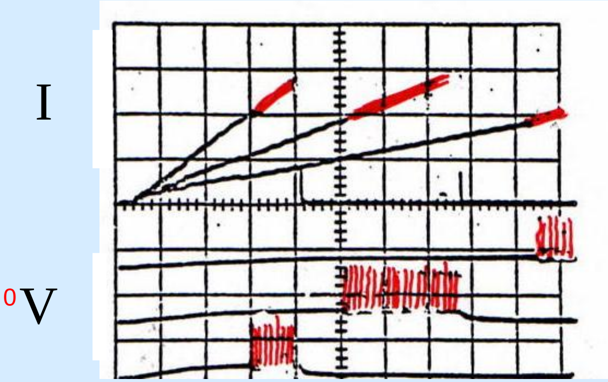
New Insights into Dynamic Bifurcation Problems with Application to Neuronal and Chemical Systems



Steven M. Baer (baer@math.la.asu.edu)
School of Mathematical and Statistical Sciences
Arizona State University, Tempe, AZ 85287

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The origin of the Slow Passage or Ramp Problem:

"Excitation is a function not only of unit intensity but also of its rate of development (dc/dt); the more rapid the change the greater the excitant effect."

— Du Bois-Reymond (1849)

In 1908 Nernst named this property of excitable tissues "accommodation."

Membrane Accommodation

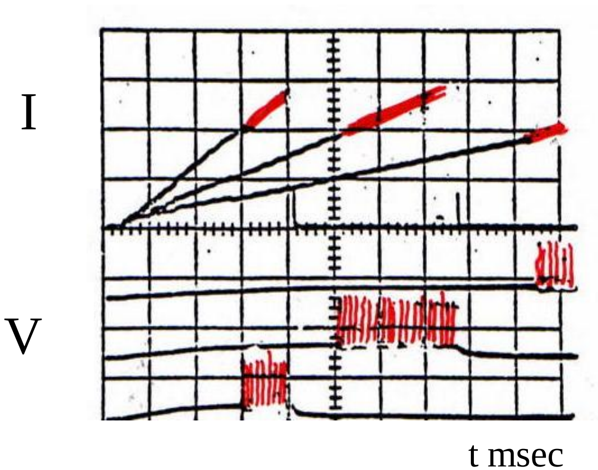
Hodgkin-Huxley (1952): Believed that their model and axons accommodated to slowly rising current and that a minimum slope existed (no calculations).

Na^+ channels are inactivating and the K^+ channels are opening while the membrane is slowly depolarized; threshold rises and stays ahead of the applied current.

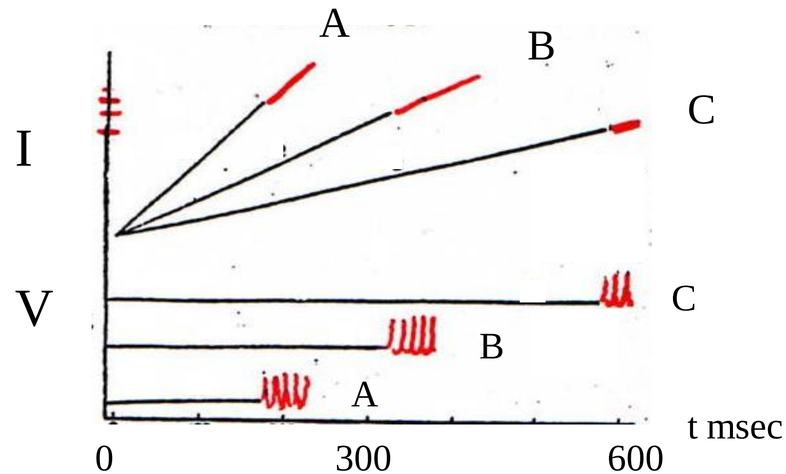
Vallbo (1964): Showed that excitable membranes exhibit accommodation and have minimum slopes.

Jakobsson and Guttman (1980): Propose a counterexample showing, experimentally and theoretically for space-clamped membrane, that accommodation reverses for very slow stimulus ramps.

Accommodation Experiments: Jakobsson & Guttman, Biophys. J., 1980

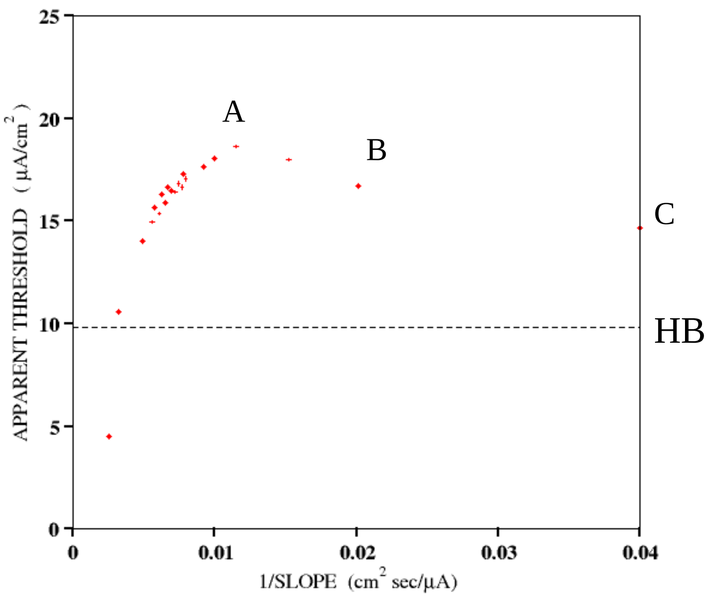


Experiment



Theory (HH eqns.)

Reverse Accommodation ?



Hodgkin-Huxley equations

$$C_m \frac{dV}{dt} = -\bar{g}_{Na} m^3 h\,(V - V_{Na}) - \bar{g}_K n^4\,(V - V_K) - g_L\,(V - V_L) + I_{APP}$$

