A slow-fast invitation

Geometric singular perturbation theory in biological practice

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Singular perturbations, background

Systems in nature often evolve on various time scales or take place on various length scales.
When studying such systems, simplifying assumptions may be of great help:

- slow processes can be assumed to stand still;
- fast processes can be assumed to adjust instantaneously to changing circumstances;
- parts of phase space can be "blown up".

Different approximations all have limited validity in space or time and need to be matched.

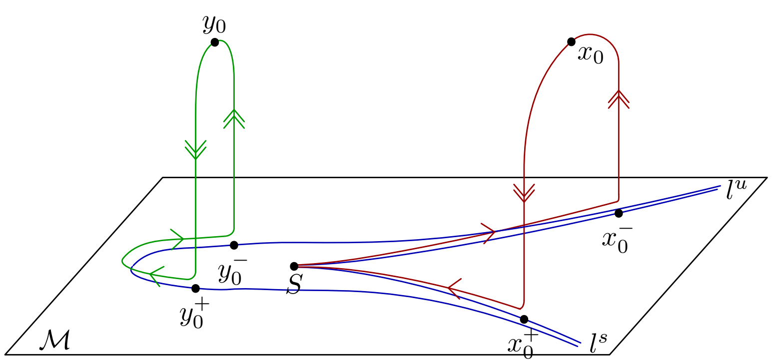
Geometric singular perturbation theory

First characterisation:

- deals with systems with clear separation of time-scales t and $\tau = \varepsilon t$, with $0 < \varepsilon \ll 1$ small parameter
- uses invariant manifolds to construct solutions of dynamical system
- combination of analysis and geometry

Schematic pictures:

- Why do these structures represent solutions/orbits?
- What is the theory validating such pictures?



Biological example (1)

Classical predator-prey model

$$\begin{cases} \dot{u} &= u\left(1 - u - \frac{av}{u+d}\right), \\ \dot{v} &= \varepsilon v\left(\frac{au}{u+d} - 1\right). \end{cases}$$

with (rescaled) numbers of prey $u \geq 0$ and predators $v \geq 0$.

- $\varepsilon > 0$ is the ratio between death rate of the predator and growth rate of the prey
- $a > 0$ and $d > 0$ determine impact of predation on the prey

If the prey reproduce much faster than the predators and the predator is rather aggressive but not so efficient,
then the ratio ε becomes a small parameter.

Biological example (2)

FitzHugh and Nagumo independently formulated the model

$$\begin{cases} u_t &= u_{xx} + f(u) - w \\ w_t &= \varepsilon(u - \gamma w) \end{cases}$$

as simplifying equations to the Hodgkin-Huxley equations that describe the generation of action potentials for an axon. Here $f(u) = u(u-a)(1-u)$ and ε is a small parameter.

The spiking potential is a travelling periodic wave that only depends on $\xi = x - ct$ and thus satisfies

$$\begin{cases} u_\xi &= v \\ v_\xi &= -cv - f(u) + w \\ w_\xi &= -\frac{\varepsilon}{c}(u - \gamma w) \end{cases}$$

augmented by fourth (slow) equation $c_\xi = 0$.

Biological example (3)

Gierer and Meinhardt modelled growth and regeneration of a fresh-water polyp, using an activator-inhibitor model

$$\begin{cases} \varepsilon^2 U_t &= U_{xx} - \varepsilon^2 \mu U + V^2 \\ V_t &= \varepsilon^2 V_{xx} - V + \frac{V^2}{U} \end{cases}$$

- U, V are concentrations, *i.e.,* $0 \leq U, V \leq 1$
- The activator $V(x,t)$ stimulates growth of a new head, the inhibitor $U(x,t)$ prevents the formation of a second head.
- At a position with a peak in activator concentration, a head will be formed.

The two components have very different diffusion rates, thus different natural length scales.
Expressed by small ratio $0 < \varepsilon^2 \ll 1$ of diffusion rates.

Biological example (3)

The existence problem for stationary solutions of the GM-equations can be written as a system of ODEs in which $x \in \mathbb{R}$ plays role of 'time':

$$\begin{cases} u' &= p \\ p' &= -v^2 + \varepsilon^2 \mu u \\ \varepsilon v' &= q \\ \varepsilon q' &= v - \frac{v^2}{u} \end{cases}$$

Solutions of interest in this talk satisfy

$$\lim_{|x| \to \infty} (U(x), V(x)) = (0, 0), \text{ so } \lim_{|x| \to \infty} (u, p, v, q) = (0, 0, 0, 0).$$

Inherent problem at $u = 0 \ldots$ (Modelling mistake?)

General slow-fast system

Systems of ODEs

(1)
$$\begin{cases} \dot{u} = f(u, v; \varepsilon), \\ \dot{v} = \varepsilon g(u, v; \varepsilon), \end{cases}$$

where $\dot{} = \frac{d}{dt}$, $u \in \mathbb{R}^k$ (fast variables), $v \in \mathbb{R}^l$ (slow variables), $k, l \geq 1$ and $0 < \varepsilon << 1$.

As long as $\varepsilon \neq 0$ equivalent with

(2)
$$\begin{cases} \varepsilon u' = f(u, v; \varepsilon), \\ v' = g(u, v; \varepsilon), \end{cases}$$

with $' = \frac{d}{d\tau}$, $\tau = \varepsilon t$ slow time.

Limiting problems

Two different limits for $\varepsilon = 0$:

(1) is singular perturbation of fast limit

$$\begin{cases} \dot{u} &= f(u, v; 0), \\ \dot{v} &= 0 \end{cases}$$

l-parameter family of k-dimensional systems

(2) is associated to slow limit

$$\begin{cases} 0 &= f(u, v; 0), \\ v' &= g(u, v; 0) \end{cases}$$

Both limiting problems are simpler and lower dimensional
$\Longrightarrow$ easier to analyse than full system (1) or (2).

