Gene Regulatory Network and Functional Analysis: Hopf Bifurcation causes by molecular movement

Mariya Ptashnyk

Division of Mathematics, University of Dundee

joined work with Mark Chaplain and Marc Sturrock

Third Scottish PDE Colloquium

June 2, 2015

UNIVERSITY OF DUNDEE

Cell signalling and Gene regulatory networks

Cell signalling: the ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis.

Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, abnormal growth in plants. By understanding cell signalling, diseases may be treated effectively.

Signaling molecules interact with a target cell as a ligand to cell surface receptors, and/or by entering into the cell through its membrane or endocytosis for intracellular signaling.

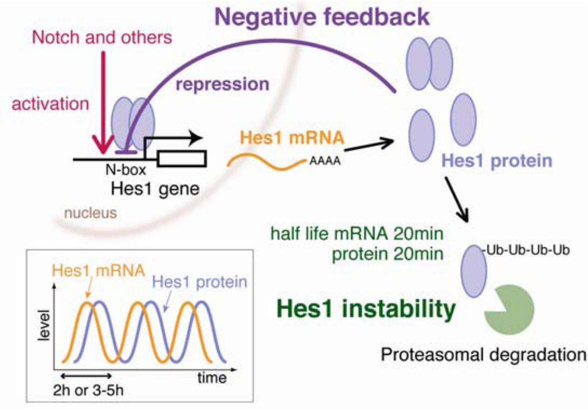
Wikipedia

Gene regulatory networks are at the heart of intercellular signal transduction and control many important cellular functions.

Biological background

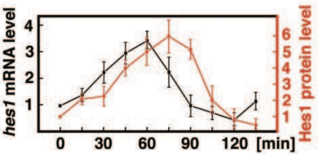
- Gene regulatory network (GRN): collection of DNA segments in a cell which interact with each other to governing the gene expression levels of mRNA and proteins
- Gene Hes1 contributes to heterogeneous differentiation responses of embryonic stem cells (nervous and digestive systems)
- Hes1 enhances the self-renewal and tumourigenicity of stem-like cancer cells in colon cancer
- Hes1 can repress its own expression by directly binding to N-box target sequences in its own promoter, thus forming a negative feedback loop

Hes1 gene expression

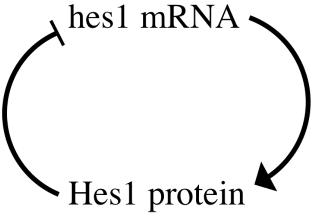


T. Kobayashi, R. Kageyama, Genes 2011

Hes1 experimental data
Hirata et al. (2002)



DDE model - Monk (2003)



$$\frac{dm(t)}{dt} = \frac{\alpha_m}{1 + (p(t)/\hat{p})^h} - \mu_m m(t)$$
$$\frac{dp(t)}{dt} = \alpha_p m(t) - \mu_p p(t)$$

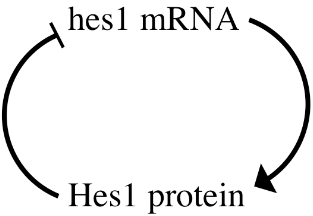
no oscillatory behaviour

stable steady state

Adding delay produces oscillatory dynamics

$$\frac{dm(t)}{dt} = \frac{\alpha_m}{1 + (p(t-\tau_m)/\hat{p})^h} - \mu_m m(t), \qquad h > 1$$
$$\frac{dp(t)}{dt} = \alpha_p m(t-\tau_p) - \mu_p p(t)$$
$$m(t) = m_0(t) \quad t \in [-\tau_m, 0], \qquad p(t) = p_0(t) \quad t \in [-\tau_p, 0]$$

DDE model - Monk (2003)



$$\frac{dm(t)}{dt} = \frac{\alpha_m}{1 + (p(t)/\hat{p})^h} - \mu_m m(t)$$
$$\frac{dp(t)}{dt} = \alpha_p m(t) - \mu_p p(t)$$