$$\tau_m(V)\frac{dm}{dt} = \phi(V)\,(m - m_\infty(V))$$

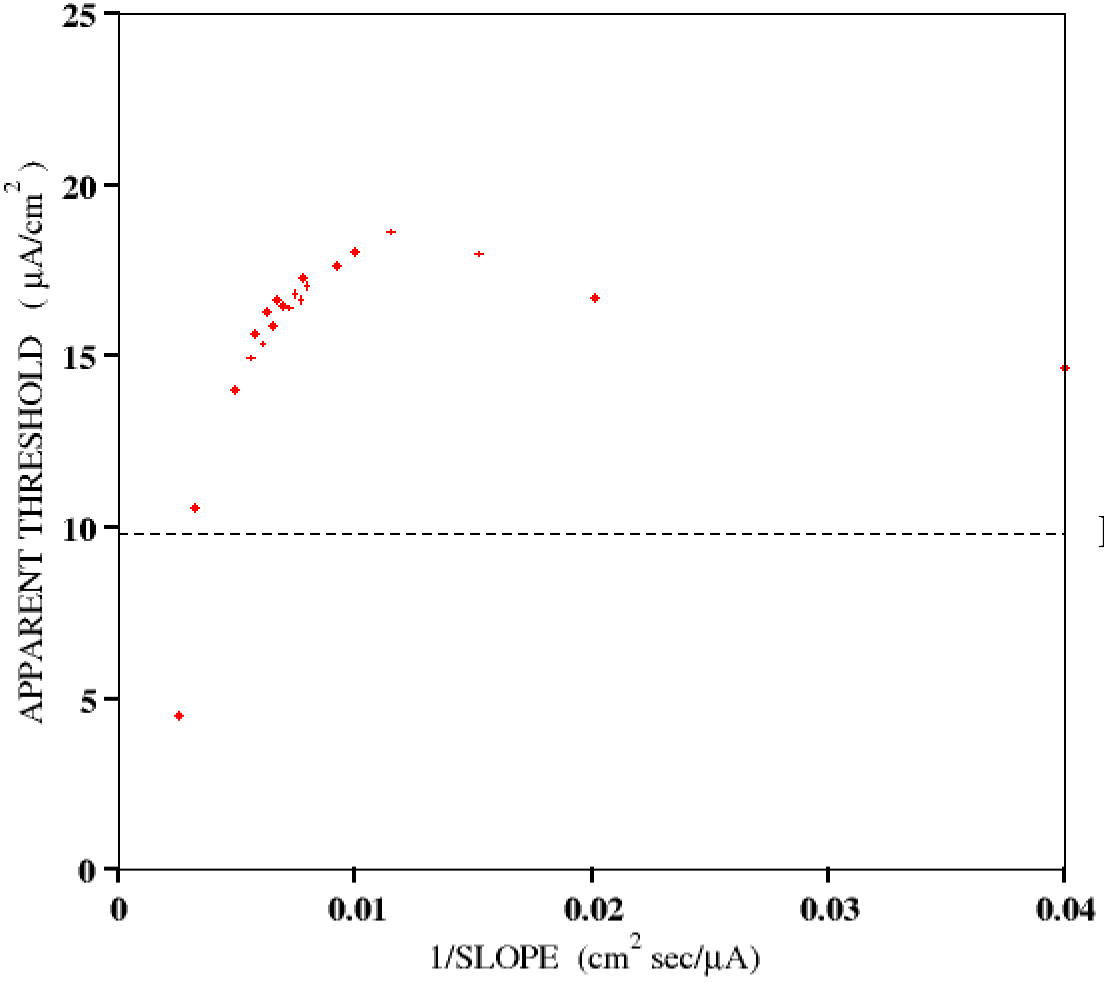
$$\tau_h(V)\frac{dh}{dt} = \phi(V)\,(h - h_\infty(V))$$

