Centre Manifold Theorem

Marek Bodnar

Institute of Applied Mathematics and Mechanics,
Faculty of Mathematics, Informatics and Mechanics,
University of Warsaw

INSTITUTE OF FUNDAMENTAL TECHNOLOGICAL RESEARCH
POLISH ACADEMY OF SCIENCES

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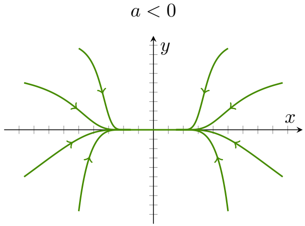
Uncoupled equations

$$\dot{x} = ax^3$$
$$\dot{y} = -y + y^2$$

- $a < 0$ then $(0, 0)$ is **stable**;
- $a > 0$ then $(0, 0)$ is **unstable**;



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$$\dot{y} = -y + y^2 + xy - x^3$$

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- But how to prove?

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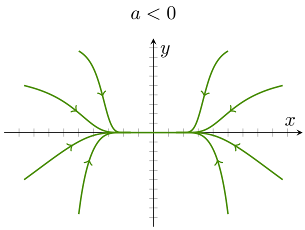

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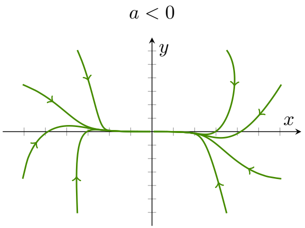

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The invariant manifold

Remark

The analysis is local, we always assume we are close to the equilibrium (usually 0).

- We want to separate equation into two, uncoupled systems;
- We have to abstract the idea of uncoupled equations;
- Interesting case: real part of some eigenvalues are 0.

Definition

A curve (or surface, or ...) $y = h(x)$ defined for small $|x|$ is called an invariant manifold for a system

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

iff solution $(x(t), y(t))$ that goes through $(x_0, h(x_0))$ stay on the manifold for small t, that is $y(t) = h(x(t))$.

The idea

$$\dot{x} = ax^3$$
$$\dot{y} = -y + y^2$$

- The invariant manifold is $y = 0$,
- so for stability of 0 solution only the equation $\dot{x} = ax^3$ is important.
- $a < 0$ then $(0, 0)$ is **stable**;
- $a > 0$ then $(0, 0)$ is **unstable**;

$$\dot{x} = ax^3 + x^2 y$$
$$\dot{y} = -y + y^2 + xy - x^3$$

We develop a theory that tells us

- there is an invariant manifold $y = h(x)$
- with $h(x) = O(x^2)$ as $x \to 0$.
- The stability can be proved studying equation

$$\dot{x} = ax^3 + x^2 h(x) = ax^3 + O(x^4).$$

- The conclusion is the same.

Existence of the Centre Manifold

We consider a system

$$\dot{x} = Ax + f(x, y)$$
$$\dot{y} = By + g(x, y) \qquad (\star)$$

- $x \in \mathbb{R}^n$, $y \in \mathbb{R}^m$; A and B — matrices;
- all eigenvalues of A have zero real parts;
- all eigenvalues of B have negative real parts;
- f, g are C^2 and contains only non-linear parts, i.e.

$$f(0,0) = 0, \quad g(0,0) = 0, \quad Df(0,0) = 0, \quad Dg(0,0) = 0.$$

(Local) Centre Manifold

An invariant manifold $\{y = h(x)\}$ of $(\star)$ is called (local) centre manifold if h is smooth, $h(0) = 0$ and $Dh(0) = 0$.

Theorem (Existence)

There exists a centre manifold for $(\star)$ $\{y = h(x)\}$, $|x| < \delta$, *for* δ *small enough, where* h *is* C^2.

Sketch of the proof:

1. Limiting equations to a ball of radius ε.
   Let $\Psi\colon \mathbb{R}^n \to [0,1]$ be a smooth function such that $\Psi(x) = 1$ for $|x| < 1$ and $\Psi(x) = 0$ for $|x| > 2$. Define

$$F(x,y) = f\left(x\frac{\Psi(x)}{\varepsilon}, y\right), \qquad G(x,y) = g\left(x\frac{\Psi(x)}{\varepsilon}, y\right)$$

   and we consider the system

$$\begin{aligned} \dot{x} &= Ax + F(x,y) \\ \dot{y} &= By + G(x,y) \end{aligned} \qquad (\diamond)$$

