The boundary of stability in nerve impulse equations

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Outline

Nerve impulse
- Hodgkin-Huxley type
- Equilibria in HH

Steady-state bifurcation in HH
- Sketch proof

Boundary of stability
- New parameters
- Old parameters

Slow manifold

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Models for nerve impulse

Ingredients:

- Difference $x \in \mathbf{R}$ of electrical potential across a nerve cell membrane (voltage) — travels along cell.
- Active transport of ions across cell's membrane through N ionic channels creates voltage.
- Channel dynamics controlled by M independent gates that open with probabilities y_i, $i = 1, \ldots, M$.

First model: Hodgkin-Huxley (1952)
$N = 2$ channels controlled by $M = 3$ gates.

Hodgkin-Huxley type: model for nerve impulse

$$\begin{cases} C_m \dfrac{\partial x}{\partial t} = a \dfrac{\partial^2 x}{\partial s^2} - I - c_0(x - V_0) - \displaystyle\sum_{j=1}^{N} c_j u_j(y)(x - V_j) \\ \\ \dfrac{\partial y_i}{\partial t} = (\gamma_i(x) - y_i)\, \tau_i(x)\ , \qquad i = 1, \dots, M \end{cases}$$

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Variables

$s \in \mathbf{R}$ distance along axon

$t \in \mathbf{R}$ time

$x \in \mathbf{R}$ voltage, observed directly

$y_i \in [0, 1]$ probabilities of gates opening

$y = (y_1, \dots, y_M)$.

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Parameters

$I \in \mathbf{R}$ stimulus intensity

$c_j > 0$ gate strength

$V_j \in \mathbf{R}$ equilibrium voltage for ion j.

Constants

$C_m \geq 0$ membrane capacity

$a \geq 0$ half the axon radius divided by electrical resistance

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Functions fitted to experimental data

$u_j(y)$ usually a monomial

$\gamma_i : \mathbf{R} \longrightarrow [0,1]$ usually monotonic $\gamma(x) = (\gamma_1, \ldots, \gamma_M)$

$\tau_i : \mathbf{R} \longrightarrow [0,1]$ usually nonzero $\tau(x) = (\tau_1, \ldots, \tau_M)$

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Special conditions

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Special conditions

Voltage clamp

$a = 0$, first equation becomes:

$$C_m \frac{\partial x}{\partial t} = -I - c_0(x - V_0) - \sum_{j=1}^{N} c_j u_j(y)(x - V_j)$$

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Special conditions

Travelling wave

$x(t,s) = X(\hat{t})$ $\qquad y_i(t,s) = Y_i(\hat{t})$ $\qquad \hat{t} = \theta t + \sigma s$

propagates forward if $\theta\sigma < 0$

Hodgkin-Huxley type: model for nerve impulse

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Special conditions

Travelling wave first equation equivalent to:

$$\begin{cases} \dfrac{\partial x}{\partial \hat{t}} = -z \\[2ex] a\sigma^2 \dfrac{\partial z}{\partial \hat{t}} = C_m \theta z - I - c_0(x - V_0) - \displaystyle\sum_{j=1}^{N} c_j u_j(y)(x - V_j) \end{cases}$$

Hodgkin-Huxley type: model for nerve impulse

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Special conditions

Travelling wave   other equations become:

$$\theta \frac{\partial y_i}{\partial t} = (\gamma_i(x) - y_i)\,\tau_i(x)$$

Equilibria for Hodgkin-Huxley type — clamped

$$\begin{cases} C_m \dfrac{\partial x}{\partial t} = -I - c_0(x - V_0) - \displaystyle\sum_{j=1}^{N} c_j u_j(y)(x - V_j) \\ \dfrac{\partial y_i}{\partial t} = (\gamma_i(x) - y_i)\,\tau_i(x)\,, \qquad i = 1, \ldots, M \end{cases}$$

equilibria

$y_i = \gamma_i(x)$

$$0 = -I - c_0(x - V_0) - \textstyle\sum_{j=1}^{N} c_j u_j(\gamma(x))(x - V_j) =$$
$$= \eta(x, I, c, V)$$