$$\tau_n(V)\frac{dn}{dt} = \phi(V)\,(n - n_\infty(V))$$

Rinzel and Baer, 1988

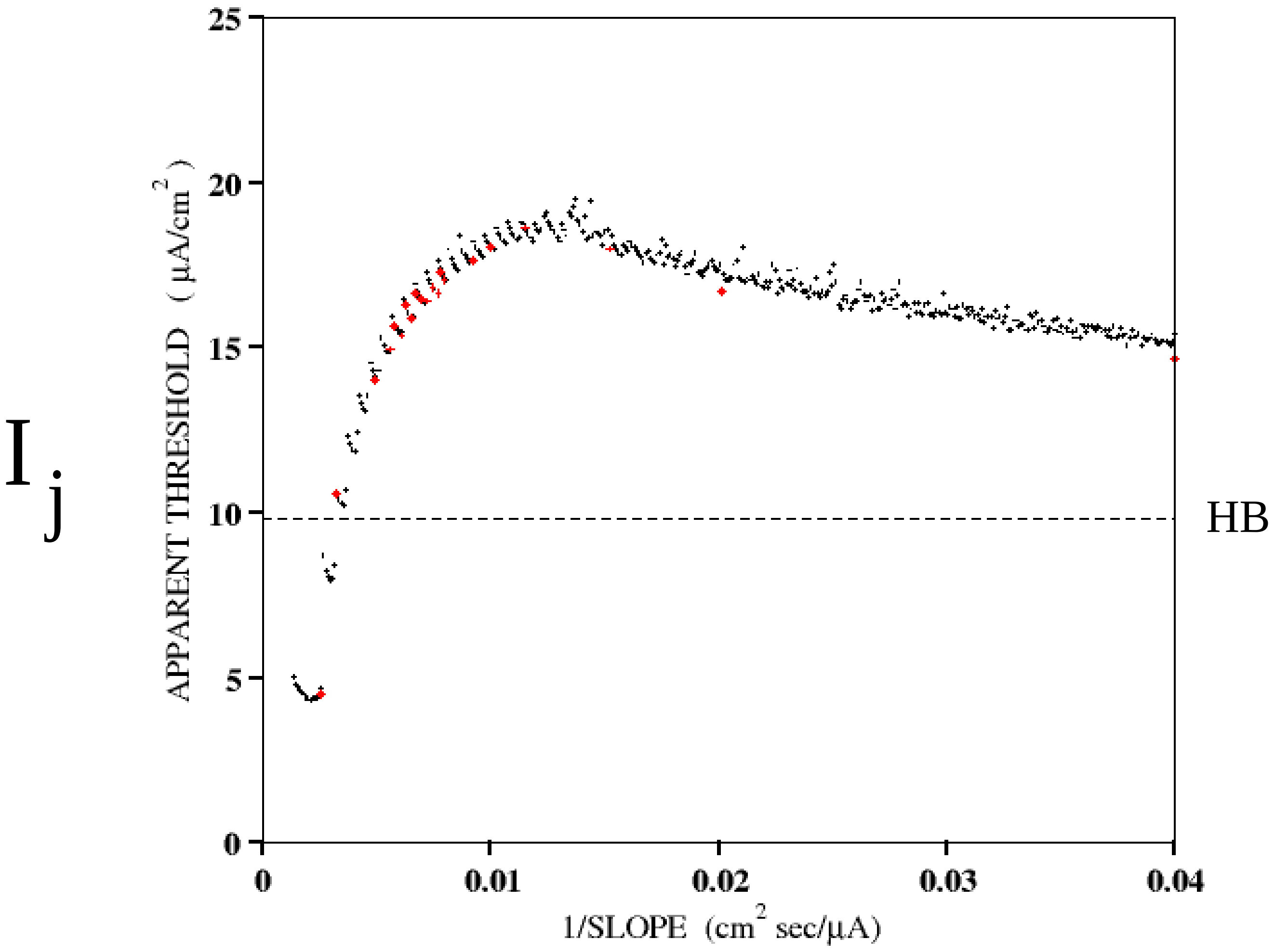
$$I_j = I_0 + \varepsilon\,(N_S T_S)$$

I_j

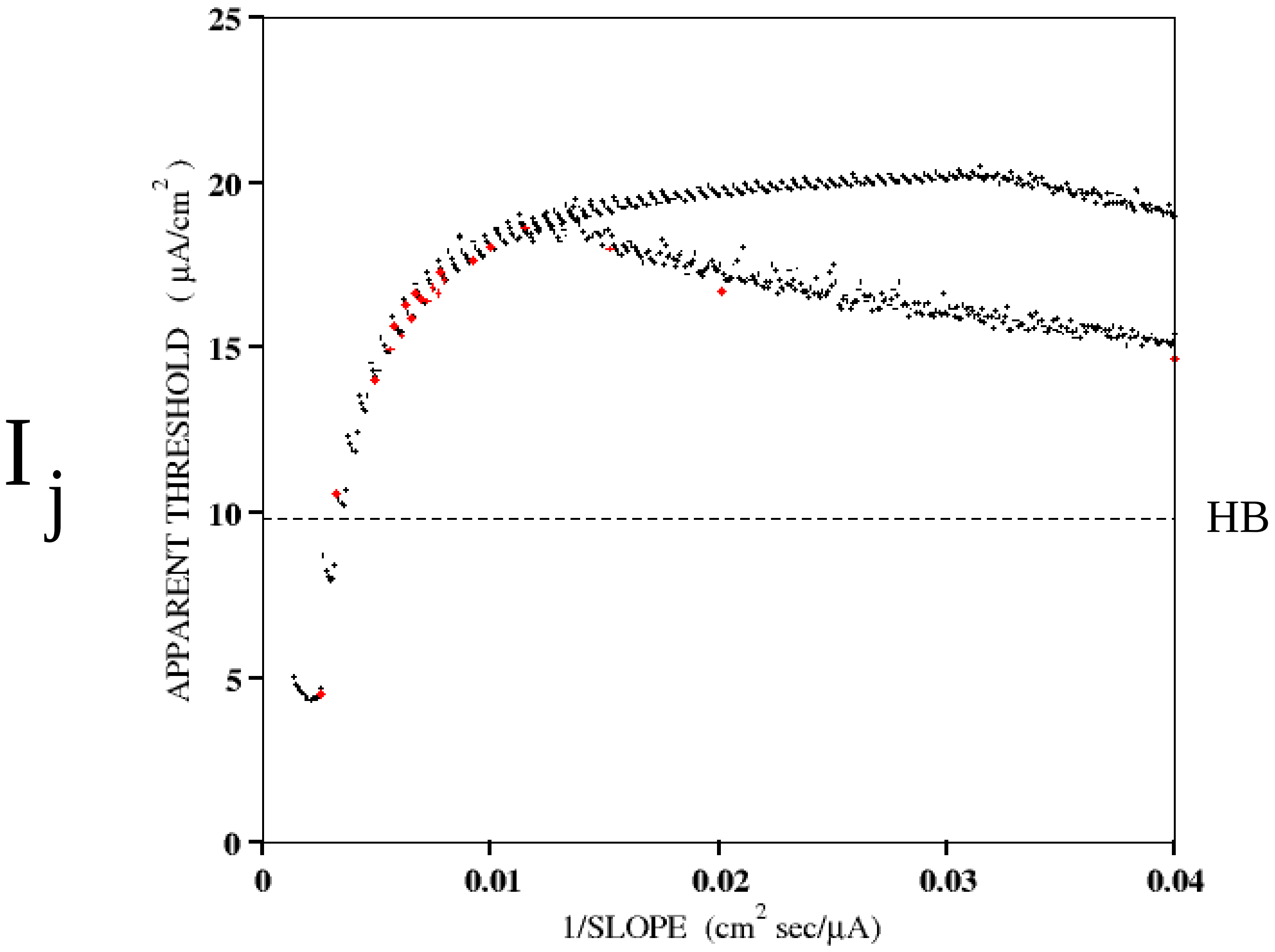


HB

Rinzel and Baer, 1988



Rinzel and Baer, 1988

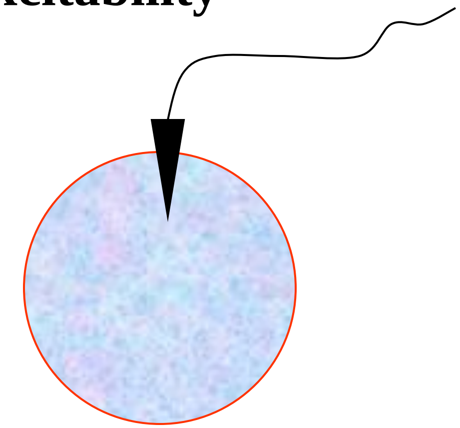


FitzHugh-Nagumo model of nerve membrane excitability

$$\frac{dv}{dt} = -f(v) - w + I,$$

$$\frac{dw}{dt} = b(v - \gamma w), \quad b << 1$$

where $f(v) = v(v-a)(v-1)$.



If $I = I_S$ is constant, the steady-state I-V relation is

$$I_S = f(v_S) + v_S / \gamma$$

Linearize about the steady-state solution (v_S, w_S) and

obtain the eigenvalue equation:

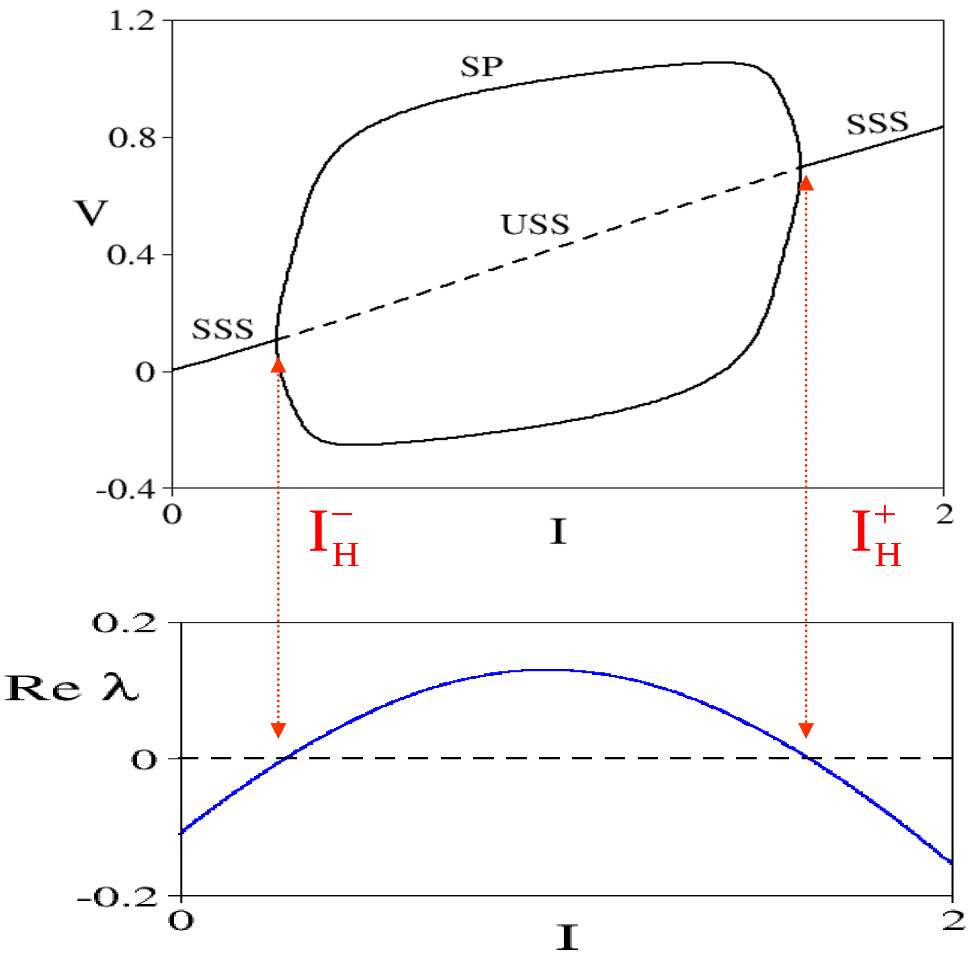
$$\begin{vmatrix} -f'(v_S) - \lambda & -1 \\ b & -b\gamma - \lambda \end{vmatrix} = 0, \quad \text{or} \quad \lambda^2 + A\lambda + B = 0$$

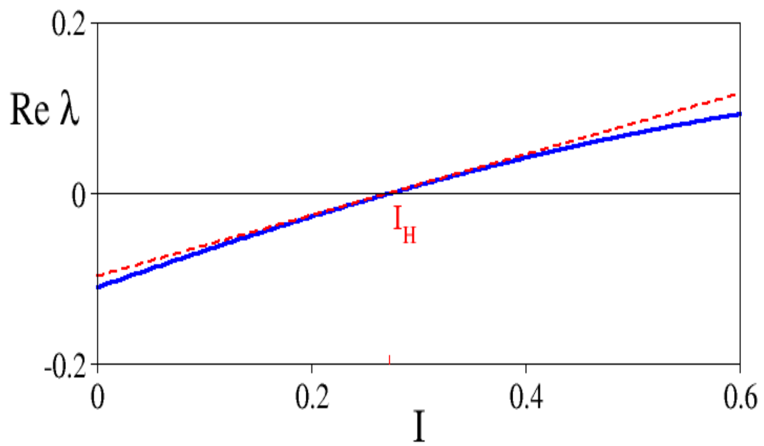
$$\begin{cases} A = f'(v_S) + b\gamma \\ B = b[1 + \gamma f'(v_S)] \end{cases}$$

There are two Hopf bifurcation points $I_H^{\pm}$ if $b\gamma < (a^2 + 1 - a)/3$.

They are found by setting $A = \mathrm{Re}\,\lambda = 0$.

Example: Supercritical bifurcation to periodic solutions:



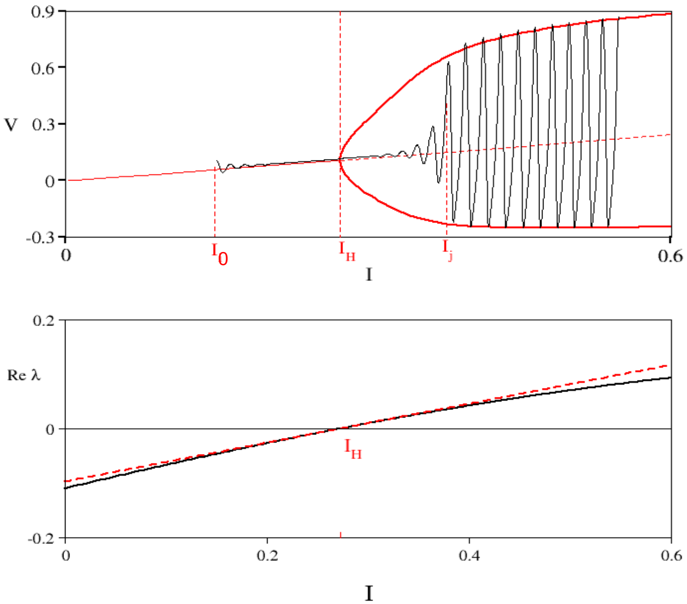


$$\mathrm{Re}\,\lambda \;\cong\; \bar{\lambda}' \;(\mathrm{I} - \mathrm{I_H})$$

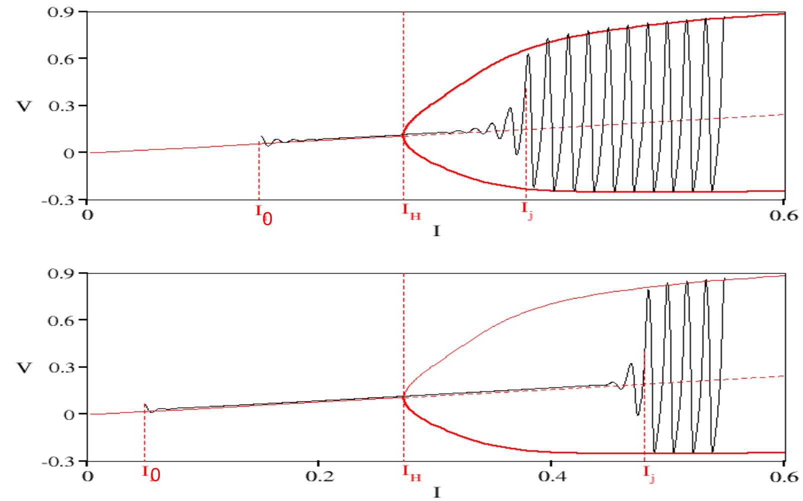
Slow passage problem

$$\frac{dv}{dt} = -f(v) - w + I,$$
$$\frac{dw}{dt} = b(v - \gamma w), \quad b << 1$$

Linear ramp: $I = I_0 + \varepsilon t$



The memory effect



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Baer, Erneux & Rinzel, The slow passage through a Hopf bifurcation: Delay, memory effects, and resonance. *SIAM J. Appl. Math*, 1989.

