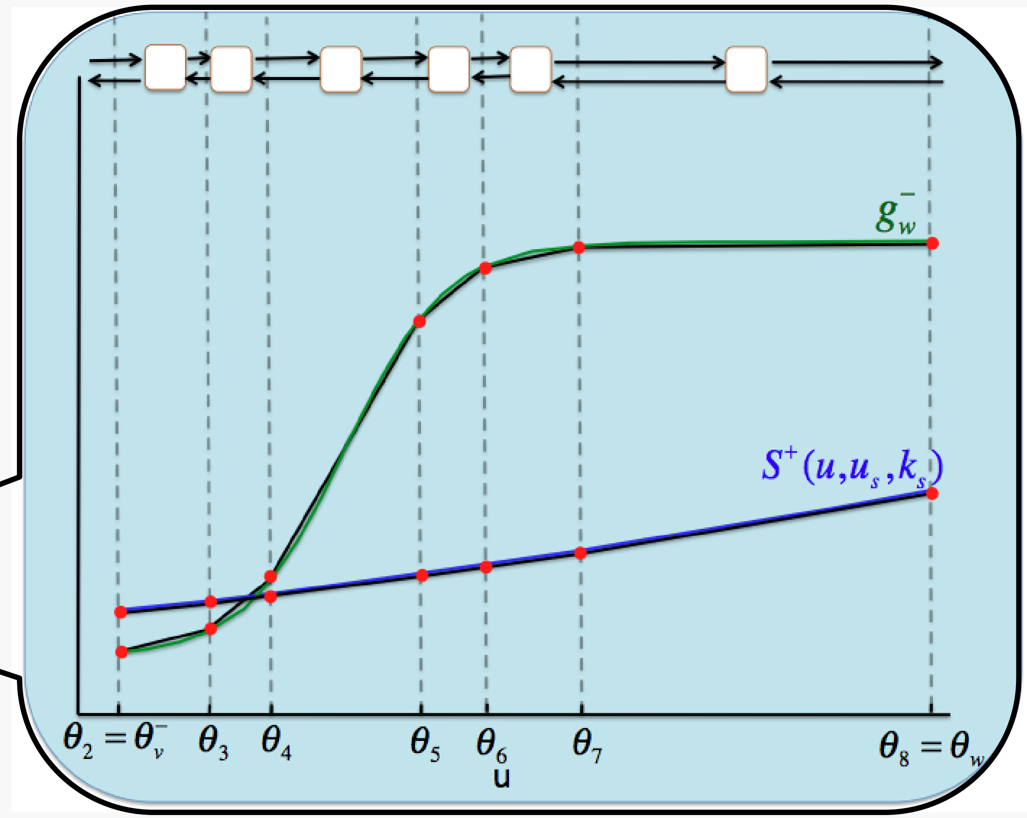

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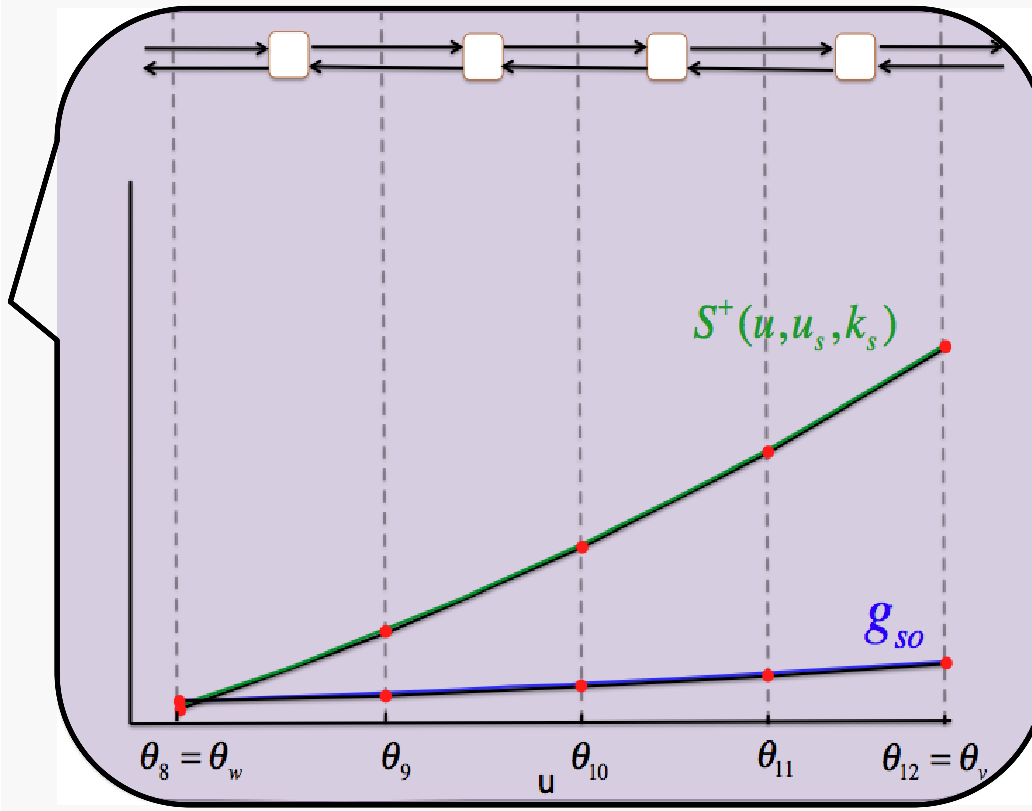
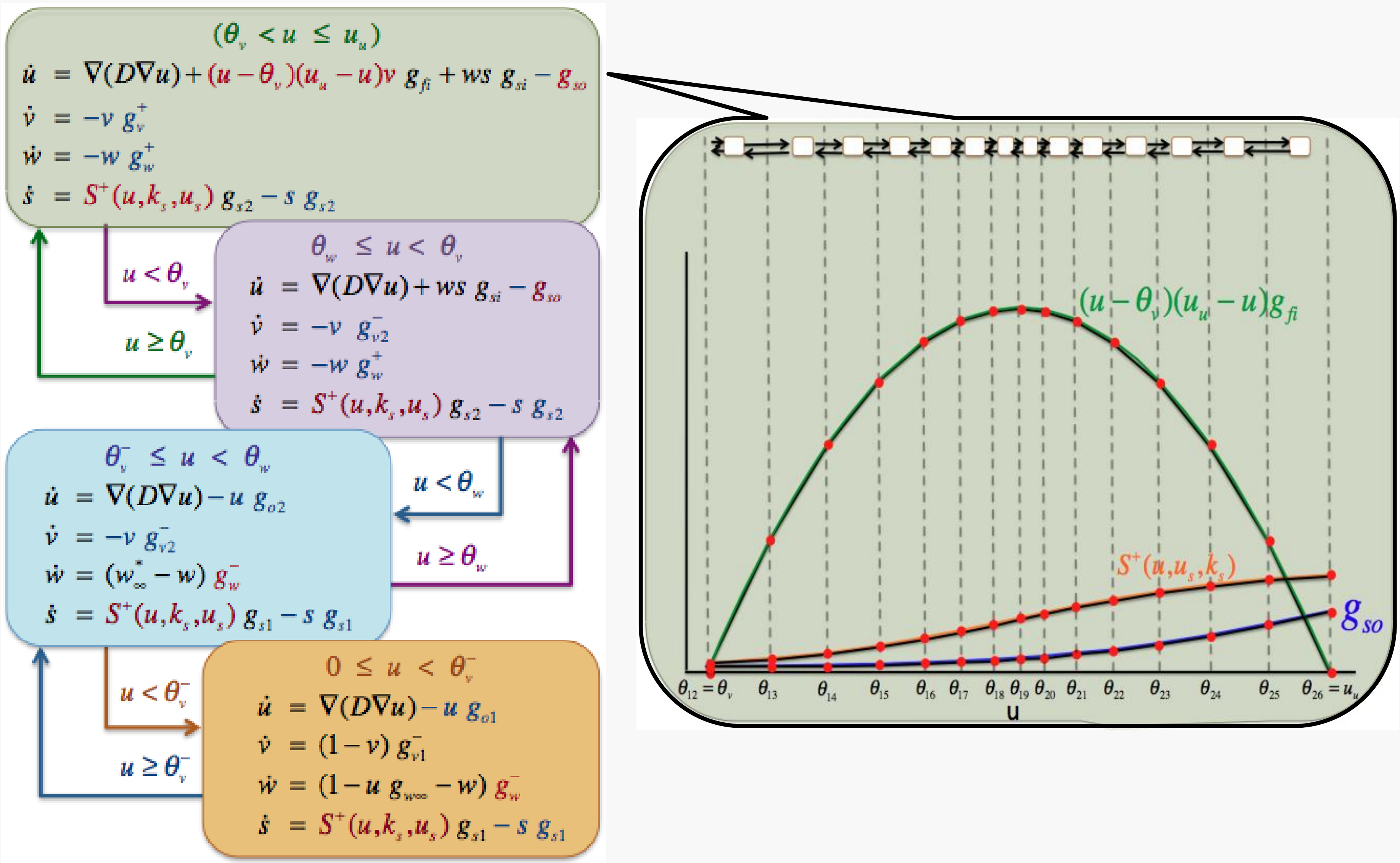