Limiting problems

However, in either formulation, one pays a price:

- fast limit has large set $\{f(u,v;0)=0\}$ of fixed points where flow is trivial
- slow limit blows flow on $\{f(u,v;0)=0\}$ up to produce non-trivial behaviour, but this limit is not defined off this set

Geometric singular perturbation theory:

- under some conditions robust geometric structure
- orbits from fast and slow $\varepsilon = 0$ limits may be glued together to singular structures that persist for $0 < \varepsilon << 1$

Robust geometric structure follows from three theorems by Fenichel (1979).

Fenichel (1)

Consider again (1)

$$\begin{cases} \dot{u} & = & f(u, v; \varepsilon) \\ \dot{v} & = & \varepsilon g(u, v; \varepsilon) \end{cases}$$

with $u \in \mathbb{R}^k$, $v \in \mathbb{R}^l$, f, g sufficiently smooth (C^{r+1}).

Suppose $\varepsilon = 0$ fast system has compact, normally hyperbolic l-dim. manifold $\mathcal{M}_0 \subset \{f(u, v; 0) = 0\}$.
Then:

↑ lin. of (1) with $\varepsilon = 0$ has exactly l eig.val. with $\mathrm{Re}(\lambda) = 0$ at $\mathcal{M}_0$

Theorem 1

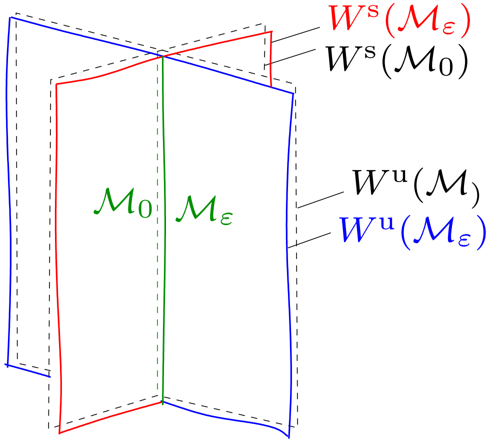
If $\varepsilon > 0$ suff. small, there exists a manifold $\mathcal{M}_\varepsilon$, $\mathcal{O}(\varepsilon)$ close to and diffeomorphic to $\mathcal{M}_0$.
$\mathcal{M}_\varepsilon$ is locally invariant under flow of (1) and C^r, including in ε.

Fenichel (2)

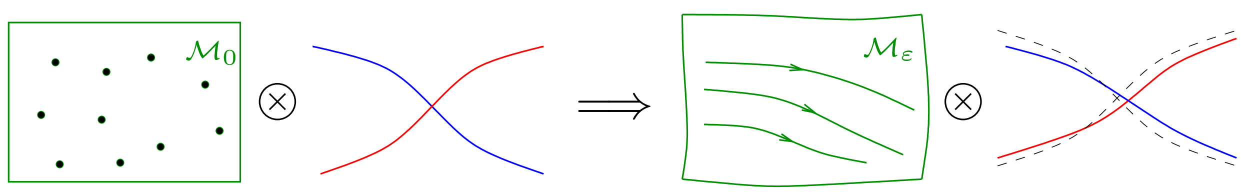
Suppose for $\varepsilon = 0$ that $\mathcal{M}_0$ has m-dim. stable manifold $W^{\mathrm{s}}(\mathcal{M}_0)$ and n-dim. unstable manifold $W^{\mathrm{u}}(\mathcal{M}_0)$ ($m + n = k$). Then:

Theorem 2

If $\varepsilon > 0$ sufficiently small, there exist stable and unstable manifolds $W^{\mathrm{s}}(\mathcal{M}_\varepsilon)$, $W^{\mathrm{u}}(\mathcal{M}_\varepsilon)$ of $\mathcal{M}_\varepsilon$, that are $\mathcal{O}(\varepsilon)$ close and diffeomorphic to $W^{\mathrm{s}}(\mathcal{M}_0)$, $W^{\mathrm{u}}(\mathcal{M}_0)$. They are locally invariant under the flow of (1) and C^r.



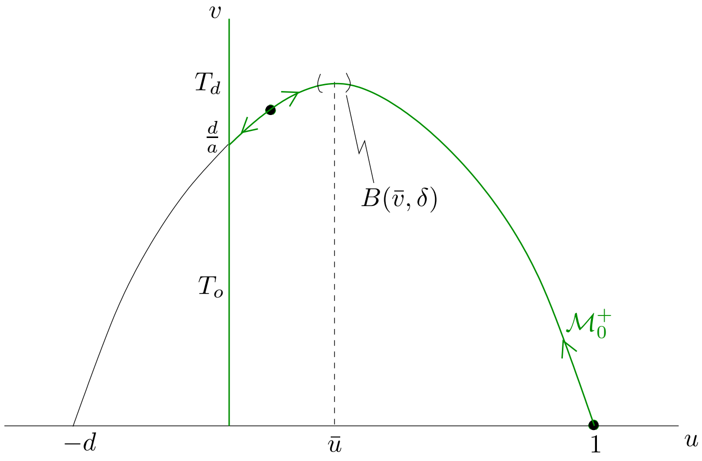
or



$\varepsilon = 0$ $\qquad$ $0 < \varepsilon \ll 1$

Example (1): predator-prey model

$$\begin{cases} \dot{u} &= u\left(1 - u - \frac{av}{u+d}\right) \\ \dot{v} &= \varepsilon v\left(\frac{au}{u+d} - 1\right) \end{cases}$$