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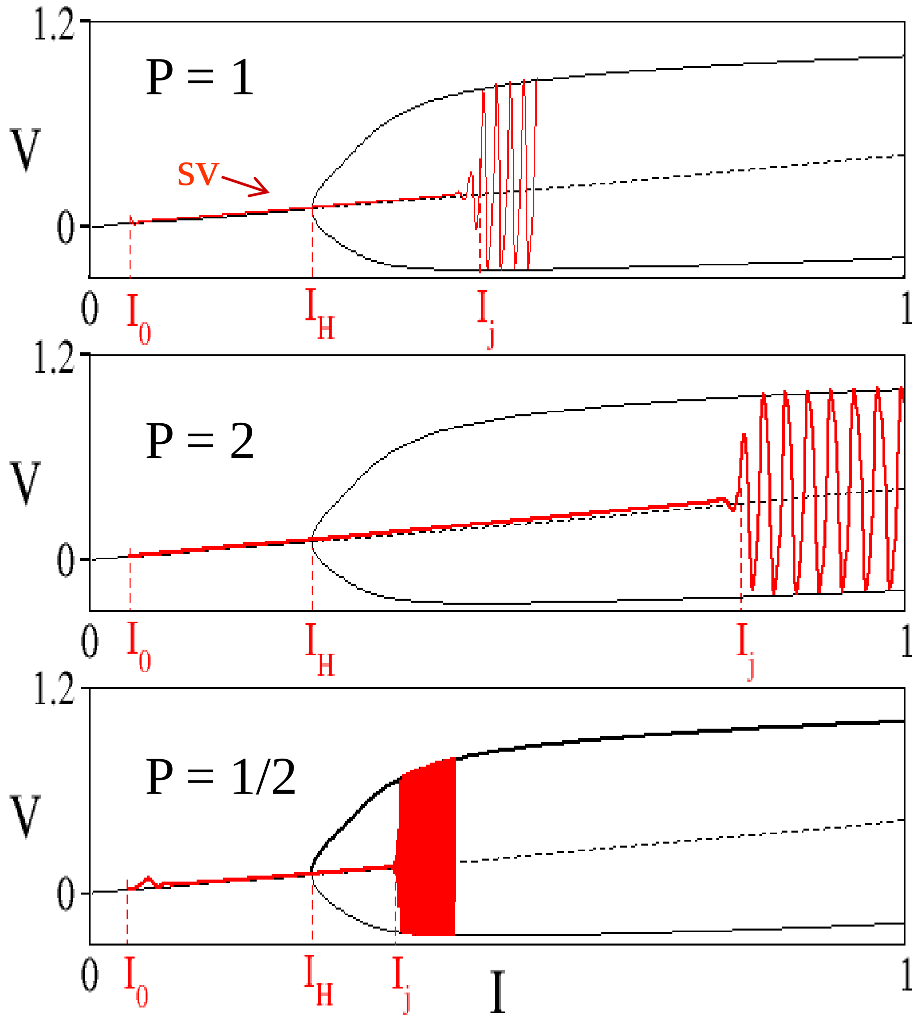
Power Ramps: $I = I_0 + (\varepsilon t)^P$, $P > 0$

$$\frac{dv}{dt} = -f(v) - w + I,$$
$$\frac{dw}{dt} = b(v - \gamma w), \quad b << 1$$



$I = I_0 + \varepsilon t$

$I_j - I_H = I_H - I_0$

$I = I_0 + (\varepsilon t)^2$

$I_j - I_H = 2\,(I_H - I_0)$

$I = I_0 + (\varepsilon t)^{1/2}$

$I_j - I_H = 1/2\,(I_H - I_0)$

Simulations suggest : $(I_j - I_H) = P\,(I_H - I_0)$, for $\varepsilon << 1$.

General nonlinear ramps

Baer & Gaekel, Physical Review E (2008)

Consider the general nth order system: $\frac{d\mathbf{x}}{dt} = \mathbf{f}\left(\mathbf{x}, I(\varepsilon t)\right), \quad (1)$

for $I = I_0 + g(\varepsilon t)$ and $\varepsilon \ll 1.$

Assume $g(0) = 0$, and $g(\varepsilon t)$ is a monotonic increasing or decreasing function.

(i) If $I = I_s$ constant, assume **(1)** has steady-state solution $\mathbf{x}_s$ given by $\mathbf{f}(\mathbf{x}_s, I) = \mathbf{0}$.

Linearize about the steady-state solution $\mathbf{x}_s$, yielding

$\frac{d\mathbf{x}}{dt} = \mathbf{J}\mathbf{x}$, where $\mathbf{J}$ is the $n \times n$ Jacobian matrix

$$\mathbf{J} = \begin{pmatrix} \partial f_1/\partial x_1 & \cdots & \partial f_1/\partial x_n \\ \vdots & \ddots & \vdots \\ \partial f_n/\partial x_1 & \cdots & \partial f_n/\partial x_n \end{pmatrix}, \quad \text{evaluated at } \mathbf{x} = \mathbf{x}_s.$$

The eigenvalues λ are found by solving $\det(\mathbf{J} - \lambda\mathbf{I}) = 0.$

Hopf point

$I = I_H$

We assume that a single pair of eigenvalues cross the imaginary axis to change the stability of the steady state, and that at criticality these eigenvalues satisfy $\operatorname{Im}\lambda \neq 0$ and the transversality condition $d\operatorname{Re}\lambda/dI \neq 0$ when $\operatorname{Re}\lambda = 0$.

(ii) If I is dynamic: $I = I_0 + g(\varepsilon t)$ and $\varepsilon \ll 1$.

There is a slowly varying solution $\mathbf{x}_{sv}$ near the static steady-state solution as I slowly changes (increases or decreases) :

$\mathbf{x}_{sv}(\tau) \sim \mathbf{x}_s(I(\tau)) + \varepsilon \mathbf{x}_1(\tau) + \cdots$ Slowly varying "steady - state"

where $\tau = g(u)$ for $u = \varepsilon t$,

and $\mathbf{x}_s(I(\tau))$ satisfies the static steady-state relation $\mathbf{f}(\mathbf{x}_s(I(\tau)), I(\tau)) = \mathbf{0}$.

To linearize (1) about $\mathbf{x}_{sv}$, first let $\mathbf{x}(t;\varepsilon) = \mathbf{x}_{sv}(\tau) + \mathbf{Z}(t,\varepsilon)$.

Substitute into (1), and for $\varepsilon \ll 1$, the slowly varying linear system is

$$\frac{d\mathbf{Z}}{dt} = \mathbf{J}\mathbf{Z},$$

This equation has the same form as the static case . The Jacobian matrix is identical and evaluated at $\mathbf{x}_s$, however, $\mathbf{x}_s = \mathbf{x}_s(I(\tau))$ is now slowly varying !

$\Longrightarrow$ J slowly varying $\Longrightarrow$ WKB

Stability of the slowly varying solution

Let I_j denote the current for which this linear system becomes unstable and the solution exhibits fast exponential growth.