Deriving the Piecewise Multi Affine Model



Deriving the Piecewise Multi Affine Model

$(\theta_v < u \le u_u)$

$$\dot{u} = \nabla(D\nabla u) + (b^{fi} + \sum_{i=12}^{i=26} a_i^{fi} R^+(u,\theta_i,\theta_{i+1}))v\, g_{fi} + ws\, g_{si} - (b^{so} + \sum_{i=12}^{i=26} a_i^{so} R^+(u,\theta_i,\theta_{i+1}))$$

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

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

$$\dot{s} = (b^s + \sum_{i=12}^{i=26} a_i^s R^+(u,\theta_i,\theta_{i+1}))\, g_{s2} - s\, g_{s2}$$

$u < \theta_v$

$u \ge \theta_v$

$\theta_w \le u < \theta_v$

$$\dot{u} = \nabla(D\nabla u) + ws\, g_{si} - (b^{so} + \sum_{i=8}^{i=12} a_i^{so} R^+(u,\theta_i,\theta_{i+1}))$$

$$\dot{v} = -v\, g_{v2}^-$$

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

$$\dot{s} = (b^s + \sum_{i=8}^{i=12} a_i^s R^+(u,\theta_i,\theta_{i+1}))\, g_{s2} - s\, g_{s2}$$

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$$\dot{w} = (b^{w1} + \sum_{i=1}^{i=2} a_i^{w1} R^+(u,\theta_i,\theta_{i+1})) - w\,(b^{w2} + \sum_{i=1}^{i=2} a_i^{w2} R^+(u,\theta_i,\theta_{i+1}))$$