2. Construction of contraction.
   Let fix $p > 0$ and $p_1 > 0$. Define X a space of Lipschitz function $h\colon \mathbb{R}^n \to \mathbb{R}^m$ with Lipschitz constant p_1 and bounded by p ($|h(x)| < p$).
   For $h \in X$, $x_0 \in \mathbb{R}^n$ we consider $x(t, x_0, h)$ a solution of

$$\dot{x} = Ax + F(x, h(x)), \quad x(0, x_0, h) = x_0.$$

   Solution exists and is unique. Define now

$$(Th)(x_0) = \int_{-\infty}^{0} \mathrm{e}^{-Bs} G\Big(x(s, x_0, h), h(x(s, x_0, h))\Big) \mathrm{d}s$$

3. T is contraction on X — some calculations and proper choice of p, p_1 and ε
4. h is C^1 — we justify that T is contraction on a subset of X consisting of Lipschitz differentiable functions
5. We need to estimate second derivatives of h and show they are continuous.

Reduction principle

On the centre manifold the flow is governed by

$$\dot{u} = Au + f(u, h(u)), \quad u(t) \in \mathbb{R}^n \qquad (\star\star)$$

Theorem (Reduction Principle)

1. *Suppose that the zero solution of $(\star\star)$ is stable (asymptotically stable)(unstable). Then the zero solution of $(\star)$ is stable (asymptotically stable) (unstable).*
2. *Suppose that the zero solution of $(\star\star)$ is stable. Let $(x(t), y(t))$ be a solution of $(\star)$ with $(x(0), y(0))$ sufficiently small. Then there exists a solution $u(t)$ of $(\star\star)$ such that as $t \to +\infty$*

$$x(t) = u(t) + O(\mathrm{e}^{-\gamma t})$$
$$y(t) = h(u(t)) + O(\mathrm{e}^{-\gamma t})$$

for some $\gamma > 0$.

Sketch of the proof, part I

Lemma

Then there exist positive constants C_1 and μ such that

$$\left|y(t) - h(x(t))\right| \leq C_1 \mathrm{e}^{-\mu t}\left|y(0) - h(x(0))\right|$$

where $(x(t), y(t))$ is solution of $(\diamond)$.

We set $z = y(t) - h(x(t))$, and calculate that

$$\dot{z} = Bz + N(x, z).$$

We estimate $|N(x, z)| < \delta(\varepsilon)|z|$ and use Gronwall Lemma.

We change basis so we have $A = A_1 + A_2$, with A_2 being nilpotent, $|\mathrm{e}^{A_1 t} x| = |x|$ and $|A_2 x| \leq \frac{\beta}{4}|x|$.

0 is unstable for $(\star\star)$ than it is also unstable for $(\star)$.

Sketch of the proof, part II

We assume that 0 is stable, we are close enough to 0 so systems $(\star)$ and $(\diamond)$ are identical.

1. Using Banach Fix Point Theorem we prove that for any $u_0 \in \mathbb{R}^n$, $z_0 \in \mathbb{R}^m$ there exists solution $(x(t), y(t))$ with $y(0) = z_0 + h(x(0))$ and $|x(t) - u(t)|$, $|y(t) - h(u(t))|$ exponentially small.
2. We define a mapping $S(u_0, z_0) = (x_0, z_0)$, with $x_0 = x(0)$. By continuous dependence of solution of ODE on initial conditions, S is continuous. We prove it is one to on, so by Invariance of Domain Theorem it is an open map so it maps a neighbourhood od $(0, 0)$ on a (different) neighbourhood of $(0, 0)$.

Approximation of the Centre Manifold

On the centre manifold we have $y(t) = h(x(t))$. We introduce it to the second equation and we get

$$Dh(x)\Big(Ax + f(x, h(x))\Big) = Bh(x) + g(x, h(x))$$

and $h(0) = 0$, $Dh(0) = 0$.

Solving this is as difficult as solving original system. But the approximation works well.

For $\varphi\colon \mathbb{R}^n \to \mathbb{R}^m$ of C^1 class, define

$$(M\varphi)(x) = D\varphi(x)\Big(Ax + f(x, \varphi(x))\Big) - B\varphi(x) - g(x, \varphi(x))$$

Theorem (Approximation)

Let $\varphi\colon \mathbb{R}^n \to \mathbb{R}^m$ be C^1 in the neighbourhood of 0 with $\varphi(0) = 0$ and $D\varphi(0) = 0$. Suppose that as $x \to 0$ $(M\varphi)(x) = O(|x|^q)$ for some $q > 1$. Then $|h(x) - \varphi(x)| = O(|x|^q)$ as $x \to 0$.