Consider the WKB (Wentzel-Kramers-Brillouin) expansion

$$\mathbf{Z}(\mathbf{t},\boldsymbol{\varepsilon}) \sim \mathbf{e}^{\frac{\boldsymbol{\sigma}(\boldsymbol{\tau})}{\boldsymbol{\varepsilon}}} \left[\mathbf{Z}_0(\tau) + \boldsymbol{\varepsilon}\, \mathbf{Z}_1(\tau) + \cdots \right] \text{ as } \varepsilon \to 0.$$

This expansion exhibits rapid exponential growth when $\mathrm{Re}\ \sigma \geq O(\varepsilon)$. That is,

to approximate I_j set

$$\boxed{\mathrm{Re}\ \sigma = 0.}$$

To find Re σ, substitute the WKB expansion into the linearized system. The resulting leading order algebraic problem has nontrivial solutions iff

$$\det\left(\mathbf{J} - \frac{\sigma'(\tau)}{(\mathrm{g}^{-1}(\tau))'}\,\mathbf{I} \right) = 0.$$

Compare to the static eigenvalue problem:

$$\det(\mathbf{J} - \lambda\, \mathbf{I}) = 0$$

$$\therefore \quad \frac{\sigma'(\tau)}{(\mathrm{g}^{-1}(\tau))'} = \lambda(I(\tau)) \Rightarrow$$ The onset occurs when $$\mathrm{Re}\ \sigma(\tau_j) = \int_0^{\tau_j} (\mathrm{g}^{-1}(\tau))' \{\mathrm{Re}\ \lambda(I(\tau))\}\, d\tau = 0$$

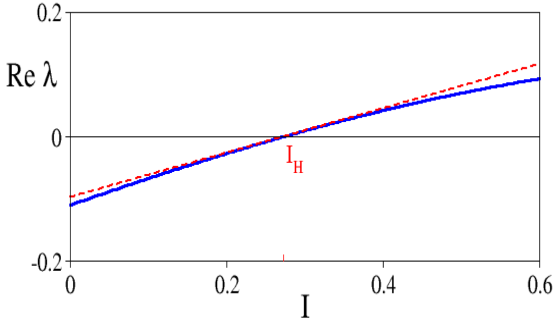
Changing variables $\boldsymbol{I} = \boldsymbol{I}_0 + \boldsymbol{\tau}$:

$$\int_{I_0}^{I_j} (\mathrm{g}^{-1}(I - I_0))' \{\mathrm{Re}\ \lambda(I)\}\, dI = 0.$$

Onset Condition

Example 1: **POWER RAMPS (FHN):** $I = I_0 + (\varepsilon t)^P$, $P > 0$

Recall that for FHN, the Re λ is approximately linear over the range of the ramp. Here



$$\mathrm{Re}\,\lambda \cong \bar{\lambda}'\ (I - I_H), \quad \text{where} \quad \bar{\lambda}' = \frac{d}{dI}\mathrm{Re}\,\lambda \Big|_{I = I_H},$$

and the onset condition simplifies to: $\int_{I_0}^{I_j} (g^{-1}(I - I_0))'\ (I - I_H)\ dI = 0.$

Integrating by parts $\Longrightarrow$

$$(I_j - I_H)\, g^{-1}(I_j - I_0) = \int_{I_0}^{I_j} g^{-1}(I - I_0)\ dI.$$

Here, $\tau = g(u) = u^P$, $u = \varepsilon t$ & $u = g^{-1}(\tau) = \tau^{1/P}$

$$\Rightarrow \quad (I_j - I_H) = P\,(I_H - I_0)$$

Example 2: SATURATING EXPONENTIAL RAMPS:

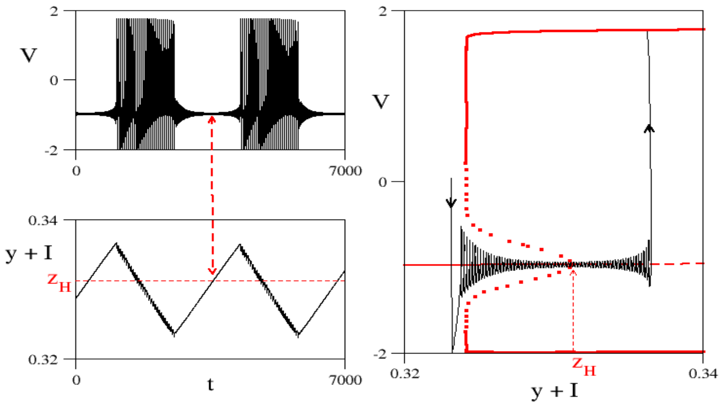
A. Neuronal (elliptic) Bursting *

FitzHugh-Rinzel (FHR) model

$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + y + I$$
$$\frac{dw}{dt} = \phi\,(v + a - b\,w)$$
Fast subsystem

$$\frac{dy}{dt} = \varepsilon(-v + c - d\,y)$$
Slow equation

Elliptic bursting was first identified in rodent trigeminal neurons controlling jaw movements (Del Negro et al, 1998).



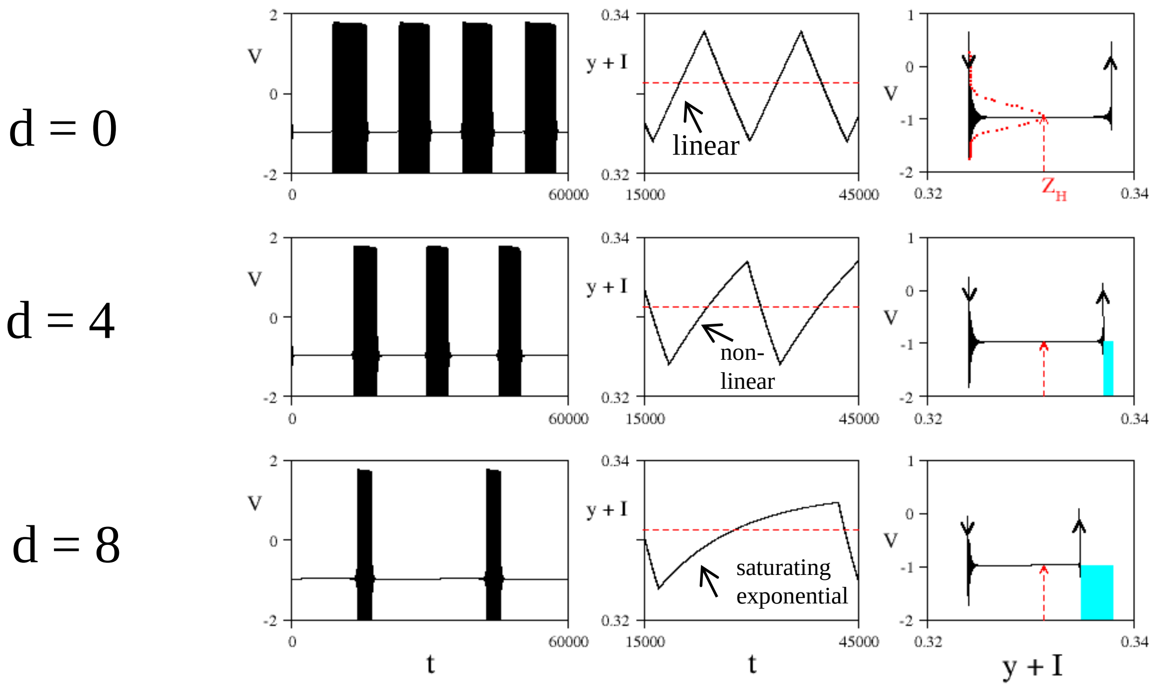
$$Z_H = y_H + I$$

(a) **Small oscillations grow in amplitude on approach to the active phase, while decaying in amplitude upon re-entering the silent phase.**