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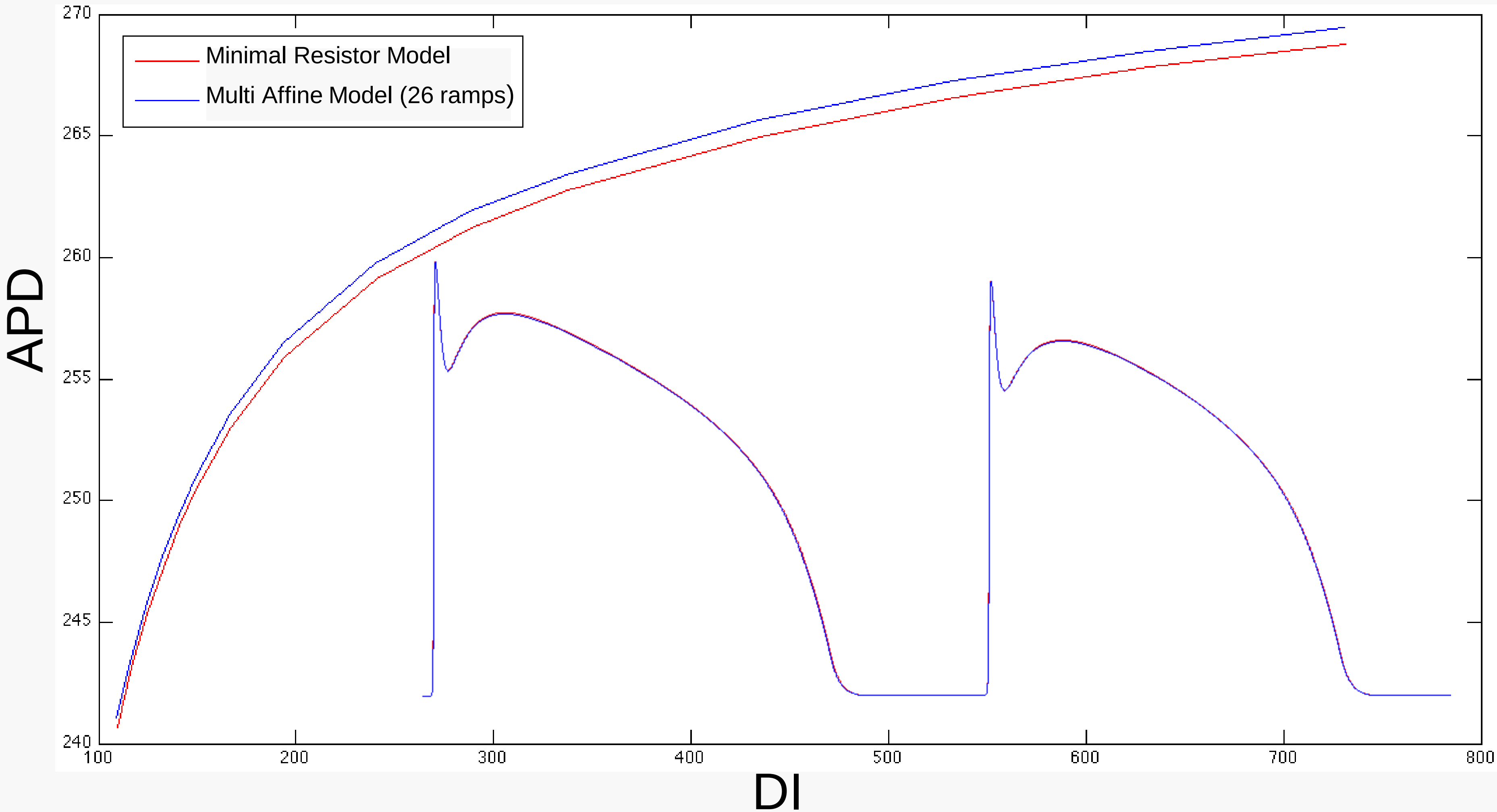
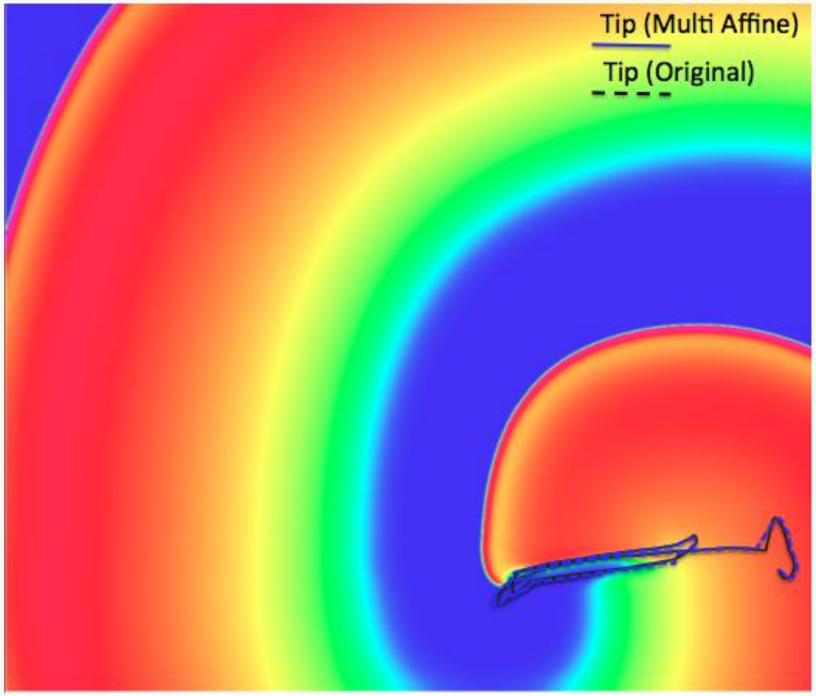
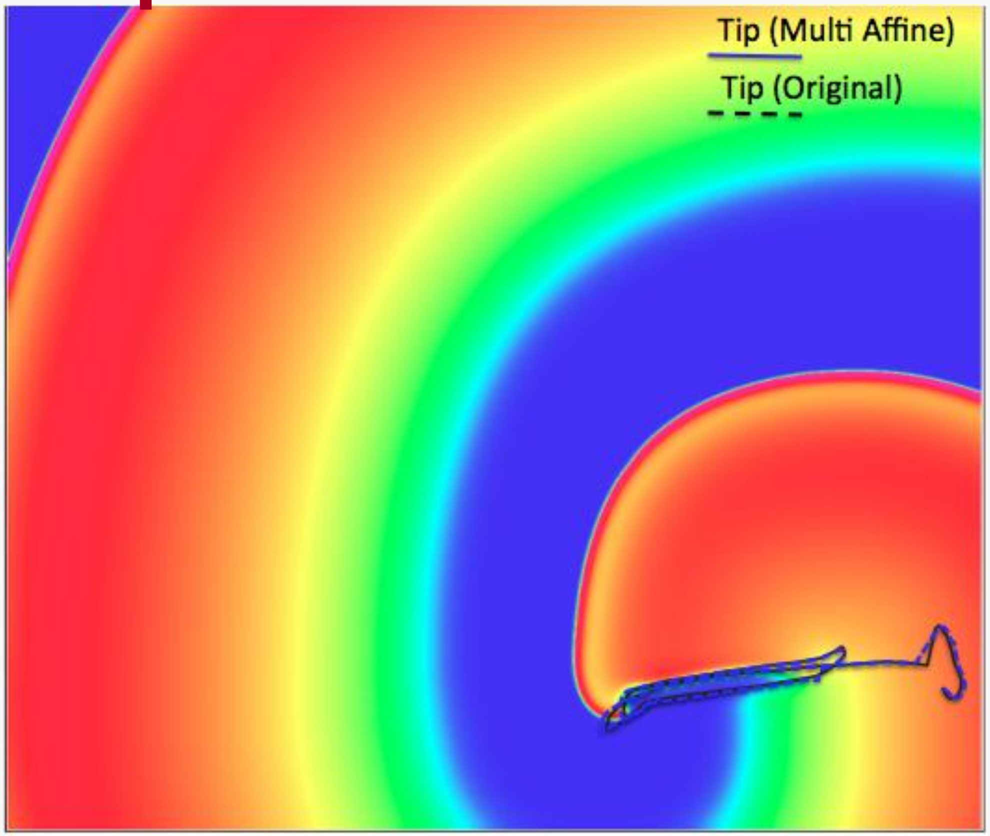
1D Cable Comparison



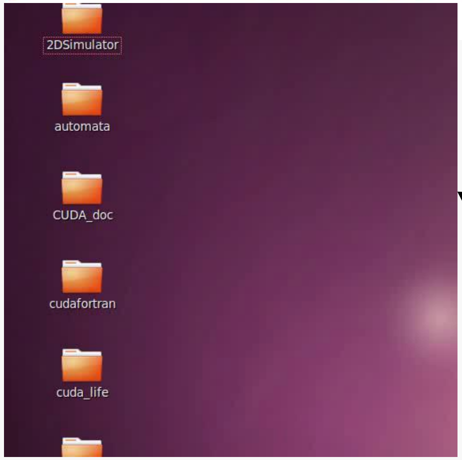
2D Comparison



Original MRM



Multi Affine (26 ramps)

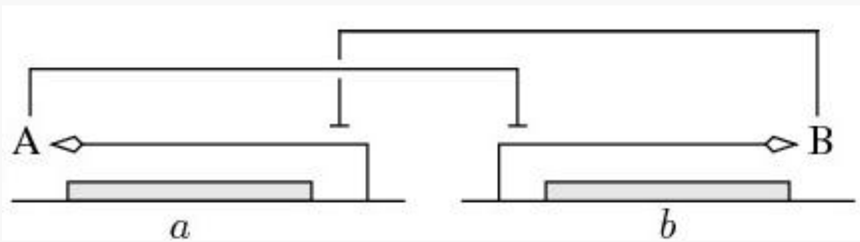


1024x1024 cells 100000 iterations 556 sec. vs. 810 sec.
(GPU Tesla C1060)