$0 < d < 1$, $a > (1+d)/(1-d)$

- for $\varepsilon = 0$, nullcline $\{f(u, v; 0) = 0, u \geq 0, v \geq 0\}$ consists of $\mathcal{M}_0^0 := \{u = 0\}$ and $\mathcal{M}_0^1 := \{v = \frac{1}{a}(1-u)(u+d)\}$, $u, v \geq 0$
- both normally hyperbolic, but not in $(0, \frac{d}{a}) \in \mathcal{M}_0^0 \cap \mathcal{M}_0^1$ and $(\bar{u}, \bar{v}) = (\frac{1-d}{2}, \frac{(1+d)^2}{4a}) \in \mathcal{M}_0^1$ for $d < 1$.
- slow $\varepsilon = 0$ system: limiting flow $v' = v\left(\frac{au}{u+d} - 1\right)$ on $\mathcal{M}_0^{0,1}$
- write $\mathcal{M}_0^1$ as graph of function in slow variable v, then $u = u(v)$ in above flow $\implies$ $v' = h(v)$ on $\mathcal{M}_0^{0,1}$

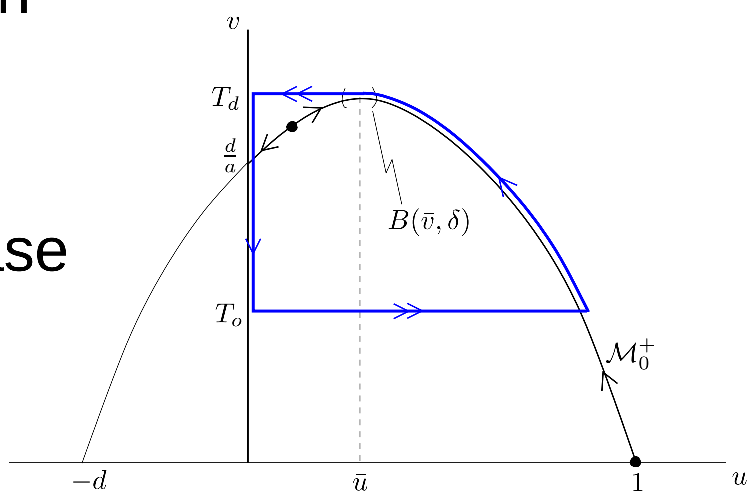
Example (1) continued

Fenichel 1: for small $\varepsilon > 0$ persistence of $\mathcal{M}_0^0$ and $\mathcal{M}_0^1$ as invariant man. $\mathcal{M}_\varepsilon^0$ and $\mathcal{M}_\varepsilon^1$ with flow $\mathcal{O}(\varepsilon)$ close to limiting flow

- nullcline $\{u = 0\}$ still invariant for $\varepsilon \neq 0 \Longrightarrow \mathcal{M}_\varepsilon^0 = \mathcal{M}_0^0$
- $\{v = \frac{1}{a}(1-u)(u+d)\}$ no longer invariant $\Longrightarrow \mathcal{M}_\varepsilon^1 \neq \mathcal{M}_0^1$

Fenichel 2: for small $\varepsilon > 0$ persistence of $W^{\mathrm{u,s}}(\mathcal{M}_0)$ as inv. man. $W^{\mathrm{u}}(\mathcal{M}_\varepsilon)$ and $W^{\mathrm{s}}(\mathcal{M}_\varepsilon)$, diff. and $\mathcal{O}(\varepsilon)$ close to $W^{\mathrm{u,s}}(\mathcal{M}_0)$

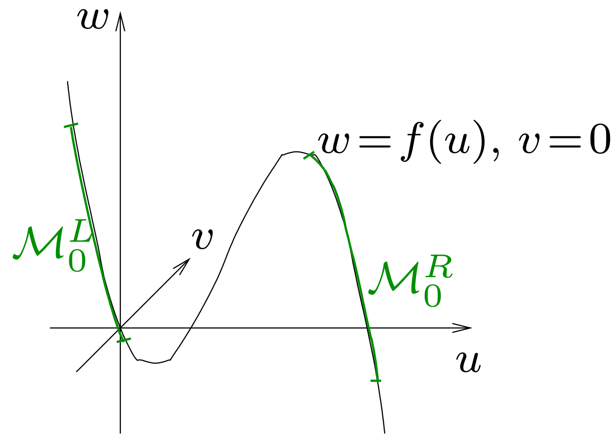
- sign of $f(u, v; \varepsilon)$ in fast equation $\dot{u} = f(u, v; \varepsilon)$ determines (in)stability of $\mathcal{M}_\varepsilon^{0,1}$
- 2D (un)st. manifolds in 2D phase space: closeness is no news



Q: construction of per. orbit?

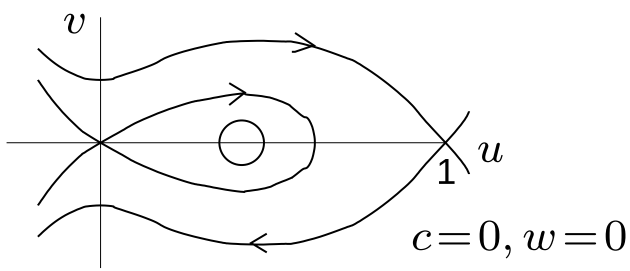
Example (2): FitzHugh-Nagumo

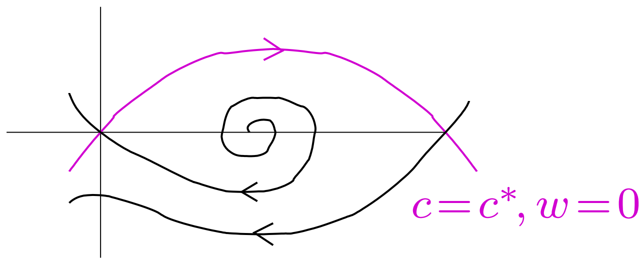
$$\begin{cases} u_\xi &= v \\ v_\xi &= -cv - f(u) + w \\ w_\xi &= -\frac{\varepsilon}{c}(u - \gamma w) \\ c_\xi &= 0 \end{cases}$$