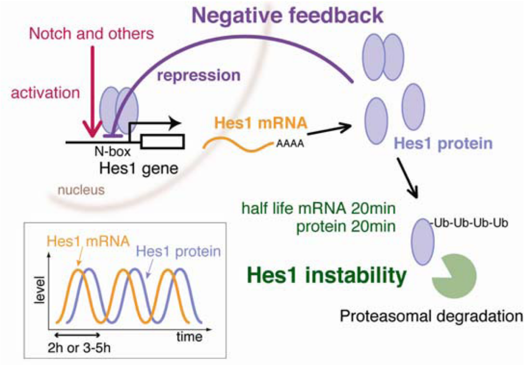
no oscillatory behaviour

stable steady state

Adding delay produces oscillatory dynamics

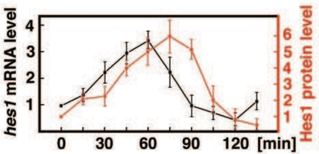
$$\frac{dm(t)}{dt} = \frac{\alpha_m}{1 + (p(t - \tau_m)/\hat{p})^h} \quad -\mu_m m(t), \qquad h > 1$$
$$\frac{dp(t)}{dt} = \alpha_p m(t - \tau_p) \quad -\mu_p p(t)$$
$$m(t) = m_0(t) \quad t \in [-\tau_m, 0], \qquad p(t) = p_0(t) \quad t \in [-\tau_p, 0]$$

Hes1 gene expression oscillation



T. Kobayashi, R. Kageyama, Genes 2011

Hes1 experimental data
Hirata et al. (2002)



Interaction between cell nucleus and cell cytoplasm:

transcription (mRNA production) in nucleus and
translation (protein production) in cytoplasm

Mathematical Model

Negative feedback loop between Hes1 protein p and its mRNA m.

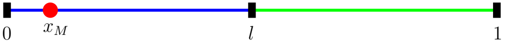
$$\frac{\partial m}{\partial t} = D\frac{\partial^2 m}{\partial x^2} + \alpha_m f(p)\delta^{\varepsilon}_{x_M}(x) - \mu_m m \qquad \text{in } (0,T)\times(0,1)$$

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} + \alpha_p g(x)\, m - \mu_p p \qquad \text{in } (0,T)\times(0,1),$$

$f : \mathbb{R} \to \mathbb{R}$ is a Hill function $f(p) = \dfrac{1}{(1+p^h)}$, with $h \geq 1$

$\delta^{\varepsilon}_{x_M}$- Dirac sequence

$$g(x) = \begin{cases} 0, & \text{if } x < l\ , \\ 1, & \text{if } x \geq l\ , \end{cases}$$



x_M- position of the centre of the gene site, $(l, 1)$- cell cytoplasm

Mathematical Model

Negative feedback loop between Hes1 protein p and its mRNA m.

$$\frac{\partial m}{\partial t} = D\frac{\partial^2 m}{\partial x^2} + \alpha_m f(p)\delta^{\varepsilon}_{x_M}(x) - \mu_m m \qquad \text{in } (0,T)\times(0,1)$$

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} + \alpha_p g(x)\, m - \mu_p p \qquad \text{in } (0,T)\times(0,1),$$

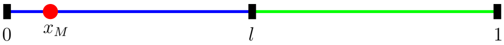
$$m_x(t,0) = m_x(t,1) = p_x(t,0) = p_x(t,1) = 0 \qquad \text{in } (0,T)$$

$$m(0,x) = m_0(x), \quad p(0,x) = p_0(x) \qquad \text{in } (0,1)$$

$f : \mathbb{R} \to \mathbb{R}$ is a Hill function $f(p) = \dfrac{1}{(1+p^h)}$, with $h \geq 1$

$\delta^{\varepsilon}_{x_M}$- Dirac sequence

$$g(x) = \begin{cases} 0, & \text{if } x < l\,, \\ 1, & \text{if } x \geq l\,, \end{cases}$$



x_M- position of the centre of the gene site, $(l,1)$- cell cytoplasm

Existence of a unique solution and estimates

Theorem

For $\varepsilon > 0$ and $m_0, p_0 \in H^2(0,1)$ with $m_0(x), p_0(x) \geq 0 \in (0,1)$:

$m^\varepsilon, p^\varepsilon \in C([0,\infty); H^2(0,1))$, $\partial_t m^\varepsilon, \partial_t p^\varepsilon \in L^2((0,T)\times(0,1))$,

$m^\varepsilon, p^\varepsilon \in C^{(\gamma+1)/2,\gamma+1}([0,T]\times[0,1])$, for some $\gamma > 0$ and any $T > 0$

$$\|m^\varepsilon\|_{L^\infty(0,T;H^1(0,1))} + \|p^\varepsilon\|_{L^2(0,T;H^2(0,1))} \leq C$$
$$\|\partial_t m^\varepsilon\|_{L^2((0,T)\times(0,1))} + \|\partial_t p^\varepsilon\|_{L^2(0,T;H^1(0,1))} \leq C$$

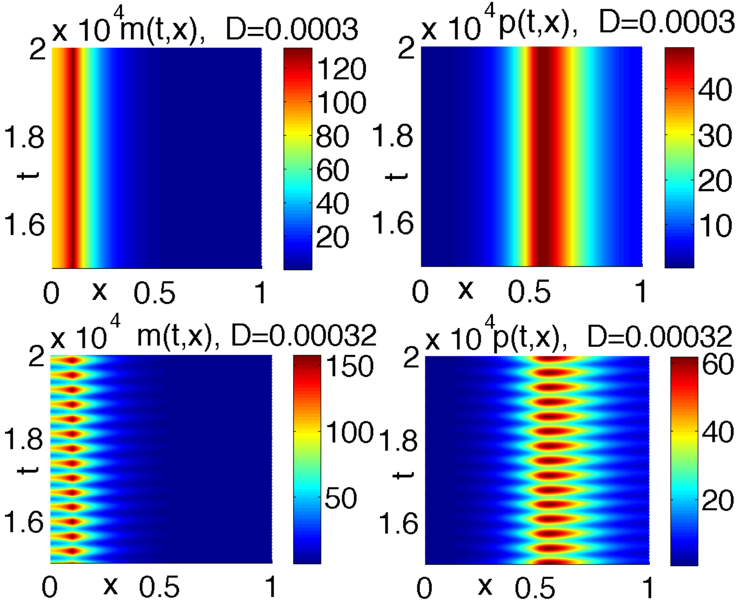
independent of ε

- Global boundedness: method of invariant regions

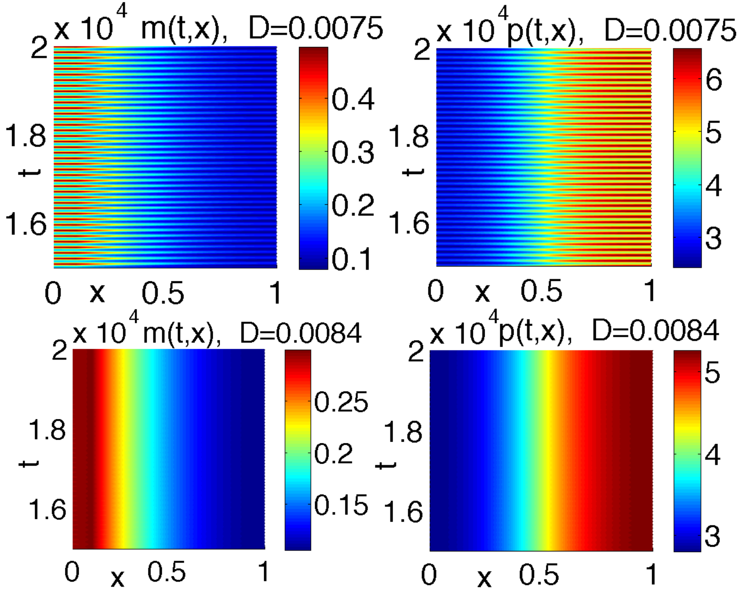
$$F_m|_{m=0} \geq 0 \quad \text{for } p \geq 0, \quad F_p|_{p=0} \geq 0 \quad \text{for } m \geq 0,$$
$$F_m|_{m=\alpha_m/(\mu\varepsilon)} \leq 0, \quad F_p|_{p=\alpha_m\alpha_p/(\mu^2\varepsilon)} \leq 0 \ \text{ for } m \leq \alpha_m/(\mu\varepsilon).$$

- Using m, p, $\partial_t m$, $\partial_t p$ and $\partial_x^2 p$ as test functions.