Equilibria for Hodgkin-Huxley type — travelling wave

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$z = 0$

$y_i = \gamma_i(x)$

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Equilibria for Hodgkin-Huxley type

Parameters:

$I, \ c_0, c_1, \ldots, c_N, \ V_0, \ldots, V_N$ in $\mathbf{R}^{2N+3} = \{(I, c, V)\}$.

Equilibrium at $x = \mu$ if $\eta(\mu, I, c, V) = 0$

Fold point at $x = \mu$ if, moreover, $\dfrac{\partial \eta}{\partial \mu}(\mu, I, c, V) = 0$

Cusp point at $x = \mu$ if, in addition, $\dfrac{\partial^2 \eta}{\partial \mu^2}(\mu, I, c, V) = 0$

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Local singular sets:

Subsets of parameter space $\mathbf{R}^{2N+3}$ where:

E_0 equilibrium exists.

F_1 equilibrium is a fold point.

F_2 equilibrium is a cusp point.

$\vdots$

Equilibria for Hodgkin-Huxley type

Equilibrium at $x = \mu$ if $\eta(\mu, I, c, V) = 0$

$$\eta(\mu, I, c, V) = -I - c_0(\mu - V_0) - \sum_{j=1}^{N} c_j u_j(\gamma(\mu))(\mu - V_j)$$

$E_0 \in \mathbf{R}^{2N+3}$ parameters where equilibrium exists,

Lemma

Under the standard hypotheses on $u_j(\mu)$ and $\gamma(y)$

$$E_0 = \mathbf{R}^{2N+3}.$$

Theorem (L. & Ruas)

For an equation of Hodgkin-Huxley type with N channels, and for generic functions $\psi_j(\mu) = u_j(\gamma(\mu))$ the local singular sets in $\mathbf{R}^{2N+3}$ satisfy:

- $\overline{F_1}$ *is a singular hypersurface with singularities at* F_2*;*
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with two local descriptions:

- *near a point where some* $c_i = 0$*,*
  $\overline{F_j}$ *meets the subspace* $\{c_i = 0\}$ *transversselly at the singular set for a HH equation with* $N - 1$ *channels;*

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- *near a point where some* $c_i = 0$,
  $\overline{F_j}$ *meets the subspace* $\{c_i = 0\}$ *transversely at the singular set for a HH equation with* $N - 1$ *channels;*
- *near points* (I, c, V) *with all* $c_j \neq 0$,
  $\overline{F_j}$ *is a ruled manifold with rulings of the form* $(\lambda I, \lambda c, V) \in \mathbf{R}^{2N+3}$.

Equilibria for Hodgkin-Huxley type

Equilibrium at $x = \mu$ if $\eta(\mu, I, c, V) = 0$

$$\eta(\mu, I, c, V) = -I - c_0(\mu - V_0) - \sum_{j=1}^{N} c_j u_j(\gamma(\mu))(\mu - V_j)$$

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New parameters $W_j = c_j V_j$ Notation: $\psi_j(\mu) = u_j(\gamma(\mu))$

Rewrite $\eta = 0$ as

$$I + \mu c_0 + \sum_{j=1}^{N} \mu \psi_j(\mu) c_j - W_0 - \sum_{j=1}^{N} \psi_j(\mu) W_j = 0$$

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then for parameters (I, c, W)

$$E_0(\mu) = (1, \mu, \mu\psi_1(\mu), \ldots, \mu\psi_N(\mu), \psi_1(\mu), \ldots, \psi_N(\mu))^{\perp}$$

Equilibria for Hodgkin-Huxley type

Equilibrium at $x = \mu$ if (I, c, W) lies in $E_0(\mu) = \mathbf{v}_0(\mu)^\perp$

$$\mathbf{v}_0(\mu) = (1, \mu, \mu\psi_1(\mu), \ldots, \mu\psi_N(\mu), \psi_1(\mu), \ldots, \psi_N(\mu))$$

$E_0 = \cup_\mu E_0(\mu) \subset \mathbf{R}^{2N+3}$ ruled manifold with codimension 1 rulings.

