

Canard Theory and Neuronal Dynamics

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Martin Wechselberger
School of Mathematics and Statistics**



Collaborators:
Michelle McCarthy, Nancy Kopell (Boston), John Mitry (Sydney).

Conductance-based models

$$c_m \frac{dV}{dt} = - \sum I_{ion}$$

$$\frac{dx}{dt} = Q_{10}^{\frac{(T-T_0)}{10}} \cdot \frac{(x_\infty(V) - x)}{\tau_x(V)}, \quad x = m, h, n, \dots$$

$$I_{ion} = g(x(V, T))(V - E_{ion})$$

- Ion channels sense their environment
(voltage, temperature, hormones, neurotransmitter, drugs,...)
- This sensitivity enables cells to produce/alter a signal
(action potential - tonic firing or bursting, calcium signal, ...)

Different time-scales

$$c_m \frac{dV}{dt} = - \sum I_{ion}$$

$$\frac{dx}{dt} = Q_{10}^{\frac{(T-T_0)}{10}} \cdot \frac{(x_\infty(V) - x)}{\tau_x(V)}, \quad x = m, h, n, \dots$$

$$I_{ion} = g(x(V, T))(V - E_{Na})$$

- Ion channels operate inherently on different time-scales
(`fast' sodium current, `delayed rectifier' potassium current,)

$$\tau_V = \frac{c_m}{g_{max}},$$

$$\tau_x = Q_{10}^{-\frac{(T-T_0)}{10}} \cdot \left(\min_{E_K < V < E_{Na}} \tau_x(V) \right)$$

Different time-scales

$$c_m \frac{dV}{dt} = - \sum I_{ion}$$

$$\frac{dx}{dt} = Q_{10}^{\frac{(T-T_0)}{10}} \cdot \frac{(x_\infty(V) - x)}{\tau_x(V)}, \quad x = m, h, n, \dots$$

$$I_{ion} = g(x(V, T))(V - E_{Na})$$

- Mathematically, we identify these **different time-scales** through dimensional analysis
- **Reference scales**
(voltage, conductance, time, temperature)

$$\tau_V = \frac{c_m}{g_{max}},$$

$$\tau_x = Q_{10}^{-\frac{(T-T_0)}{10}} \cdot \left(\min_{E_K < V < E_{Na}} \tau_x(V) \right)$$

Slow-fast systems

$$c_m \frac{dV}{dt} = - \sum I_{ion}$$

$$\frac{dx}{dt} = Q_{10}^{\frac{(T-T_0)}{10}} \cdot \frac{(x_\infty(V) - x)}{\tau_x(V)}, \quad x = m, h, n, \dots$$

- Based on dimensional analysis, we might group gating variables into **slow and fast gates** (voltage is usually a fast variable)
- This gives a **slow-fast (dimensionless) system**

$$\begin{aligned}\varepsilon \dot{v} &= f(v, y, z, \varepsilon) && \text{voltage } v \\ \varepsilon \dot{y} &= h(v, y, z, \varepsilon) && \text{fast gates } y = m, \dots \\ \dot{x} &= g(v, y, z, \varepsilon) && \text{slow gates } x = n, h, \dots\end{aligned}\qquad \varepsilon \ll 1$$

Geometric singular perturbation theory

$$\left. \begin{array}{rcl} \dot{x} & = & g(x, z, \varepsilon) \\ \varepsilon \dot{z} & = & f(x, z, \varepsilon) \end{array} \right\} (S) \quad \left. \begin{array}{rcl} x' & = & \varepsilon g(x, z, \varepsilon) \\ z' & = & f(x, z, \varepsilon) \end{array} \right\} (F)$$

slow time t

$$x \in \mathbb{R}^k, \quad z \in \mathbb{R}^m, \quad \varepsilon \ll 1$$

$$f : \mathbb{R}^k \times \mathbb{R}^m \times \mathbb{R} \rightarrow \mathbb{R}^m, \quad g : \mathbb{R}^k \times \mathbb{R}^m \times \mathbb{R} \rightarrow \mathbb{R}^k$$

fast time $\tau = t/\varepsilon$

Geometric singular perturbation theory

$$\left. \begin{array}{l} \dot{x} = g(x, z, \varepsilon) \\ \varepsilon \dot{z} = f(x, z, \varepsilon) \end{array} \right\} (S) \quad \left. \begin{array}{l} x' = \varepsilon g(x, z, \varepsilon) \\ z' = f(x, z, \varepsilon) \end{array} \right\} (F)$$

slow time t

$$x \in \mathbb{R}^k, \quad z \in \mathbb{R}^m, \quad \varepsilon \ll 1$$

$$f : \mathbb{R}^k \times \mathbb{R}^m \times \mathbb{R} \rightarrow \mathbb{R}^m, \quad g : \mathbb{R}^k \times \mathbb{R}^m \times \mathbb{R} \rightarrow \mathbb{R}^k$$

singular limit $\varepsilon \rightarrow 0$

$$\left. \begin{array}{l} \dot{x} = g(x, z, 0) \\ 0 = f(x, z, 0) \end{array} \right\} (R) \quad \left. \begin{array}{l} x' = 0 \\ z' = f(x, z, 0) \end{array} \right\} (L)$$

reduced problem (k-dim)

layer problem (m-dim)

$$(R) + (L) \Rightarrow (S) \text{ resp. } (F)$$

Geometric singular perturbation theory

singular limit $\varepsilon \rightarrow 0$

$$\begin{aligned}\dot{x} &= g(x, z, 0) \\ 0 &= f(x, z, 0)\end{aligned}\left.\right\} (R)$$

$$\begin{aligned}x' &= 0 \\ z' &= f(x, z, 0)\end{aligned}\left.\right\} (L)$$

reduced problem (k-dim)

layer problem (m-dim)

critical manifold (k-dim)

$$S := \{(x, z) \in \mathbb{R}^k \times \mathbb{R}^m \mid f(x, z, 0) = 0\}$$

is the interface between limiting problems

Dynamic changes

$$c_m \frac{dV}{dt} = - \sum I_{ion} - \sum I_{syn} + I_{appl}(t)$$

- Synaptic currents or (experimentally) applied currents will alter the inherent dynamics of a cell.
- Again, these currents could be slow or fast.
- Ionic and synaptic currents sense their environment (voltage, temperature, hormones, neurotransmitter, drugs,...)
- In particular, temperature, hormones, neurotransmitter, drugs,... may change the dynamics of the gating variables significantly

Neuron model with GABAa current

- Focus on a potassium current (M-current) and the role of inhibitory synaptic current (GABAa)

$$c_m \frac{dV}{dt} = -I_{Na} - I_K - I_L - I_M - I_{syn} + I_{app}$$

$$\frac{dx}{dt} = \frac{(x_\infty(V) - x)}{\tau_x(V)}, \quad x = m, h, n, w$$

$$\frac{ds}{dt} = -s/\tau_s$$

$$I_{Na} = \bar{g}_{Na} m^3 h (V - E_{Na})$$

$$I_K = \bar{g}_k n^4 (V - E_k)$$

$$I_L = \bar{g}_L (V - E_L)$$

$$I_M = \bar{g}_m w (V - E_k)$$

$$I_{syn} = \bar{g}_i s (V - E_i)$$

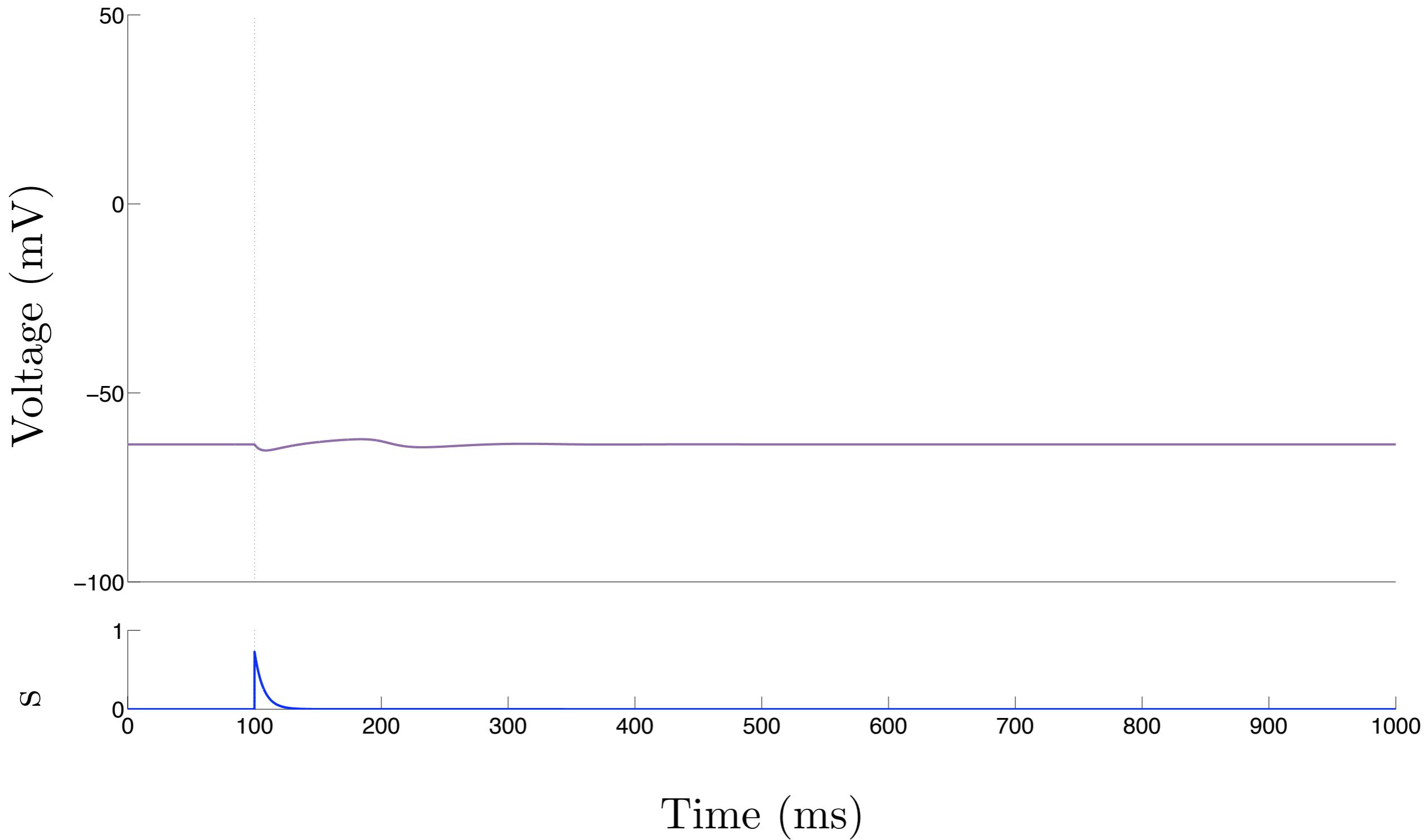
Propofol and GABAa current (McCarthy et al)

$$\begin{aligned}c_m \frac{dV}{dt} &= -I_{Na} - I_K - I_L - I_M - I_{syn} + \cancel{I_{app}} \\ \frac{dx}{dt} &= \frac{(x_\infty(V) - x)}{\tau_x(V)}, \quad x = m, h, n, w \\ \frac{ds}{dt} &= -s/\tau_s\end{aligned}$$

- Propofol potentiates GABAa receptors, i.e. it changes the time scale of the synaptic (inactivation) gate s. It slows down the inactivation of the synaptic current.
- Paradoxically, low doses of propofol causes excitation!

