CMACS

Computational Modeling and Analysis for Complex Systems

Simulating the Cornell's Minimal Model (4 variables)

Ezio Bartocci, PhD

SUNY at Stony Brook

January 14, 2011

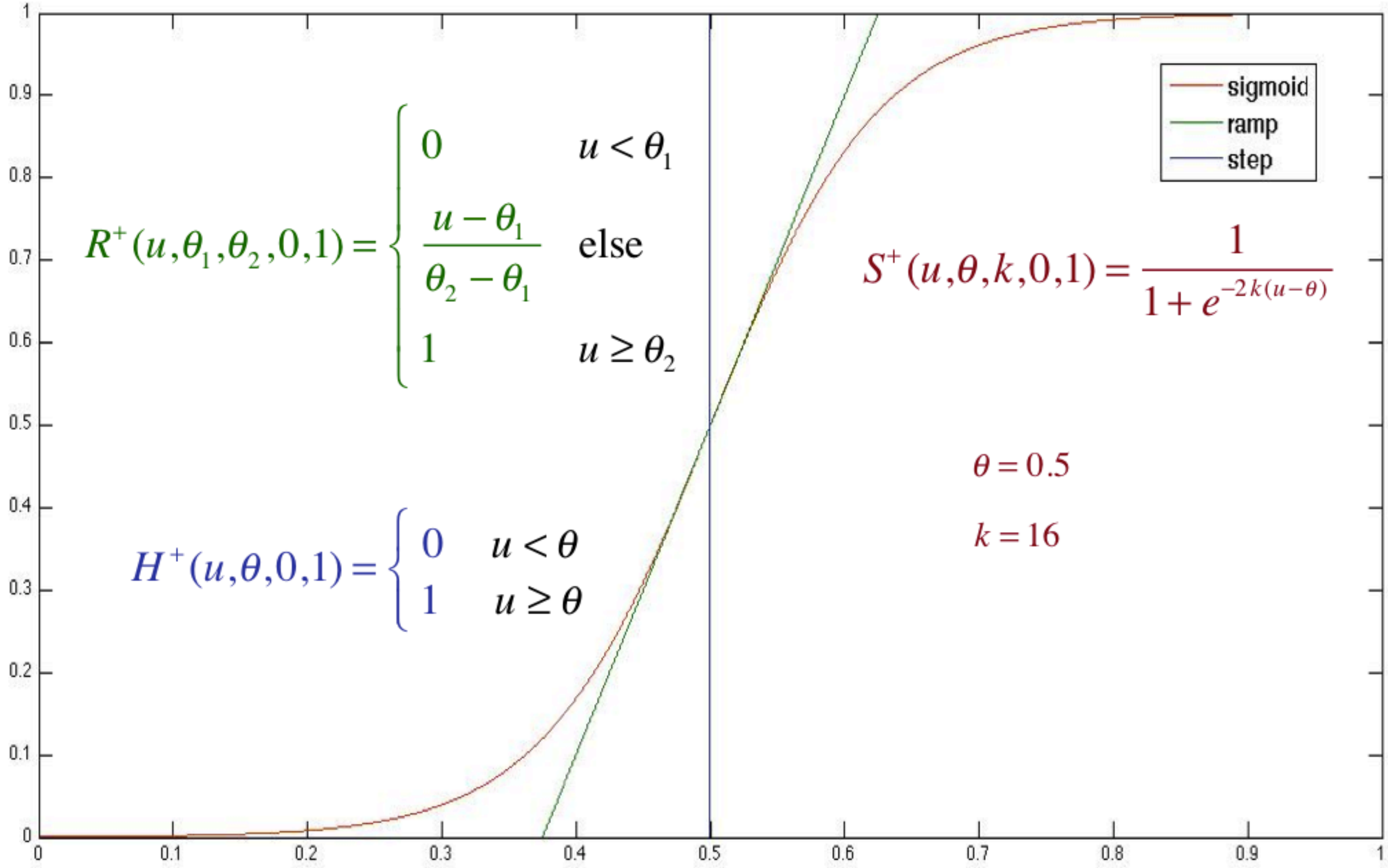
Today's agenda

- Biological Switching
  - Heaviside, Ramp, Sigmoid
  - Gene Regulatory Networks
- Minimal Resistor Model
- Minimal Conductance Model

Existing Models

- Detailed ionic models:
  - Luo and Rudi: (14 variables)
  - Tusher, Noble and Panfilov: (17 variables)
  - Priebe and Beuckelman: (22 variables)
  - Iyer, Mazhari and Winslow: (67 variables)
- Approximate models:
  - The cost of communication
  - Amdahl's Law

Biological Switching



Biological Switching

- **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 (GNR)