Example 1

We consider a system

$$\dot{x} = xy + ax^3 + by^2x$$
$$\dot{y} = -y + cx^2 + dx^2y$$

The system has a centre manifold $y = h(x)$. To approximate h we take

$$(M\varphi)(x) = \varphi'(x)\Big(x\varphi(x) + ax^3 + bx\varphi^2(x)\Big) + \varphi(x) - cx^2 - dx^2\varphi(x).$$

If $\varphi(x) = O(x^2)$ then $(M\varphi)(x) = \varphi(x) - cx^2 + O(x^4)$.
Therefore (by Approximation Theorem), $h(x) = cx^2 + O(x^4)$ and the dynamics on the centre manifolds reads

$$\dot{u} = uh(u) + au^3 + buh^2(u) = (a + c)u^3 + O(u^5).$$

By reduction Principle we have

- $a + c < 0$ then steady state is stable
- $a + c > 0$ then steady state is unstable

Example 1, the case $a + c = 0$

Let

$$\varphi(x) = cx^2 + \psi(x), \quad \psi(x) = O(x^4).$$

We have thus,

$$(M\varphi)(x) = \varphi'(x)\Big(x\varphi(x) + ax^3 + bx\varphi^2(x)\Big) + \varphi(x) - cx^2 - dx^2\varphi(x).$$

Thus, we have $\varphi(x) = cx^2 + cdx^4 + O(x^6)$ and the stability of the zero solution is determined by

$$\dot{u} = uh(u) + au^3 + buh^2(u) = (cd + bc^2)u^5 + O(u^7).$$

If $a + c = 0$ and

- $cd + bc^2 < 0$ then steady state is stable
- $cd + bc^2 > 0$ then steady state is unstable

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If $a + c = 0$ and

- $cd + bc^2 < 0$ then steady state is stable
- $cd + bc^2 > 0$ then steady state is unstable

Example 2 — a model of CAR-T therapy

$$\dot{T} = (\rho_T f(T) - \alpha_T C)T$$
$$\dot{C} = \left(\frac{aT}{1+T} - \frac{bT}{1+C} - 1\right)C + k \qquad (\clubsuit)$$

- T — tumour cells;
- C — CAR-T cells, that is chimeric antigen receptor T cells modified in laboratory to recognise tumour cells.
- f — growth function (constant for Mathusian growth and $1 - T/K$ for the logistic one).
- k — parameter responsible for external influx of CAR-T cells (treatment).

M. Bodnar, *et al.*, *On the analysis of a mathematical model of CAR–T cell therapy for glioblastoma*, *International Journal of Applied Mathematics and Computer Science*, **33**, 379–394 (2023).

Example 2

$$\dot{T} = (\rho_T f(T) - \alpha_T C)T$$
$$\dot{C} = \left(\frac{aT}{1+T} - \frac{bT}{1+C} - 1\right)C + k \qquad (\clubsuit)$$

with $f(0) = 1$. The Jacobi Matrix for the steady state $(0, k)$ reads

$$\begin{pmatrix} \rho_T - \alpha_T k & 0 \\ \left(a - \frac{b}{1+k}\right)k & -1 \end{pmatrix} \xrightarrow{k\alpha_T = \rho_T} \begin{pmatrix} 0 & 0 \\ \left(a - \frac{b}{1+k}\right)k & -\eta_C \end{pmatrix}$$

In order to eliminate the linar term connected to the first variable from the second equation we use

$$T = x, \quad C = k + y + \beta x, \quad \beta = \left(a - \frac{b}{1+k}\right)k$$

and the system becomes

$$\dot{x} = \big(\rho_T f(x) - \alpha_T(k + y + \beta x)\big)x$$
$$\dot{y} = \left(\frac{ax}{1+x} - \frac{bx}{1+k+\beta x+y} - 1\right)(k + \beta x + y) + k + \beta\dot{x}$$

Stability of the steady state

Let $f(x) = 1 - \gamma_1 x + O(x^2)$, $\gamma_1 = -f'(0) \geq 0$. By F_x and F_y we denote right-hand sides of the first and the second equation. Assume also that $\varphi = O(x^2)$ then we have

$$F_x(x, \varphi(x)) = \Big(\rho_T(1 - \gamma_1 x + O(x^2)) - \alpha_T(k + \varphi(x) + \beta x)\Big)x$$
$$= -(\rho_T\gamma_1 + \alpha_T\beta)x^2 + O(x^3).$$