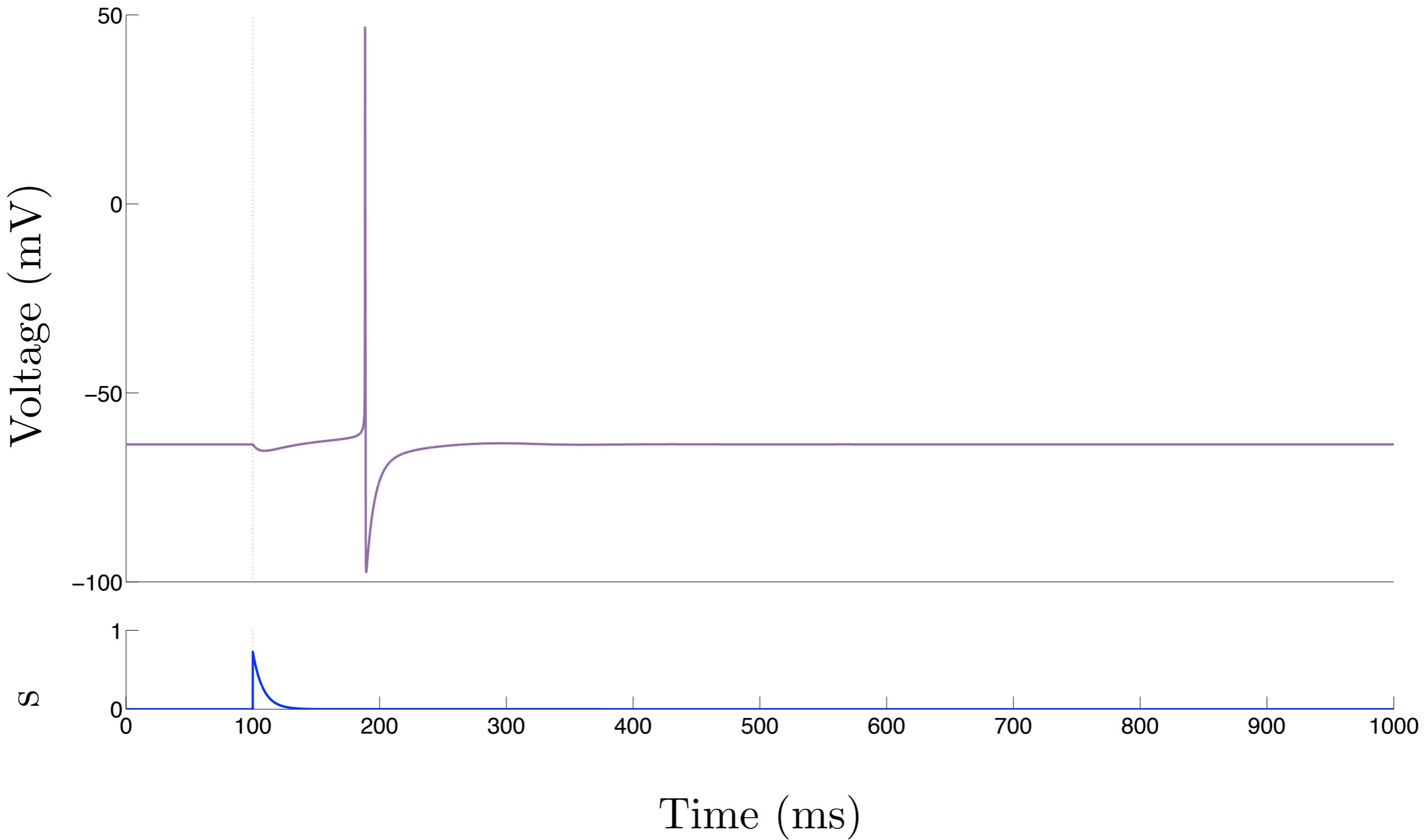
Propofol and inhibitory GABAa current

$$\tau_s = 7$$



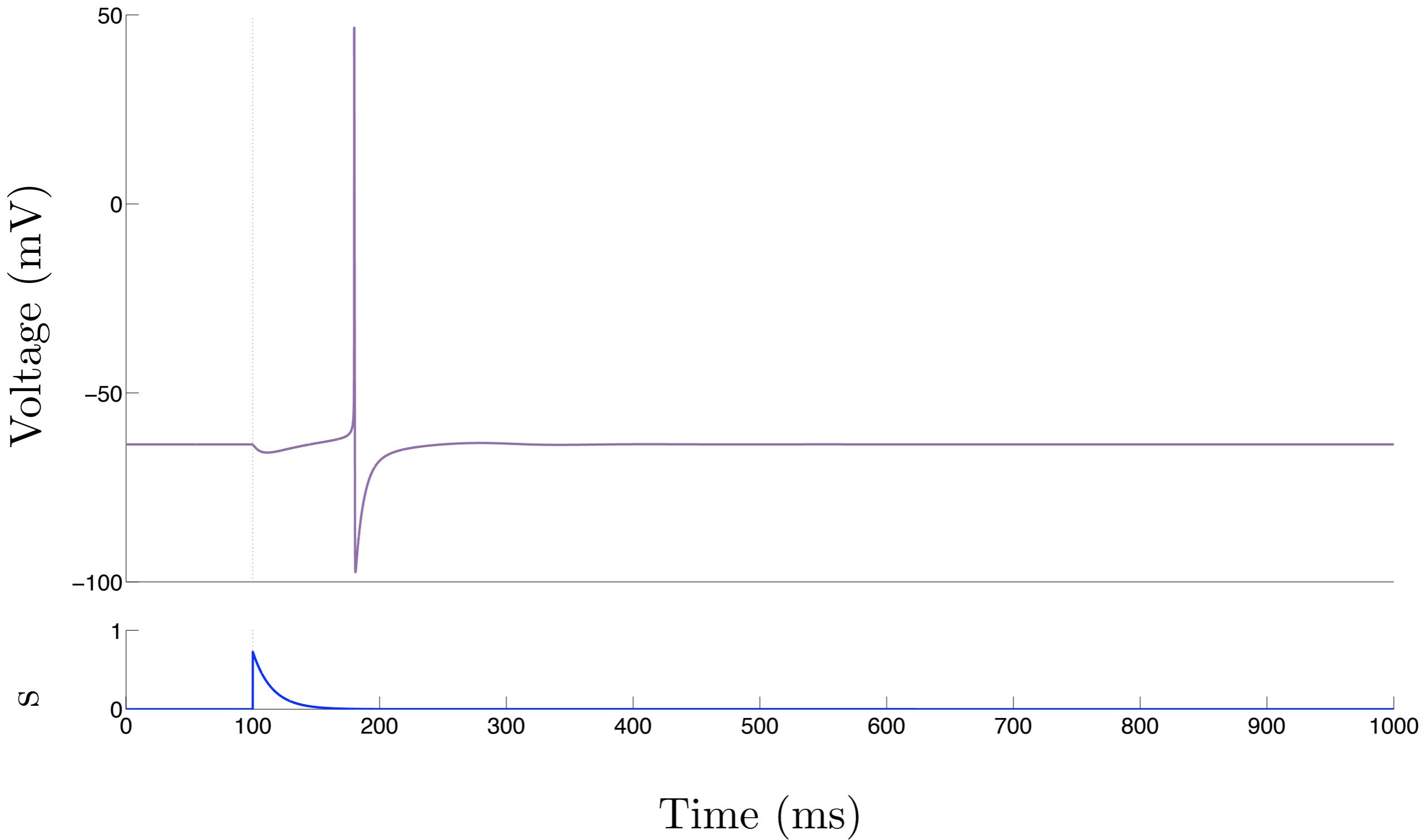
Propofol and inhibitory GABAa current

$$\tau_s = 8$$



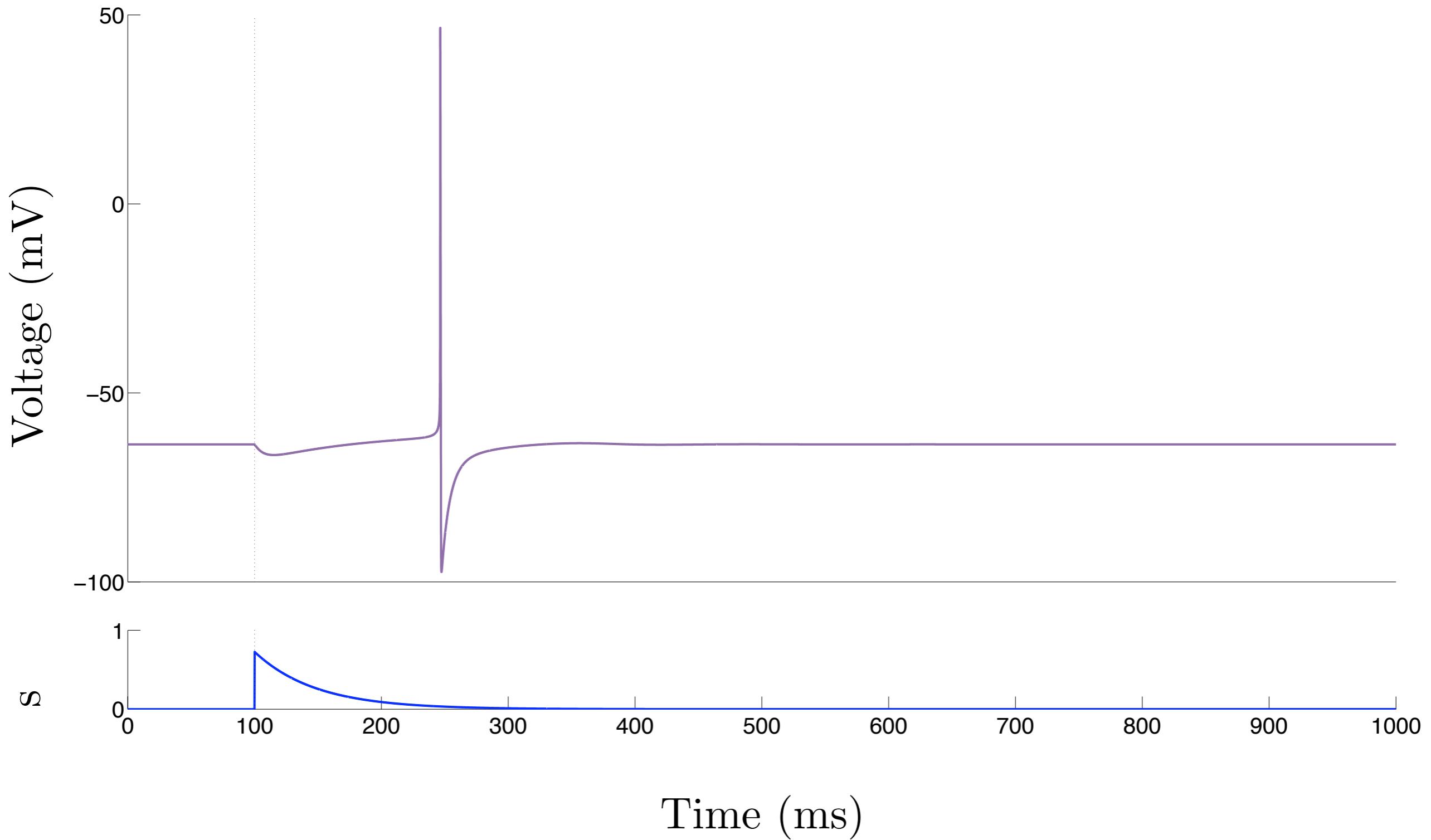
Propofol and inhibitory GABAa current

$$\tau_s = 15$$



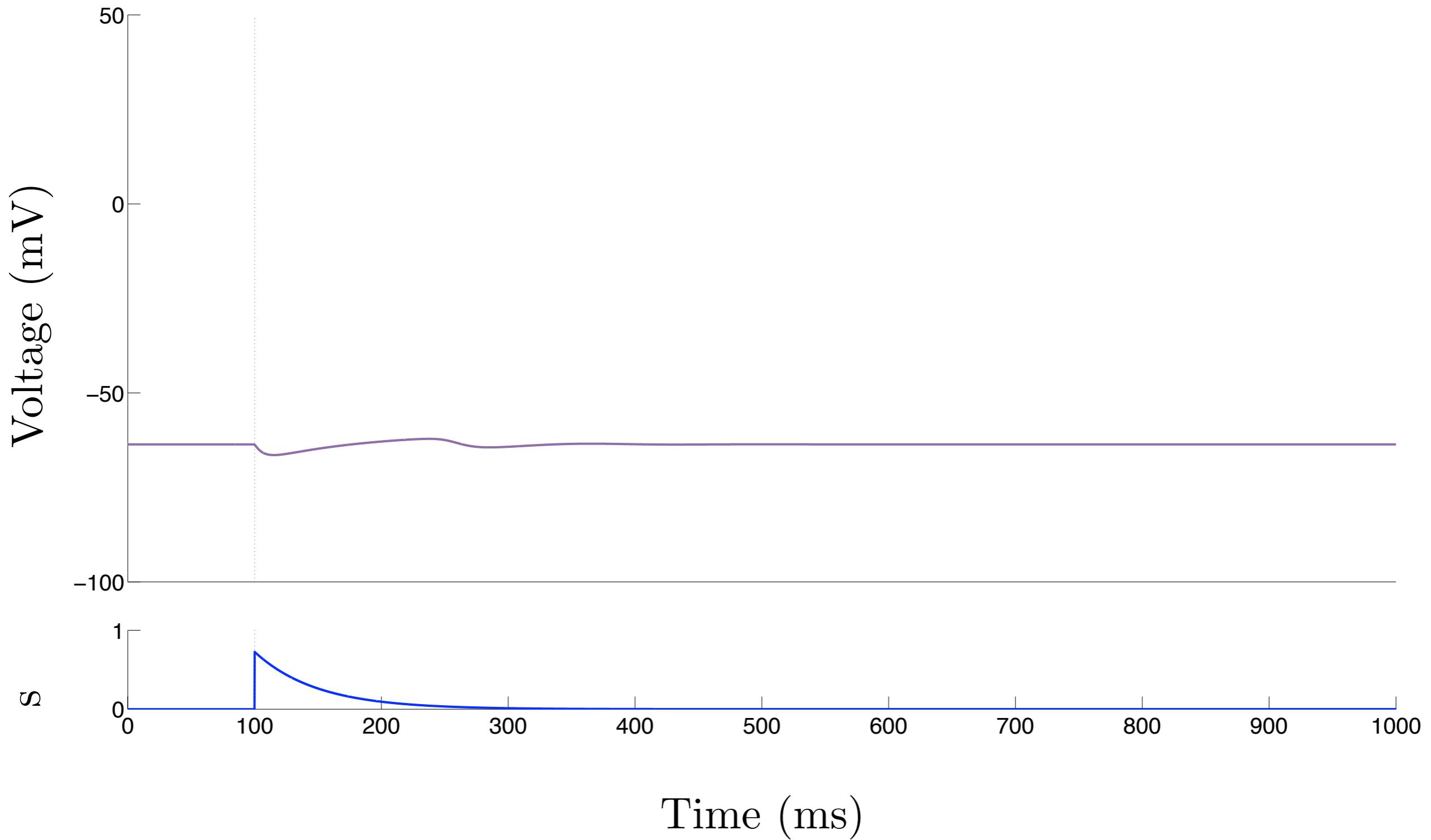
Propofol and inhibitory GABAa current

$$\tau_s = 48$$



Propofol and inhibitory GABAa current

$$\tau_s = 49$$



Contrast: inhibitory applied step current

- The dynamic nature of the inhibitory synapse makes the response significantly different to a inhibitory step protocol!

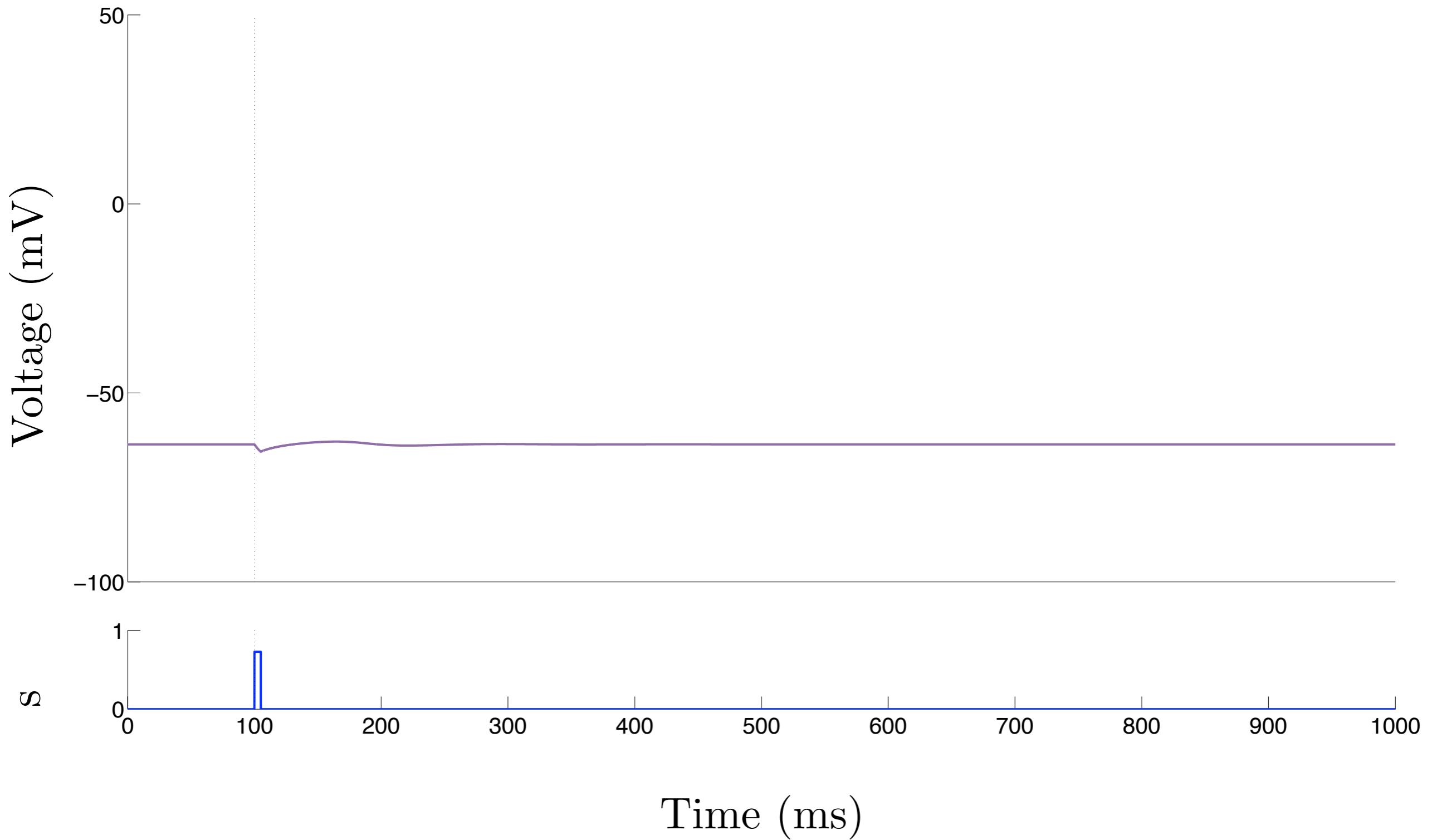
$$c_m \frac{dV}{dt} = -I_{Na} - I_K - I_L - I_M - \cancel{I_{syn}} + I_{app}$$

$$\frac{dx}{dt} = \frac{(x_\infty(V) - x)}{\tau_x(V)}, \quad x = m, h, n, w$$

$$\frac{ds}{dt} = -s/\tau_s$$

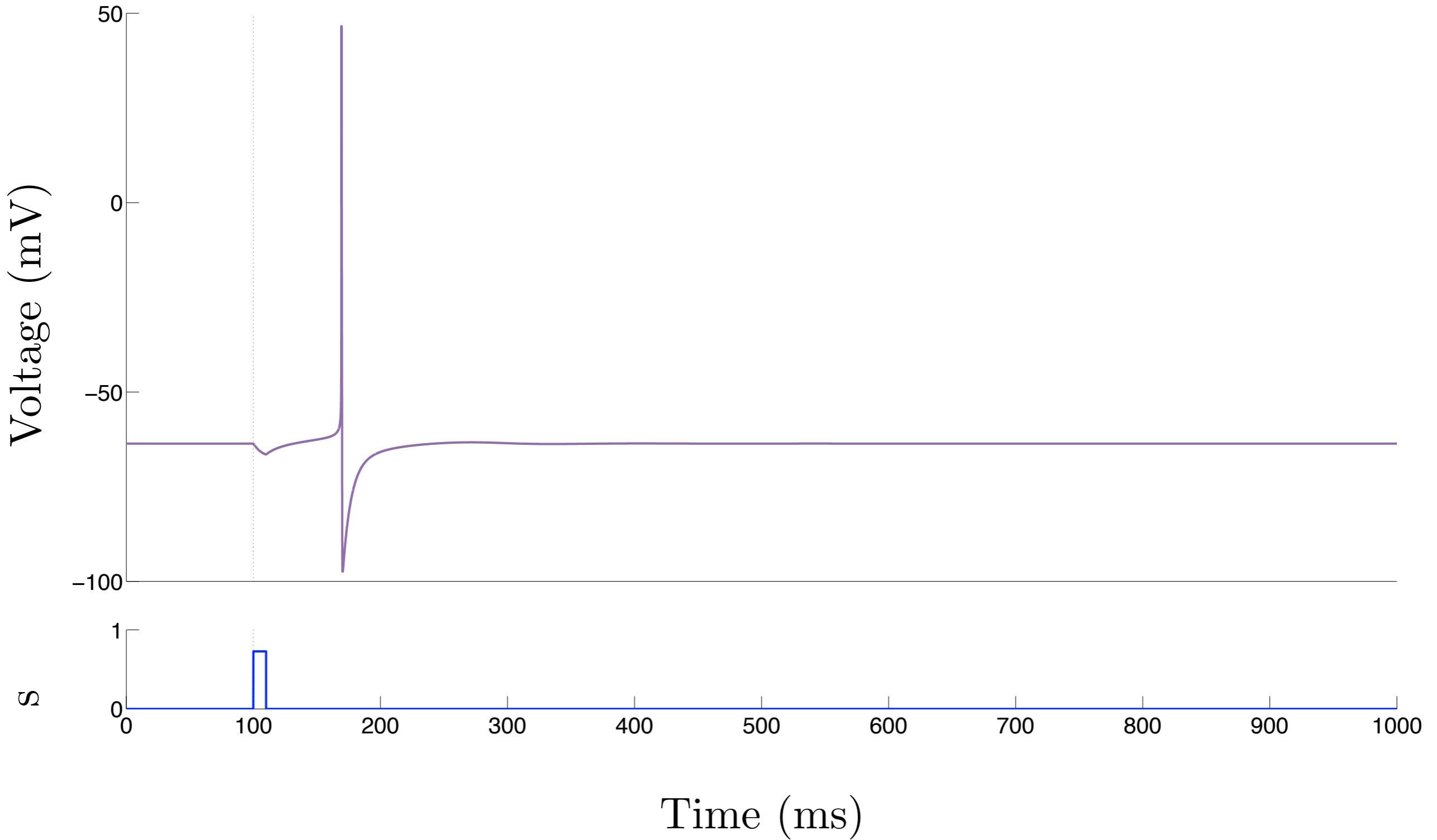
Contrast: inhibitory applied step current

step duration = 5



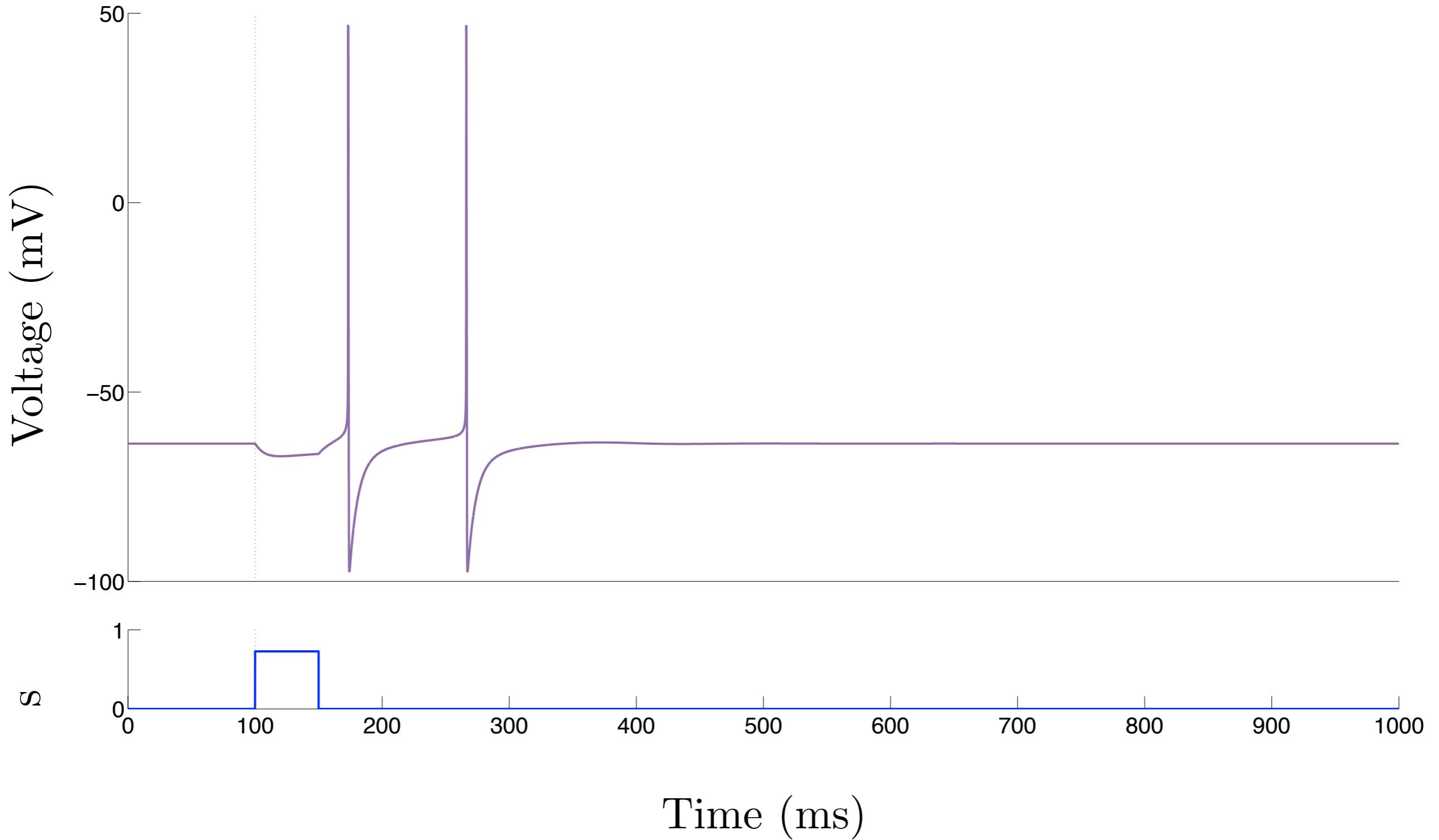
Contrast: inhibitory applied step current

step duration = 10



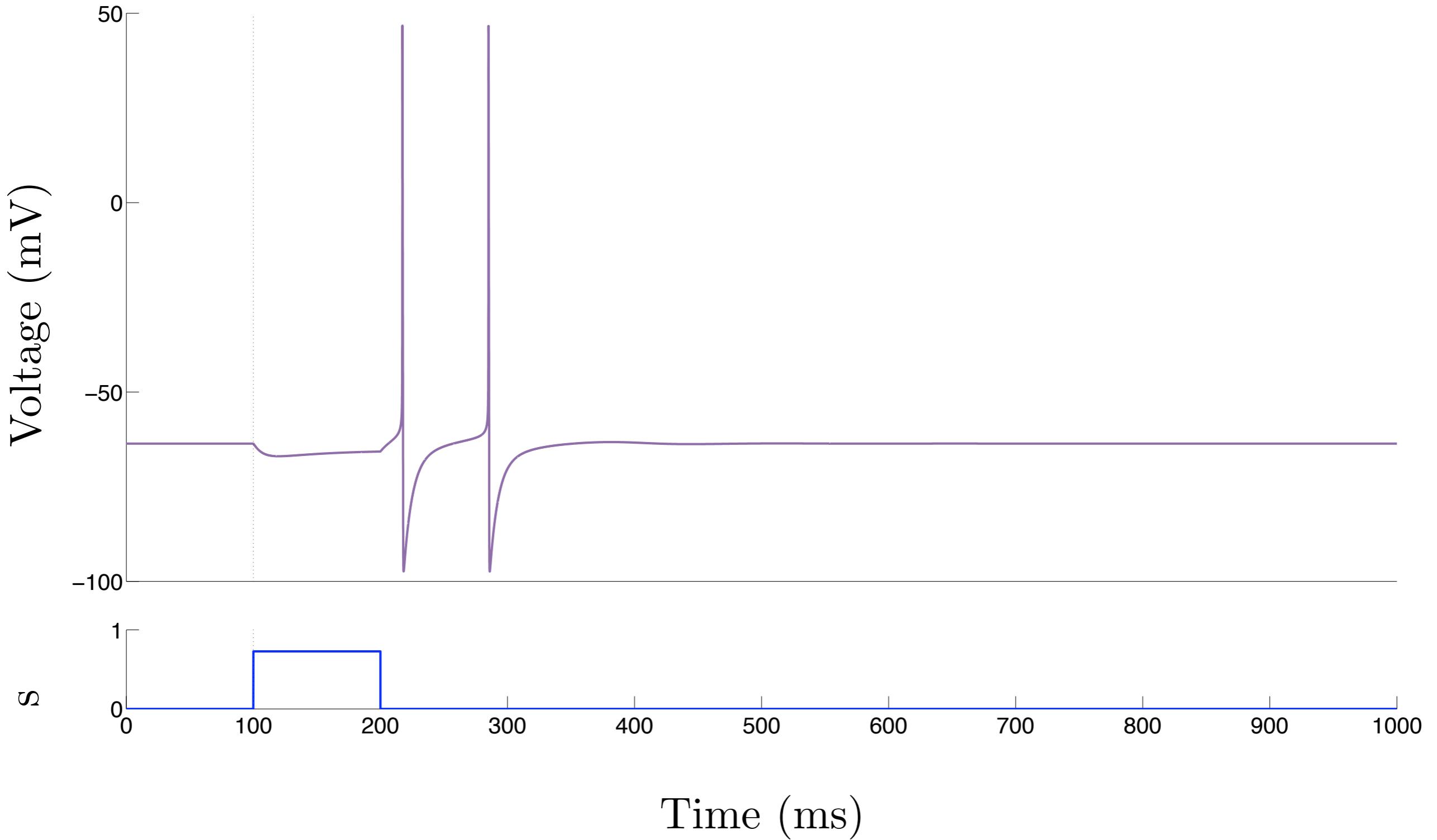
Contrast: inhibitory applied step current

