Two time-scales and application to nerve impulse

School on Singularity Theory
Mini-course on applications of singularities

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Method — Models with two time scales $\dot{z} = \frac{dz}{dt}$

$$\begin{cases} \varepsilon\dot{x} = f(x,y) & \text{fast equation} \\ \dot{y} = g(x,y) & \text{slow equation} \end{cases} \qquad 0 < \varepsilon \ll 1$$

Study the two time scales separately (singular limit).

Slow time τ — Rescale time: $t = \varepsilon\tau$, $z' = \frac{dz}{d\tau}$

$$\begin{cases} x' = f(x,y) \\ y' = \varepsilon g(x,y) \end{cases} \qquad \varepsilon \to 0 \qquad \begin{cases} x' = f(x,y) \\ y' = 0 \end{cases}$$

fast equation dominates

Fast time t

$$\varepsilon \to 0 \qquad \begin{cases} 0 = f(x,y) & \text{slow manifold} \\ \dot{y} = g(x,y) & \text{slow equation} \end{cases}$$

Models with two time scales

$$\begin{cases} \varepsilon \dot{x} &= f(x,y) \qquad \text{fast equation} \qquad x \in \mathbf{R}^r \\ \dot{y} &= g(x,y) \qquad \text{slow equation} \qquad y \in \mathbf{R}^\ell \end{cases}$$

For $\varepsilon > 0$ small:

- When $f(x,y)$ is far from 0, then

$$|\dot{x}(t)| = \frac{1}{\varepsilon}|f(x,y)| \gg |\dot{y}(t)| = |g(x,y)|$$

- A good approximation is to take $y(t) \approx$ constant, and then study the solutions $x(t)$ of

$$\dot{x}(t) = \frac{1}{\varepsilon}f(x,y)$$

  that have the same qualitative behaviour as the solutions of the layer equation:

$$\dot{x}(t) = f(x,y)$$

- Get a different differential equation for each $y \in \mathbf{R}$.

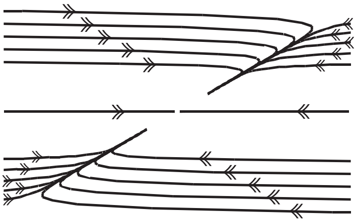
Models with two time scales

$$\begin{cases} \varepsilon\dot{x} = f(x,y) & \text{fast equation} \\ \dot{y} = g(x,y) & \text{slow equation} \end{cases}$$

Example 1

$$\begin{cases} \varepsilon\dot{x} = -(x-y) & \text{fast equation} \\ \dot{y} = -y & \text{slow equation} \end{cases}$$

Phase portrait $(x(t), y(t))$ with $\varepsilon = 1/20$



Models with two time scales

$$\begin{cases} \varepsilon\dot{x} &= f(x,y) \qquad \text{fast equation} \\ \dot{y} &= g(x,y) \qquad \text{slow equation} \end{cases}$$

For $0 < \varepsilon \ll 1$ we start with the analysis of the layer equation:

$$\dot{x} = f(x,y) \qquad \text{with } y \text{ constant}$$

x_* is an equilibrium of the layer equation when $f(x_*, y) = 0$

Example 1

$$\begin{cases} \varepsilon \dot{x} &= -(x-y) = f(x,y) \\ \dot{y} &= -y \end{cases}$$

fast equation
slow equation

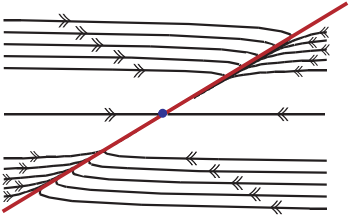
For $0 < \varepsilon \ll 1$ we start with the analysis of the layer equation:

$$\dot{x} = f(x,y) = -(x-y) \qquad \text{with } y \text{ constant}$$

$x_* = y$ is the equilibrium of the layer equation.

$$\frac{\partial f}{\partial x}(x_*, y) = -1 < 0$$

Solutions of the layer equation approach the line $x = y$.



x_* is an attracting equilibrium of the layer equation.