Moreover $(M\varphi)(x) = \varphi'(x)F_x(x, \varphi(x)) - F_y(x, \varphi(x)) = O(x^2)$. Thus, by reduction principle stability of the steady state is determined by stability of zero solution of

$$\dot{u} = -\left(\rho_T\gamma_1 + \alpha_T\left(a - \frac{b}{1+k}\right)k\right)u^2 + O(u^3)$$
$$= -\rho_T\left(\gamma_1 + a - \frac{b}{1+k}\right)u^2 + O(u^3)$$

- **Conclusion:** If $\rho_T = k\alpha_T$ then the steady state is stable if

$$k > \frac{b}{a + |f'(0)|} - 1$$

Lack of uniqueness

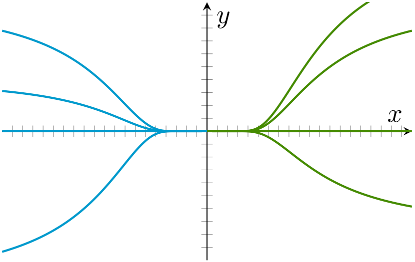
Consider the system

$$\dot{x} = -x^3, \quad \dot{y} = -y.$$

Any curve of the form

$$h(x, c_1, c_2) = \begin{cases} c_1 \exp\left(-\frac{1}{x^2}\right), & x > 0 \\ 0 & x = 0 \\ c_2 \exp\left(-\frac{1}{x^2}\right), & x < 0 \end{cases}$$

is centre manifold.



We can combine any left branch with any right branch.

If h_1 and h_2 are centre manifold, than by Approximation Theorem, $h_1(x) - h_2(x) = O(x^q)$ as $x \to 0$ for all $q > 1$.

Some properties of centre manifold

- If the function f and g (of the right-hand side) are C^k class, then centre manifold is of the same class, but it is not analytic in general even if f and g are. Example:

$$\dot{x} = -x^3, \qquad \dot{y} = -y + x^2$$

- Centre manifold need not be unique, but if an equilibrium point or periodic orbit lies on one centre manifold, it has to lie on every centre manifold.
- If the dynamics ($\star$) is defined on some subspace $S \subset \mathbb{R}^{n+m}$, then Redaction Principle is also valid on S.
- Analogous theorems are valid for difference equations

$$\begin{aligned} x_{n+1} &= Ax_n + f(x_n, y_n) \\ y_{n+1} &= By_n + g(x_n, y_n) \end{aligned}$$

Consider

$$\ddot{r} + \dot{r} + f(r) = 0$$

where f is a smooth function such that

$$f(r) = r^3 + ar^5 + O(r^7) \quad \text{as} \quad r \to 0.$$

It is possible to construct Liapunov function. However, the rate of decay cannot be determined by linearization. We show how centre manifolds can be used to estimate the decay rate.

Let $x = r + \dot{r}$, and $y = \dot{r}$. Then we have

$$\begin{aligned} \dot{x} &= -f(x-y) \\ \dot{y} &= -y - f(x-y). \end{aligned}$$

$$\begin{aligned} \dot{x} &= -f(x-y) \\ \dot{y} &= -y - f(x-y). \end{aligned} \qquad \text{(DE)}$$

- (DE) has a centre manifold $y = h(x)$
- The Reduction Principle says equation

$$\dot{u} = -f(u - h(u))$$

  determines the asymptotic behaviour of small solutions of (DE).
- Using definition of f and $h = O(u^2)$ we get

$$\dot{u} = -u^3 + O(u^4).$$

- Assume that $u(t) > 0$ for all t. Using d'Hôspital rule we have

$$-1 = \lim_{t\to+\infty} \frac{\dot{u}}{u^3} = \lim_{t\to+\infty} \frac{1}{t} \int_1^{u(t)} \frac{1}{s^3} \mathrm{d}s$$

Let w be a solution of

$$\dot{w} = -w^3, \quad w(0) = 1, \quad \Longrightarrow \quad w(t) = \frac{1}{\sqrt{2t}} + \frac{C}{t\sqrt{t}} + O(t^{-5/2}).$$

Then $u(t) = w\big(t + o(t)\big)$. Thus, we get

$$u(t) = \frac{1}{\sqrt{2t}} + o\left(\frac{1}{\sqrt{t}}\right).$$

To get further terms in the asymptotic expansion of u, we need an approximation to $h(u)$.