Numerical simulations for $D = 3 \cdot 10^{-4}$ and $D = 3.2 \cdot 10^{-4}$



Numerical simulations for $D = 7.5 \cdot 10^{-3}$ and $D = 8.4 \cdot 10^{-3}$



Stationary solutions

$$D\frac{d^2 m_\varepsilon^*}{dx^2} + \alpha_m f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon(x) - \mu_m m_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

$$D\frac{d^2 p_\varepsilon^*}{dx^2} + \alpha_p g(x)\, m_\varepsilon^* - \mu_p p_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

+ homogeneous Neumann b.c.

$$\tilde{\mathcal{A}}_{0,j} = \left(D\frac{d^2}{dx^2} - \mu_j\right),\ j = m, p$$

with $\mathcal{D}(\tilde{\mathcal{A}}_{0,j}) = \{v \in H^2(0,1) :\ v'(0) = v'(1) = 0\}$

is invertible and

$$m_\varepsilon^*(x,D) = \alpha_m(-\tilde{\mathcal{A}}_{0,m})^{-1}(f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon)$$

$$p_\varepsilon^*(x,D) = \alpha_m\alpha_p(-\tilde{\mathcal{A}}_{0,p})^{-1}(g(x)\,(-\tilde{\mathcal{A}}_{0,m})^{-1}(f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon))$$

For $\quad K(p) = \alpha_m\alpha_p(-\tilde{\mathcal{A}}_{0,p})^{-1}\left[g(x)(-\tilde{\mathcal{A}}_{0,m})^{-1}\left[\delta_{x_M}^\varepsilon f(p)\right]\right]$

$$p_\varepsilon^*(x,D) = K(p_\varepsilon^*(x,D))$$

Stationary solutions

$$D\frac{d^2 m_\varepsilon^*}{dx^2} + \alpha_m\, f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon(x) - \mu_m\, m_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

$$D\frac{d^2 p_\varepsilon^*}{dx^2} + \alpha_p\, g(x)\, m_\varepsilon^* - \mu_p\, p_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

$+$ homogeneous Neumann b.c.

$$\tilde{\mathcal{A}}_{0,j} = \left(D\frac{d^2}{dx^2} - \mu_j\right),\ j = m, p$$

with $\mathcal{D}(\tilde{\mathcal{A}}_{0,j}) = \{v \in H^2(0,1):\ v'(0) = v'(1) = 0\}$

is invertible and

$$m_\varepsilon^*(x,D) = \alpha_m(-\tilde{\mathcal{A}}_{0,m})^{-1}(f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon)$$

$$p_\varepsilon^*(x,D) = \alpha_m\alpha_p(-\tilde{\mathcal{A}}_{0,p})^{-1}(g(x)\,(-\tilde{\mathcal{A}}_{0,m})^{-1}(f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon))$$

For $\quad K(p) = \alpha_m\alpha_p(-\tilde{\mathcal{A}}_{0,p})^{-1}\left[g(x)(-\tilde{\mathcal{A}}_{0,m})^{-1}\left[\delta_{x_M}^\varepsilon f(p)\right]\right]$

$$p_\varepsilon^*(x,D) = K(p_\varepsilon^*(x,D))$$

Stationary solutions

$$D\frac{d^2 m_\varepsilon^*}{dx^2} + \alpha_m f(p_\varepsilon^*)\, \delta_{x_M}^\varepsilon(x) - \mu_m m_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

$$D\frac{d^2 p_\varepsilon^*}{dx^2} + \alpha_p g(x)\, m_\varepsilon^* - \mu_p p_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