Recall

$V(x)$ vector field of class C^k, $k \geq 1$ with $x \in U \subset \mathbf{R}^n$, open
$\overline{x} \in U$ equilibrium of V
$\varphi(t, x_0)$ the solution of $\dot{x} = V(x)$ such that $\varphi(0, x_0) = x_0$

Definition

the equilibrium $\overline{x}$ of $\dot{x} = V(x)$ is an attractor if
$\exists \eta > 0$ such that,
if $|x - \overline{x}| < \eta$ and $t > 0$ then $\varphi(t, x)$ is well defined and
$\lim_{t \to \infty} \varphi(t, x) = \overline{x}$.

the equilibrium $\overline{x}$ of $\dot{x} = V(x)$ is a repellor if
$\exists \eta > 0$ such that,
if $|x - \overline{x}| < \eta$ and $t < 0$ then $\varphi(t, x)$ is well defined and
$\lim_{t \to -\infty} \varphi(t, x) = \overline{x}$.

Recall

$V(x)$ vector field of class C^k, $k \geq 1$ with $x \in U \subset \mathbf{R}^n$, open
$\overline{x} \in U$ equilibrium of V
$\varphi(t, x_0)$ the solution of $\dot{x} = V(x)$ such that $\varphi(0, x_0) = x_0$

Definition

The equilibrium $\overline{x}$ of V is hyperbolic if all the eigenvalues of $DV(\overline{x})$ have non-zero real parts.

If all the eigenvalues have negative real parts, then $\overline{x}$ is an attractor.
If all the eigenvalues have positive real parts, then $\overline{x}$ is a repellor.

Models with two time scales

$$\begin{cases} \varepsilon\dot{x} &= f(x,y) \qquad \text{fast equation} \\ \dot{y} &= g(x,y) \qquad \text{slow equation} \end{cases}$$

Definition

The slow manifold L is the set of points where $f = 0$, i.e. the set of equilibria of the layer equation, given by

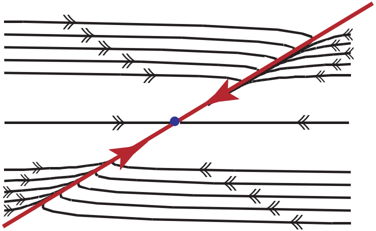
$$L = \{(x,y): \quad f(x,y) = 0\}$$

The layer equation is not a good approximation near the slow manifold, where $f(x,y) \approx 0$.
Near the slow manifold the dynamics follows the slow equation.

Example 1

$$\begin{cases} \varepsilon \dot{x} &= -(x-y) = f(x,y) \qquad \text{fast equation} \\ \dot{y} &= -y \qquad \text{slow equation} \end{cases}$$

Slow manifold $L = \{(x,y): \quad f(x,y) = 0\} = \{(x,y): \quad x = y\}$
$y = 0$ is the only equilibrium of the slow equation in L and it is an attractor.



The slow manifold is not flow-invariant.

Example 2

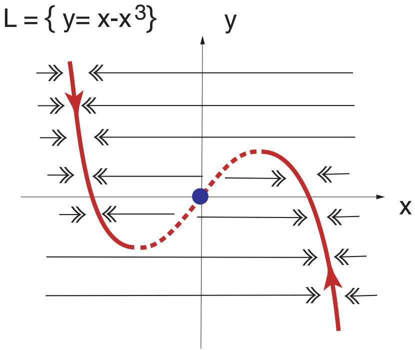
$$\begin{cases} \varepsilon \dot{x} &= x - x^3 - y \\ \dot{y} &= x \end{cases}$$