step duration = 50



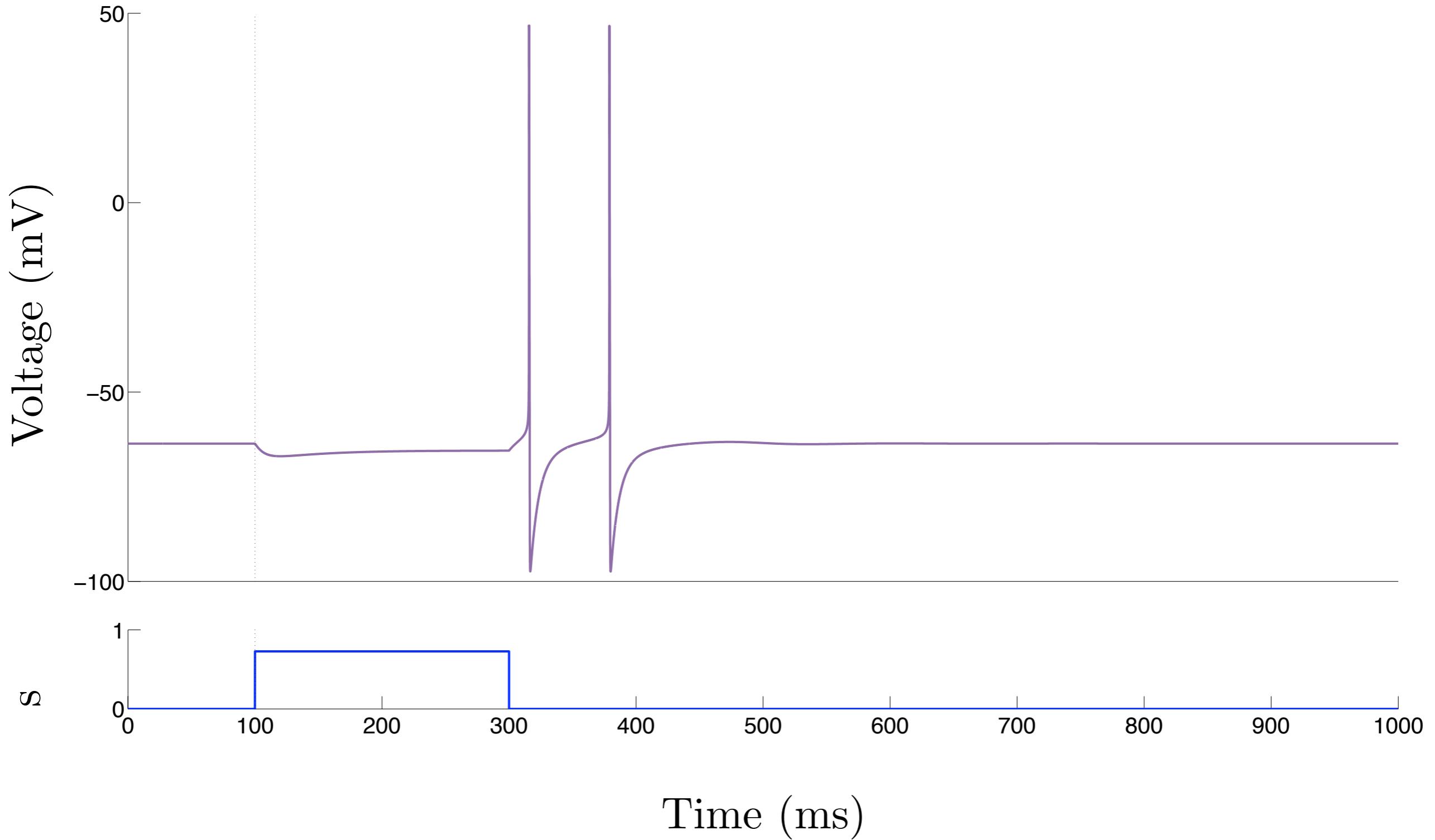
Contrast: inhibitory applied step current

step duration = 100



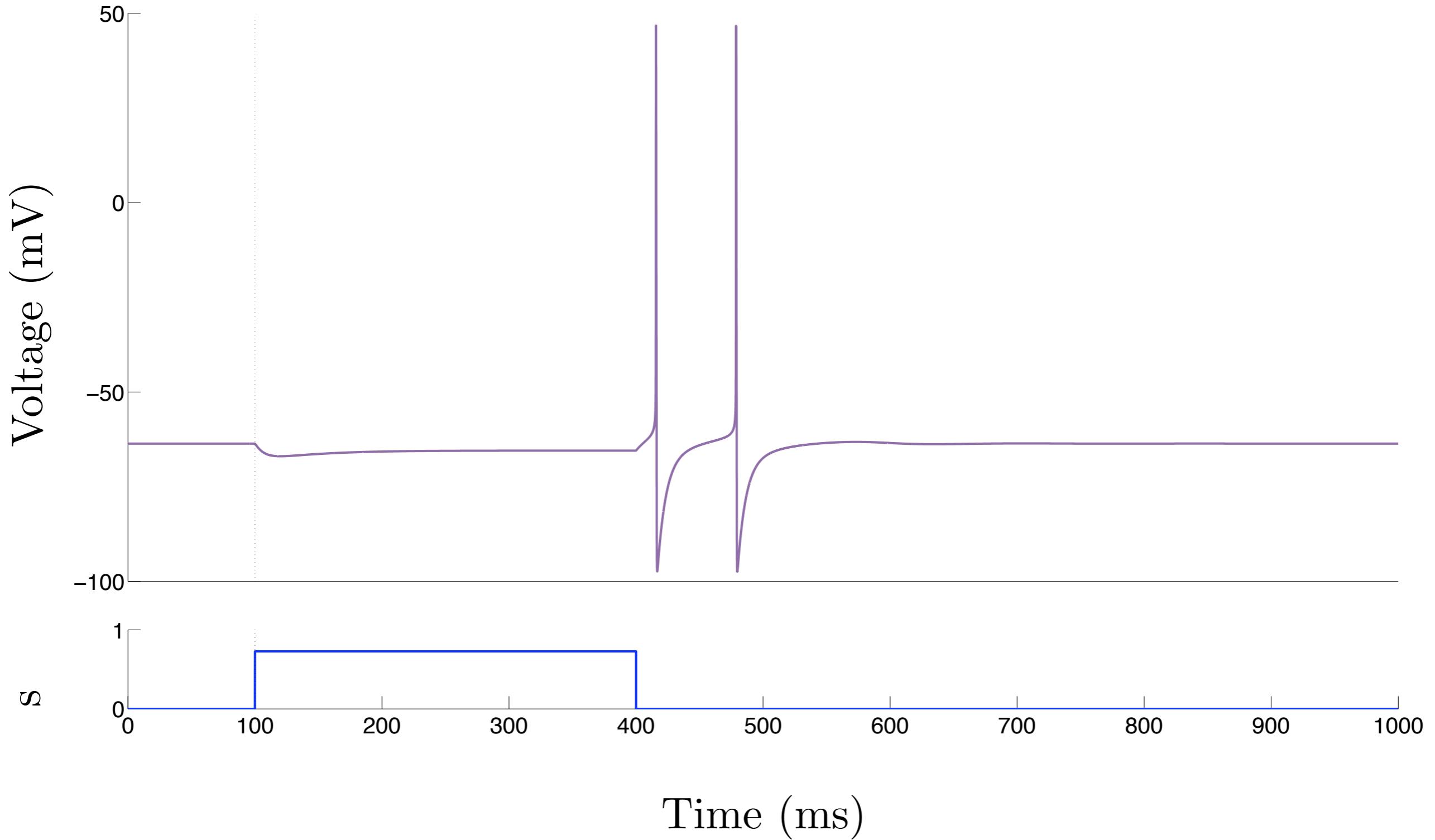
Contrast: inhibitory applied step current

step duration = 200



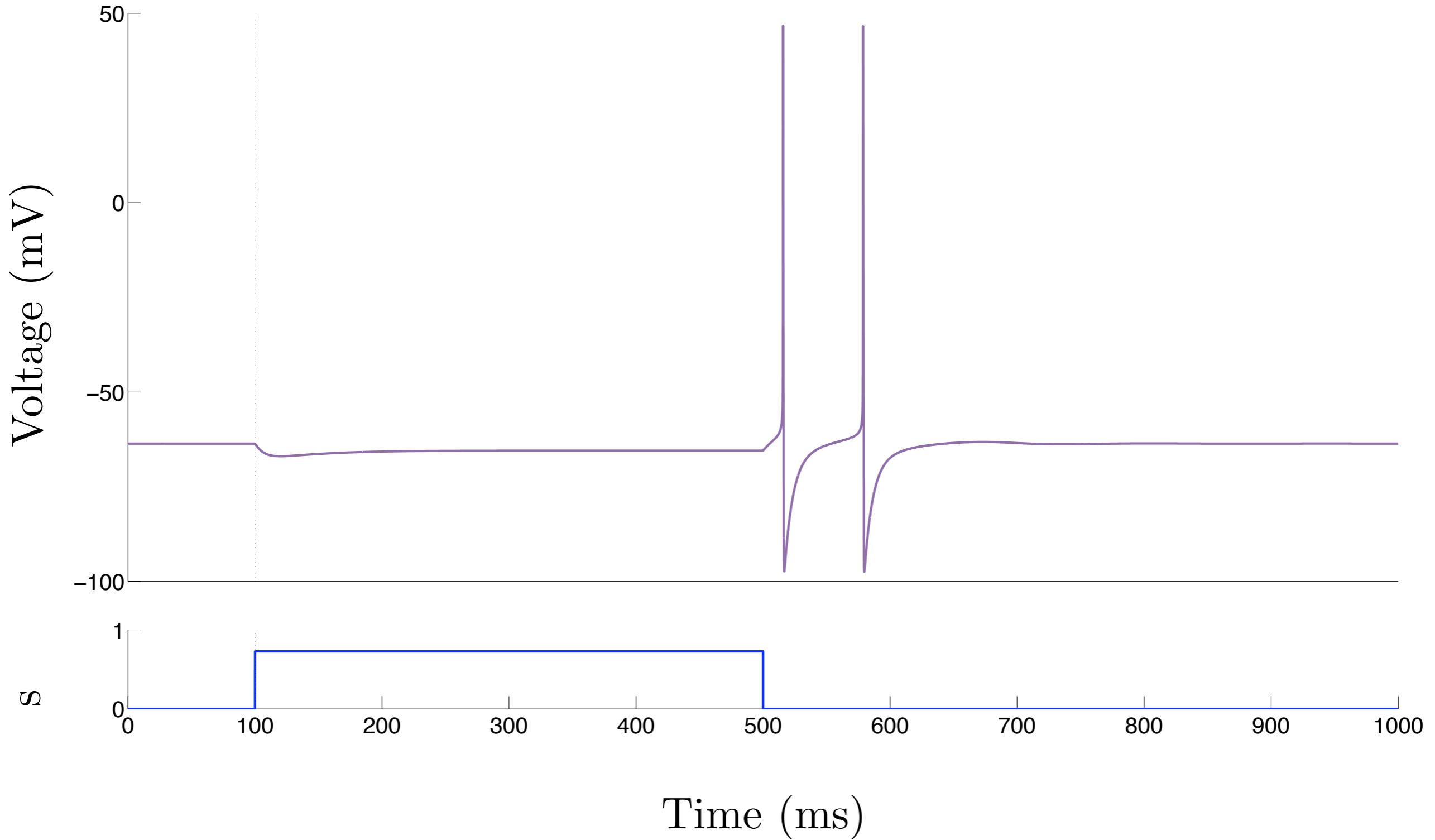
Contrast: inhibitory applied step current

step duration = 300



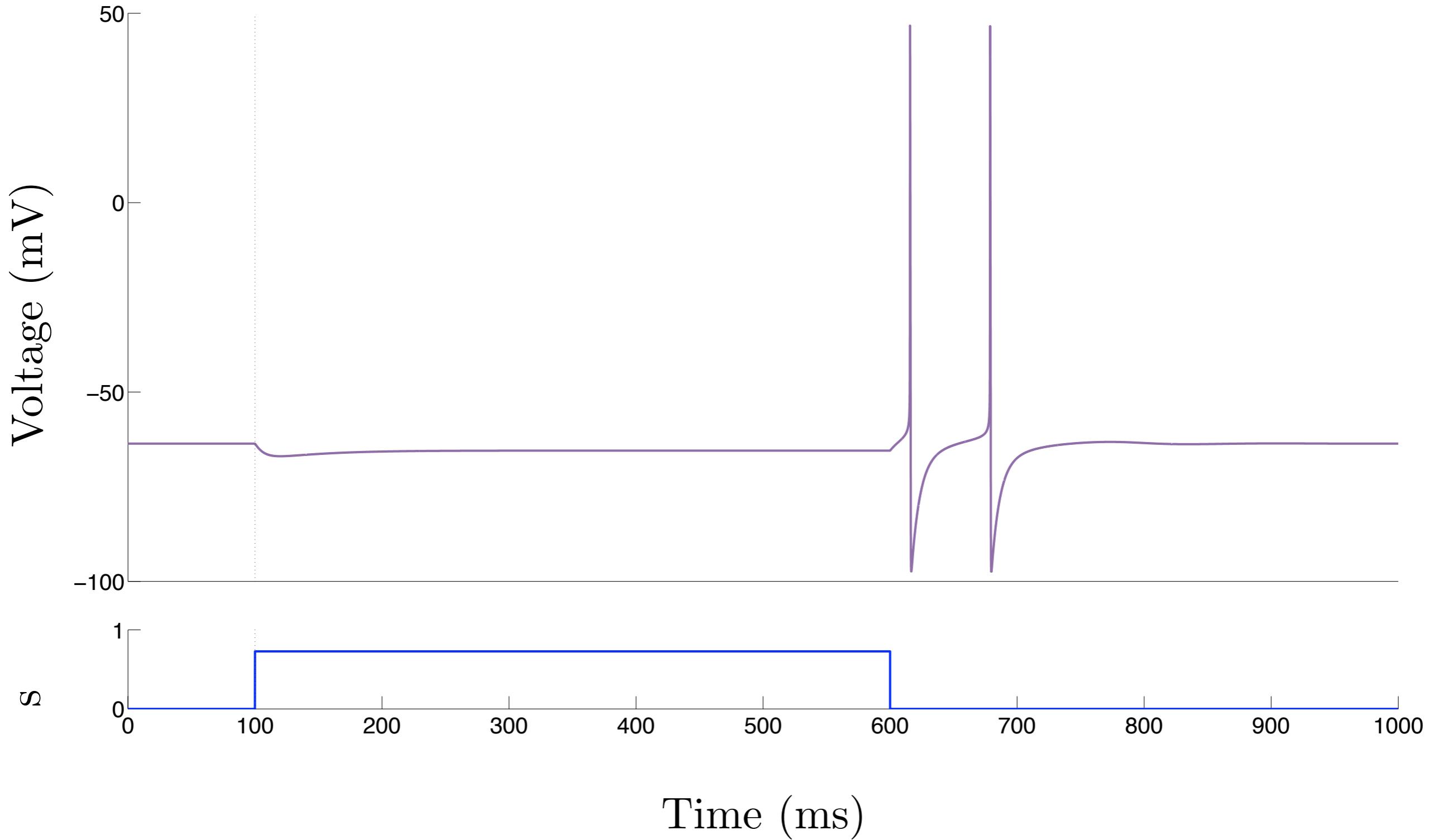
Contrast: inhibitory applied step current

step duration = 400

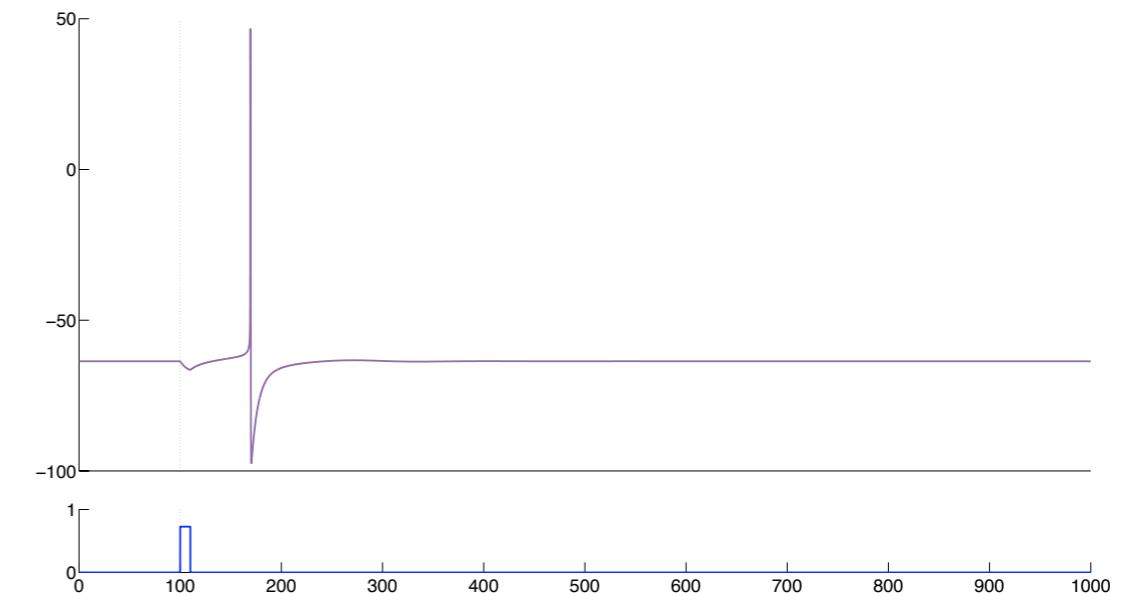
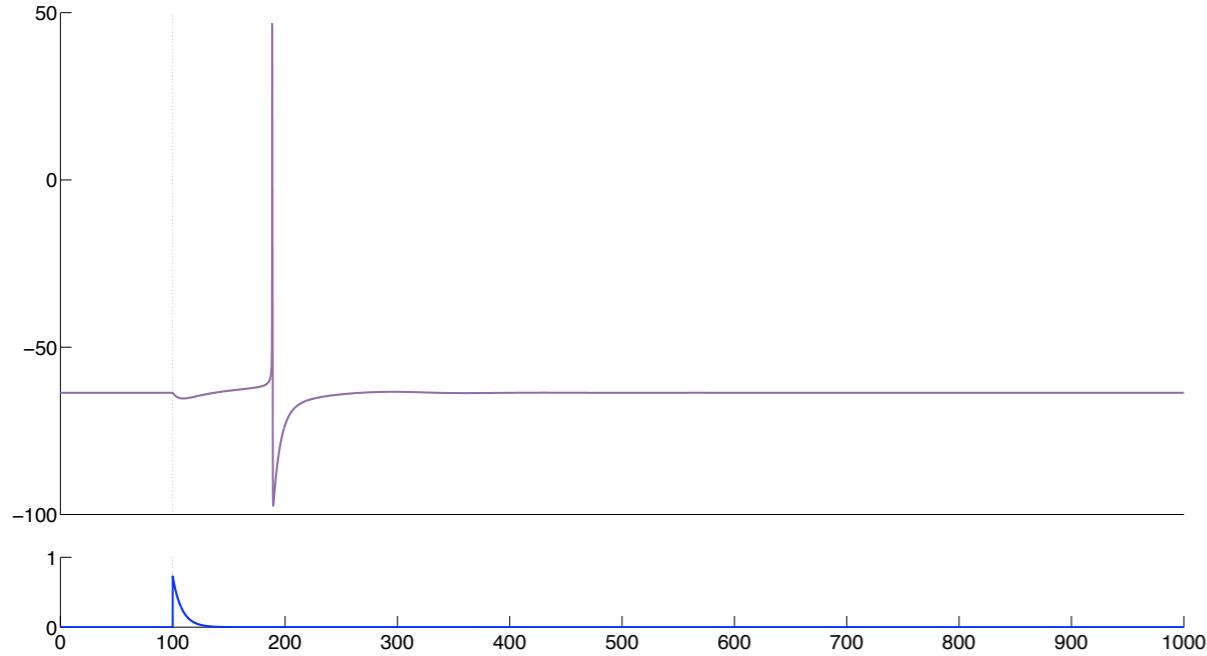