$+$ homogeneous Neumann b.c.

$$\tilde{\mathcal{A}}_{0,j} = \left(D\frac{d^2}{dx^2} - \mu_j\right),\ j = m, p$$

with $\mathcal{D}(\tilde{\mathcal{A}}_{0,j}) = \{v \in H^2(0,1) :\ v'(0) = v'(1) = 0\}$

is invertible and

$$m_\varepsilon^*(x, D) = \alpha_m (-\tilde{\mathcal{A}}_{0,m})^{-1}(f(p_\varepsilon^*)\, \delta_{x_M}^\varepsilon)$$

$$p_\varepsilon^*(x, D) = \alpha_m \alpha_p (-\tilde{\mathcal{A}}_{0,p})^{-1}(g(x)\, (-\tilde{\mathcal{A}}_{0,m})^{-1}(f(p_\varepsilon^*)\, \delta_{x_M}^\varepsilon))$$

For $\quad K(p) = \alpha_m \alpha_p (-\tilde{\mathcal{A}}_{0,p})^{-1} \left[g(x)(-\tilde{\mathcal{A}}_{0,m})^{-1} \left[\delta_{x_M}^\varepsilon f(p)\right]\right]$

$$p_\varepsilon^*(x, D) = K(p_\varepsilon^*(x, D))$$

Stationary solutions

$$D\frac{d^2 m_\varepsilon^*}{dx^2} + \alpha_m\, f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon(x) - \mu_m\, m_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

$$D\frac{d^2 p_\varepsilon^*}{dx^2} + \alpha_p\, g(x)\, m_\varepsilon^* - \mu_p\, p_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

$+$ homogeneous Neumann b.c.

$$\tilde{\mathcal{A}}_{0,j} = \left(D\frac{d^2}{dx^2} - \mu_j\right),\ j = m, p$$

with $\mathcal{D}(\tilde{\mathcal{A}}_{0,j}) = \{v \in H^2(0,1):\ v'(0) = v'(1) = 0\}$

is invertible and

$$m_\varepsilon^*(x,D) = \alpha_m(-\tilde{\mathcal{A}}_{0,m})^{-1}(f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon)$$

$$p_\varepsilon^*(x,D) = \alpha_m\alpha_p(-\tilde{\mathcal{A}}_{0,p})^{-1}(g(x)\,(-\tilde{\mathcal{A}}_{0,m})^{-1}(f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon))$$

For $\quad K(p) = \alpha_m\alpha_p(-\tilde{\mathcal{A}}_{0,p})^{-1}\left[g(x)(-\tilde{\mathcal{A}}_{0,m})^{-1}\left[\delta_{x_M}^\varepsilon f(p)\right]\right]$

$$p_\varepsilon^*(x,D) = K(p_\varepsilon^*(x,D))$$

Stationary solutions

For $$K(p) = \alpha_m \alpha_p (-\tilde{\mathcal{A}}_{0,p})^{-1} \left[g(x)(-\tilde{\mathcal{A}}_{0,m})^{-1} \left[\delta^{\varepsilon}_{x_M} f(p) \right] \right]$$

$$p^*_\varepsilon(x, D) = K(p^*_\varepsilon(x, D))$$

- $K : C([0,1]) \to C([0,1])$ is compact
- $\mathcal{Q} = \{p \in C([0,1]) : 0 \leq p(x) \leq C + 1 \text{ for } x \in [0,1]\}$ closed convex bounded subset of $C([0,1])$
- $K(p) > 0$ for $p \geq 0$ $\quad \Longrightarrow \quad$ $p - K(p) \neq 0$ for $p \in \partial\mathcal{Q}$.
- Leray-Schauder degree theory guarantees the existence of a positive stationary solution.

For nonnegative stationary solutions we have *a priori* estimates

$$\|m^*_\varepsilon\|_{H^1(0,1)} + \|m^*_\varepsilon\|_{C([0,1])} + \|p^*_\varepsilon\|_{H^1(0,1)} + \|p^*_\varepsilon\|_{H^2(0,1)} \leq C$$

uniformly in ε.