- **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**

Cornell's Minimal Resistor Model

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

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

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

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

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

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

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

Cornell's Minimal Resistor Model

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

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

$$-H^{+}(u,\theta,0,1) \quad ws/\tau_{si}$$

$$J_{so} \quad ,1) \quad ,0,1)/\tau_{so}$$

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

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

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

Slow output current

Slow input current

voltage

Diffusion Laplacian

Fast input current

Cornell's Minimal Resistor Model

Heaviside (step)

Activation Threshold

Fast input Gate

Piecewise Nonlinear

Resistance Time Cst

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

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

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

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

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

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

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

Cornell's Minimal Resistor Model

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

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

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

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

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

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

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

Slow Output Gate

Piecewise Bilinear

Piecewise Nonlinear

Sigmoid (s-step)

Piecewise Linear

Nonlinear

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

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

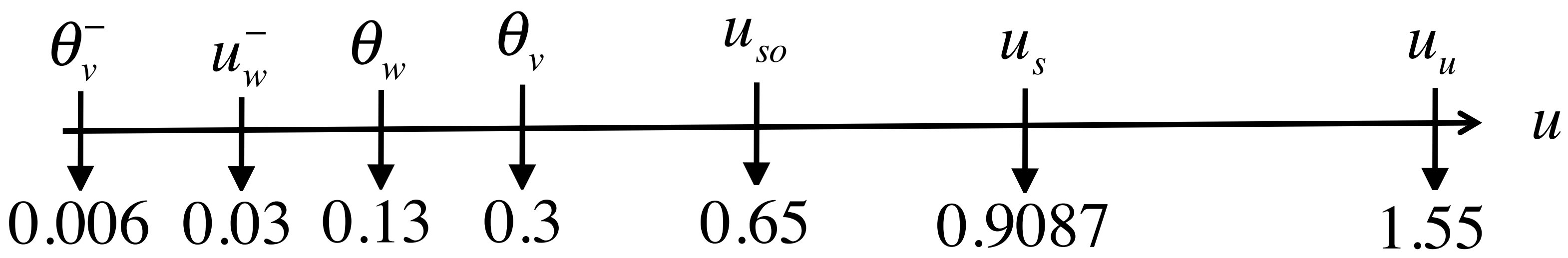
$$\tau_{so} = S^+(u, k_{so}^-, u_{so}^-, \tau_{so1}^-, \tau_{so2}^-)$$