Contrast: inhibitory applied step current

step duration = 500



Synapse versus Step Protocol



- Synapse
- Dynamic response
- Explanation:
Canards
- Step Protocol
- Discontinuous response
- Explanation:
Post-Inhibitory Rebound

Identifying different scales in the model

- Dimensionless model:

$$\begin{aligned} \delta \ll 1 \quad & \delta \frac{dv}{dt} = f_1(v, m, h, n, w, s) \\ & \delta \frac{dm}{dt} = f_2(v, m) \\ & \frac{dh}{dt} = f_3(v, h) \\ & \frac{dn}{dt} = f_4(v, n) \\ & \frac{dw}{dt} = \epsilon g_1(v, w) \\ & \frac{ds}{dt} = \epsilon g_2(s) \quad \epsilon \ll 1 \end{aligned}$$

- Identify three different time scales: super-fast, fast, slow

Identifying different scales in the model

- Place super-fast and fast variables into one ‘fast’ group
- Slow-fast system with 4 fast (v, m, h, n) and 2 slow (w, s) variables

$$\begin{aligned}v' &= f_1(v, m, h, n, w, s) \\m' &= f_2(v, m) \\h' &= f_3(v, h) \\n' &= f_4(v, n) \\w' &= \epsilon g_1(v, w) \\s' &= \epsilon g_2(s)\end{aligned}\quad \epsilon \ll 1$$

Geometric singular perturbation analysis

$\begin{aligned} v' &= f_1(v, m, h, n, w, s) \\ m' &= f_2(v, m) \\ h' &= f_3(v, h) \\ n' &= f_4(v, n) \\ w' &= \epsilon g_1(v, w) \\ s' &= \epsilon g_2(s) \end{aligned}$	$\begin{aligned} \epsilon \dot{v} &= f_1(v, m, h, n, w, s) \\ \epsilon \dot{m} &= f_2(v, m) \\ \epsilon \dot{h} &= f_3(v, h) \\ \epsilon \dot{n} &= f_4(v, n) \\ \dot{w} &= g_1(v, w) \\ \dot{s} &= g_2(s) \end{aligned}$
fast time $\tau = t/\epsilon$	slow time t

singular limit $\epsilon \rightarrow 0$

$\begin{aligned} v' &= f_1(v, m, h, n, w, s) \\ m' &= f_2(v, m) \\ h' &= f_3(v, h) \\ n' &= f_4(v, n) \\ w' &= 0 \\ s' &= 0 \end{aligned}$	$\begin{aligned} 0 &= f_1(v, m, h, n, w, s) \\ 0 &= f_2(v, m) \\ 0 &= f_3(v, h) \\ 0 &= f_4(v, n) \\ \dot{w} &= g_1(v, w) \\ \dot{s} &= g_2(s) \end{aligned}$
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layer problem (4D)

reduced problem (2D)

Layer problem

$$\begin{aligned}v' &= f_1(v, m, h, n, w, s) \\m' &= f_2(v, m) \\h' &= f_3(v, h) \\n' &= f_4(v, n) \\w' &= 0 \\s' &= 0\end{aligned}$$

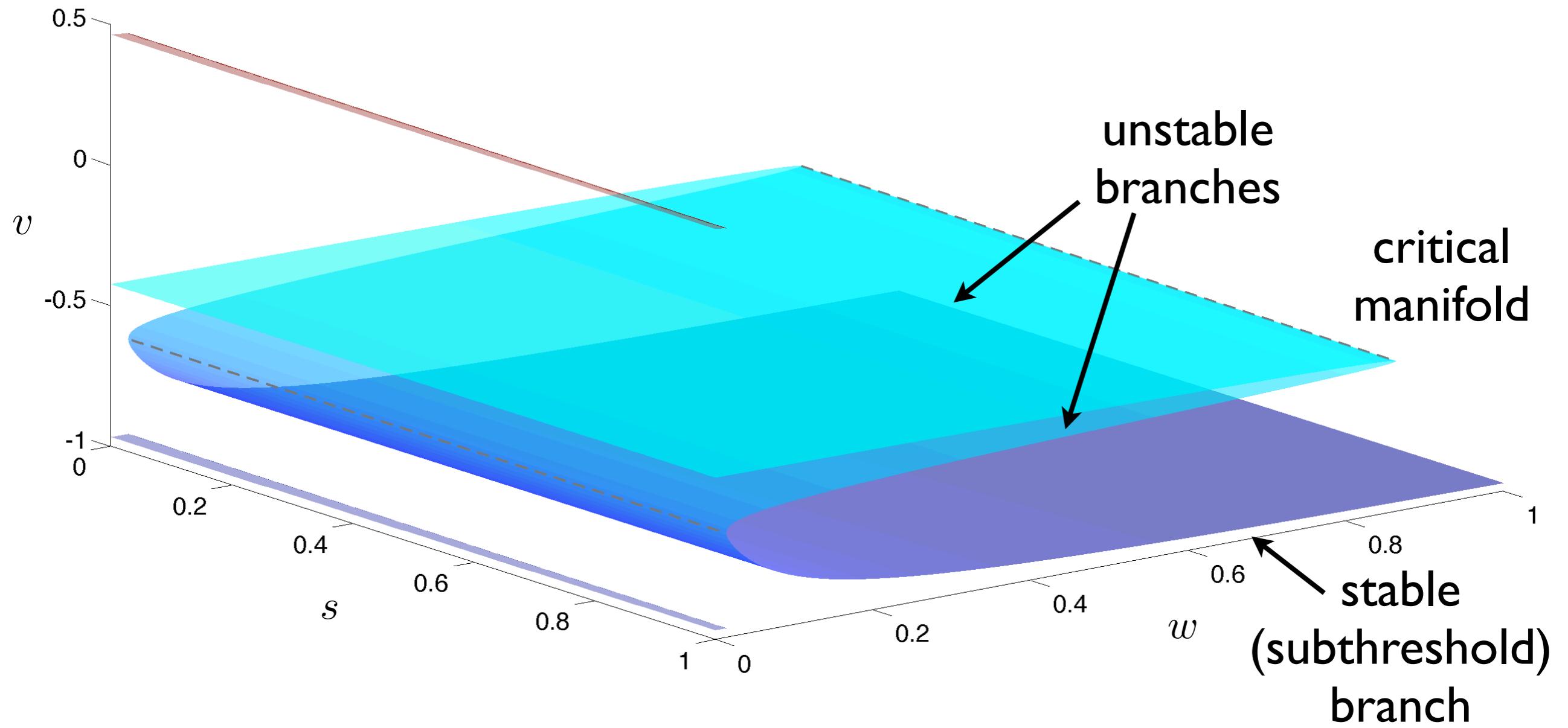
$$\begin{aligned}S_0 &= \{ (v, m, h, n, w, s) \mid f_1 = f_2 = f_3 = f_4 = 0 \}. \\&= \{ (v, m, h, n, w, s) \mid f_1(v, m_\infty(v), h_\infty(v), n_\infty(v), w, s) = 0 \}.\end{aligned}$$

- The 2D critical manifold is the manifold of equilibrium states
- The layer problem describes flow towards/away from critical manifold
- The slow variables **(w,s)** are bifurcation parameters

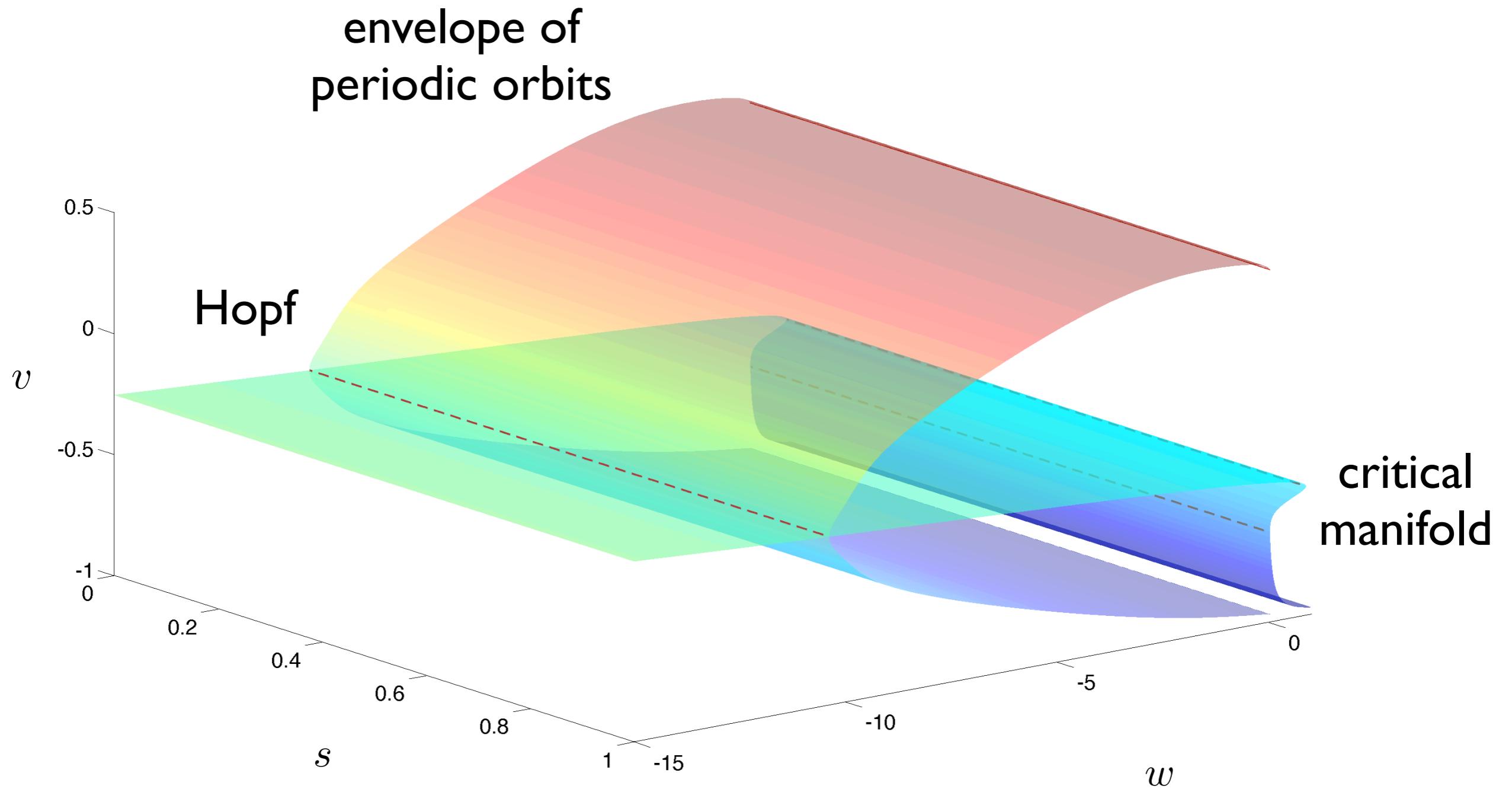
Layer problem

$$S_0 = \{ (v, m, h, n, w, s) \mid f_1 = f_2 = f_3 = f_4 = 0 \}.$$

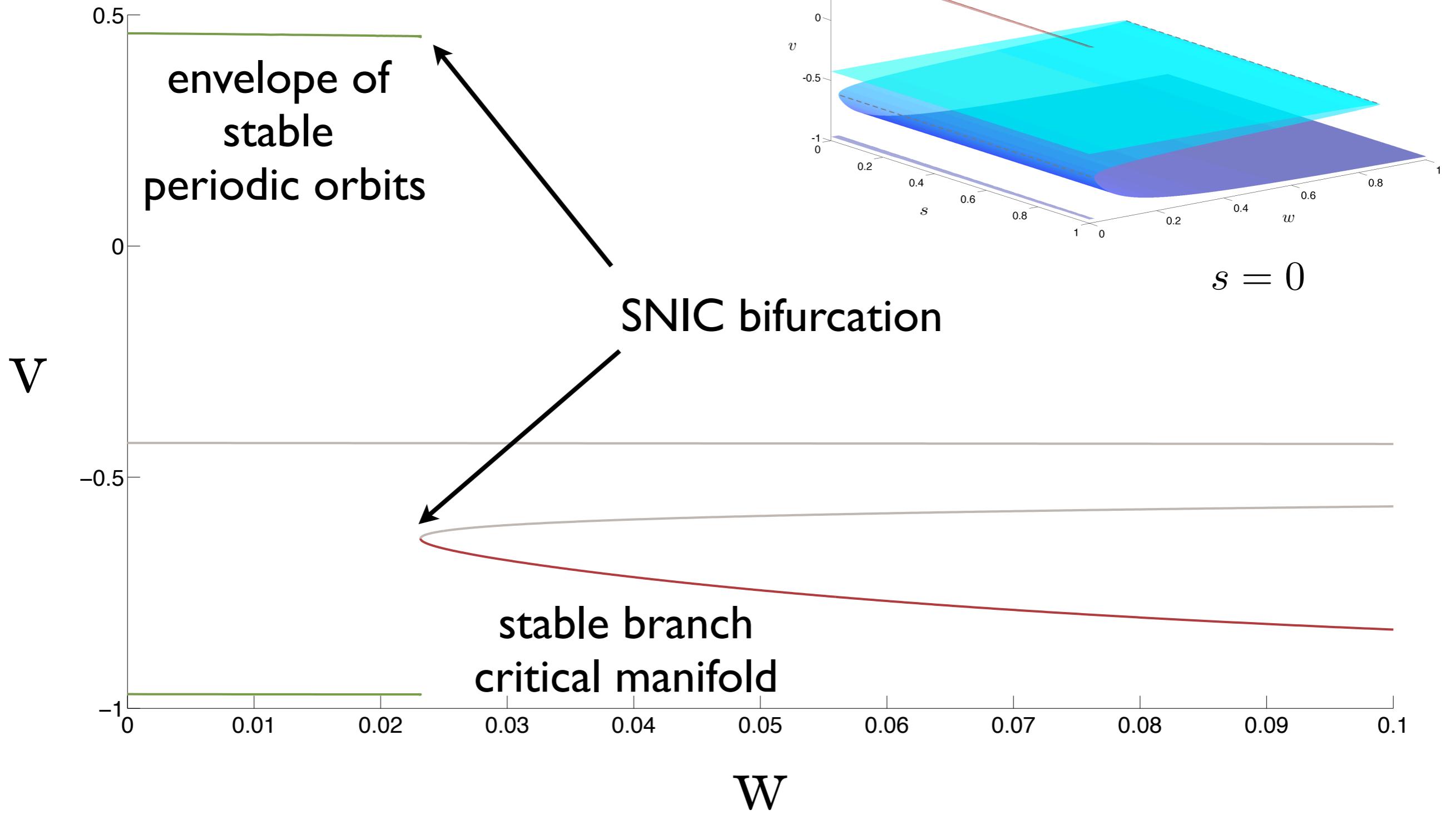
$$= \{ (v, m, h, n, w, s) \mid f_1(v, m_\infty(v), h_\infty(v), n_\infty(v), w, s) = 0 \}.$$



Layer problem



Layer problem



Geometric singular perturbation analysis

$$\begin{aligned} v' &= f_1(v, m, h, n, w, s) \\ m' &= f_2(v, m) \\ h' &= f_3(v, h) \\ n' &= f_4(v, n) \\ w' &= \epsilon g_1(v, w) \\ s' &= \epsilon g_2(s) \end{aligned}$$

fast time $\tau = t/\epsilon$

$$\begin{aligned} \epsilon \dot{v} &= f_1(v, m, h, n, w, s) \\ \epsilon \dot{m} &= f_2(v, m) \\ \epsilon \dot{h} &= f_3(v, h) \\ \epsilon \dot{n} &= f_4(v, n) \\ \dot{w} &= g_1(v, w) \\ \dot{s} &= g_2(s) \end{aligned}$$

slow time t

singular limit $\epsilon \rightarrow 0$

$$\begin{aligned} v' &= f_1(v, m, h, n, w, s) \\ m' &= f_2(v, m) \\ h' &= f_3(v, h) \\ n' &= f_4(v, n) \\ w' &= 0 \\ s' &= 0 \end{aligned}$$

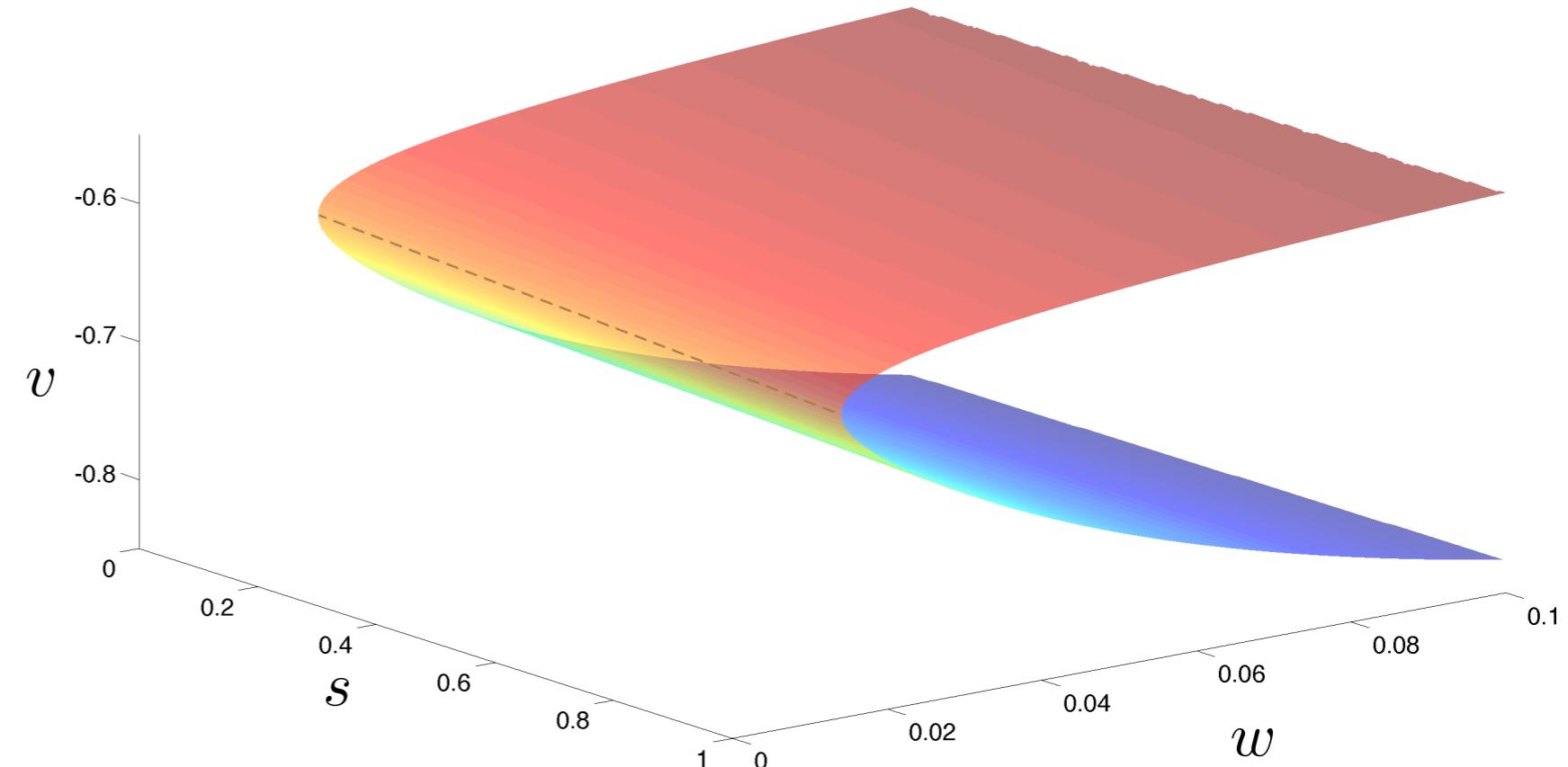
layer problem

$$\begin{aligned} 0 &= f_1(v, m, h, n, w, s) \\ 0 &= f_2(v, m) \\ 0 &= f_3(v, h) \\ 0 &= f_4(v, n) \\ \dot{w} &= g_1(v, w) \\ \dot{s} &= g_2(s) \end{aligned}$$

reduced problem

Reduced problem in subthreshold regime

$$\begin{aligned}0 &= f_1(v, m, h, n, w, s) \\0 &= f_2(v, m) \\0 &= f_3(v, h) \\0 &= f_4(v, n) \\\dot{w} &= g_1(v, w) \\\dot{s} &= g_2(s)\end{aligned}$$