(b) **Projection of the burst in the slow-fast variable phase plane. Superimposed is a bifurcation diagram of the fast subsystem, for static values of the slow variable.**

* **This kind of bursting was first identified by Rinzel and Troy (1982) and first classified by Rinzel in 1987.**

Nonlinear ramping influences burst pattern



Observations:

1. Independent of *d*, the initial values $y_0 + I$ for each silent phase are approximately equal.
2. During the silent phase, V is approximately constant, and its value $\bar{V}$ is independent of d.

Therefore the slow subsystem, during the silent phase, can be modeled by the following initial value problem :

$$\frac{dy}{dt} = \varepsilon(-\bar{v} + c - d\, y), \quad y(0) = y_0$$

Silent phase duration T

Our observations suggest that the silent phase dynamics is determined by the fast subsystem forced by the solution to the initial value problem for y; that is,

$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + y + I$$

$$\frac{dw}{dt} = \phi(v + a - bw)$$

where

$$y = y_0 + (y_m - y_0)(1 - e^{-(\varepsilon d)t}), \qquad y_m = \frac{c - \bar{v}}{d}. \qquad (1)$$

Let $\tau = g(u) = (y_m - y_0)(1 - e^{-u}), \quad u = (\varepsilon d)t,$

$$\Rightarrow u = g^{-1}(\tau) = \ln\left(\frac{y_m - y_0}{y_m - y_0 - \tau}\right)$$

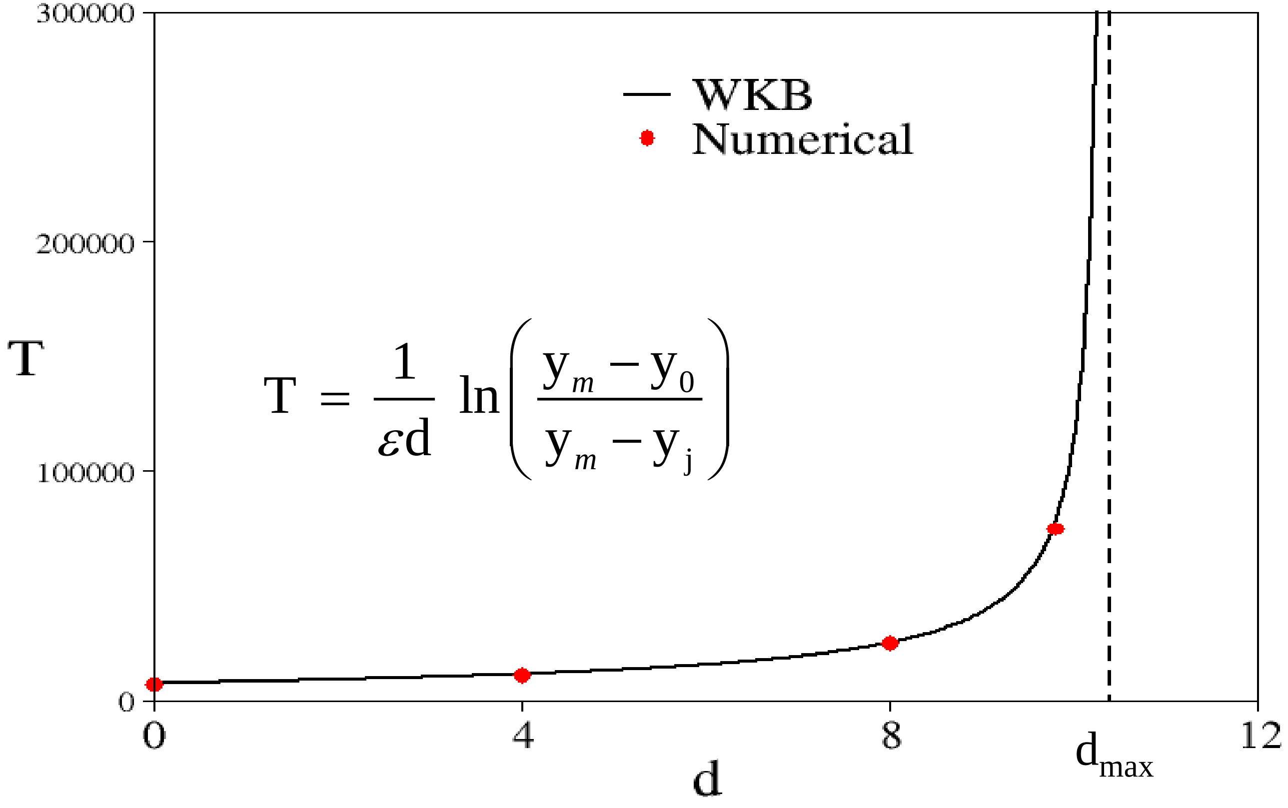
Assuming $\mathrm{Re}\,\lambda \cong \bar{\lambda}'\,(y - y_H)$ the onset condition reduces to

$$y_j - y_H = (y_m - y_H) - (y_m - y_0)\, e^{-\left(\frac{y_j - y_0}{y_m - y_H}\right)}$$

Find y_j by iteration, substitute for y in (1), and then solve for T:

$$T = \frac{1}{\varepsilon d} \ln\left(\frac{y_m - y_0}{y_m - y_j}\right)$$

Analytic vs numerical estimate of silent phase duration T



$$T = \frac{1}{\varepsilon d} \ln\left(\frac{y_m - y_0}{y_m - y_j}\right)$$

B. Target nucleation: Formation of pacemakers in the unstirred BZ reaction*

The Belousov-Zhabotinsky (BZ) reaction is the prototype oscillatory chemical system. During the induction period the medium appears red with outward concentric waves of blue. After the induction period , pacemaker sites oscillate between blue (high ferriin) and red (low ferriin).