Stationary solutions: Isolate and Unique

$$D\frac{d^2 m_\varepsilon^*}{dx^2} + \alpha_m f(p_\varepsilon^*)\, \delta_{x_M}^\varepsilon(x) - \mu_m m_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

$$D\frac{d^2 p_\varepsilon^*}{dx^2} + \alpha_p g(x)\, m_\varepsilon^* - \mu_p p_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

The linearised equations at the steady state $(m_\varepsilon^*, p_\varepsilon^*)$:

$$\mathcal{A}\begin{pmatrix} u_1 \\ u_2 \end{pmatrix} = 0, \qquad \mathcal{A} = \mathcal{A}_0 + \mathcal{A}_1,$$

where
$$\mathcal{A}_0 = \begin{pmatrix} D\frac{d^2}{dx^2} - \mu_m & 0 \\ 0 & D\frac{d^2}{dx^2} - \mu_p \end{pmatrix}$$

with $\mathcal{D}(\mathcal{A}_0) = \{v \in H^2(0,1) \times H^2(0,1) : \; v'(0) = 0, \; v'(1) = 0\}$

and the bounded operator

$$\mathcal{A}_1 = \begin{pmatrix} 0 & \alpha_m f'(p_\varepsilon^*(x,D))\, \delta_{x_M}^\varepsilon(x) \\ \alpha_p g(x) & 0 \end{pmatrix}$$

If $\mathcal{A}$ is invertible

$\Longrightarrow$ Family in $D \in [d_1, d_2]$ of isolated positive stationary solutions.

Stationary solutions: Isolate and Unique

$$D\frac{d^2 m_\varepsilon^*}{dx^2} + \alpha_m f(p_\varepsilon^*)\,\delta_{x_M}^\varepsilon(x) - \mu_m m_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

$$D\frac{d^2 p_\varepsilon^*}{dx^2} + \alpha_p g(x)\, m_\varepsilon^* - \mu_p p_\varepsilon^* = 0 \qquad \text{in } (0,1)$$

The linearised equations at the steady state $(m_\varepsilon^*, p_\varepsilon^*)$:

$$\mathcal{A}\begin{pmatrix} u_1 \\ u_2 \end{pmatrix} = 0, \qquad \mathcal{A} = \mathcal{A}_0 + \mathcal{A}_1,$$

where
$$\mathcal{A}_0 = \begin{pmatrix} D\frac{d^2}{dx^2} - \mu_m & 0 \\ 0 & D\frac{d^2}{dx^2} - \mu_p \end{pmatrix}$$

with $\mathcal{D}(\mathcal{A}_0) = \{v \in H^2(0,1)\times H^2(0,1) :\ v'(0) = 0,\ v'(1) = 0\}$

and the bounded operator

$$\mathcal{A}_1 = \begin{pmatrix} 0 & \alpha_m f'(p_\varepsilon^*(x,D))\,\delta_{x_M}^\varepsilon(x) \\ \alpha_p g(x) & 0 \end{pmatrix}$$

If $\mathcal{A}$ is invertible

$\Longrightarrow$ Family in $D \in [d_1, d_2]$ of isolated positive stationary solutions.

Stationary solutions: Isolate and Unique

- Show that $\mathcal{A}$ is invertible by contradiction

If $\mathcal{A}$ is not invertible, then from the linearised equations:

$$\tilde{A}_{0,m}\, u_1 + \alpha_m f'(p^*_\varepsilon(x, D))\, \delta^\varepsilon_{x_M}(x)\, u_2 = 0,$$
$$\tilde{A}_{0,p}\, u_2 + \alpha_p g(x)\, u_1 = 0,$$

where

$$\tilde{A}_{0,j} = \Big(D\frac{d^2}{dx^2} - \mu_j \Big), \quad j = m, p$$

we have for $x \in (x_M - \varepsilon, x_M + \varepsilon)$, since $f'(p^*_\varepsilon) < 0$,

$$u_2(x) - \alpha_m \alpha_p (-\tilde{A}_{0,p})^{-1} \Big(g(x)\, (-\tilde{A}_{0,m})^{-1} \big(f'(p^*_\varepsilon) \delta^\varepsilon_{x_M} u_2 \big) \Big)(x) > 0$$

$\succ$ a contradiction, since u_2 is a solution.