Sigmoidal

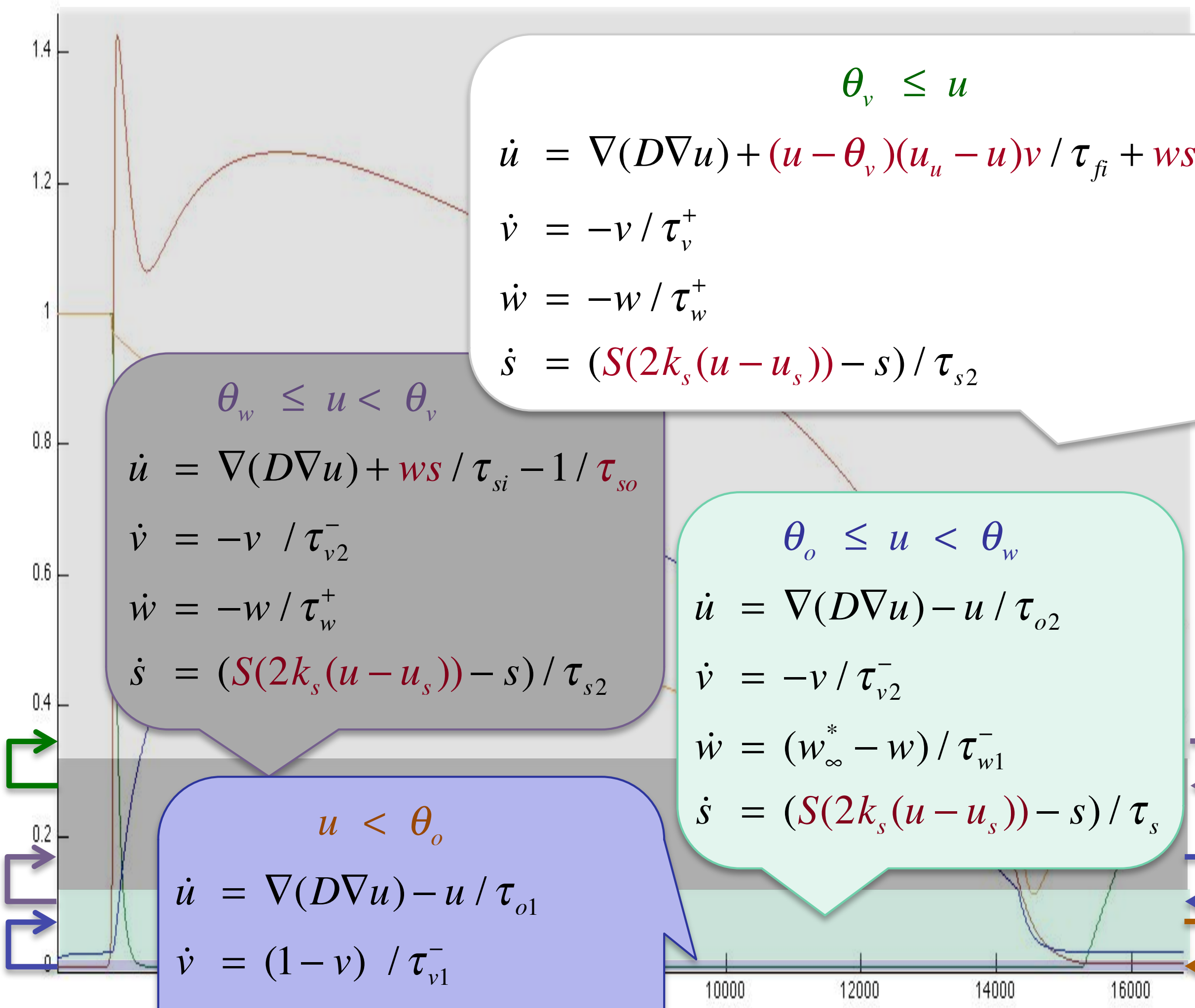
$$v_\infty = h^-(u, \theta_v^-, 0, 1)$$

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

Piecewise Linear



Cornell's Minimal Resistance Model



$\theta_v \leq u$

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

$\theta_w \leq u < \theta_v$

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

$\theta_o \leq u < \theta_w$

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

$u < \theta_o$

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

$u \geq \theta_v$

$u \geq \theta_w$

$u \geq \theta_o$

$u < \theta_v = 0.3$

$u < \theta_w = 0.13$

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

Sigmoid Closure

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

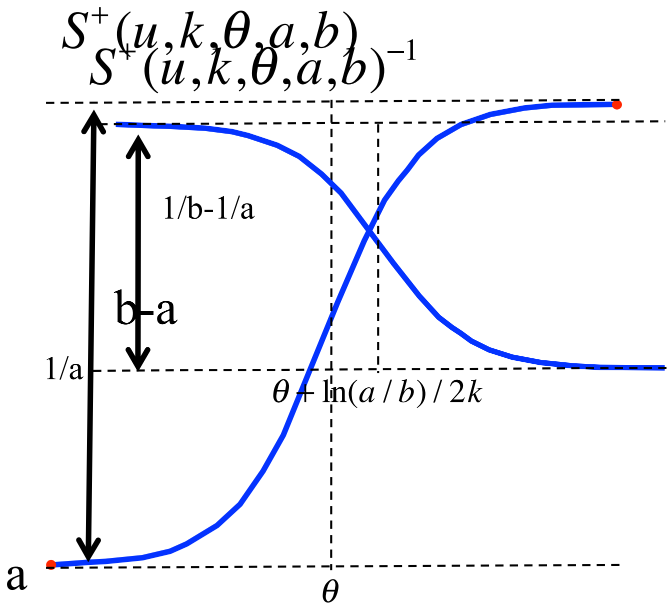
$$S^+(u,k,\theta,a,b)^{-1} = S^-(u,k,\theta+\ln(a/b)/2k,b^-,a^-)$$

Proof

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

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

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



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

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

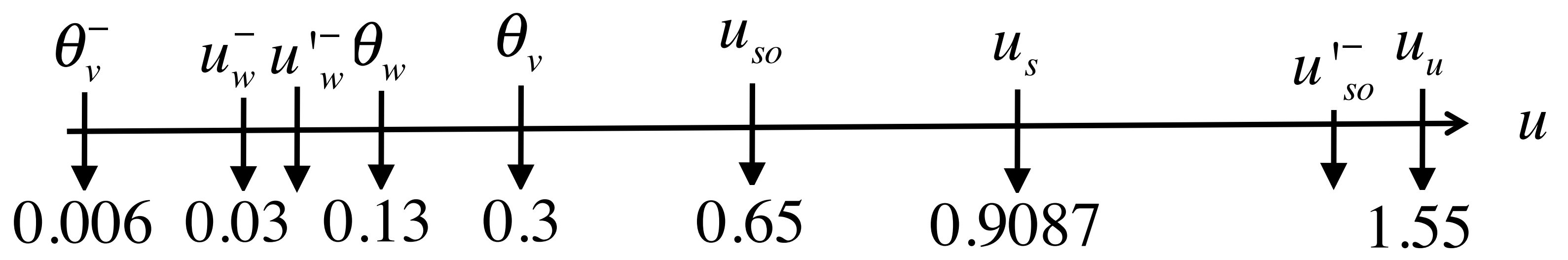
$$\tau_v^- = H^+(u, \theta_v^-, \tau_{v1}^-, \tau_{v2}^-) \qquad g_v^- = 1/\tau_v^- = H^-(u, \theta_v^-, g_{v1}^-, g_{v2}^-)$$