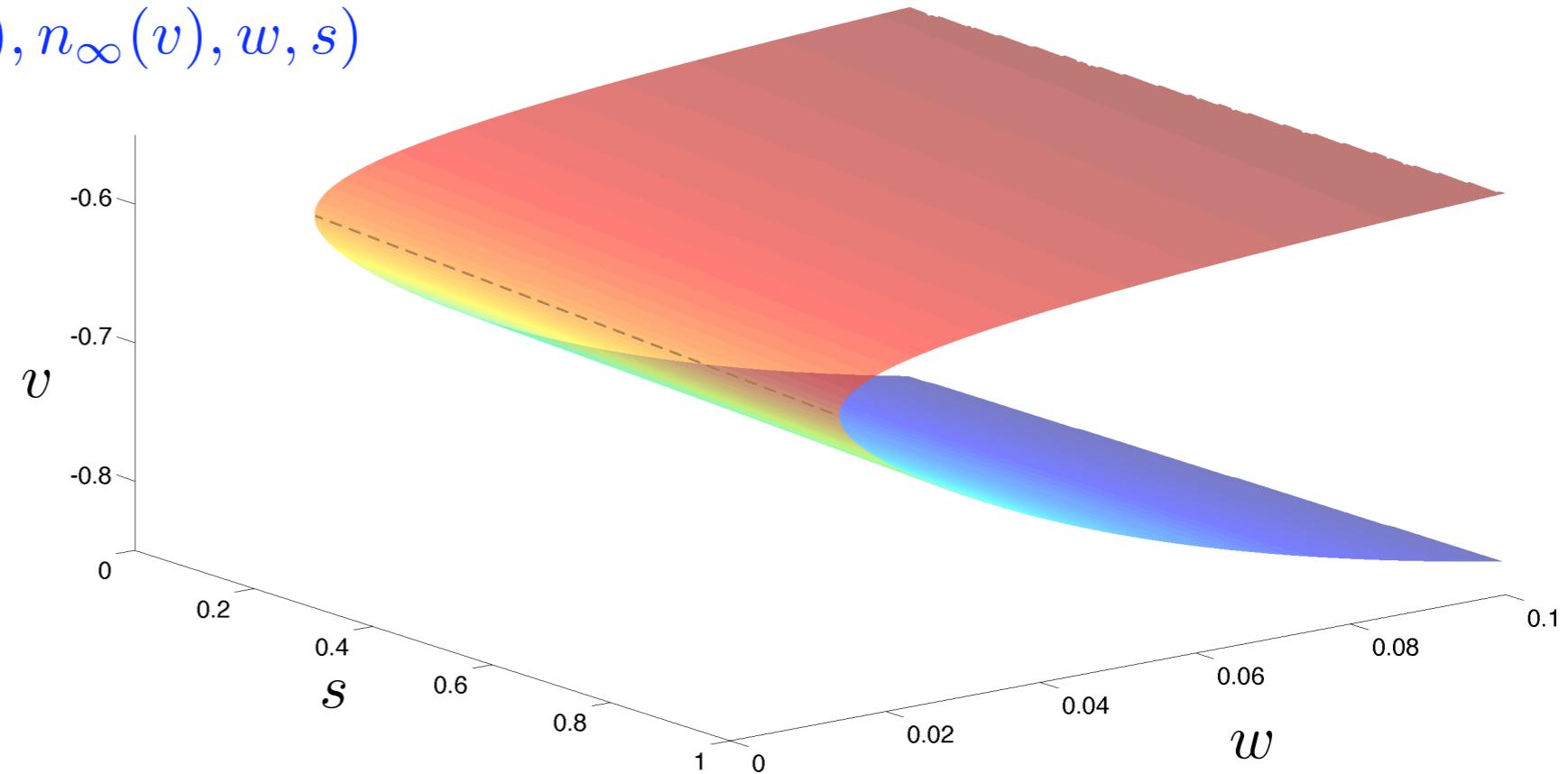
- The reduced flow is restricted to the 2D critical manifold
- It is a Differential-Algebraic System
- The critical manifold is a graph over (v, s) , i.e. $w=w(v, s)$

Reduced problem in subthreshold regime

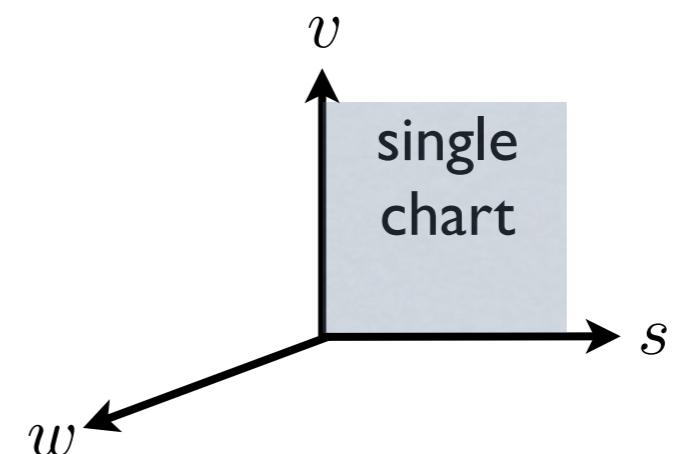
$$0 = f_1(v, m_\infty(v), h_\infty(v), n_\infty(v), w, s)$$

$$\frac{dw}{dt} = g_1(v, w)$$

$$\frac{ds}{dt} = g_2(s).$$



- Since $w=w(v,s)$, we project onto (v,s) -space to study the reduced flow in one single chart



Reduced problem

$$\begin{aligned}-\frac{\partial f_1}{\partial v}v' &= \frac{\partial f_1}{\partial w}g_1(v, w) + \frac{\partial f_1}{\partial s}g_2(s) \\ s' &= g_2(s).\end{aligned}$$

- Note that the reduced problem is singular along the fold
- We can circumvent this problem by rescaling time which gives the corresponding desingularised problem



$$\begin{aligned}v' &= \frac{\partial f_1}{\partial w}g_1(v, w) + \frac{\partial f_1}{\partial s}g_2(s) \\ s' &= -\frac{\partial f_1}{\partial v}g_2(s).\end{aligned}$$

- The desingularised flow has to be reversed on the repelling side of the critical manifold to obtain the corresponding reduced flow.

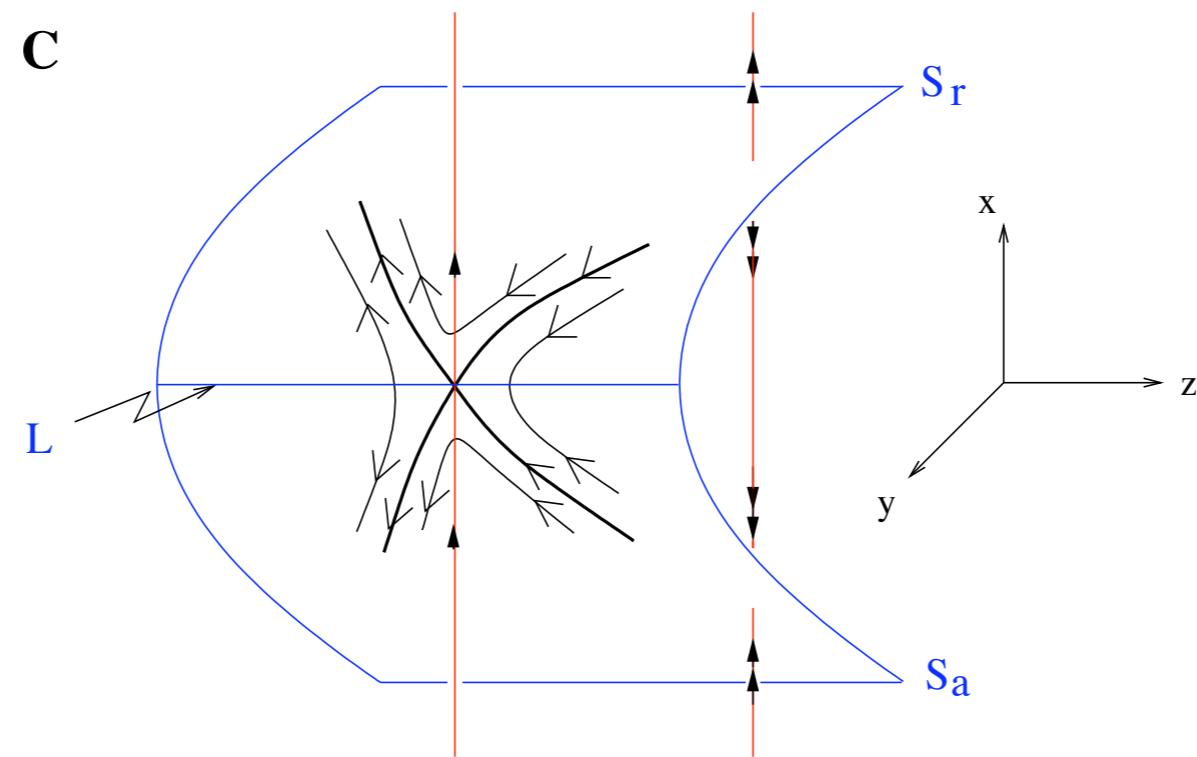
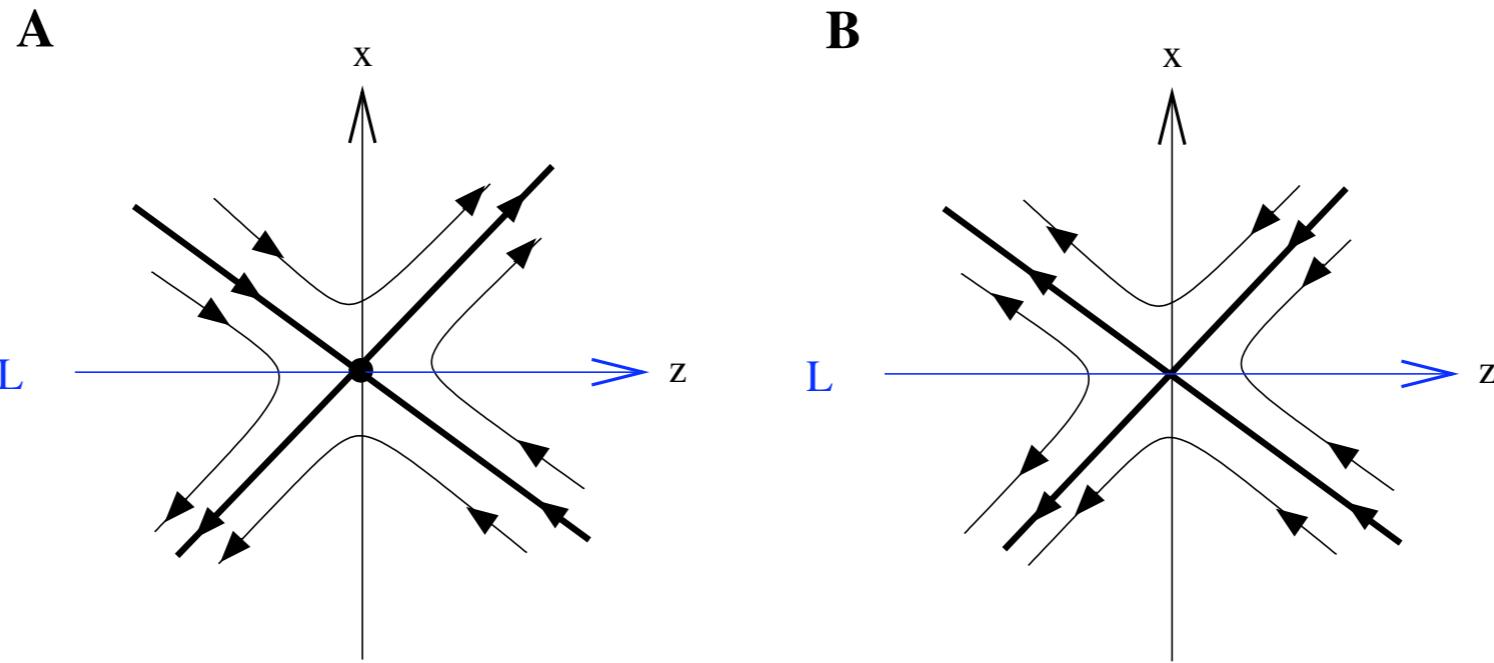
The desingularised problem

$$\begin{aligned}v' &= \frac{\partial f_1}{\partial w} g_1(v, w) + \frac{\partial f_1}{\partial s} g_2(s) \\s' &= -\frac{\partial f_1}{\partial v} g_2(s).\end{aligned}$$

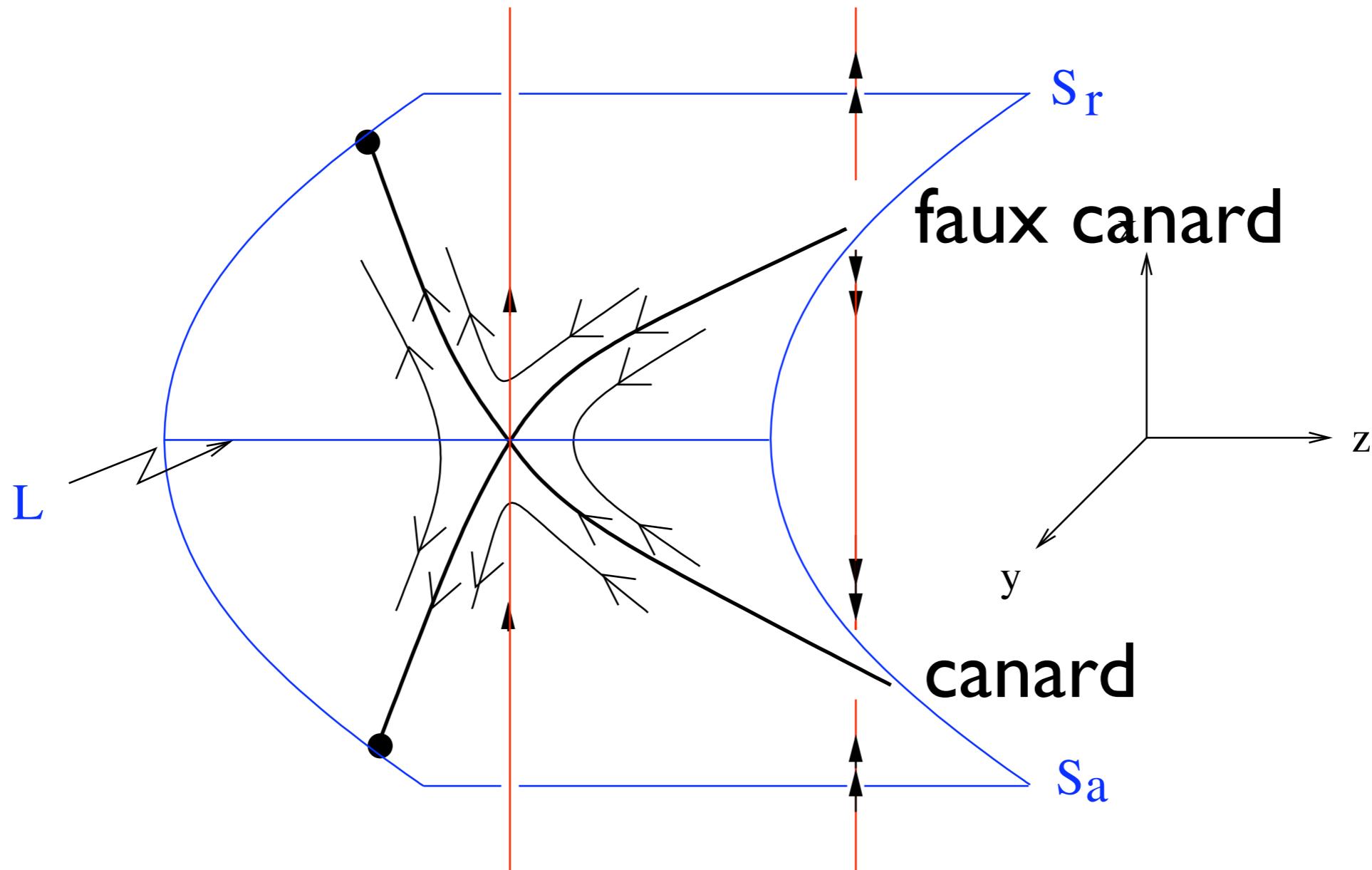
- Ordinary singularities away from the fold are defined by
 $g_1 = g_2 = 0$
- There are special singularities of the desingularised problem constrained to the fold (called folded singularities) defined by:

$$\frac{\partial f_1}{\partial v} = 0 \quad \text{and} \quad \left(\frac{\partial f_1}{\partial w} g_1 + \frac{\partial f_1}{\partial s} g_2 \right) = 0$$