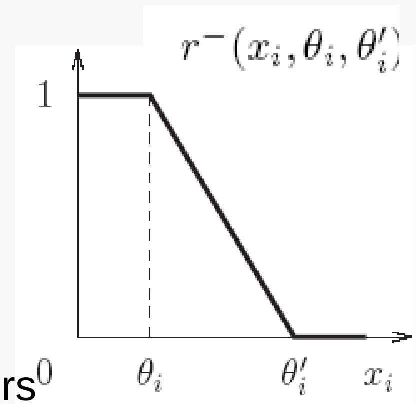
Simulation of the Multi Affine Model is computational efficient (1.43 x)

Parameter Identification

Genetic Regulatory Networks



cross-inhibition network



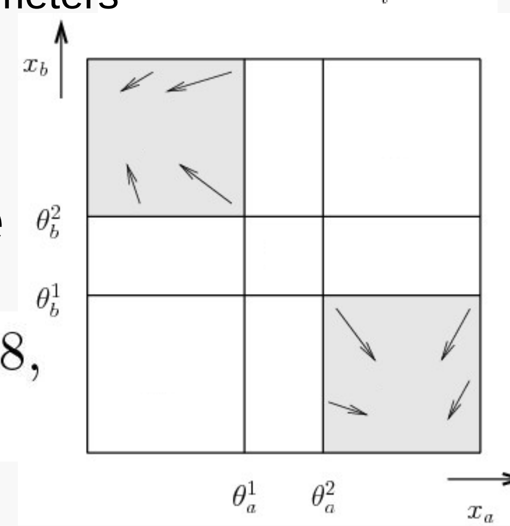
$$\dot{x}_a = \kappa_a r^-(x_b, \theta_b^1, \theta_b^2) - \gamma_a x_a$$
$$\dot{x}_b = \kappa_b r^-(x_a, \theta_a^1, \theta_a^2) - \gamma_b x_b$$

x: protein concentration

$\theta_a^1, \theta_a^2, \theta_b^1, \theta_b^2$ threshold concentration

$k_a, k_b, \gamma_a, \gamma_b$: rate parameters

G. Batt, C. Belta and R. Weiss (2008) **Temporal logic analysis of gene networks under parameter uncertainty**



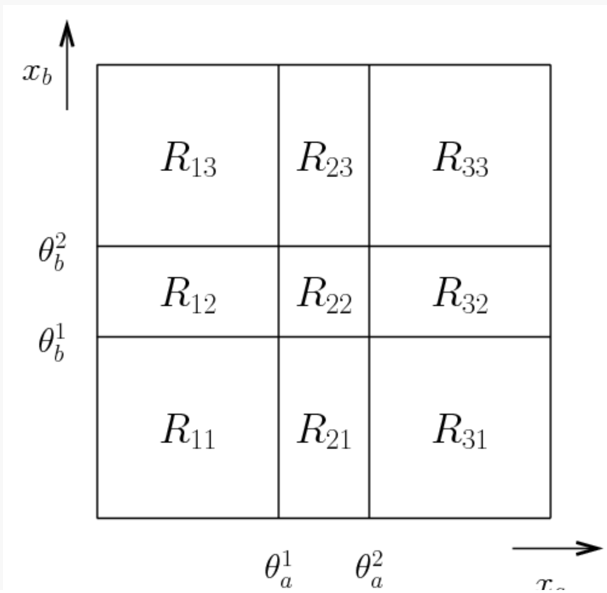
- Find parameters such that network is bistable

$$p = (\kappa_a, \kappa_b) \in \mathcal{P} = [0, 40] \times [0, 20]$$

$$\gamma_a = 1,\ \gamma_b = 2,\ \theta_a^1 = 8,$$
$$\theta_b^1 = 8,\ \theta_a^2 = \theta_b^2 = 12$$

Genetic Regulatory Networks

- Partition of the state space: rectangles $R \in \mathcal{R}$



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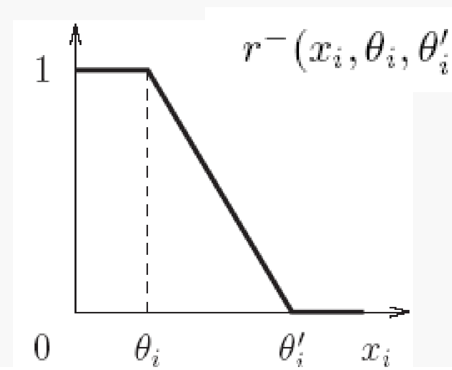
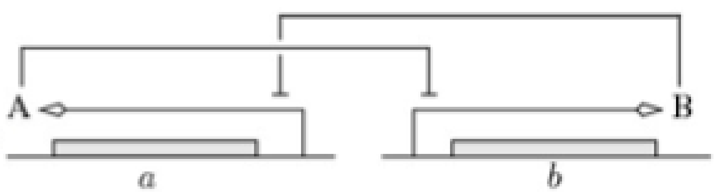


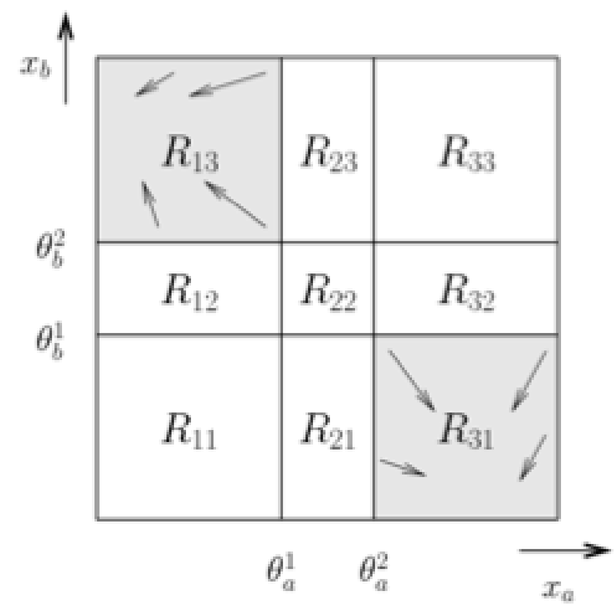
- Differential equation models $\dot{x} = f(x, p)$, with
  - f is **piecewise-multiaffine** (PMA) function of state **variables** x
  - f is **affine** function of rate **parameters** p k_a, k_b

    (multiaffine functions: products of different state variables allowed)