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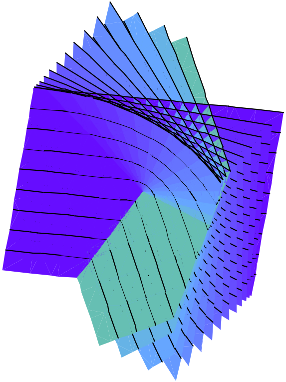

2-d rulings
sweep open subset of $\mathbf{R}^3$

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This proves — recall $\psi_j(\mu) = u_j(\gamma(\mu))$:

Lemma

Under the standard hypotheses on $u_j(\mu)$ and $\gamma(y)$

$$E_0 = \mathbf{R}^{2N+3}.$$

Sketch proof of the Theorem

- $E_0(\mu) \in \mathbf{R}^{2N+3}$ parameters where $x = \mu$ is equilibrium.
  $F_1(\mu) \subset E_0(\mu)$ μ is a fold point.
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- Parameters $(I, c, W) \qquad W_j = c_j V_j$.
- $E_0(\mu) = \{(I, c, W) \quad \eta(\mu, I, c, V) = 0\}$

$$\overline{F_1(\mu)} = \{(I, c, W) \quad \eta = 0, \quad \frac{\partial \eta}{\partial \mu} = 0\}$$

$$\overline{F_2(\mu)} = \{(I, c, W) \quad \eta = 0 \quad \frac{\partial \eta}{\partial \mu} = 0 \quad \frac{\partial^2 \eta}{\partial \mu^2} = 0\}$$

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- $E_0(\mu) = \{(I, c, W) \quad \eta(\mu, I, c, V) = 0\}$
  $= \langle \mathbf{v}_0(\mu) \rangle^\perp$

  $$\overline{F_1(\mu)} = \{(I, c, W) \quad \eta = 0, \quad \frac{\partial \eta}{\partial \mu} = 0\}$$

  $$= \langle \mathbf{v}_0(\mu), \frac{d\mathbf{v}_0}{d\mu} \rangle^\perp$$

  $$\overline{F_2(\mu)} = \{(I, c, W) \quad \eta = 0 \quad \frac{\partial \eta}{\partial \mu} = 0 \quad \frac{\partial^2 \eta}{\partial \mu^2} = 0\}$$

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  $\overline{F_2(\mu)} = \langle \mathbf{v}_0(\mu), \dfrac{d\mathbf{v}_0}{d\mu}, \dfrac{d^2\mathbf{v}_0}{d\mu^2} \rangle^\perp$
- $\mathbf{v}_0(\mu), \dfrac{d\mathbf{v}_0}{d\mu}, \ldots, \dfrac{d^L\mathbf{v}_0}{d\mu^L}$, $L = 2N + 3$
  are linearly independent
  for $\psi_j(\mu) = u_j(\gamma(\mu))$ in a residual set.

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  are linearly independent
  for $\psi_j(\mu) = u_j(\gamma(\mu))$ in a residual set.
- $\overline{F_j} = \cup_\mu \overline{F_j(\mu)} \subset \mathbf{R}^{2N+3}$ cone-like manifold
  codimension $j + 1$ rulings $\quad$ singularities in $\overline{F_{j+1}}$

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If $c_j \neq 0$ then

$(I, c, W) \mapsto (I, c, V)$

$$(I, c_0, \ldots, c_N, W_0, \ldots, W_N) \mapsto (I, c_0, \ldots, c_N, \frac{W_0}{c_0}, \ldots, \frac{W_N}{c_N})$$

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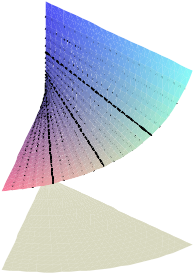
blows up the cone into a ruled manifold.