fast equation $0 < \varepsilon \ll 1$

slow equation

Slow manifold $L = \{(x, y) : \quad y = \varphi(x) = x - x^3\}$

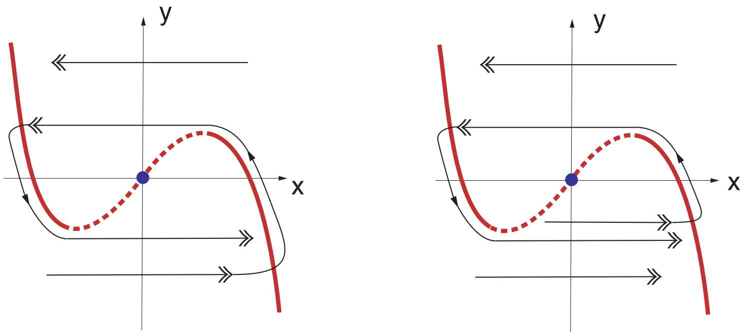
Dynamics on the slow manifold, (dashed: repellor)



Example 2

$$\begin{cases} \varepsilon \dot{x} = x - x^3 - y & \text{fast equation} \quad 0 < \varepsilon \ll 1 \\ \dot{y} = x & \text{slow equation} \end{cases}$$

Slow manifold $L = \{(x, y) : \quad y = \psi(x) = x - x^3\}$



L cannot be written globally as a graph $x = \Phi(y)$.

Models with two time scales — singularities

$$\begin{cases} \varepsilon \dot{x} = f(x,y) & \text{fast equation} & x \in \mathbf{R}^r \\ \dot{y} = g(x,y) & \text{slow equation} & y \in \mathbf{R}^\ell \end{cases}$$

Slow manifold $L = \{(x,y) : \quad f(x,y) = 0\}$
Generically L is a regular ℓ-dimensional submanifold of $\mathbf{R}^{r+\ell}$
(if rank $\dfrac{\partial f}{\partial x} = r$)

In one parameter families, L may have singular points.

Projection $P : \mathbf{R}^{r+\ell} \longrightarrow \mathbf{R}^\ell$
Singularities of of P restricted to L

- If $\ell = 1$, generically, singularities of P restricted to L are folds.
- If $\ell = 2$, generically, singularities of P restricted to L are folds and cusps.
- If $\ell = 3$ ...

Models with two time scales — singularities

Dynamics on the slow manifold:

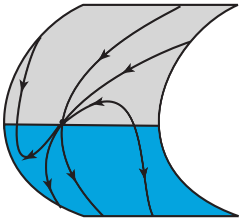
$$\begin{cases} 0 = f(x,y) & x \in \mathbf{R}^r \\ \dot{y} = g(x,y) & y \in \mathbf{R}^\ell \end{cases}$$

Generically, equilibria of the slow equation are not singularities of the projection
but in one-parameter families, equilibria may occur at fold points.

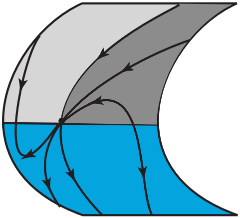
Singularity theory provides a classification of folded equilibria of slow equation.

Generically they are folded saddles and folded nodes.

Folded node

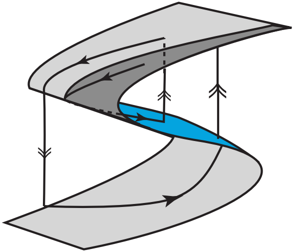


Folded node



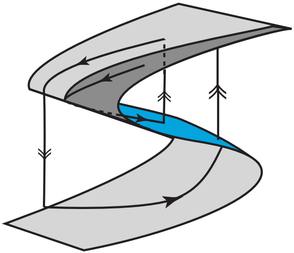
Trapping region.

Folded node



Trajectories that reach the trapping region get funneled into repelling part of slow manifold and jump back.