Specifications of dynamical properties

- Dynamical properties expressed in **temporal logic** (LTL)
  - set of atomic proposition Π : $x_i < \lambda_i,\ x_i > \lambda_i$
  - usual logical operators $\neg\phi, \quad \phi_1 \wedge \phi_2, \quad \phi_1 \vee \phi_2, \quad \phi_1 \rightarrow \phi_2, \quad \ldots$
  - temporal operators $\mathrm{X}\,\phi, \quad \mathrm{F}\,\phi, \quad \mathrm{G}\,\phi, \quad \phi_1\,\mathrm{U}\,\phi_2, \quad \ldots$





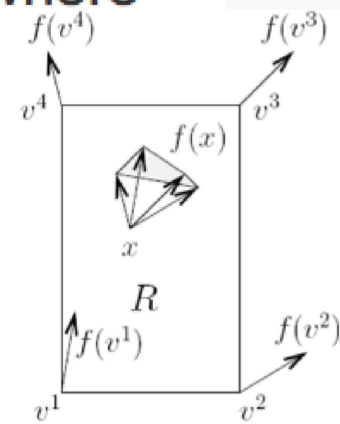
bistability property:

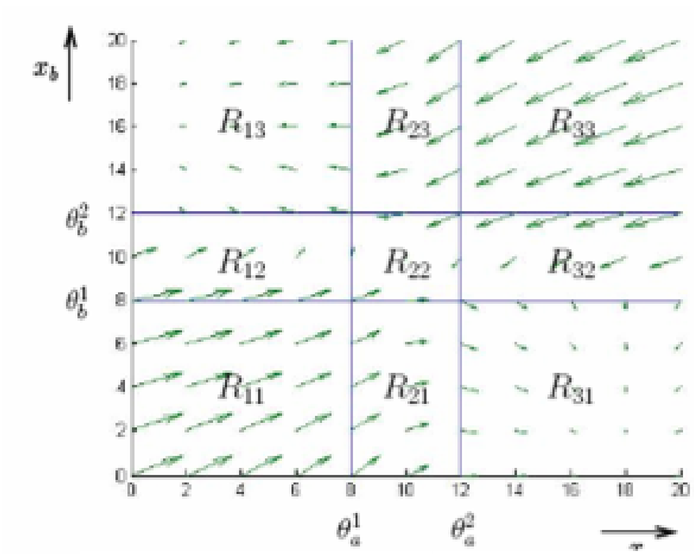
$$\begin{aligned}\phi_1 = \quad & (x_a < \theta_a^1 \wedge x_b > \theta_b^2 \rightarrow \mathrm{G}\,(x_a < \theta_a^1 \wedge x_b > \theta_b^2)) \\ & \wedge (x_b < \theta_b^1 \wedge x_a > \theta_a^2 \rightarrow \mathrm{G}\,(x_b < \theta_b^1 \wedge x_a > \theta_a^2))\end{aligned}$$

How to define that the system satisfies an LTL property ?

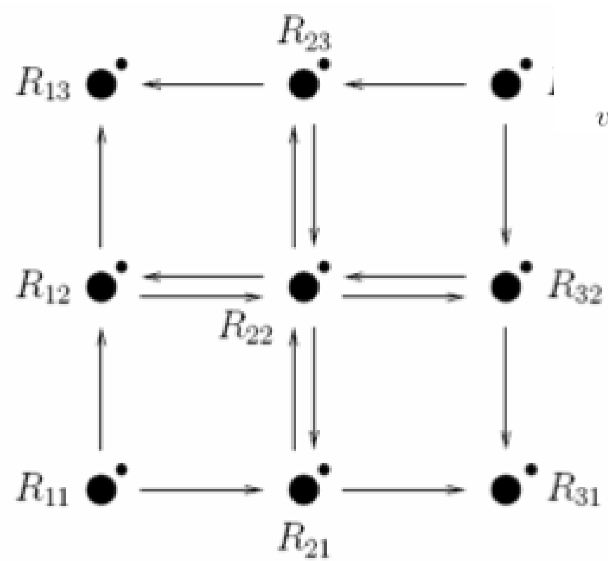
❖ Discrete transition system, $T_{\mathcal{R}}(p) = (\mathcal{R}, \rightarrow_{\mathcal{R},p}, \models_{\mathcal{R}})$, where

- $\mathcal{R}$ finite set of rectangles $\quad \forall x \in R,\ f(x) \in \text{hull}(\{f(v) \mid v \in \mathcal{V}_R\}$
- $\rightarrow_{\mathcal{R},p}$ quotient transition relation
- $\models_{\mathcal{R}}$ quotient satisfaction relation





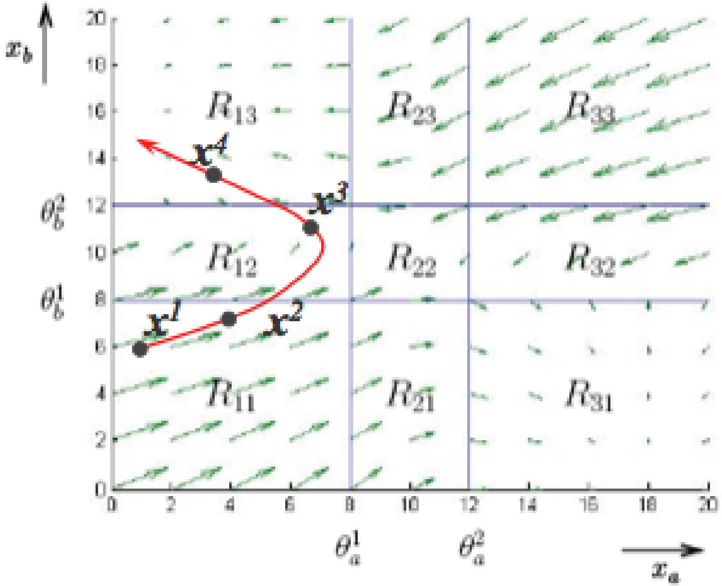
$$R_{11} \rightarrow_{\mathcal{R},p} R_{21},\ R_{21} \rightarrow_{\mathcal{R},p} R_{31}$$
$$R_{11} \rightarrow_{\mathcal{R},p} R_{11},$$



$$R_{11} \models_{\mathcal{R}} x_a < \theta_a^1,\quad R_{11} \models_{\mathcal{R}} x_b < \theta_b^1$$

Embedding transition system

- **PMA system,** $\Sigma = (f, \Pi)$ associated with **embedding transition system,** $T_{\mathcal{X}}(p) = (\mathcal{X}_{\mathcal{R}}, \rightarrow_{\mathcal{X},p}, \models_{\mathcal{X}})$, where
  - $\mathcal{X}_{\mathcal{R}}$ continuous state space
  - $\rightarrow_{\mathcal{X},p}$ transition relation
  - $\models_{\mathcal{X}}$ satisfaction relation