Introductory example

Consider

$$\dot{x} = \varepsilon x - x^3 + xy$$
$$\dot{y} = -y + y^2 - x^2.$$

We want to study dynamics of this system near the origin for small $|\varepsilon|$ (later we will apply this for the bifurcation theory).

We cannot apply developed theory directly, as eigenvalues of the system are -1 and ε. But we may write

$$\begin{aligned}\dot{x} &= \varepsilon x - x^3 + xy \\ \dot{y} &= -y + y^2 - x^2 \\ \dot{\varepsilon} &= 0.\end{aligned} \qquad (\heartsuit)$$

This system has eigenvalues 0, 0, and -1 (the term εx is now non-linear).

Centre manifold for the system (♡)

$$\dot{x} = \varepsilon x - x^3 + xy$$
$$\dot{y} = -y + y^2 - x^2$$
$$\dot{\varepsilon} = 0.$$

The system has centre manifold of the form $y = h(x, \varepsilon)$ for small $|x|$ and $|\varepsilon|$.

We are looking for an approximation φ of the manifold h. We have

$$\begin{aligned}(M\varphi)(x, \varepsilon) &= \partial_x \varphi(x, \varepsilon)\dot{x} + \partial_\varepsilon \dot{\varepsilon} + \varphi(x, \varepsilon) - \varphi^2(x, \varepsilon) + x^2 \\ &= \partial_x(\varepsilon x - x^3 + x\varphi(x, \varepsilon)) + \varphi(x, \varepsilon) - \varphi^2(x, \varepsilon) + x^2\end{aligned}$$

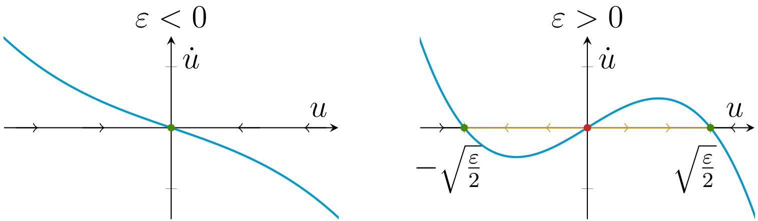
If $\varphi(x, \varepsilon) = -x^2$ then $(M\varphi)(x, \varepsilon) = O(C(x, \varepsilon))$, where C is homogeneous cubic in x and ε.

Thus, the Approximation Theorem implies that $h(x, \varepsilon) = -x^2 + O(C(x, \varepsilon))$ and the Reduction Principle we can consider only a system

$$\dot{u} = \varepsilon u - 2u^3 + O(|u|C(u, \varepsilon))$$
$$\dot{\varepsilon} = 0$$

- $\varepsilon < 0$, small $\implies$ stable
- $\varepsilon > 0$, small $\implies$ unstable

$$\dot{u} = u\Big(\varepsilon - 2u^2 + O(C(u,\varepsilon))\Big)$$



- For $\varepsilon < 0$ the zero solution is locally asymptotically stable;
- For $\varepsilon > 0$ the solutions of the equation for u consist of two orbits connecting 0 and $\pm\sqrt{\frac{\varepsilon}{2}}$. Hence, the stable manifold of the original system forms a separatrix, while the unstable one consists of the orbit connecting $(0,0)$ with two other equilibria.

The model arise from a model of the kinetics of enzyme reactions.

$$\dot{y} = -y + (y + c)z$$
$$\varepsilon\dot{z} = y - (y + 1)z$$

where $\varepsilon > 0$ is small, $0 < c < 1$. Quasi-stationary approximation gives

$$z = \frac{y}{y+1} \implies \dot{y} = \frac{-\lambda y}{1+y}, \ \lambda = 1 - c.$$

Using perturbation techniques it can be shown that for small ε solutions of both systems are close to each other.

We get similar result using centre manifold.

F.G. Heinenken, H.M. Tsuchiya and R. Aris, On the mathematical status of the pseudo-steady state hypothesis of biochemical kinetics, *Math. Biosci*, **1**, 95–113, (1967).