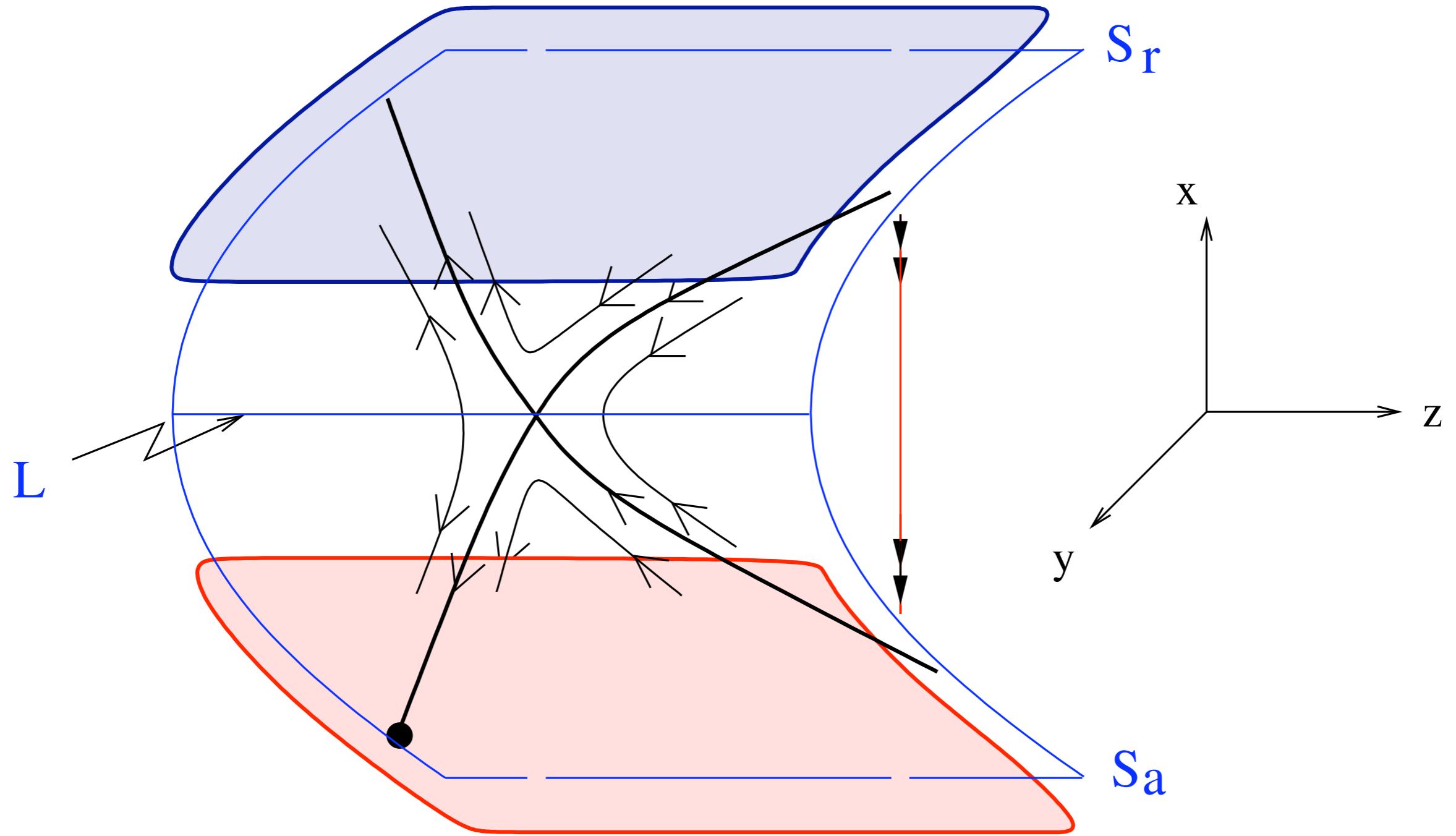
Folded saddle



Canard of folded saddle type



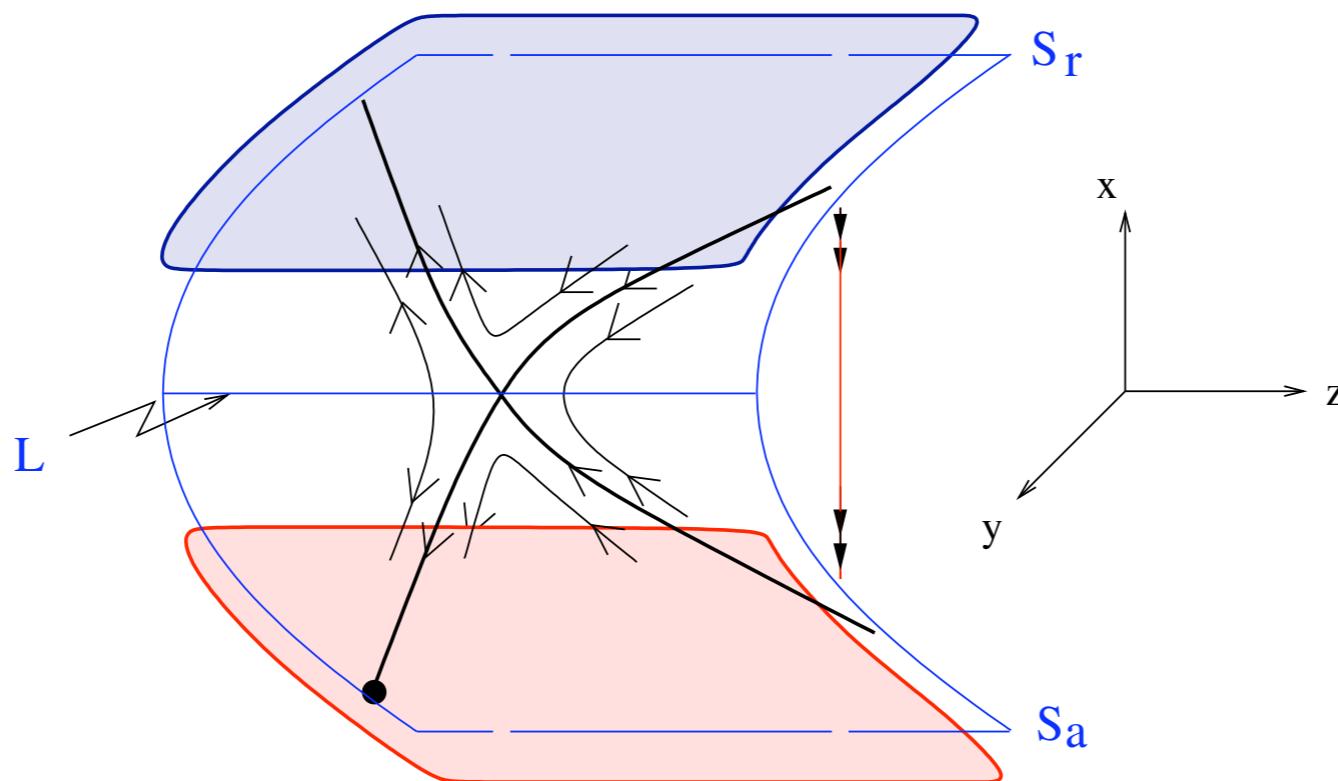
Canard of folded saddle type



Geometric singular perturbation theory

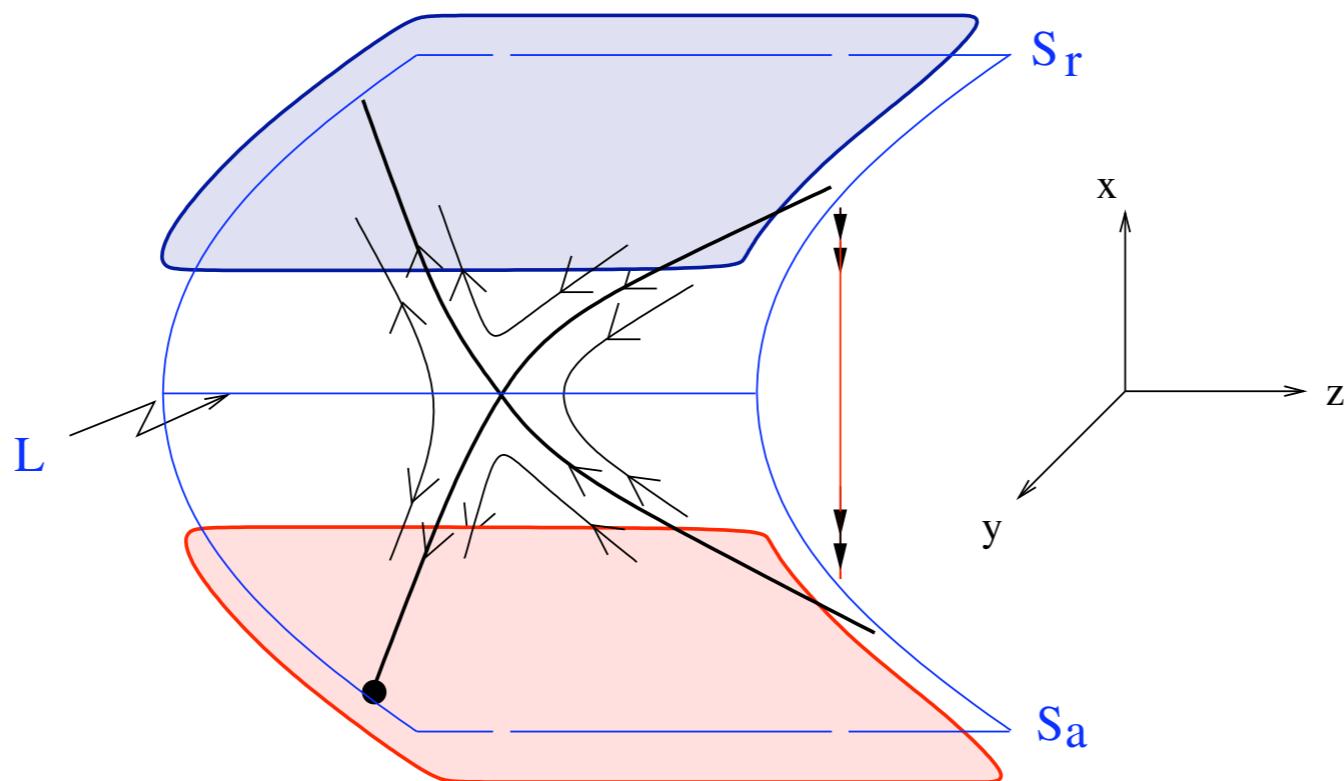
We ask the question if **singular canards** persist as **canards of the full system**.

[Definition] A maximal canard corresponds to the intersection of the manifolds $S_{a,\varepsilon}$ and $S_{r,\varepsilon}$ extended by the flow into the neighborhood of the fold.

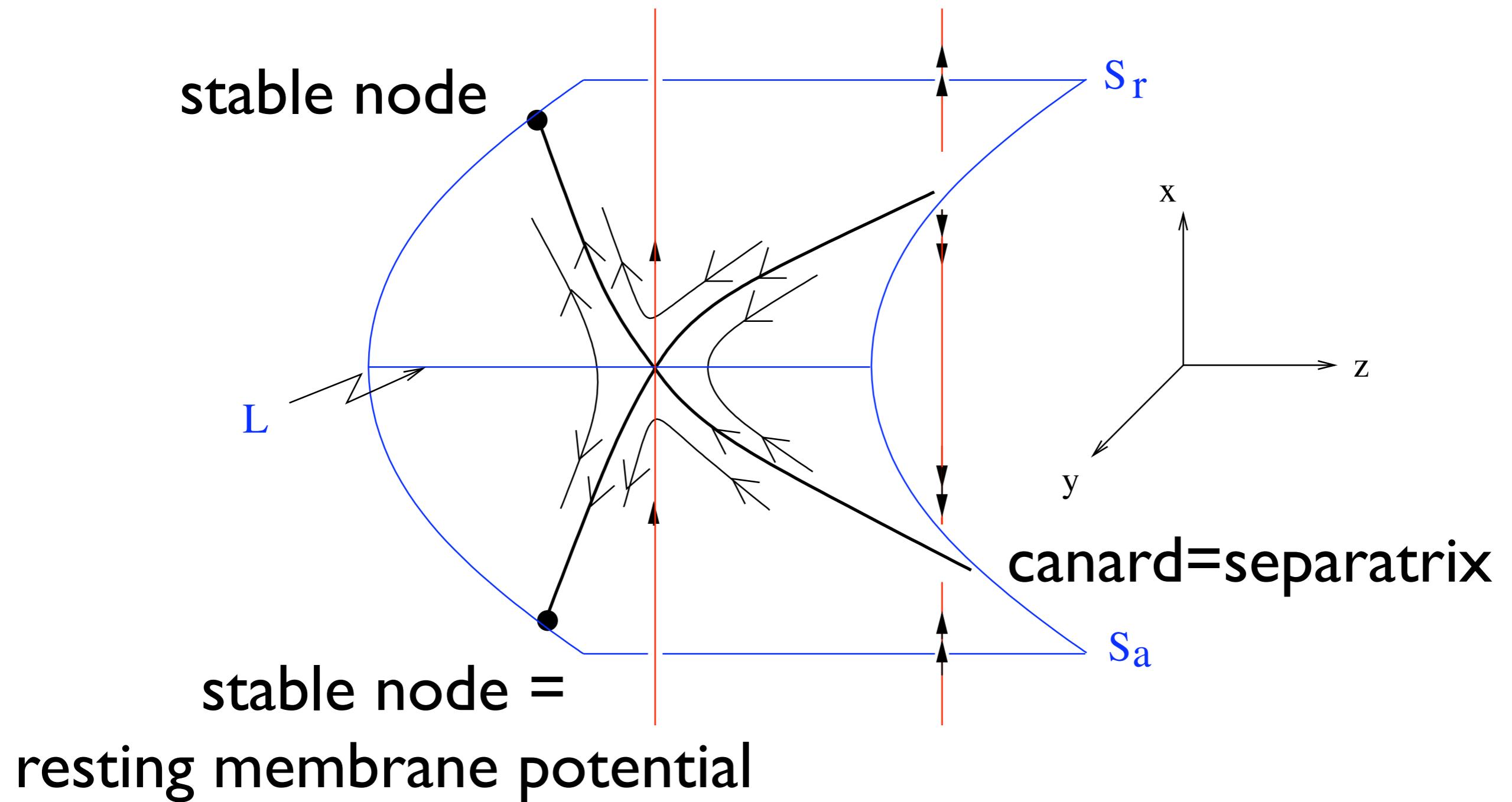


Geometric singular perturbation theory

[Theorem: Szmolyan, Wechselberger 2001] A singular canard of folded saddle type persists as a maximal canard, i.e. as a transverse intersection of the manifolds $S_{a,\varepsilon}$ and $S_{r,\varepsilon}$ extended by the flow into the neighborhood of the fold.