Folded node

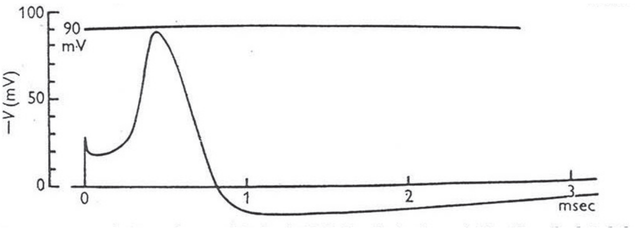


Trajectories that reach the trapping region get funneled into repelling part of slow manifold and jump back.

Canard

A solution that moves in the attracting part of the slow manifold, passes close to the fold line,
and then follows the repelling part of the slow manifold for some time.

Nerve Impulse



from: Hodgkin e Huxley, 1952

Action potential: experimental plot of voltage as a function of time in squid giant axon.

Expect to find in models:

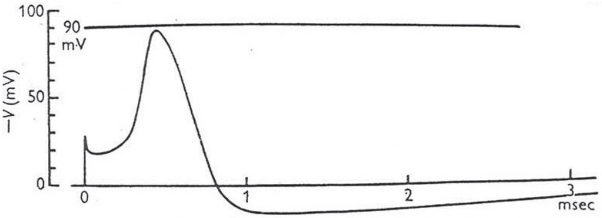
- single action potentials
- trains of action potentials, periodic solutions
- more complicated behaviour

depending on choices of parameters.

Models for nerve impulse

Qualitative properties:

- Attracting equilibrium.
- Action potentials of a well defined size.
- Threshold for triggering an action.
- Jump action.
- Slow return to equilibrium.



Use two time scales to create a model

First model — FitzHugh-Nagumo equation

$$\begin{cases} \varepsilon \dot{x} &= \varphi(x) - y \\ \dot{y} &= x - \gamma y - \delta \end{cases}$$

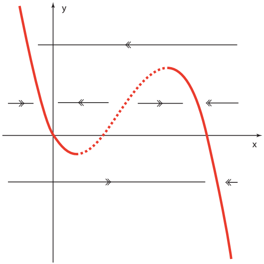
fast equation

slow equation $\qquad \varepsilon \ll 1$

$\varphi(x) = -x(x-a)(x-b) \qquad 0 < a < b \qquad \delta \in \mathbf{R} \qquad \gamma > 0$

Layer equation $\dot{x} = \varphi(x) - y$

Two fold points on slow manifold.



slow manifold

First model — FitzHugh-Nagumo equation

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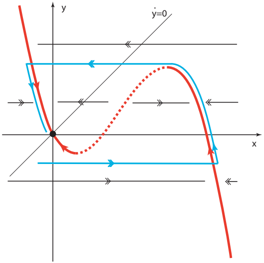
$\varphi(x) = -x(x-a)(x-b) \qquad 0 < a < b \qquad \delta \in \mathbf{R} \qquad \gamma > 0$



γ small, $\delta \approx 0$

Large transient
$y \ll 0$, jump to action

Jump return
to equilibrium

Slow return to equilibrium is not possible in the plane.

First model — FitzHugh-Nagumo equation

$$\begin{cases} \varepsilon\dot{x} = \varphi(x) - y & \text{fast equation} \\ \dot{y} = x - \gamma y - \delta & \text{slow equation} \end{cases} \qquad \varepsilon \ll 1$$

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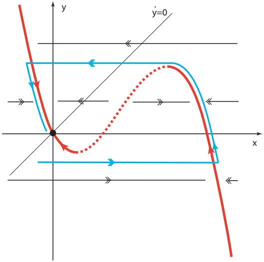
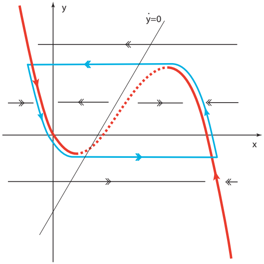


γ small, $\delta \approx 0$



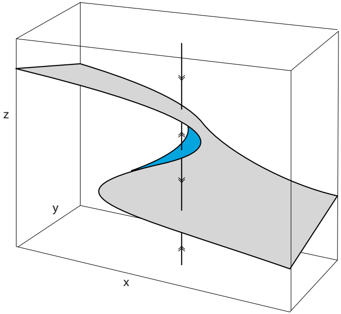
γ small, $\delta \gg 0$

δ increases — equilibrium moves to repelling part of slow manifold.