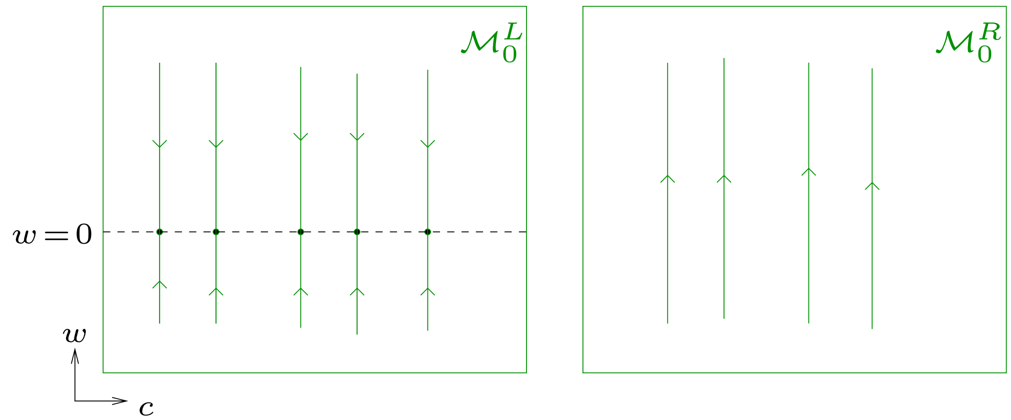
with $f(u) = u(1-u)(u-a)$, $a < \frac{1}{2}$

$\varepsilon = 0$ fast flow:





$\varepsilon = 0$ slow flow on $\mathcal{M}_0^{L,R}$:

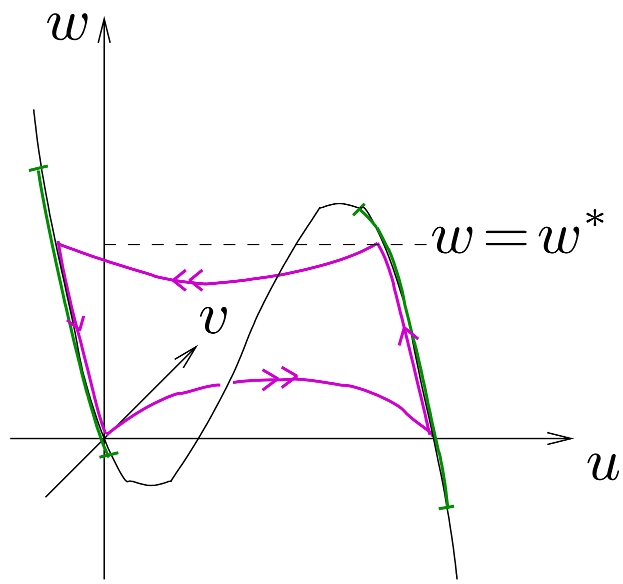


return orbit for $c = c^*, w = w^*$

Example (2) continued

Picture in subspace $c = c^*$:

Based on two slow parts along $\mathcal{M}_0^{L,R}$ and two fast parts, one can formally construct a singular periodic orbit.



Question: Does this singular structure persist for $0 < \varepsilon \ll 1$?

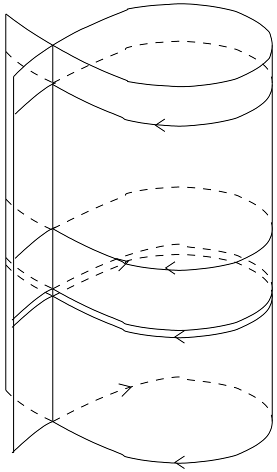
- Fenichel 1,2 guarantee that 2D $\mathcal{M}_0^{L,R}$ along with 3D $W^{\mathrm{u,s}}(\mathcal{M}_0^{L,R})$ persist for sufficiently small $\varepsilon \neq 0$
- $\varepsilon = 0$ heteroclinic orbits at $w = 0, c = c^*$ and $w = w^*, c = c^*$ correspond to transversal intersections $W^{\mathrm{u}}(\mathcal{M}_0^L) \cap W^{\mathrm{s}}(\mathcal{M}_0^R)$ and v.v. which are robust under perturbations

Q: Do perturbed heteroclinic jumps still hit $\mathcal{M}_\varepsilon^{L,R}$ at right place?

Fibering of manifolds

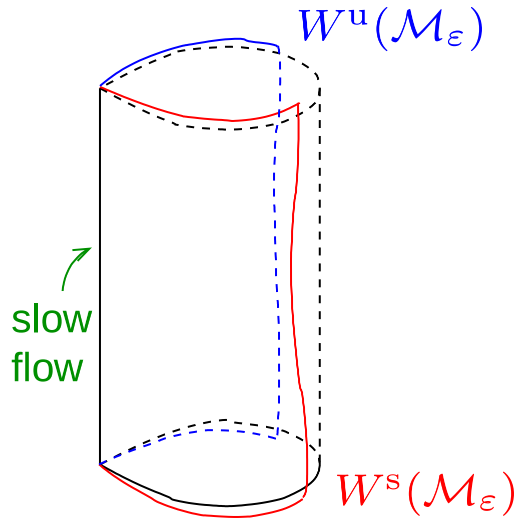
Imagine example
$$\dot{x} = y$$
$$\dot{y} = x - x^2 + \varepsilon h_1(x, y, z; \varepsilon)$$
$$\dot{z} = \varepsilon h_2(x, y, z; \varepsilon)$$

$\varepsilon = 0$



$\Longrightarrow$

$\varepsilon > 0$



fibering of $W^{\mathrm{u,s}}(\mathcal{M}_0)$ by $W^{\mathrm{u,s}}(v_0)$ of points $v_0 \in \mathcal{M}_0$

Questions:

- Do $W^{\mathrm{u,s}}(v_0)$ perturb to analogous objects?
- Relative position of $W^{\mathrm{u}}(\mathcal{M}_\varepsilon)$ and $W^{\mathrm{s}}(\mathcal{M}_\varepsilon)$?