Let $\tau = \varepsilon t, \quad f(y, w) = -y + (y + c)(y - w), \quad w = y - z$

$$f(y, w) = -\lambda y - cw + y(y - w)$$

$$\begin{aligned} \dot{y} &= -y + (y + c)z \\ \varepsilon \dot{z} &= y - (y + 1)z \end{aligned} \quad \Longrightarrow \quad \begin{aligned} y' &= \varepsilon f(y, w), \\ w' &= -w + y^2 - yw + \varepsilon f(y, w) \\ \varepsilon' &= 0 \end{aligned}$$

By the Existence Theorem, there exists centre manifold $w = h(y, \varepsilon)$

We are looking for approximation of the manifold.

$$(M\varphi)(y, \varepsilon) = \varepsilon \partial_y \varphi(y, \varepsilon) f(y, \varphi) + \varphi(y, \varepsilon) - y^2 + y\varphi(y, \varepsilon) - \varepsilon f(y, \varphi)$$

If $\varphi = y^2 - \lambda \varepsilon y$ then $(M\varphi)(y, \varepsilon) = O(|y|^3 + |\varepsilon|^3)$ so

$$h(y, \varepsilon) = y^2 - \lambda \varepsilon y + O(|y|^3 + |\varepsilon|^3)$$

By reduction principle the dynamics is governed by

$$u' = \varepsilon f(u, h(u, \varepsilon)),$$

reverting to the original time scale

$$\dot{u} = f(u, h(u, \varepsilon)) = -\lambda(u - u^2) + O(|\varepsilon u| + |u|^3)$$

and for sufficiently small $y(0)$ and $z(0)$ there exists a solution u and parameter $\gamma > 0$ such that

$$y(t) = u(t) + O(\mathrm{e}^{-\gamma t/\varepsilon})$$
$$z(t) = y(t) - h(y(t), \varepsilon) + O(\mathrm{e}^{-\gamma t/\varepsilon})$$

Making the result great again

Our result is local. But we can extend it.

Assume that $\bar{y} \neq -1$. Then

$$
\begin{aligned}
y' &= \varepsilon f(y,w),\\
w' &= -w + y^2 - yw + \varepsilon f(y,w)\\
\varepsilon' &= 0
\end{aligned}
$$

$$\left(\bar{y}, \frac{\bar{y}^2}{1+\bar{y}}, 0\right)$$ is a curve of the equilibrium points.

We expect that there is an invariant manifold $w = h(y,\varepsilon)$ defined for small ε and $0 \leq y \leq m = O(1)$ with h close to the curve

$$w = \frac{y^2}{1+y}.$$

For initial data close to that curve, the stability properties of the oryginal system are the same as the stability properties of the reduced equation.

Global Invariant Manifolds

$$
\begin{aligned}
x' &= Ax + \varepsilon f(x, y, \varepsilon) \\
y' &= By + \varepsilon g(x, y, \varepsilon) \\
\varepsilon' &= 0
\end{aligned}
$$

Theorem

- *Eigenvalues of A have zero real parts*
- *eigenvalues of B have negative real parts*
- $x \in \mathbb{R}^n$, $y \in \mathbb{R}^m$, $\varepsilon \in \mathbb{R}$,
- f, g *are* C^2 *with* $f(0, 0, 0) = g(0, 0, 0) = 0$

Let $a > 0$. *Then,*

- *there is* $\delta > 0$ *such that*
- *the system has invariant manifold* $y = h(x, \varepsilon)$ *for* $|x| < a$, $|\varepsilon| < \delta$,
- $|h(x, \varepsilon)| < C|\varepsilon|$.
- *The constant* C *depends on* a, A, B, f *and* g.

- Define smooth cut-off function $\Psi(x) = 1$ for $|x| < a$ and $\Psi(x) = 0$ for $|a| > a + 1$.
- Take $F(x, y, \varepsilon) = \varepsilon f(x\Psi(x), y, \varepsilon)$ and $G(x, y, \varepsilon) = \varepsilon g(x\Psi(x), y, \varepsilon)$.
- Like in the proof of existence of the centre manifold we prove the existence of the manifold for

$$\begin{aligned} x' &= Ax + F(x, y, \varepsilon) \\ y' &= Ay + G(x, y, \varepsilon) \end{aligned}$$

for $|\varepsilon|$ small enough.