$\Longrightarrow$ A family in $D \in [d_1, d_2]$ of isolated positive stationary solutions.

Stationary solutions: Isolate and Unique

- Show that $\mathcal{A}$ is invertible by contradiction

If $\mathcal{A}$ is not invertible, then from the linearised equations:

$$\begin{aligned} \tilde{A}_{0,m}\, u_1 + &\quad \alpha_m f'(p^*_\varepsilon(x,D))\, \delta^\varepsilon_{x_M}(x)\; u_2 = 0, \\ \tilde{A}_{0,p}\, u_2 + &\quad \alpha_p g(x)\; u_1 = 0, \end{aligned}$$

where

$$\tilde{A}_{0,j} = \Big(D\frac{d^2}{dx^2} - \mu_j \Big), \quad j = m, p$$

we have for $x \in (x_M - \varepsilon, x_M + \varepsilon)$, since $f'(p^*_\varepsilon) < 0$,

$$u_2(x) - \alpha_m \alpha_p (-\tilde{A}_{0,p})^{-1} \Big(g(x)\, (-\tilde{A}_{0,m})^{-1} \big(f'(p^*_\varepsilon) \delta^\varepsilon_{x_M} u_2 \big) \Big)(x) > 0$$

$\succ$ a contradiction, since u_2 is a solution.

$\Longrightarrow$ A family in $D \in [d_1, d_2]$ of isolated positive stationary solutions.

Stationary solutions as $\varepsilon \to 0$

A priori estimate $\Longrightarrow$

$$m_\varepsilon^* \rightharpoonup m_0^* \text{ in } H^1(0,1), \quad p_\varepsilon^* \rightharpoonup p_0^* \text{ in } H^2(0,1)$$

Then

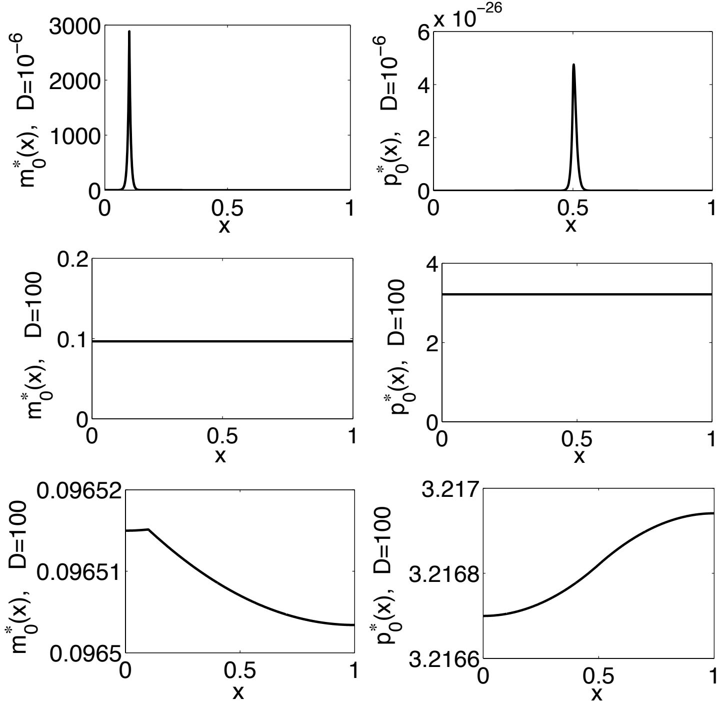
$$m_0^*(x,D) = \alpha_m G_\mu(x,x_M) f(p_0^*(x_M,D)) \; ,$$
$$p_0^*(x,D) = \alpha_m \alpha_p f(p_0^*(x_M,D)) \int_0^1 g(y)\, G_\mu(x,y)\, G_\mu(y,x_M)\, dy,$$