First answer: Fenichel fibering

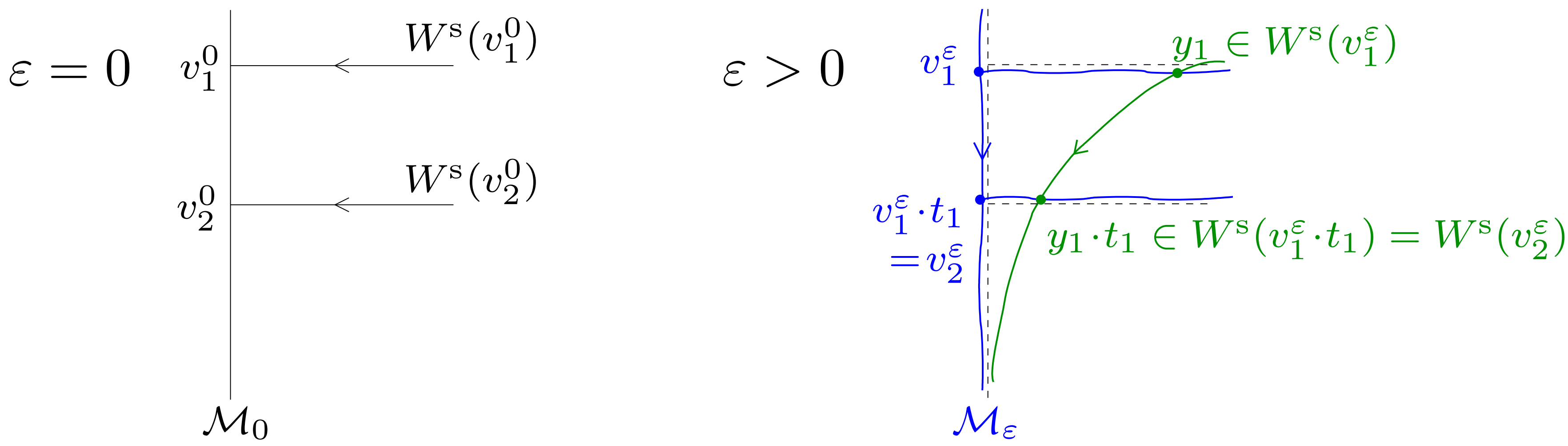
Fenichel (3): fibering

Theorem 3

$\forall v_\varepsilon \in \mathcal{M}_\varepsilon$ there is an m-dim. manifold $W^{\mathrm{s}}(v_\varepsilon) \subset W^{\mathrm{s}}(\mathcal{M}_\varepsilon)$ $\mathcal{O}(\varepsilon)$-close and diffeomorphic to $W^{\mathrm{s}}(v_0)$ and C^r in v and ε

The family $\{W^{\mathrm{s}}(v_\varepsilon) | v_\varepsilon \in \mathcal{M}_\varepsilon\}$ is invariant in the sense that $W^{\mathrm{s}}(v_\varepsilon) \cdot t \subset W^{\mathrm{s}}(v_\varepsilon \cdot t)$ $\forall t > 0$ (fibers are no longer orbits!)

evolution:
if $v_\varepsilon = v(0)$, then $v_\varepsilon \cdot t = v(t)$



Analogous for $W^{\mathrm{u}}(v_\varepsilon)$

Construction of global orbits

Questions:

- Construction of periodic orbit in predator-prey system?
- Perturbed homoclinic manifold $W^{\mathrm{u}}(\mathcal{M}_0) = W^{\mathrm{s}}(\mathcal{M}_0)$: relative positions of $W^{\mathrm{u}}(\mathcal{M}_\varepsilon)$ and $W^{\mathrm{s}}(\mathcal{M}_\varepsilon)$?
- Construction of pulse for FitzHugh-Nagumo?

Answers:

- Compute time that orbit spends near $\mathcal{M}_\varepsilon = \{u = 0\}$ (delayed loss of stability)
- Melnikov-type measures of distance
- Tracking of manifolds using Fenichel normal form. Consider 1D $\mathcal{S} = \{u = v = w = 0, |c - c^*| < \delta\} \subset \mathcal{M}_0^L$, track 2D $W^{\mathrm{u}}(\mathcal{S})$, proof that it intersects the 3D $W^{\mathrm{s}}(\mathcal{M}_0^L)$ transversally: 1D intersection (orbit!) for c, w close to c^*, w^*.