- The flow on he invariant manifold is given by the equation

$$u' = Au + \varepsilon f(u, h(u, \varepsilon), \varepsilon)$$

- The Approximation Theorem:
  - $\varphi \colon \mathbb{R}^{n+1} \to \mathbb{R}^m$, $\varphi(0, 0) = 0$.
  - $|(M\varphi)(x, \varepsilon)| < C|\varepsilon|^p$, $p > 1$ for $|x| < a$ and

$$(M\varphi) = D_x\varphi\Big(Ax - \varepsilon f(x, \varphi, \varepsilon)\Big) - B\varphi - \varepsilon g(x, \varphi, \varepsilon)$$

Then

- $\Big|h(x, \varepsilon) - \varphi(x, \varepsilon)\Big| < C_1|\varepsilon|^p$

for $|x| < a$ and some constant C_1.

Immune response to a replicating antigen

- The model originates from the work of: S.J. Merrill, A model of the stimulation of B-cells by replicating antigen I, *Mathematical Biosciences*, **41**(1–2), 125–141 (1978).
- Describes the interaction between:
  - replicating antigen,
  - antigen-specific B-cells,
  - antibodies.
- Explains immune activation and high-zone tolerance via nonlinear feedback mechanisms.

The model description was prepared by ChatGPT as I could not get the digital version of the Merrill's paper.

Reduced dynamical system

The model description was prepared by ChatGPT as I could not get the digital version of the Merrill's paper.

$$\begin{aligned}\varepsilon\dot{x} &= -\left(x^3 + \left(a - \frac{1}{2}\right)x + b - \frac{1}{2}\right),\\ \dot{a} &= \frac{1}{2}\delta(1-x) - a - \gamma_1 ab,\\ \dot{b} &= -\gamma_1 ab + \gamma_2 b.\end{aligned} \tag{IM}$$

- x – immune activation variable representing the effective level of immune stimulation
  - it does not correspond to a single biological population;
  - encodes the global state of the immune response;
  - $|x| < 1$;
- $a \geq 0$ – effective population of antigen-specific B-cells.
- $b \geq 0$ – antibody (or antigen–antibody complexes) concentration.

- It was used a quasi-stationary approximation getting $x = F(a,b)$
- In the system

$$\dot{a} = \frac{1}{2}\delta(1 - F(a,b)) - a - \gamma_1 ab,$$
$$\dot{b} = -\gamma_1 ab + \gamma_2 b.$$

  the existence of the Hopf bifurcation was proved using δ as a parameter.
- By appealing to a result in singular perturbation theory, it was concluded that for ε sufficiently small, (IM) also has a periodic solution.

Let $(\bar{x}, \bar{a}, \bar{b})$ be an equilibrium point of (IM). From the last equation(assuming $\bar{b} > 0$):

$$\gamma_1 \bar{a}\bar{b} = \gamma_2 \bar{b} \implies \bar{a} = \frac{\gamma_2}{\gamma_1}.$$

Thus,

$$\begin{aligned} \bar{x}^3 + \left(\frac{\gamma_2}{\gamma_1} - \frac{1}{2}\right)\bar{x} + \bar{b} - \frac{1}{2} &= 0 \\ \frac{1}{2}\delta(1 - \bar{x}) - \frac{\gamma_2}{\gamma_1} - \gamma_2 \bar{b} &= 0 \end{aligned} \qquad (\spadesuit)$$

We assume that $|\bar{x}| < 1$, $\bar{b} \geq 0$ and $\bar{a} = \frac{\gamma_2}{\gamma_1}$ and define

$$y = a - \bar{a}, \quad z = b - \bar{b}, \quad w = -\psi(\bar{x}, \bar{a})(x - \bar{x}) - \bar{x}y - z,$$

with $\psi(\bar{x}, \bar{a}) = 3\bar{x}^2 + \bar{a} - \frac{1}{2}$.

A system after change of variables

Assuming $\psi \neq 0$ we get

$$\begin{aligned} \varepsilon \dot{w} &= g(w, y, z, \varepsilon), \\ \dot{y} &= f_2(w, y, z, \varepsilon), \\ \dot{z} &= f_3(w, y, z, \varepsilon), \end{aligned}$$

where

$$\begin{aligned} g(w, y, z, \varepsilon) &= f_1(w, y, z, \varepsilon) - \varepsilon \bar{x} f_2(w, y, z, \varepsilon) - \varepsilon f_3(w, y, z, \varepsilon) \\ f_1(w, y, z, \varepsilon) &= -\psi w + N(w + \bar{x} y + z, y) \\ f_2(w, y, z, \varepsilon) &= \left(\frac{\delta \bar{x}}{2\psi} - 1 - \gamma_1 \bar{b} \right) y + \left(\frac{\delta}{2\psi} - \gamma_2 \right) z + \frac{\delta}{2\psi} w - \gamma_1 y z \\ f_3(w, y, z, \varepsilon) &= -\gamma_1 \bar{b}\, y - \gamma_1 y z \\ N(\theta, y) &= -\frac{\theta^3}{\psi^{-2}} + \frac{3\theta^2 \bar{x}}{\psi^{-1}} - y\theta \end{aligned}$$