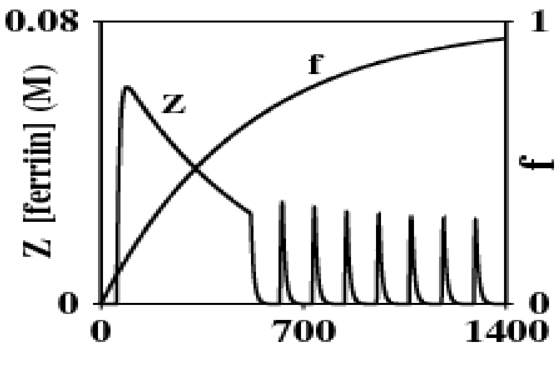
$$\frac{dx}{dt} = k_3[\mathrm{BrO_3^-}][\mathrm{H^+}]^2\, y - k_2[\mathrm{H^+}]\, xy + k_5[\mathrm{BrO_3^-}][\mathrm{H^+}]\, x - 2k_4 x^2$$

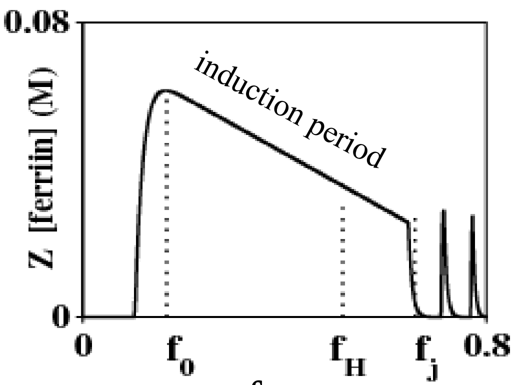
$$\frac{dy}{dt} = -k_3[\mathrm{BrO_3^-}][\mathrm{H^+}]^2\, y - k_2[\mathrm{H^+}]\, xy + \frac{\mathrm{f}(t)}{2} k_c[\mathrm{MA}]_0\, z$$

$$\frac{dz}{dt} = 2k_5[\mathrm{BrO_3^-}][\mathrm{H^+}]\, x - k_c[\mathrm{MA}]_0\, z,$$

where $\mathrm{f}(t) = \mathrm{f}_\infty(1 - e^{-k_f t}), \quad t \ge 0.$ (saturating exponential)

The stoichiometric factor f increases with bromination of malonic acid





***Sobel, Hastings & Field, J. Phys. Chem. A **110,** 5 (2006)

To track the induction period from f_0 to f_j, rewrite f as

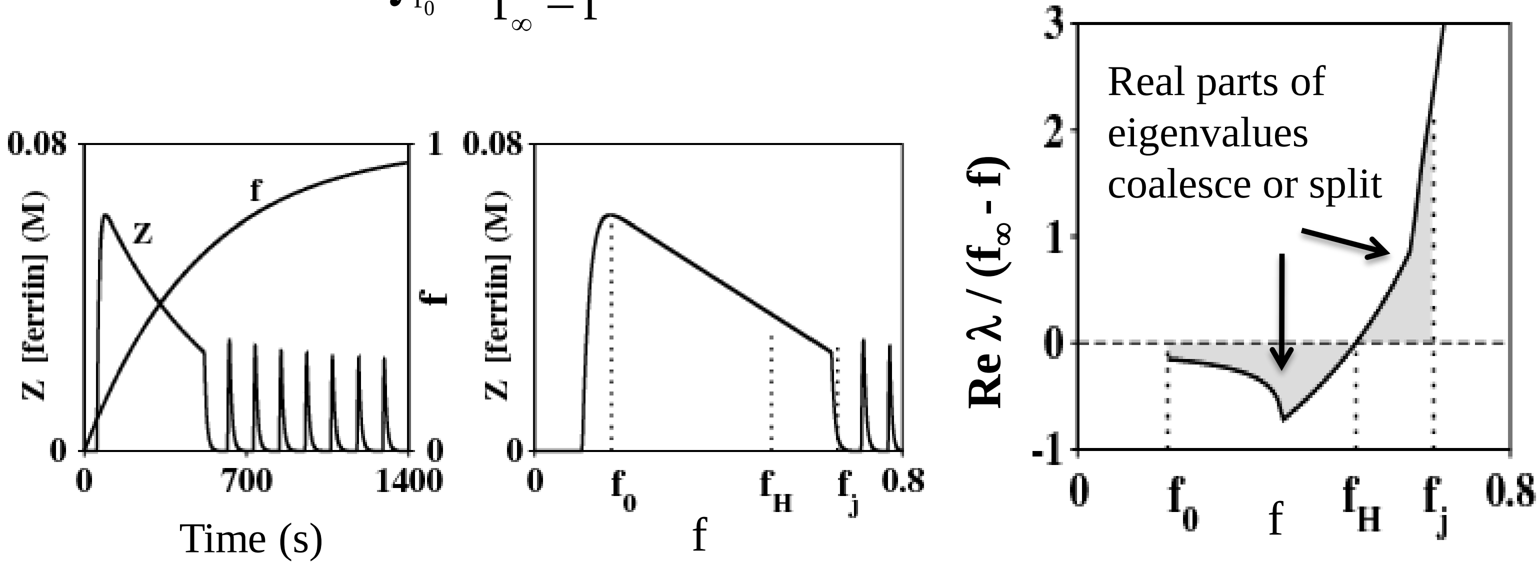
$$f = f_0 + (f_\infty - f_0)(1 - e^{-k_f (t - t_0)}), \quad t \ge t_0.$$

Let $\tau = g(u) = (f_\infty - f_0)(1 - e^{-u}), \quad u = k_f (t - t_0)$

$$\Rightarrow u = g^{-1}(\tau) = \ln\left(\frac{f_\infty - f_0}{f_\infty - f_0 - \tau} \right)$$

Here the onset condition, $\int_{f_0}^{f_j} (g^{-1}(f - f_0))' \{\mathrm{Re}\, \lambda(f)\}\, df = 0,$

reduces to $\int_{f_0}^{f_j} \frac{\{\mathrm{Re}\, \lambda(f)\}}{f_\infty - f}\, df = 0.$



Ongoing Research and Open Problem Areas

1. Apply the WKB analysis to ramping in reaction diffusion equations such as Hodgkin-Huxley cables and passive dendrites with excitable spines (ongoing with Ph.D. student Lydia Bilinsky).

   Computational challenges: Hundreds of eigenvalues need to be followed and numerical error associated with the slow ramp is compounded for these problems.

2. Generalize the slow passage problem to include slow non-monotonic ramps.

3. Extend the stochastic analysis of Kuske (1999, 2000) and Kuske and Baer (2002) to monotonic nonlinear ramps.

4. Extend the analysis of Holden and Erneux (1993) for slow passage from oscillatory to steady-state solutions for nonlinear ramps

5. Extend the analysis to other applications in chemistry, biology, engineering, and physics; to any system where a parameter (applied or natural) passes slowly through a Hopf bifurcation.