Example (4): coupled Ginzburg-Landau

Equations with similar geometry as Gierer-Meinhardt, but no singularity in $u = 0$:

$$\begin{aligned} A_t &= A_{xx} - (1 - \mu B)A + A|A|^2 \\ \varepsilon^2 \tau B_t &= \tfrac{1}{\varepsilon^2} B_{xx} - \varepsilon^2 \alpha B + \nu |A|^2 + \beta |A|^2 B \end{aligned}$$

ODE for **standing pulse solutions**, which satisfy $\lim_{x\to\pm\infty} A(x) = \lim_{x\to\pm\infty} B(x) = 0$:

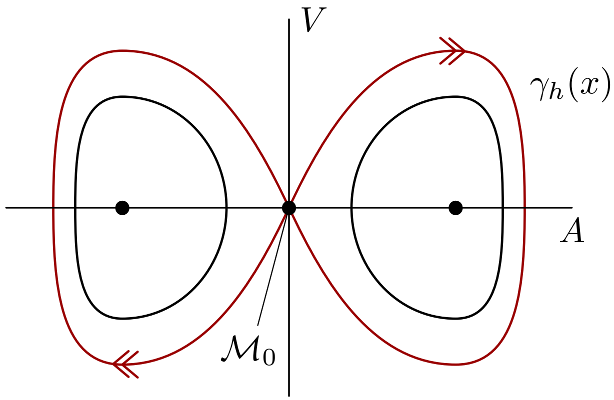
$$\left\{ \begin{aligned} A' &= V \\ V' &= A - A^3 - \mu A B \\ B' &= \varepsilon D \\ D' &= \varepsilon(\varepsilon^2 \alpha B - \nu A^2 - \beta B A^2) \end{aligned} \right.$$

The pulse solutions correspond to homoclinic solutions γ_h that satisfy $\lim_{x\to\pm\infty} \gamma_h(x) = (0, 0, 0, 0)$.

The unperturbed GL-pulse

Fast $\varepsilon = 0$ limit

$$\begin{cases} A' &= V \\ V' &= (1-\mu B_0)A - A^3 \\ B' &= 0 \\ D' &= 0 \end{cases}$$



2D normally hyperbolic manifold $\mathcal{M}_0 = \{A = V = 0\}$

Saddle points $(0, 0, B_0, D_0) \in \mathcal{M}_0$ with $B_0 < 1/\mu$ connected to themselves via homoclinic orbits $\gamma_h(x; B_0, D_0)$

$\mathcal{M}_0$ has 3D stable and unstable manifolds $\mathcal{W}^s(\mathcal{M}_0)$ and $\mathcal{W}^u(\mathcal{M}_0)$ that coincide (union of all orbits $\gamma_h(x; B_0, D_0)$).

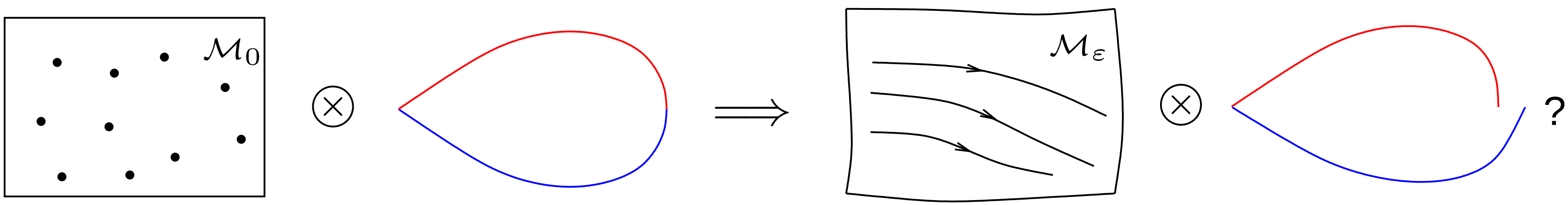
Question: Will any homoclinic orbit persist for small $\varepsilon > 0$?

Example (4) continued

Fenichel 1,2: normally hyperbolic manifold $\mathcal{M}_0$ and $\mathcal{W}^{s,u}(\mathcal{M}_0)$ persist for $0 < \varepsilon \ll 1$.

$\Longrightarrow$ locally invariant manifold $\mathcal{M}_\varepsilon$ and manifolds $\mathcal{W}^{s,u}(\mathcal{M}_\varepsilon)$, diffeomorphic to and $\mathcal{O}(\varepsilon)$ close to their $\varepsilon = 0$ counterparts.

Recall: this does not guarantee that $\mathcal{W}^s(\mathcal{M}_\varepsilon)$ and $\mathcal{W}^u(\mathcal{M}_\varepsilon)$ still coincide.



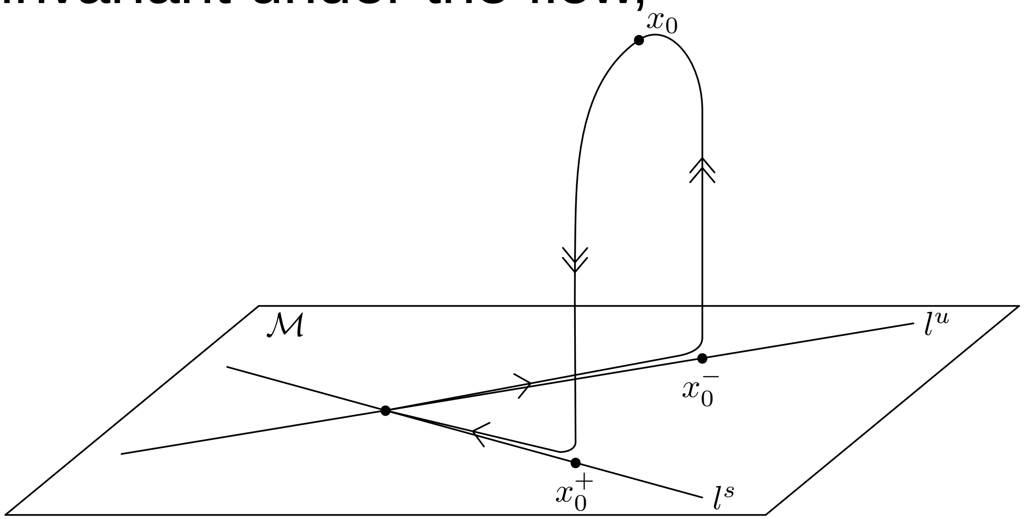
$\varepsilon = 0$

$0 < \varepsilon \ll 1$

Melnikov method:
measure $\mathcal{O}(\varepsilon)$ distance between $W^{\mathrm{u}}(\mathcal{M}_\varepsilon)$ and $W^{\mathrm{s}}(\mathcal{M}_\varepsilon)$ in some reference hyperplane.