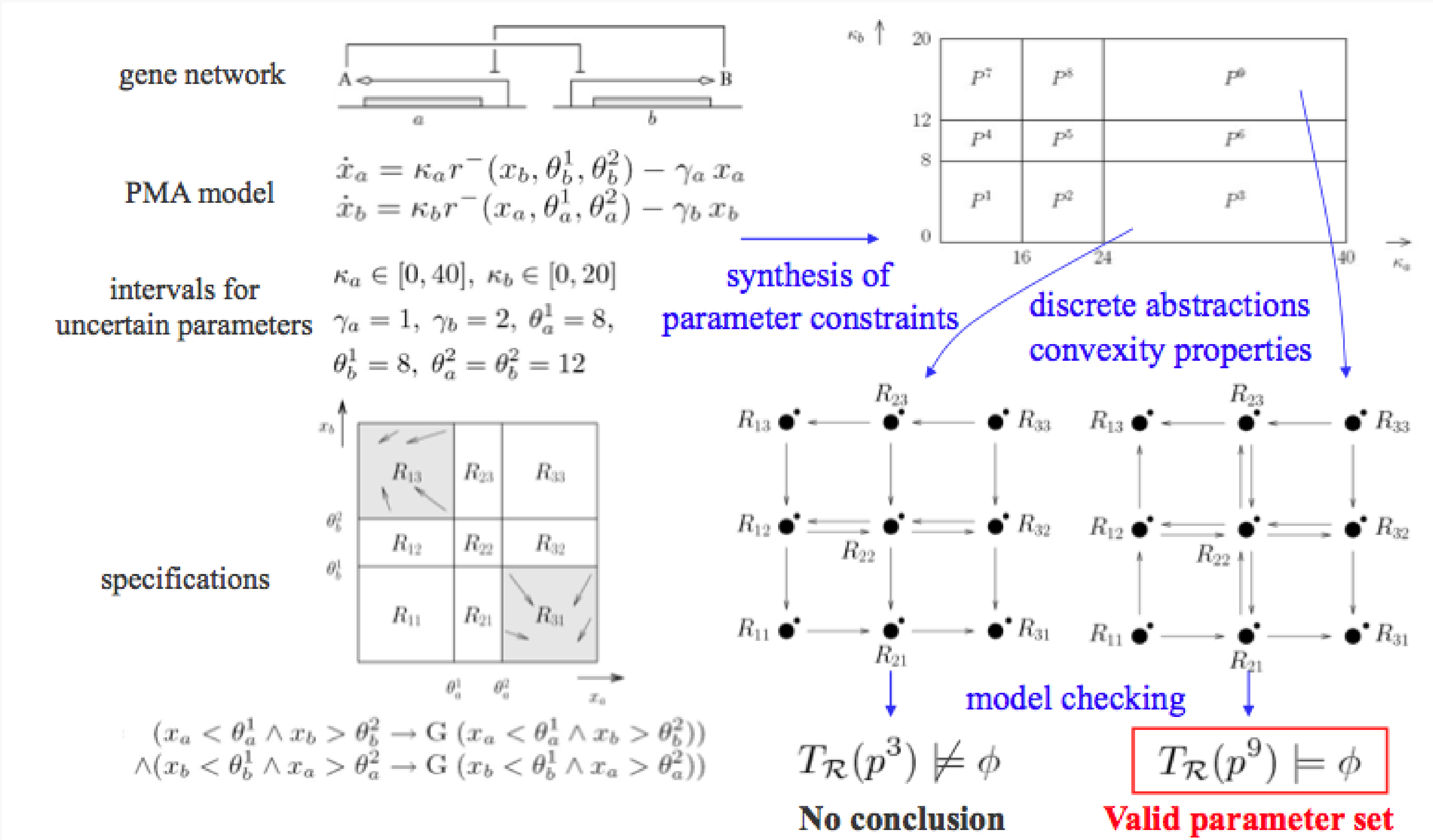
$$x^1 \rightarrow_{\mathcal{X},p} x^2, \quad x^1 \rightarrow_{\mathcal{X},p} x^3,$$

$$x^2 \rightarrow_{\mathcal{X},p} x^3, \quad x^3 \rightarrow_{\mathcal{X},p} x^4$$

$$x^1 \models_{\mathcal{X}} x_a < \theta_a^1, \quad x^1 \models_{\mathcal{X}} x_b < \theta_b^1,$$

$$x^4 \models_{\mathcal{X}} x_a < \theta_a^1, \quad x^4 \models_{\mathcal{X}} x_b > \theta_b^1$$

Iterative exploration of parameter space



Parameter Idenfication for APD

$(\theta_v < u \le u_u)$

$$\dot{u} = \nabla(D\nabla u) + (b^{fi} + \sum_{i=12}^{i=26} a_i^{fi} R^+(u,\theta_i,\theta_{i+1}))v\, g_{fi} + ws\, g_{si} - (b^{so} + \sum_{i=12}^{i=26} a_i^{so} R^+(u,\theta_i,\theta_{i+1}))$$
$$\dot{v} = -v\, g_v^+$$
$$\dot{w} = -w\, k_b g_w^+$$
$$\dot{s} = (b^s + \sum_{i=12}^{i=26} a_i^s R^+(u,\theta_i,\theta_{i+1}))\, g_{s2} - s\, g_{s2}$$

$u < \theta_v$

$u \ge \theta_v$

$\theta_w \le u < \theta_v$

$$\dot{u} = \nabla(D\nabla u) + ws\, g_{si} - (b^{so} + \sum_{i=8}^{i=12} a_i^{so} R^+(u,\theta_i,\theta_{i+1}))$$
$$\dot{v} = -v\, g_{v2}^-$$
$$\dot{w} = -w\, k_b g_w^+$$
$$\dot{s} = (b^s + \sum_{i=8}^{i=12} a_i^s R^+(u,\theta_i,\theta_{i+1}))\, g_{s2} - s\, g_{s2}$$

$u < \theta_w$

$u \ge \theta_w$

$\theta_v^- \le u < \theta_w$

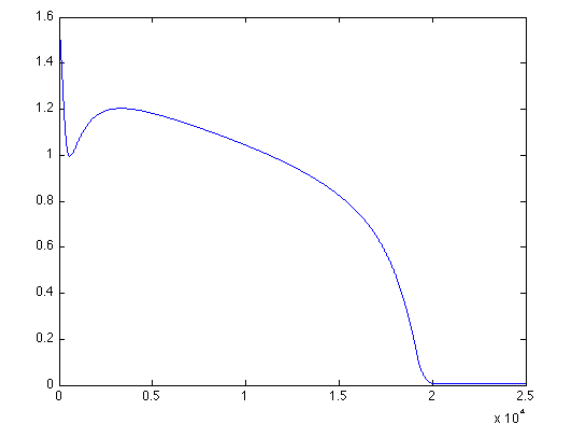
$$\dot{u} = \nabla(D\nabla u) - u\, g_{o2}$$
$$\dot{v} = -v\, g_{v2}^-$$
$$\dot{w} = (w_\infty^* - w)\, k_a (b^w + \sum_{i=2}^{i=8} a_i^w R^+(u,\theta_i,\theta_{i+1}))$$
$$\dot{s} = (b^s + \sum_{i=2}^{i=8} a_i^s R^+(u,\theta_i,\theta_{i+1}))\, g_{s1} - s\, g_{s1}$$