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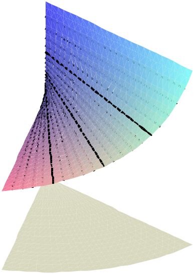

If $c_j = 0$ then $W_j = 0$

Hodgkin-Huxley type without the j-th channel.

Boundary of stability for equilibria

$G(Y, \lambda)$ parametrized family of o.d.e.s in $\mathbf{R}^n$

$$\dot{Y} = G(Y, \lambda) \qquad G(Y_*, \lambda) = 0$$

Stability of Y_* determined by the signs of the real parts of eigenvalues of the linearisation

$$D_Y G(Y_*, \lambda)$$

Boundary of stability $\quad \Sigma \quad$ values of λ where linearisation $D_Y G(Y_*, \lambda)$ has eigenvalues with real part $= 0$.

$\Sigma = E_1 \cup H_1$

$E_1 \quad$ eigenvalue $= 0$

H_1 eigenvalues $= \pm i\sqrt{(B)}$, $B > 0$

Boundary of stability for equilibria

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Stability of Y_* determined by the signs of the real parts of eigenvalues of the linearisation

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Boundary of stability Σ values of λ where linearisation $D_Y G(Y_*,\lambda)$ has eigenvalues with real part $= 0$.

$\Sigma = E_1 \cup H_1$ usually

E_1 eigenvalue $= 0$ folds

H_1 eigenvalues $= \pm i\sqrt{(B)},\ B > 0$ Hopf bifurcations

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Boundary of stability for equilibria

Σ: values of λ where
$p(X)$ characteristic polynomial of $D_Y G(Y_*, \lambda)$
has roots with real part $= 0$.

$\Sigma = E_1 \cup H_1$

$E_1 \supset E_2 \supset \cdots E_j \cdots \supset E_n$ 0 is a root of multiplicity j

$H_1 \supset H_2 \supset \cdots H_j \cdots \supset H_{[n/2]}$

$\pm i\sqrt(B)$, $B > 0$ is a root of multiplicity j

Boundary of stability for equilibria

Σ: values of λ where
$p(X)$ characteristic polynomial of $D_Y G(Y_*, \lambda)$
has roots with real part $= 0$.

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$\overline{H_j} = H_j \cup E_{2j}$ and $E_1 = F_1$.

Linearisation of Hodgkin-Huxley type

At equilibrium $x = \mu, \quad \eta(\mu, I, c, V) = 0$

$$D\ HH(\mu) = \begin{bmatrix} A_0 & A_1 & \cdots & A_M \\ \gamma_1' \tau_1 & -\tau_1 & \cdots & 0 \\ \vdots & \vdots & & \vdots \\ \gamma_M' \tau_M & 0 & \cdots & -\tau_M \end{bmatrix}.$$

where

$$A_0 = -c_0 - \sum_{j=1}^{N} c_j u_j(\gamma(\mu))$$

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New parameters $A = (A_0, A_1, \ldots, A_M)$

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Theorem (L. & Rito)

For an equation of Hodgkin-Huxley type with M channel dynamics, for all functions $\gamma_i(\mu)$, such that $\gamma_i'(\mu) \neq 0$, and for generic functions $\tau_i(\mu)$, the singular sets H_1, H_2 and E_2 for parameters A are singular ruled submanifolds of in $\mathbf{R}^{M+1}$:

- *E_2 is a singular hypersurface with codimension 2 rulings;*
- *regular points in H_1 form an open set in $\mathbf{R}^{M+1}$ covered by codimension 2 affine subspaces;*
- *regular points in H_2 form a codimension 2 manifold covered by codimension 4 affine subspaces.*