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

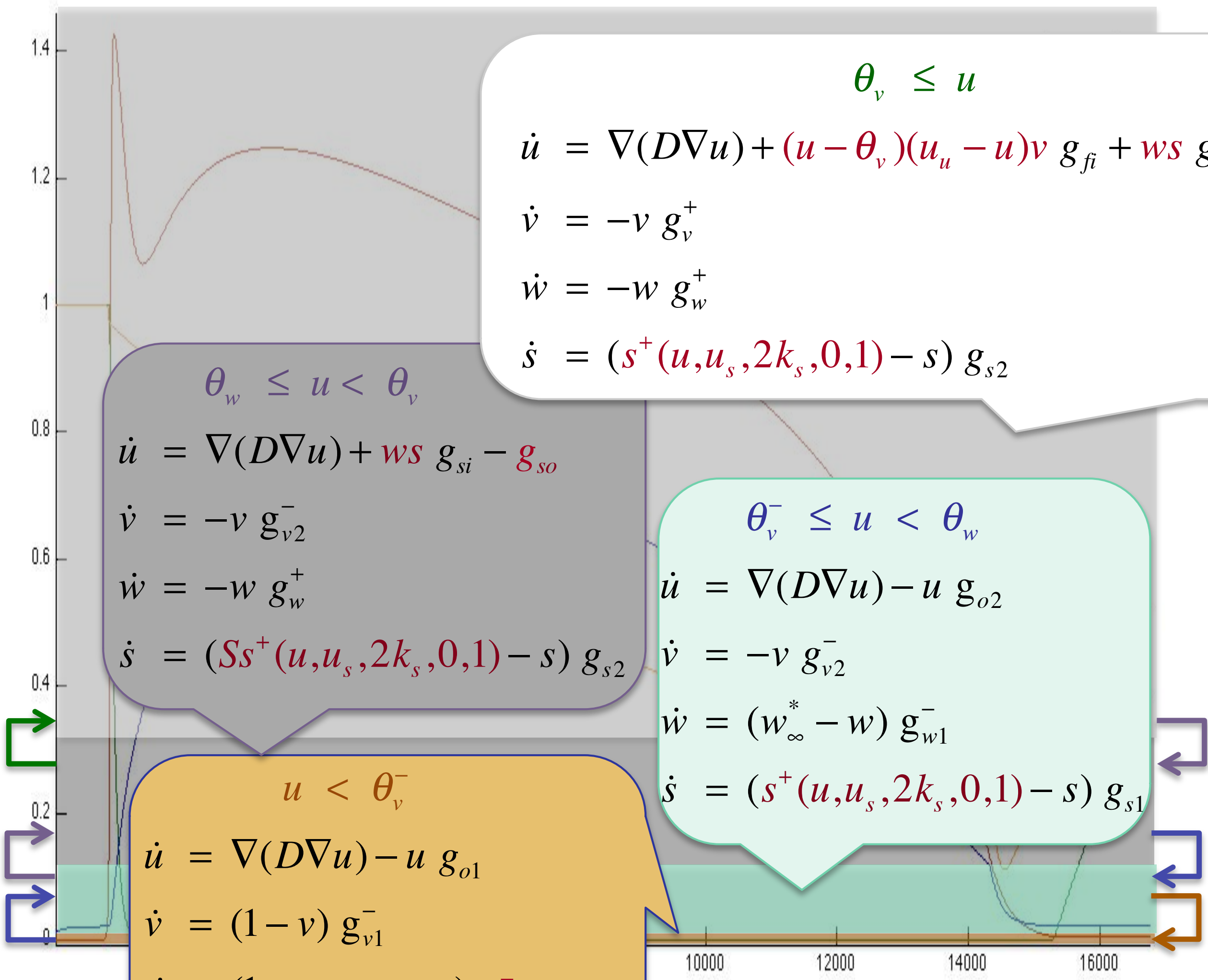
$$\tau_s = H^+(u, \theta_w, \tau_{s1}, \tau_{s2}) \qquad g_s = 1/\tau_s = H^-(u, \theta_w, g_{s1}, g_{s2})$$

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

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



Conductances Minimal Model



$\theta_v \le u$

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

$\theta_w \le u < \theta_v$

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

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

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

$u < \theta_v^{-}$

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

$u \ge \theta_v$

$u \ge \theta_w$

$u \ge \theta_o$

$u < \theta_v = 0.3$

$u < \theta_w = 0.13$

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