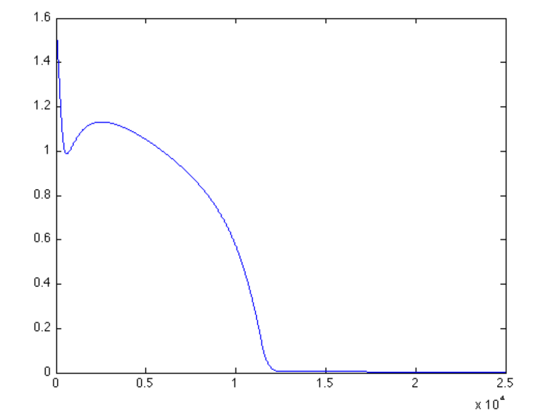
$u < \theta_v^-$

$u \ge \theta_v^-$

$0 \le u < \theta_v^-$

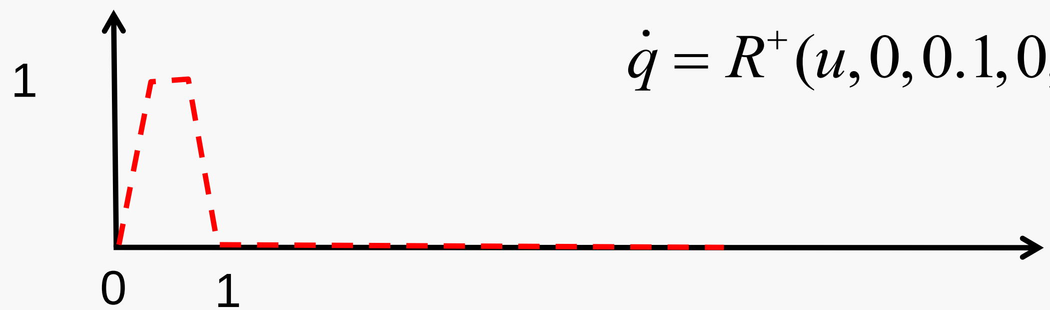
$$\dot{u} = \nabla(D\nabla u) - u\, g_{o1}$$
$$\dot{v} = (1 - v)\, g_{v1}^-$$
$$\dot{w} = k_a (b^{w1} + \sum_{i=1}^{i=2} a_i^{w1} R^+(u,\theta_i,\theta_{i+1})) - w k_a\, (b^{w2} + \sum_{i=1}^{i=2} a_i^{w2} R^+(u,\theta_i,\theta_{i+1}))$$
$$\dot{s} = (b^s + \sum_{i=1}^{i=2} a_i^s R^+(u,\theta_i,\theta_{i+1}))\, g_{s1} - s\, g_{s1}$$





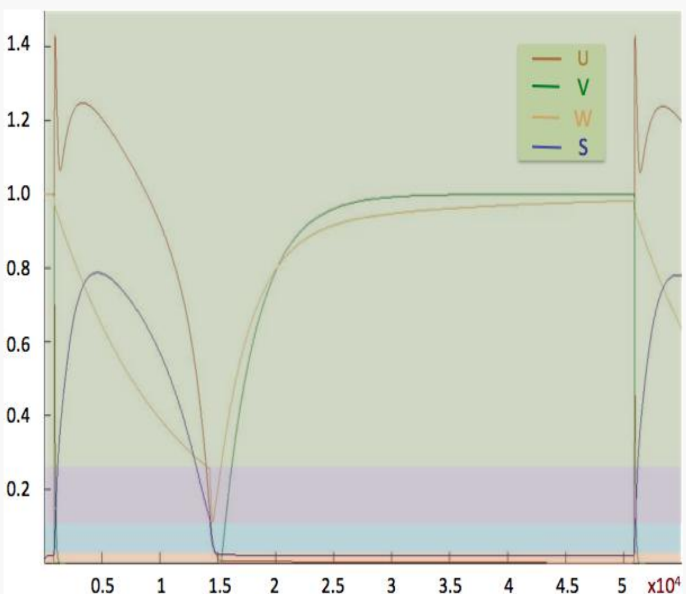
Encoding a Property on the APD

Introducing a new state variable for the stimulus:



$$\dot{q} = R^{+}(u,0,0.1,0,1) + R^{-}(u,0.9,1,1,0)$$

Measuring the APD with another state variable: $\dot{z} = R^{+}(u,0.3,0.3,0,1)$

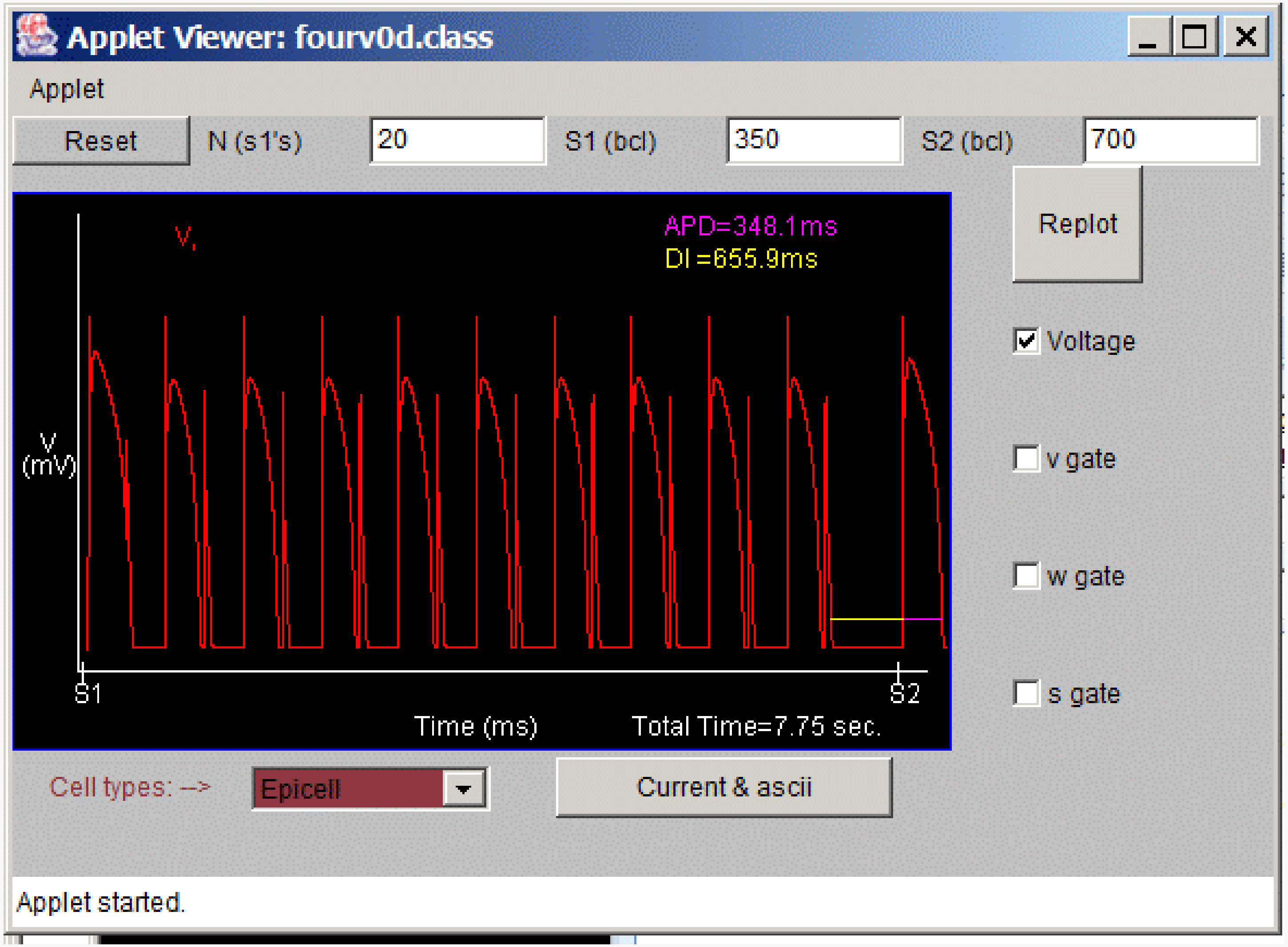


Property: starting with initial conditions u=0,w=0.8,v=1.0,s=0.0 the cell will fire an action potential with APD between 200 and 300 ms

LTL FORMULA:

$$\phi = (u = 0 \wedge w = 0.8 \wedge v = 1.0 \wedge s = 0.0) \rightarrow F(z > 200 \wedge z < 300)$$

Alternans



Applet Viewer: fourv0d.class
Applet
Reset
N (s1's)
20
S1 (bcl)
350
S2 (bcl)
700
Replot
APD=348.1ms
DI =655.9ms
V
V (mV)
S1
S2
Time (ms)
Total Time=7.75 sec.
Voltage
v gate
w gate
s gate
Cell types: -->
Epicell
Current & ascii
Applet started.

Future Works

- Performing experiments with Rovergene
- Encoding more sophisticated properties
- Discriminate healthy/unhealthy tissues using model checking

Thanks for the attention

```
function [e,a,b,xb] = optimalLinearApproximation(x,y,S)
Input:
   x,y:  Curves given as an x-points vector and a vector of y-points vectors
     S:  Number >= 2 of desired segments
Output:
     e:  Errors matrix
   a,b:  Line-segment-coefficients matrix
    xb:  x-coordinate at breaking point matrix
Initialization
z1   = size(x);  P = z1(2);    Get number of points in each curve
z2   = size(y);  C = z2(1);    Get number of digitized curves
se = zeros(1,C);               Initialize vector of errors, one error for each curve
Cost tables
cost   = ones(P,S) * inf;   cost(30,4) = min cost to pt 30 with 4-segm polyline
error = ones(P,P) * inf;   error(i, n)  = cached error of line segment (i,n)
cost(2,1) = 0;               1-segment-polyline cost of polyline (1,2) = 0
Predecessor table
father = ones(P,S) * inf;  father(30,4) = pred of pt 30 on a 4-segm polyline
Computation of optimal segmentation
Initialize cost and father for 1-segment-polyline, from pt 1 to all other pts
for p = 2:P                    Traverse all  other points
    for c = 1:C                   Traverse all curves
       se(c) = segmentError(x(1:p), y(c,1:p));  (1,p)-line-segment appr error
    end; for c
    cost(p,1) = max(se);      Maximum error among all curves
    father(p,1) = 1;            All 1-segment polylines have father point 1
end; for p
```

```
Compute s-segm-polyline cost from point 1 to all other points
for s = 2:S                          Number of segments in the polyline
   for p = 3:P                       Next-point-number to consider
      minErr = cost(p-1,s-1); minIndex = p-1; Error of (p-1,p) = 0
      for i = s:p-2                  Next-intermediate-point to consider
         if (error(i,p) == Inf)      Error of line segment (i,n) not cashed
            for c = 1:C              Next curve-number to consider
               se(c) = segmentError(x(i:p), y(k,i:p)); (i,p)-segment error
            end; for k
            error(i,p) = max(se);  Maximum line segment error
         end; if
         currErr = cost(i,s-1) + error(i,p);   s-segment-polyline error
         if (currErr < minErr)                 Smaller error?
            minErr = currErr; minIndex = i;  Update error and parent
         end; if
      end; for i
      cost(p,s) = minErr;          s-segment-polyline minimal cost
      father(p,s) = minIndex;    Last point's father on the polyline
   end; for p
end; for s
[e,a,b,xb] = ExtractAnswer;
end
```

```
function [e,a,b] = segmentError(x,y)
Input:
   x,y:  Digitized curve-segment as an x-vector and an y-vector
Output:
      e:  Error of the line segment between the first and last point
   a,b:  The coeficients defining this segment
Initialization:
z = size(x); P = s(2);   Find out the number of points of x,y
Compute 1-segment linear-interpolation of (x,y) coefficients
a = (y(n) - y(1)) / (x(n) - x(1));
b = (y(1) * x(n) - y(n) * x(1)) / (x(n) - x(1));
Compute perpendicular-distance error for above line segment
e = 0;            Initialize Error
for p = 1:P      Compute error for the each point on the curve
   e = e + (y(p) - a * x(p) - b)^2  / (a^2 +1);  Accumulate least square
end;
end
```

```
function [e,a,b,xb] = ExtractAnswer
Output:
    e,a,b,xb:  As in the output of optimalLinearApproximation
Initialization:
ib = zeros(S,S+1); xb = zeros(S,S+1);  yb = zeros(C, S,S+1);  Points matrices
a = zeros(C, S,S);    b = zeros(C, S,S);    er = zeros(C, S,S); Coefficients/error
Extract error and coefficient matrices
for s = S:-1:1       Traverse polyline segments in inverse order
   ib(s,s+1)  = P;                      Get last point number
   xb(s,s+1) = x(ib(s,s+1));    Get x-value for this point
   for c = 1:C       Traverse all curves
      yb(c,s,s+1) = y(c,ib(s,s+1));  Get y-value for this point
   end;
   for i = s:-1:1       Traverse predecessor points in inverse order
      ib(s,i) = father(ib(j,i+1),i);    Get predecessor point number
      xb(s,i) = x(ib(s,i));                Get x-value  for this point
      for c = 1:C      Traverse all curves
         yb(c,s,i) = y(c,ib(s,i));        Get y-value for this point
         [er(c,s,i), a(c,s,i), b(c,s,i)] = Compute err, a and b for segm (x,y)
            segmentError( x(ib(s,i):ib(s,i+1)), y(c,ib(s,i):ib(s,i+1)) );
      end
   end;
end;
end
```