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There are two types of singular points in H_j:

- *affine subspaces corresponding to isolated values of $\mu = \mu_*$ where $\tau_i(\mu_*) = \tau_j(\mu_*)$, $i \neq j$;*
- *affine subspaces contained in $Hj + 1$.*

Sketch proof

Linearisation of Hodgkin-Huxley type

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$A \mapsto f_\mu(A)$ coefficients of characteristic polynomial

$f_\mu(A) = \hat{f}(\mu) \cdot A + \tilde{f}(\mu)$

$\hat{f}(\mu) \qquad (M+1) \times (M+1)$ matrix

$\det\left(\hat{f}(\mu)\right) = 0$ iff $\tau_i(\mu) = \tau_j(\mu)$, $i \neq j$;

Sketch proof

The polynomial

$$P_\alpha(X) = \alpha_0 + \alpha_1 X + \cdots + \alpha_{n-1}X^{n-1} \pm X^n.$$

satisfies $P_\alpha(i\sqrt{B}) = 0$ iff

$$(\alpha_0, \alpha_1, \cdots, \alpha_{n-1}, \pm 1) \perp \langle \mathbf{v}_E(B), \mathbf{v}_O(B)\rangle$$

where

$$\mathbf{v}_E(B) = (1, 0, -B, 0, B^2, 0, \ldots)$$

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$i\sqrt{B}$ is a double root iff

$$(\alpha_0, \alpha_1, \cdots, \alpha_{n-1}, \pm 1) \perp \langle \mathbf{v}_E, \mathbf{v}_O, \frac{d\mathbf{v}_E}{dB}, \frac{d\mathbf{v}_O}{dB} \rangle$$

Sketch proof

For each μ:

$E_2(\mu)$ double eigenvalue $= 0$ for A at

$$f_\mu(A) \perp \langle (1,0,0,\dots),(0,1,0,\dots)\rangle$$

Sketch proof

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For each μ and each $B>0$:

$H_1(\mu,B)$ eigenvalue $i\sqrt{B}$ for A at

$$f_\mu(A) \perp \langle \mathbf{v}_E(B), \mathbf{v}_O(B)\rangle$$

$H_2(\mu,B)$ double eigenvalue $i\sqrt{B}$ for A at

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Sketch proof

$$E_2(\mu) \qquad f_\mu(A) \perp \langle (1,0,0,\dots),(0,1,0,\dots)\rangle$$

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$E_2(\mu)$ $\quad f_\mu(A) \perp \langle (1,0,0,\dots),(0,1,0,\dots)\rangle$

E_2 singular hypersurface with codimension 1 rulings

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$H_1(\mu, B)$ $\quad f_\mu(A) \perp \langle \mathbf{v}_E(B), \mathbf{v}_O(B)\rangle$

$H_1(\mu, B)$ sweeps an open set with codimension 2 rulings

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H_2 singular codimension 2 manifold with codimension 4 rulings

New/Old parameters

New parameters $A = (A_0, A_1, \ldots, A_M)$

$$A_0 = -c_0 - \sum_{j=1}^{N} c_j u_j(\gamma(\mu))$$

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rewrite: $A = \mathcal{M}(\mu) \cdot (I, c, W)$

$\mathcal{M}(\mu)$ an $(M+1) \times (2N+3)$ matrix

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For old parameters

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$\hat{f}(\mu) \cdot \mathcal{M}(\mu) \cdot (I, c, W) + \tilde{f}(\mu) \perp \langle (1, 0, 0, \dots), (0, 1, 0, \dots) \rangle$

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$H_2(\mu, B)$
$\hat{f}(\mu) \cdot \mathcal{M}(\mu) \cdot (I, c, W) + \tilde{f}(\mu) \perp \langle \mathbf{v}_E, \mathbf{v}_O, \frac{d\mathbf{v}_E}{dB}, \frac{d\mathbf{v}_O}{dB} \rangle$

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$A = \mathcal{M}(\mu) \cdot (I, c, W) \quad \mathcal{M}(\mu)$ an $(M+1) \times (2N+3)$ matrix

If $M \leq 2N+2$ (no more than two dynamics per channel)

the sets E_2, H_1, H_2 have the same structure as in the Theorem.