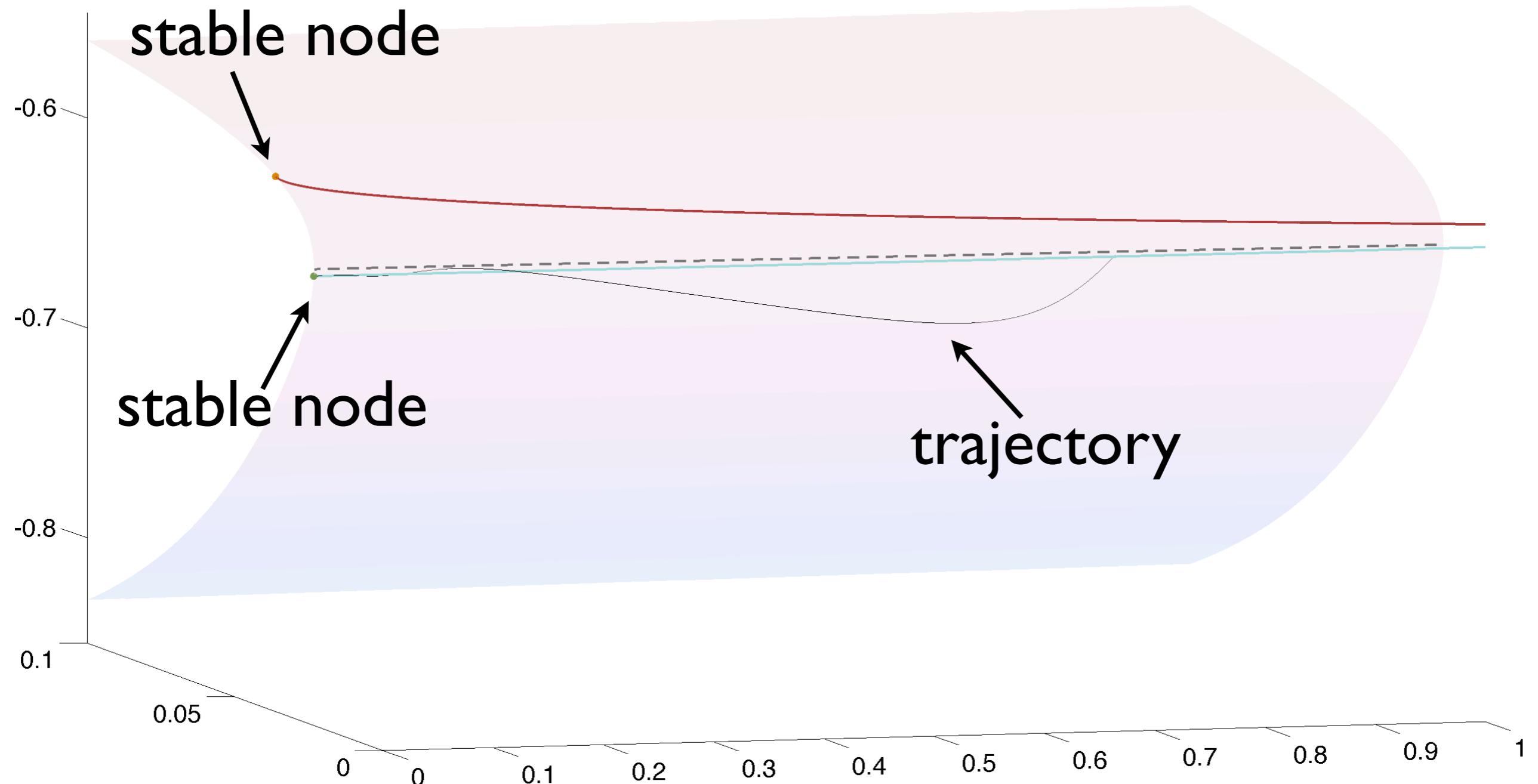


Model: Stable Equilibria + Folded saddle

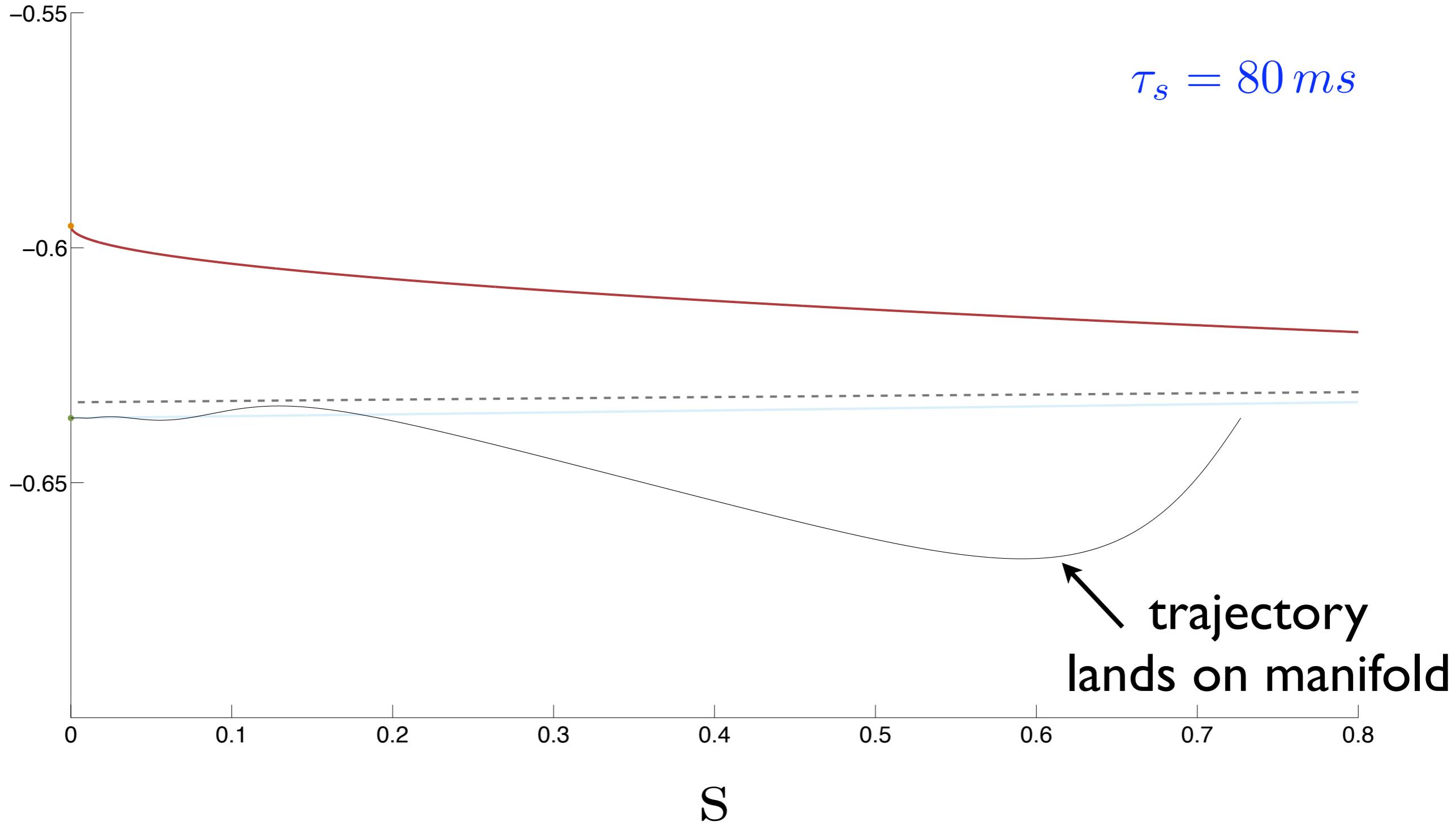


Slow inactivation: no action potential

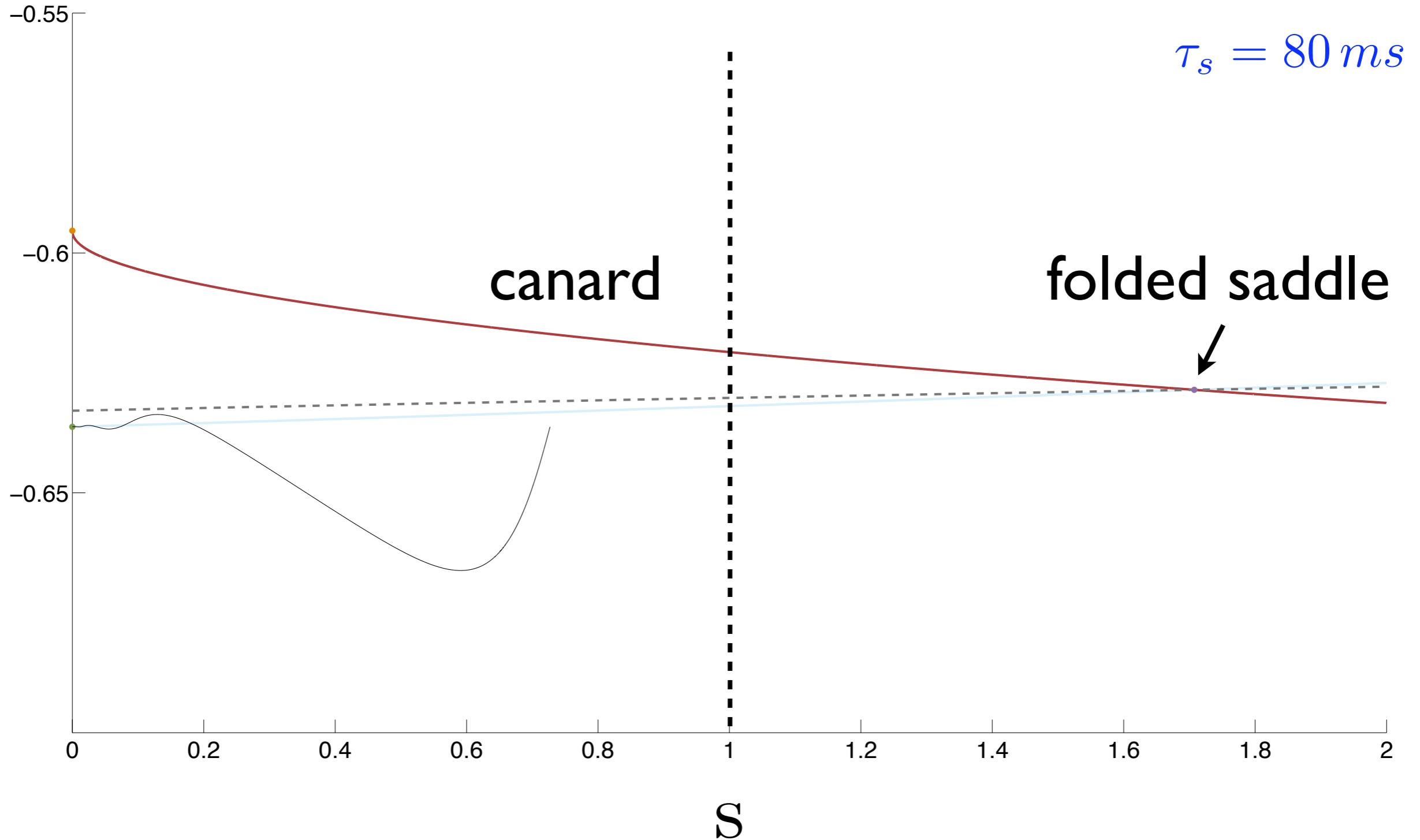
$$\tau_s = 80 \text{ ms}$$



Slow inactivation: no action potential

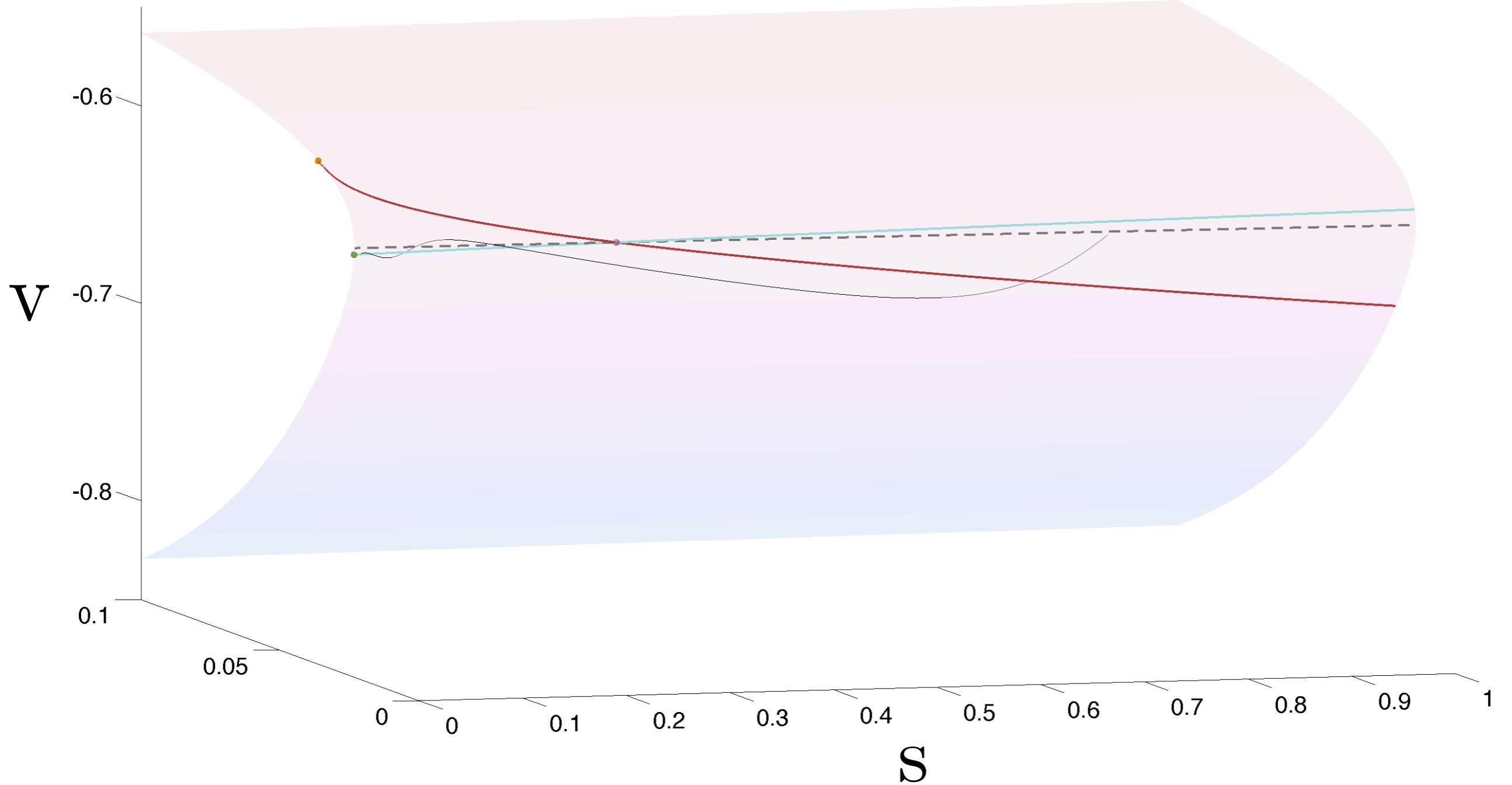


Slow inactivation: no action potential

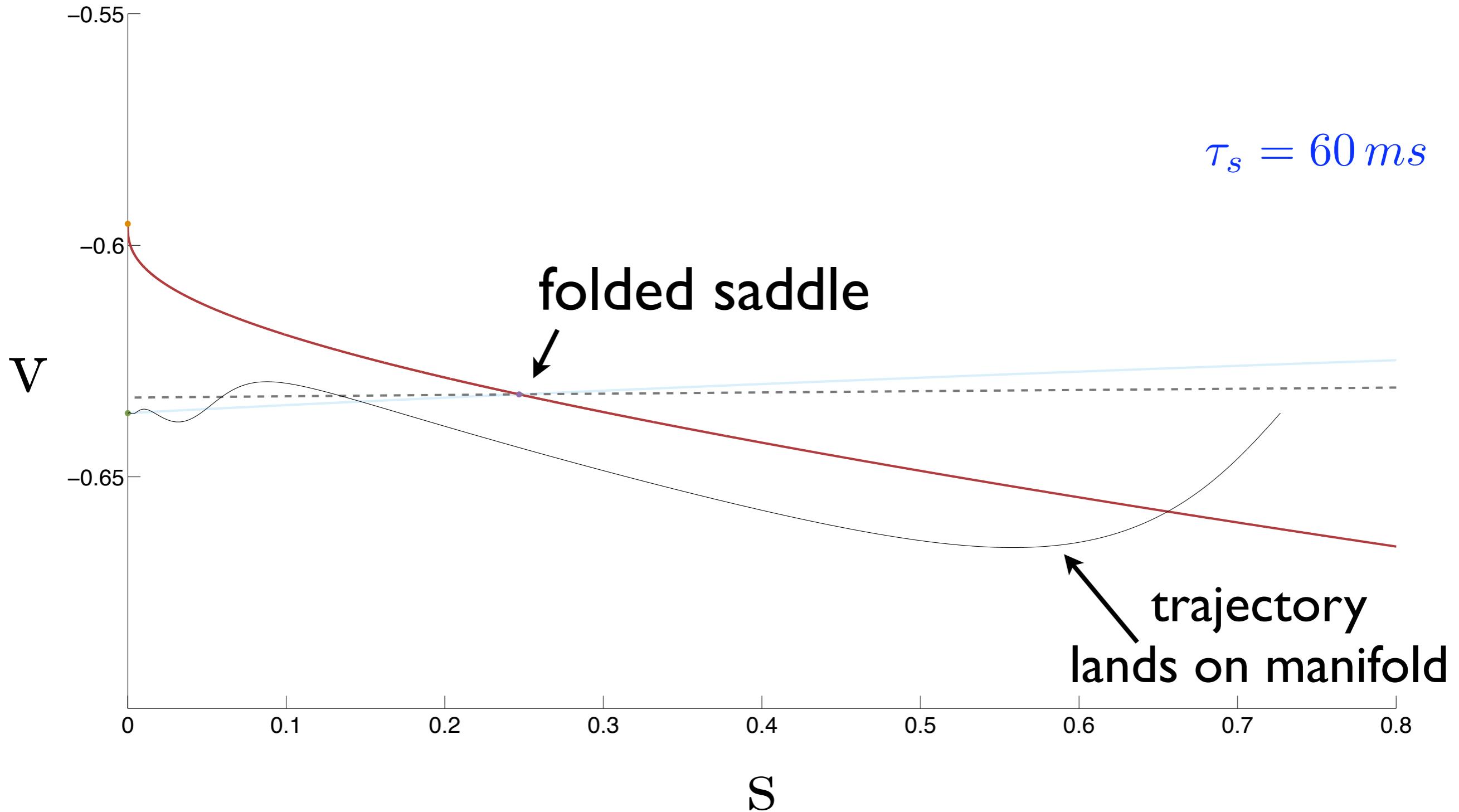


No action potential, but folded saddle in physiological regime

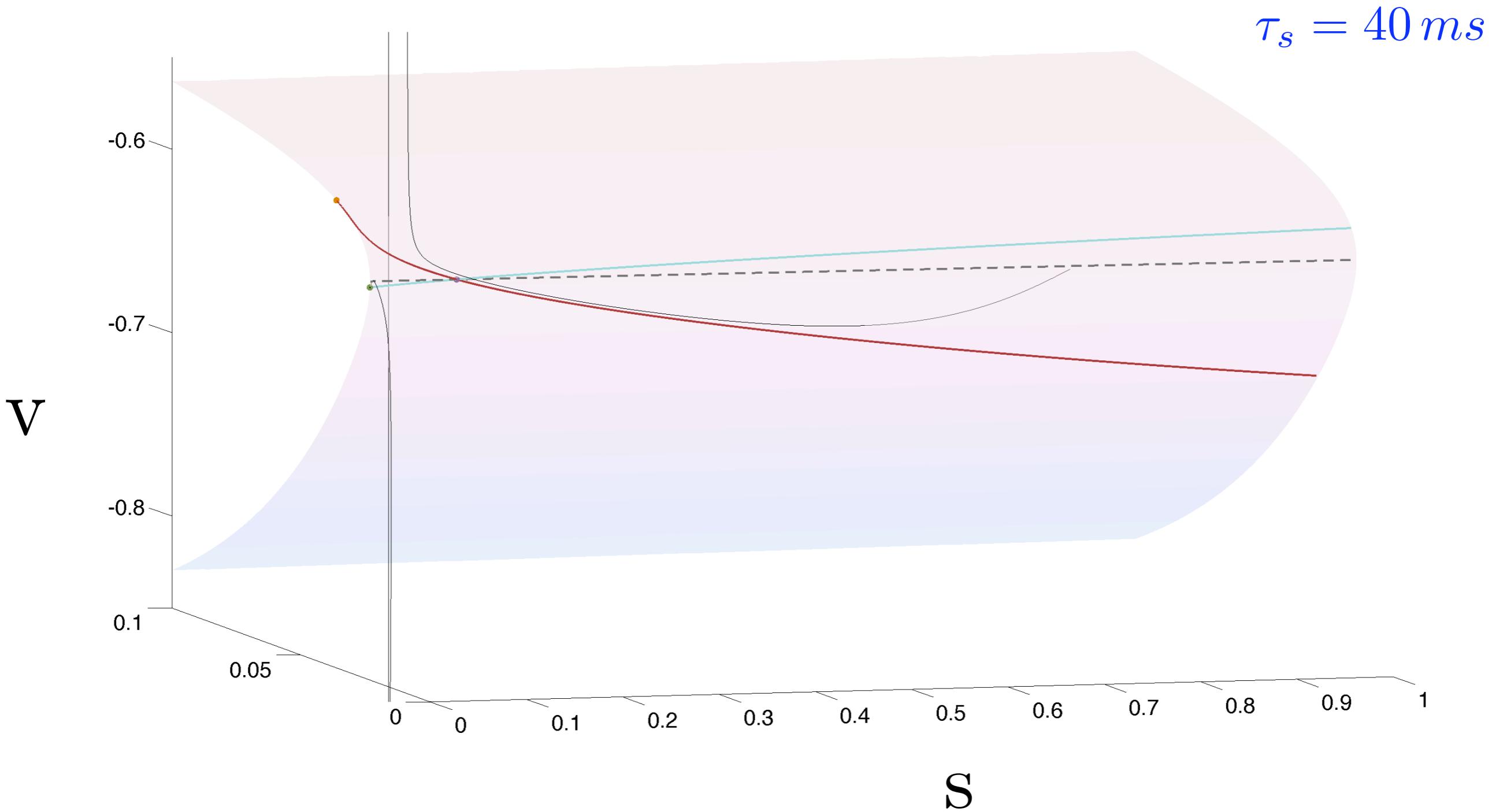
$\tau_s = 60\text{ ms}$



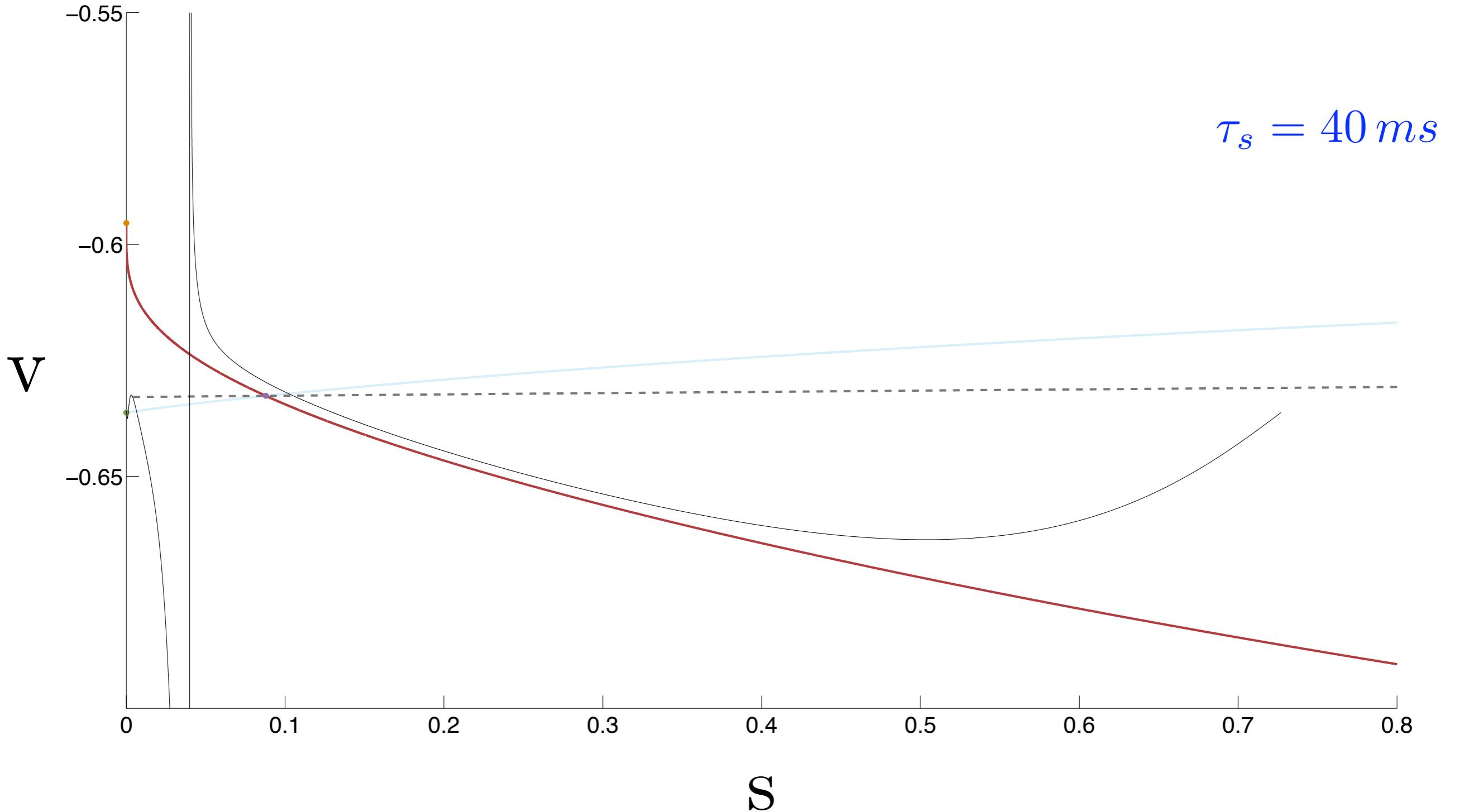
No action potential, but folded saddle in physiological regime