Dynamics on $\mathcal{M}_\varepsilon$

In this example, $\mathcal{M}_0$ is still invariant under the flow, i.e., $\mathcal{M}_\varepsilon = \mathcal{M}_0$.



Substitute $A = V = 0$ to obtain flow on $\mathcal{M}_\varepsilon$:

$$\begin{cases} B' &= \varepsilon D \\ D' &= \varepsilon^3 \alpha B \end{cases}$$

Fixed point $(B, D) = (0, 0)$ clearly has saddle structure if $\alpha > 0$.

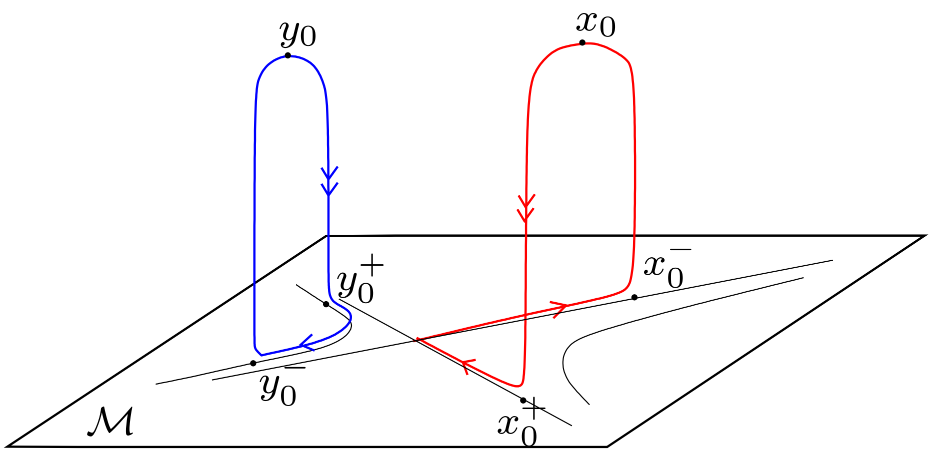
If a homoclinic orbit exists, curves l^u and l^s must serve as approximate trajectories as it reaches $(0, 0)$.

Persistent fast connections (1)

3D manifolds $\mathcal{W}^s(\mathcal{M}_\varepsilon)$ and $\mathcal{W}^u(\mathcal{M}_\varepsilon)$ in $\mathbb{R}^4$
$\Longrightarrow$ expect 2D intersection(s) $\mathcal{W}^s(\mathcal{M}_\varepsilon) \cap \mathcal{W}^u(\mathcal{M}_\varepsilon)$,
a 1-parameter family of orbits.

Melnikov function: single zeroes correspond to transversal intersections by smoothness of $W^{\mathrm{u}}(\mathcal{M}_\varepsilon)$, $W^{\mathrm{s}}(\mathcal{M}_\varepsilon)$ (Fenichel 2).
Computation based on known unperturbed hom. orbits γ_h.
$\Longrightarrow D = 0$ at leading order for orbits homoclinic to $\mathcal{M}_\varepsilon$.

$$x_0 \in \mathcal{W}^u(\mathcal{M}_\varepsilon) \cap \mathcal{W}^s(\mathcal{M}_\varepsilon) \cap \{V = 0\}$$

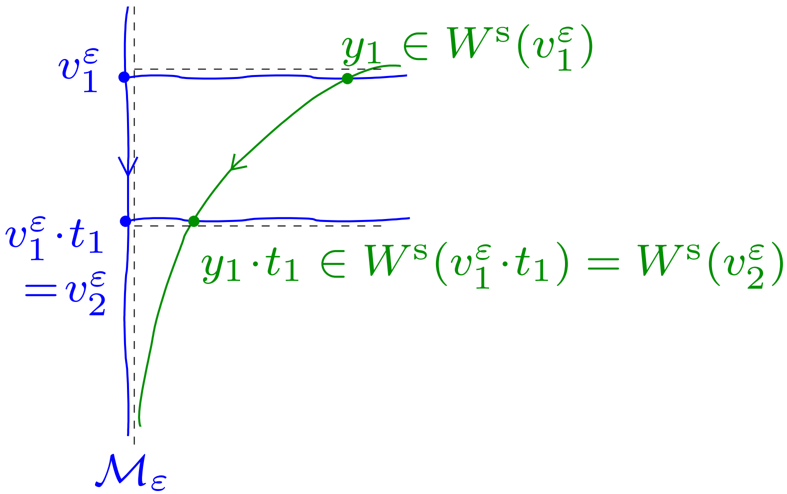


Q. Can these orbits be homoclinic to the critical point $(0,0,0,0)$?

Answer: Determined by Fenichel fibers

Take off, touch down

Recall fibers:

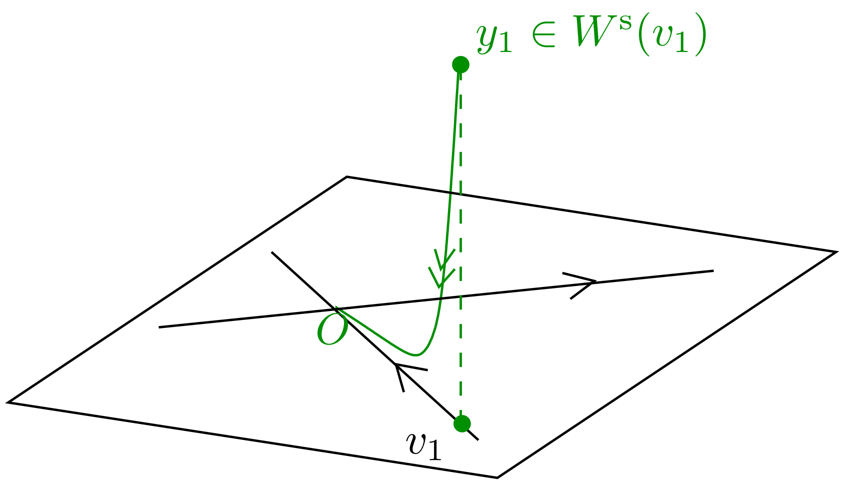


v_1 basepoint of y_1:

$\|v_1 \cdot T - y_1 \cdot T\| = \mathcal{O}(e^{-\kappa/\varepsilon})$

$\forall T > \mathcal{O}(\frac{1}{\varepsilon})$

In this case we wish:



If $\exists y_1$ with basepoint $v_1 \in l^s$:

$\|y_1 \cdot t - O\| \to 0$ as $t \to \infty$

Apply to determine homoclinic orbit to O.

Persistent fast connections (2)

Any $y_0 \in W^{\mathrm{u}}(\mathcal{M}_\varepsilon) \cap W^{\mathrm{s}}(\mathcal{M}_\varepsilon) \cap \{v = 0\}$ has basepoints $y_0^\pm \in \mathcal{M}_\varepsilon$. Define T_o and T_d as collections of all basepoints:

$$T_o = \bigcup_{y_0} y_0^-, \quad T_d = \bigcup_{y_0} y_0^+$$

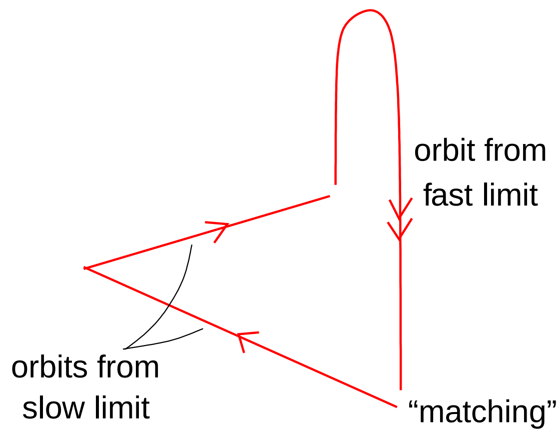
Note: depend on reference plane $\{v = 0\}$, but variation of points y_0 along fast pulse (i.e., to other ref. plane) only yields $\mathcal{O}(\varepsilon)$ variation of basepoints $y_0^\pm$, and hence of curves T_o, T_d

If $T_o \cap l^u$ and $T_d \cap l^s$ are transversal intersections, then implicit function theorem guarantees existence of orbit with basepoints on $l^{u,s}$.

For homoclinic orbit to 0, curve T_o has to intersect l^u at same B-coordinate where T_d intersects l^s.
Here automatically satisfied due to reversibility symmetry.

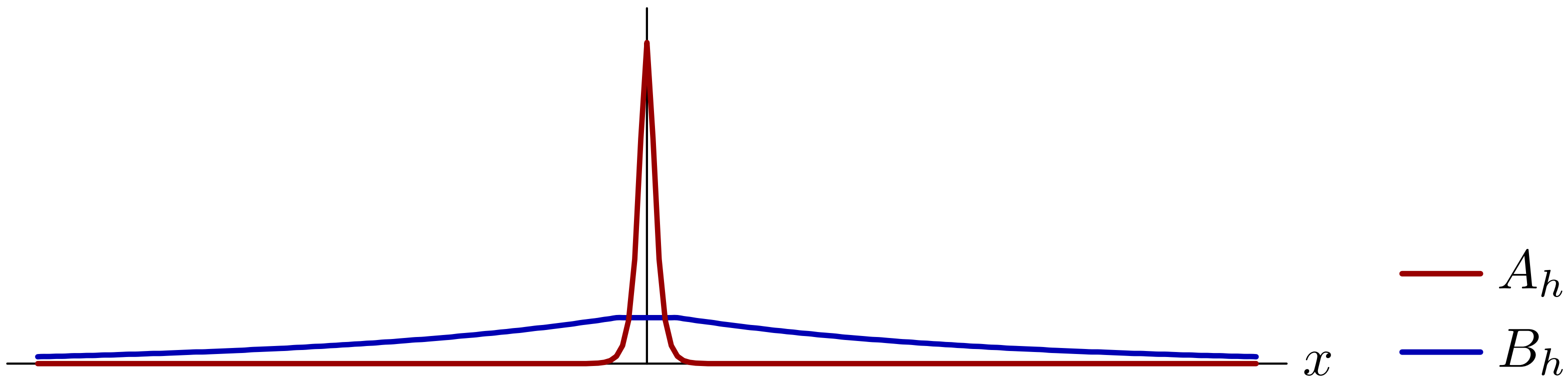
Persistence results

Results:
Homoclinic orbits with singular structure as $\varepsilon = 0$ limit:



$\beta = 0$: there is a unique pulse solution.

$\beta \neq 0$: induces bifurcations. There are open regions in parameter space with zero, one or two pulse solutions. These regions are separated by a manifold of bifurcations.



Conclusions

- Geometric singular perturbation theory is strong instrument
- Determine precise geometry and obtain results by combination of analysis and geometrical insight
- For many results more than only Fenichel's theorems needed
- Schematic pictures help a lot!