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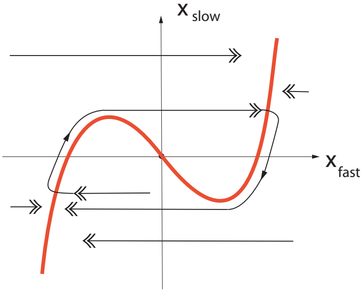
In the original parameters (I, c, V) with $W_i = c_i V_i$,
the sets E_2, H_1, H_2 have a similar structure but no rulings.

Two time-scales

$$\begin{cases} \dot{x}_f = \frac{1}{\varepsilon} f_{fast}(x_f, x_s) & \text{fast equation} \\ \dot{x}_s = f_{slow}(x_f, x_s) & \text{slow equation} \end{cases}$$



Slow manifold:
$f_{fast}(x_f, x_s) = 0$.

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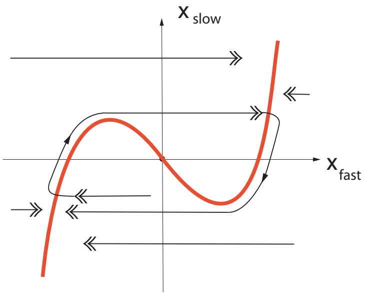

Slow manifold:
$f_{fast}(x_f, x_s) = 0.$

Non trivial dynamics associated to folds on the slow manifold: $\det\left(\frac{df_{fast}}{dx_f}\right) = 0$

Hodgkin-Huxley type

$$\begin{cases} C_m \dfrac{dx}{dt} = -I - c_0(x - V_0) - \displaystyle\sum_{j=1}^{N} c_j u_j(y)(x - V_j) \\ \\ \dfrac{dy_i}{dt} = (\gamma_i(x) - y_i)\, \tau_i(x) \qquad i = 1, \ldots, M \end{cases}$$

Only one fast variable:

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Only one fast variable:

$x_{fast} = y_i$ slow manifold is $y_i = \gamma_i(x)$ no folds

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Only one fast variable:

$x_{fast} = x$ slow manifold is

$\left(I + c_0 + \sum_{j=1}^{N} c_j u_j(y)\right) x = c_0 V_0 + \sum_{j=1}^{N} c_j u_j(y) V_j$

no folds if $c_j \geq 0$ and $u_j(y) \in [0, 1]$.

Hodgkin-Huxley type

$$\begin{cases} C_m \dfrac{dx}{dt} = -I - c_0(x - V_0) - \displaystyle\sum_{j=1}^{N} c_j u_j(y)(x - V_j) \\[2ex] \dfrac{dy_i}{dt} = (\gamma_i(x) - y_i)\,\tau_i(x) \qquad i = 1, \dots, M \end{cases}$$

Only one fast variable:

No folds.

Hodgkin-Huxley type

$$
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Scenario: two fast variables: $x_{fast} = (x, y_1)$

Hodgkin-Huxley type

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Simple case: $u_1(y) = y_1^m$, and

$j > 1 \quad \Rightarrow \quad u_j(y)$ does not depend on y_1.

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Fold points of $f_{fast} = 0$ correspond to fold points of HH type, with $N = 1$ channel, $M = 1$ channel dynamics and new parameters:

$$\widehat{\mathbf{c_0}} = c_0 + \sum_{j=2}^{N} c_j u_j(y) \qquad \widehat{\mathbf{W_0}} = c_0 V_0 + \sum_{j=2}^{N} c_j u_j(y) V_j$$