Zeeman's model for the nerve impulse (1972)

$$\begin{cases} \dot{x} = -1 - y & \text{slow equation} \\ \dot{y} = -2(y + z) & \text{slow equation} \\ \varepsilon\dot{z} = -(x + yz + z^3) & \text{fast equation} \end{cases} \qquad \varepsilon \ll 1$$

The slow manifold



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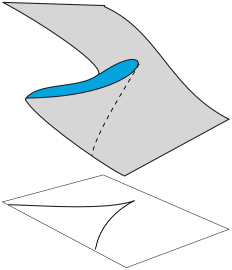
Slow manifold $f(x,y,z) = -(x + yz + z^3) = 0$

Not regular: $\dfrac{\partial f}{\partial z} = -3z^2 - y = 0$

Folds: $\dfrac{\partial f}{\partial z} = 0$

$(x,y,z) = (2z^3, -3z^2, z) \quad z \neq 0$

$\dfrac{\partial^2 f}{\partial z^2} = -6z \neq 0$



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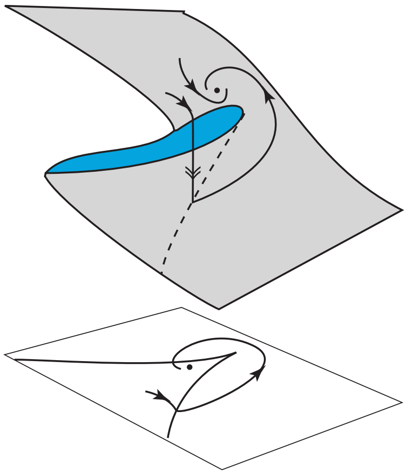
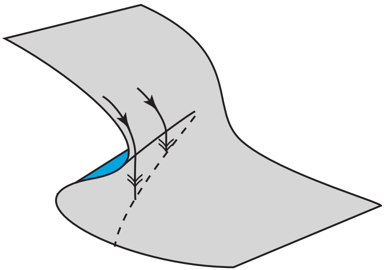


To get a jump, slow trajectories must run into the fold line.

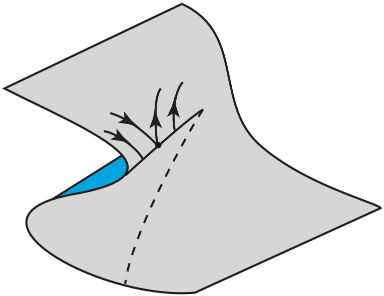


If this happens all the way to the cusp, get arbitrarily small action potentials.

The model avoids this by having an equilibrium of the slow equation on the fold line.

Action potentials of well defined size

Equilibrium at the fold line — folded saddle
also creates threshold



Action potentials of well defined size

Equilibrium at the fold line — folded saddle
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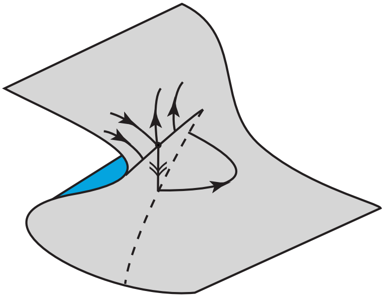
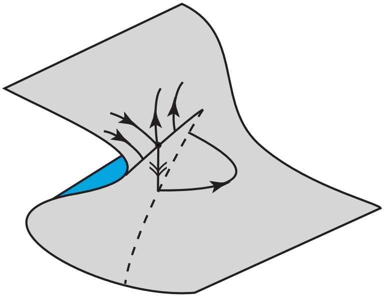


Some trajectories will jump more than once:
fast return to equilibrium!