Getting periodic solution

- We change time scale $t = \varepsilon s$ and get the system

$$w' = g(w, y, z\varepsilon), \quad y' = \varepsilon f_2(w, y, z\varepsilon), \quad z' = \varepsilon f_3(w, y, z\varepsilon), \quad \varepsilon' = 0.$$

- The system has a centre manifold $w = h(y, z, \varepsilon)$ and the local behavior of solutions is determined by the equation (in terms of the original time scale)

$$\dot{y} = f_2\big(h(y, z, \varepsilon), y, z\varepsilon\big)$$
$$\dot{z} = f_3\big(h(y, z, \varepsilon), y, z\varepsilon\big)$$

- Now we show that this system has periodic solution bifurcating from the origin for certain values of the parameters

The linearization near $y = 0$, $z = 0$ gives

$$J(\varepsilon) = \begin{bmatrix} \frac{\delta \bar{x}}{2\psi} - 1 - \gamma_1 \bar{b} & \frac{\delta}{2\psi} - \gamma_2 \\ -\gamma_1 \bar{b} & 0 \end{bmatrix} + O(\varepsilon)$$

For the Hopf bifurcation we need $\mathrm{tr} J(\varepsilon) = 0$ and $\frac{\delta}{2\psi} - \gamma_2 > 0$.
Clearly, $\bar{x}$ and $\bar{b}$ must be solution of (♠) with $|\bar{x}| < 1$ and $\bar{b} > 0$

Lemma

Let $\gamma_1 < 2\gamma_2$. Then for each $\varepsilon > 0$ there exist $\delta(\varepsilon)$, $\bar{x}(\varepsilon)$, $\bar{b}(\varepsilon)$ such that

- $0 < 2\bar{x}(\varepsilon) < 1, \quad \bar{b}(\varepsilon) > 0, \quad \psi > 0$
- $\delta(\varepsilon) > 2\psi\gamma_2, \quad \mathrm{tr} J(\varepsilon) = 0$
- (♠) *is satisfied.*

Getting periodic solution

- Denoting by $\bar{x}(\varepsilon,\delta)$, $\bar{b}(\varepsilon,\delta)$ solution of (♠) with δ close to $\delta(\varepsilon)$ we calculate
$$\frac{\partial}{\partial\delta}\mathrm{tr}J(\varepsilon,\delta)\bigg|_{\delta=\delta(\varepsilon)} < 0$$
- With $\ell(\varepsilon) = \sqrt{\gamma_1\bar{b}} + O(\varepsilon)$, $m(\varepsilon) = \sqrt{\frac{\delta}{2\psi} - \gamma_2} + O(\varepsilon)$, setting $y_1 = \ell(\varepsilon)z$, $z_1 = m(\varepsilon)y$ we transform the system into
$$\dot{y}_1 = -\omega_0 z_1 - \frac{\gamma_1}{m_1}y_1 z_1$$
$$\dot{z}_1 = \omega_0 y_1 + \frac{m\delta}{2\psi}h(y,z,\varepsilon) - \frac{\gamma_1}{\ell}y_1 z_1$$
with
$$\omega_0^2 = \gamma_1\bar{b}\left(\frac{\delta}{2\psi} - \gamma_2\right) + O(\varepsilon).$$
- Changing into polar coordinates we get expression for the limit cycle. The stability of the periodic solution can be also calculated.

After some calculations we get

$$h(y,z) = \varphi_2 - \frac{(\bar{x}y+z)^3}{\psi^3} + 6\frac{\bar{x}(\bar{x}y+z)}{\psi^2}\varphi_2 - \frac{y}{\psi}\varphi_2 + O(y^4+z^4)$$

where

$$\varphi_2(y,z) = \frac{3\bar{x}(\bar{x}y+z)^2}{\psi^2} - \frac{y(\bar{x}y+z)}{\psi}$$

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Thank you!