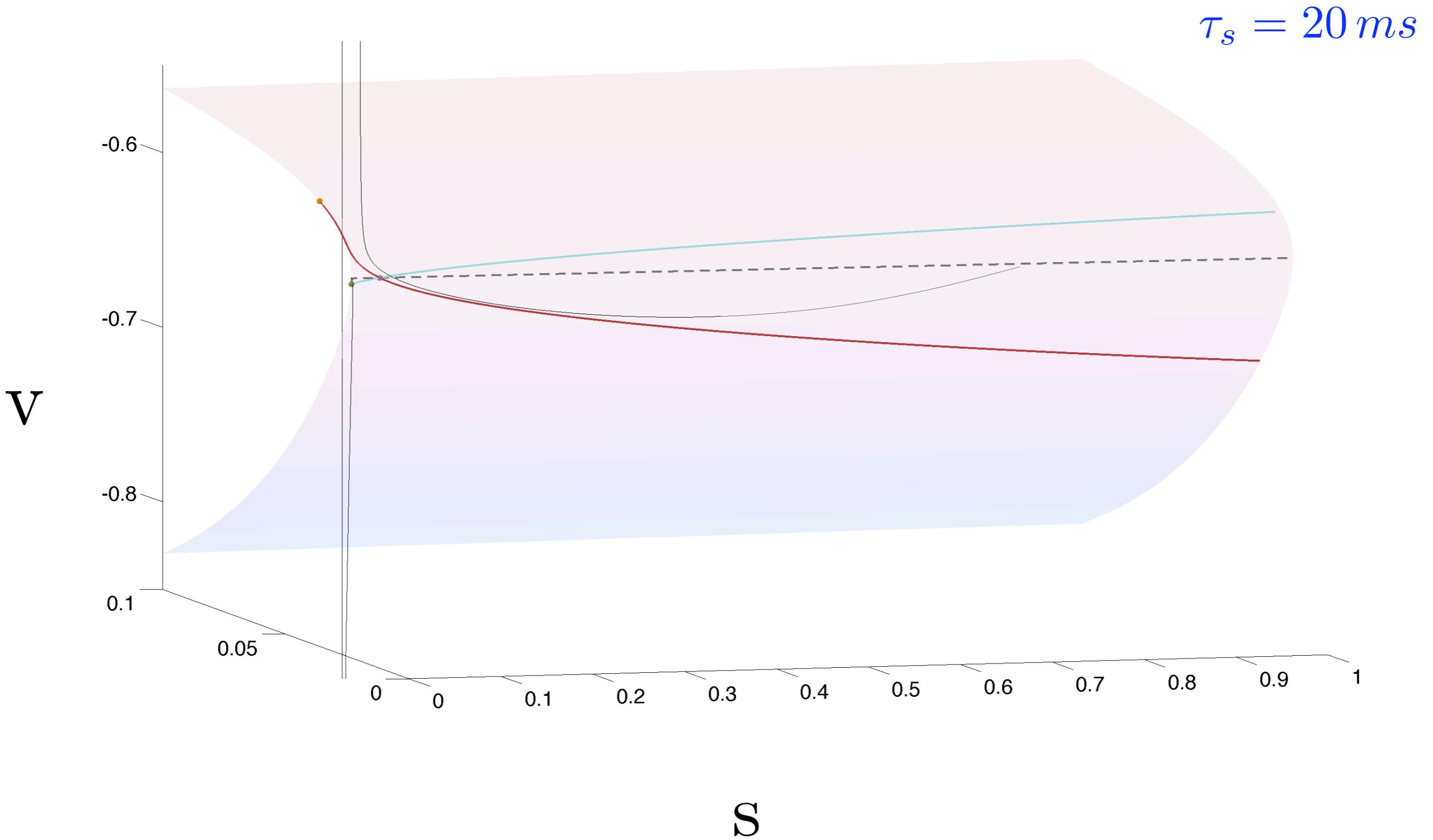
Action potential! trajectory ‘lands on’ other side of canard



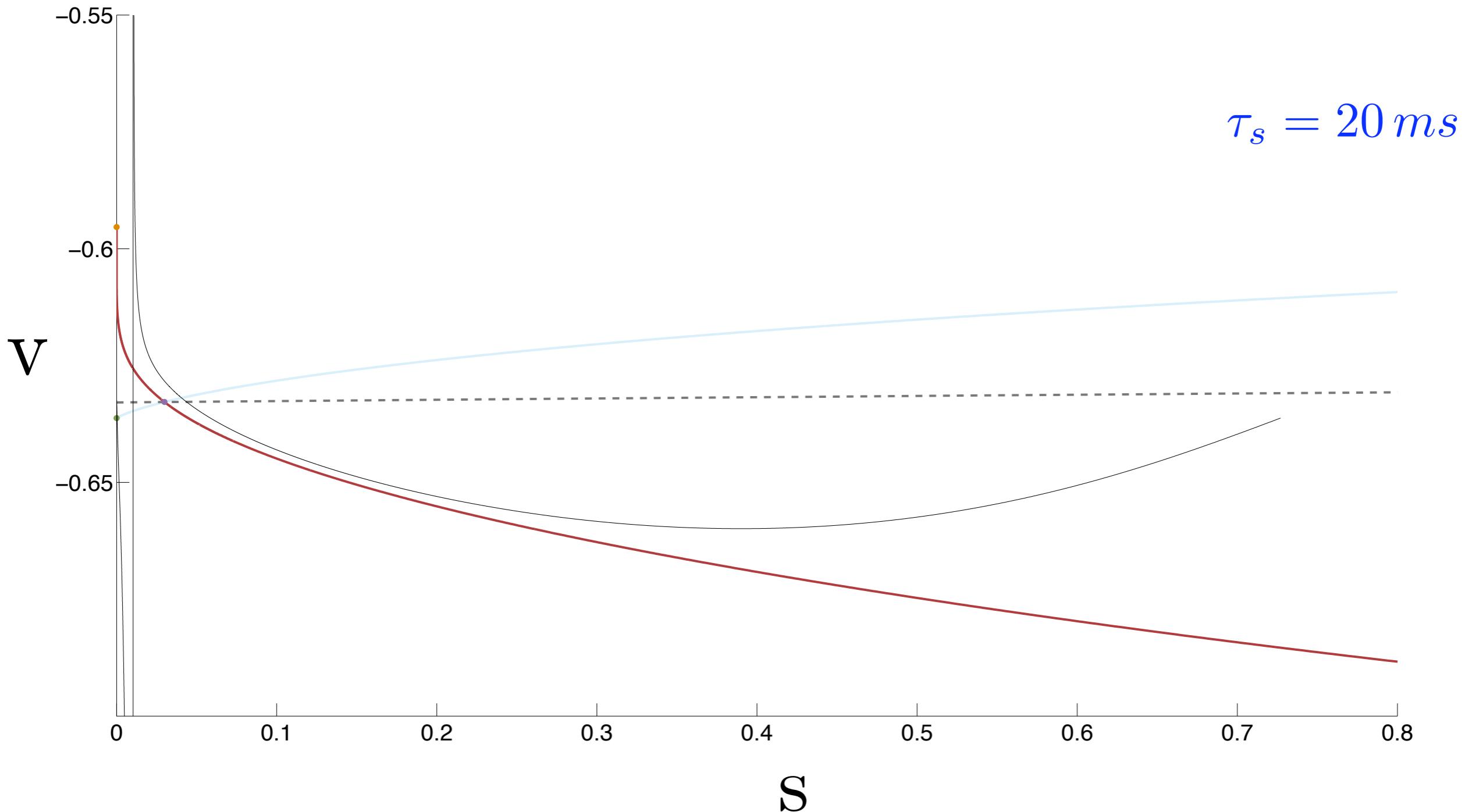
Action potential! trajectory ‘lands on’ other side of canard



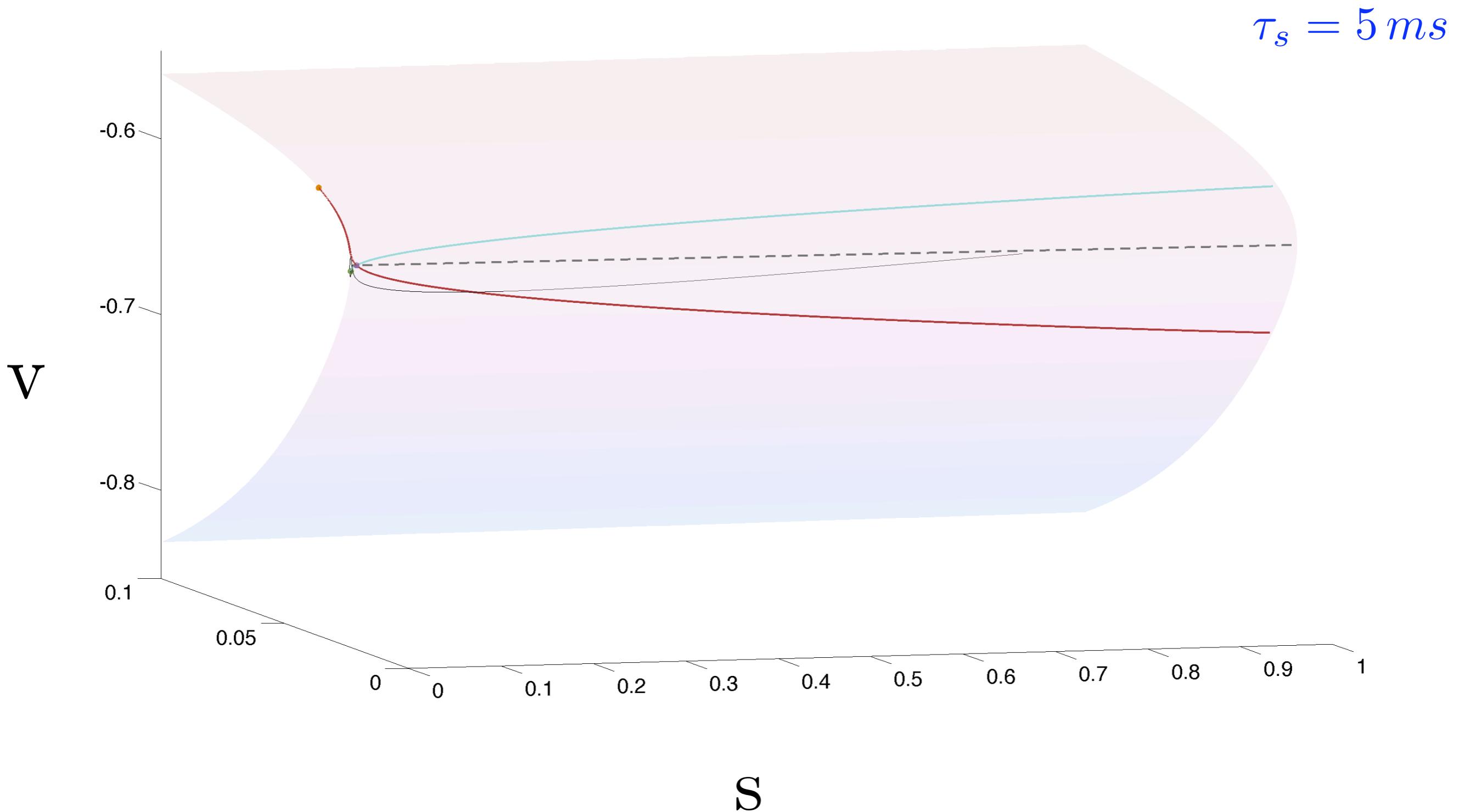
Action potential! trajectory ‘lands on’ other side of canard



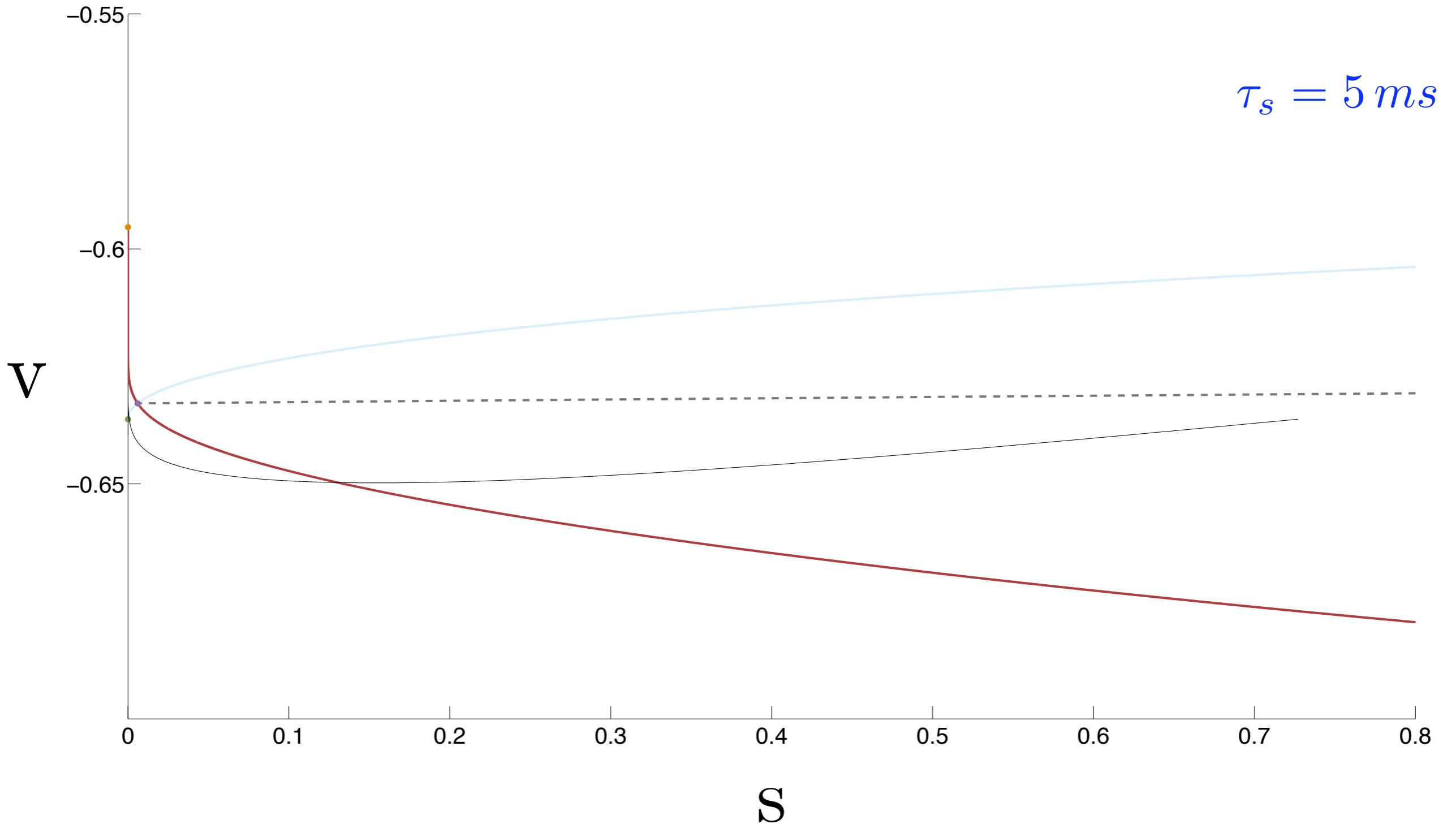
Action potential!
trajectory ‘lands on’ other side of canard



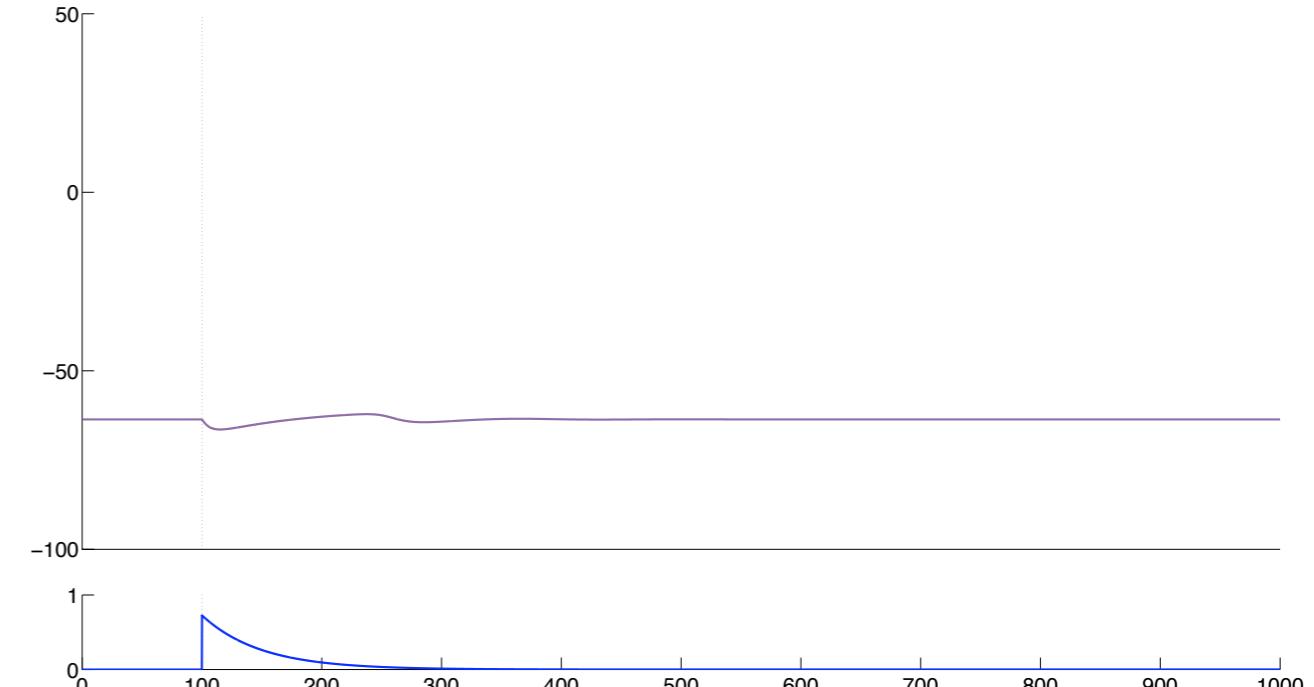
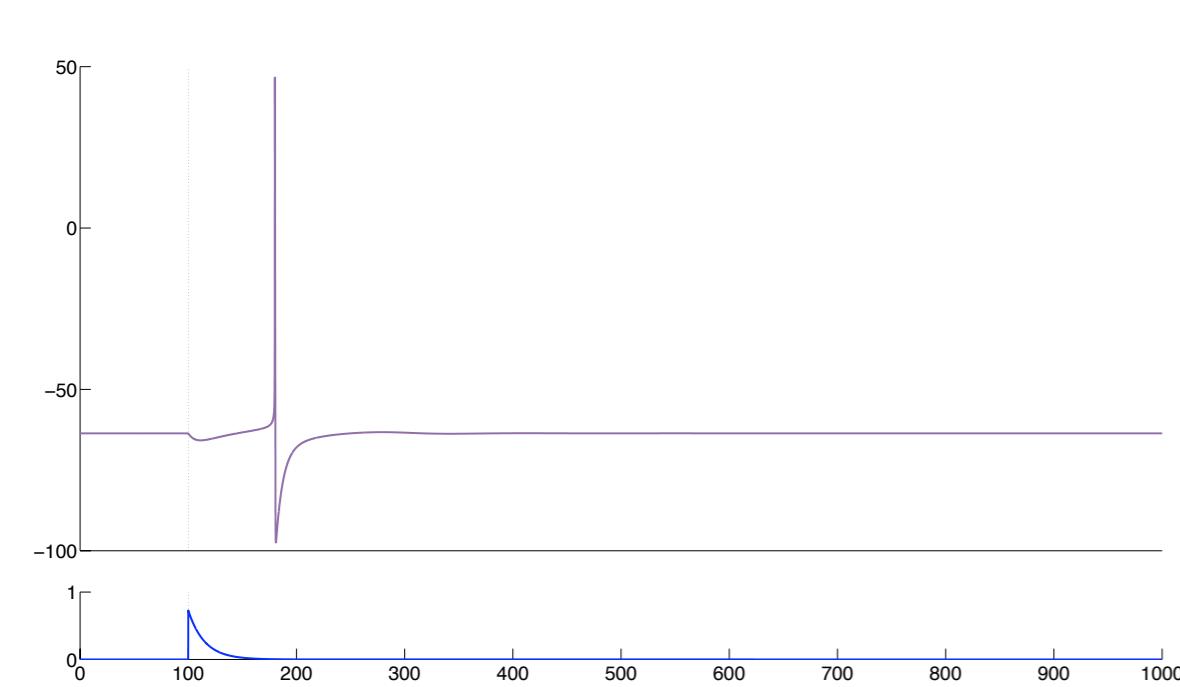
No action potential!
synapse too fast



No action potential!
synapse too fast



Summary: dynamic changes and canards



- A canard reflects the dynamic nature of this GABAergic synapse.
- A canard forms an excitation separatrix on the subthreshold manifold.
- A canard is a generic object in slow-fast system with 2 (or more) slow variables.

Canards and MMOs in biophysical models

- Hodgkin-Huxley model (squid giant axon)
(Rubin, Wechselberger, Biol. Cybern. 2007; Chaos 2008)
- Self-coupled FitzHugh-Nagumo model
(Wechselberger, SIAM J. Appl. Dyn. Syst. 2005)
- Stellate cell model (entorhinal cortex): Acker et al.
(Rotstein, Wechselberger, Kopell, SIAM J. Appl. Dyn. Syst. 2008)
(Wechselberger, Weckesser, Physica D 2009; DCDS-S 2009)
- Interneuron model (incl. network properties): Erisir
(Ermentrout, Wechselberger; SIAM J. Appl. Dyn. Syst. 2009)
- Intracellular calcium models: Atri, Politi-Hoefer, Dupont
(Harvey, Kirk, Osinga, Sneyd, Wechselberger; Chaos 2010)
- Pituitary lactotroph model:
(Vo, Bertram, Tabak, Wechselberger, J. Comp. Neurosci. 2010, DCDS-A 2012)
(Teka, Vo, Wechselberger, Bertram, J. Math. Neurosci. 2012)
- MMO review:
(Desroches, Guckenheimer, Krauskopf, Kuehn, Osinga, Wechselberger; SIAM Review 2012)