Action potentials of well defined size

Equilibrium at the fold line — folded saddle
also creates threshold



Some trajectories will jump more than once:
fast return to equilibrium!

(although the jumps are very small)

The model has to be adjusted.

Hodgkin-Huxley type: models for nerve impulse from experiments

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

Variables

$t \in \mathbf{R}$ time

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

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

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

Hodgkin-Huxley type: models for nerve impulse from experiments

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Parameters

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

$c_j > 0$ ionic gate strength

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

Hodgkin-Huxley type: models for nerve impulse from experiments

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

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 $\tau(x) = (\tau_1, \ldots, \tau_M)$

Hodgkin-Huxley type: models for nerve impulse from experiments

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

Original Hodgkin-Huxley model

$N = 2 \qquad M = 3$

ionic gates:

Na^+ controlled by $u_1(y_1, y_2) = y_1^3 y_2$

K^+ controlled by $u_2(y_3) = y_3^4$

Hodgkin-Huxley type: models for nerve impulse from experiments

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

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ionic gates:

Na^+ controlled by $u_1(y_1, y_2) = y_1^3 y_2$

K^+ controlled by $u_2(y_3) = y_3^4$

x (voltage) and y_1 (Na^+ activation) faster.

Hodgkin-Huxley type

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

One fast variable:

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

Hodgkin-Huxley type

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

One fast variable:

$x_{fast} = x$ slow manifold is

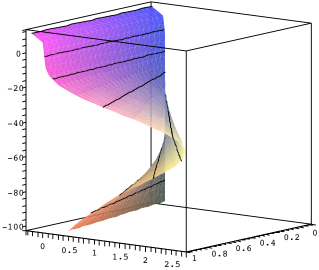
$$\left(c_0 + \sum_{j=1}^{N} c_j u_j(y)\right) x = -I + c_0 V_0 + \sum_{j=1}^{N} c_j u_j(y) V_j$$

Since $c_j \geq 0$ and $u_j(y) \in [0, 1]$:

No folds. Need at least two fast variables.

Hodgkin-Huxley model

$$\begin{cases} \dfrac{dx}{dt} = -I - c_0(x - V_0) - \displaystyle\sum_{j=1}^{2} c_j u_j(y)(x - V_j) \\ \dfrac{dy_i}{dt} = (\gamma_i(x) - y_i)\,\tau_i(x) \qquad i = 1, \dots, 3 \end{cases}$$



two fast variables: x, y_1

original model:
$u_1(y) = y_1^3 y_2$, $u_2(y) = y_3^4$

graph: slow manifold
(y_2, y_3^4, x) for $I = -10$

Hodgkin-Huxley model

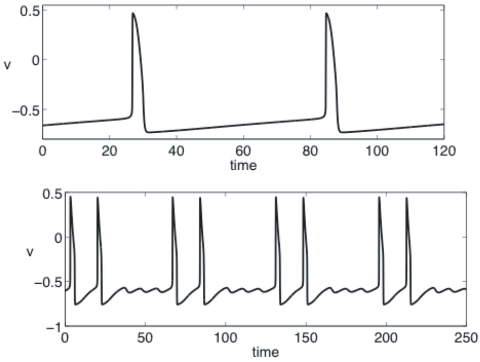
$$\begin{cases} \dfrac{dx}{dt} = -I - c_0(x - V_0) - \displaystyle\sum_{j=1}^{2} c_j u_j(y)(x - V_j) \\ \dfrac{dy_i}{dt} = (\gamma_i(x) - y_i)\,\tau_i(x) \qquad i = 1, \ldots, 3 \end{cases}$$

slow manifold has:

- folds
- cusps
- a folded node

Get

- action potentals
- trains of action potentials
- canards



voltage as a function of time for Hodgkin-Huxley model numerical plots

From Rubin and Wechselberger (2007)

Tomorrow — symmetries

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