We compute for $x = x_M$

$$p_0^*(x_M,D) = f(p_0^*(x_M,D)) \frac{\alpha_p \alpha_m}{4} \frac{\cosh^2(\theta\, x_M)}{\mu\, D\, \theta\, \sinh^2(\theta)} \Big[\theta + \sinh(\theta)\Big].$$

The polynomial in $p_0^*(x_M,D)$ has a uniques positive solution

$\Longrightarrow$ uniques positive (m_0^*, p_0^*) and also unique positive $(m_\varepsilon^*, p_\varepsilon^*)$.



$m_0^*(x)$, D=10^{-6}
3000
2000
1000
0
0
0.5
1
x
x 10^{-26}
$p_0^*(x)$, D=10^{-6}
6
4
2
0
0
0.5
1
x
$m_0^*(x)$, D=100
0.2
0.1
0
0
0.5
1
x
$p_0^*(x)$, D=100
4
2
0
0
0.5
1
x
$m_0^*(x)$, D=100
0.09652
0.09651
0.0965
0
0.5
1
x
$p_0^*(x)$, D=100
3.217
3.2168
3.2166
0
0.5
1
x

Linearized stability of the steady-state solution

$$\frac{\partial m}{\partial t} = D\frac{\partial^2 m}{\partial x^2} + \alpha_m f(p)\delta^{\varepsilon}_{x_M}(x) - \mu_m m \qquad \text{in } (0,T)\times(0,1)$$
$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} + \alpha_p g(x)\, m - \mu_p p \qquad \text{in } (0,T)\times(0,1)$$

- $-\mathcal{A}_0$ is sectorial with $\sigma(\mathcal{A}_0) \subset (-\infty, -\mu]$, where $\mu = \min\{\mu_m, \mu_p\}$
- $X^s = ((-\mathcal{A}_0)^s)$ Hilbert subspace of $H^{2s}(0,1)\times H^{2s}(0,1)$
- $\tilde{f} : \mathbb{R}^2_+ \to \mathbb{R}^2_+$ is smooth and

$$\tilde{f}(y+z) = \tilde{f}(y) + B(y)z + r(y,z),$$

where

$$\|r(y,z)\|_{\mathbb{R}^2} \le C_\varepsilon(y)\|z\|^2_{\mathbb{R}^2}, \qquad B(y) = \begin{pmatrix} 0 & \alpha_m f'(y_2)\delta^{\varepsilon}_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- $B(u^*_\varepsilon) : X^s \to X$ - bounded linear, for $s \in (0,1)$, $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon) \in H^1 \times H^2$
- For $s \in [5/6, 1)$: estimates uniform in ε

$$\|B(u^*_\varepsilon)z\|_X \le C\|z\|_{X^s}, \qquad \|r(u^*_\varepsilon, z)\|_X \le C\|z\|^2_{X^s}.$$

- $\Longrightarrow$ We can apply linearised stability analysis

e.g. Henry D. Geometric Theory of Semilinear parabolic equations. 1981

Linearized stability of the steady-state solution

For $\mathcal{A}_{0,j} = (D\frac{d^2}{dx^2} - \mu_j)I$ and $\tilde{f}(u) = (\alpha_m f(p)\delta^{\varepsilon}_{x_M}(x), \alpha_p g(x)m)^T$

$$\partial_t u = \mathcal{A}_0 u + \tilde{f}(u), \qquad u = (m,p)^T$$

- $-\mathcal{A}_0$ is sectorial with $\sigma(\mathcal{A}_0) \subset (-\infty, -\mu]$, where $\mu = \min\{\mu_m, \mu_p\}$
- $X^s = ((-\mathcal{A}_0)^s)$ Hilbert subspace of $H^{2s}(0,1) \times H^{2s}(0,1)$
- $\tilde{f} : \mathbb{R}^2_+ \to \mathbb{R}^2_+$ is smooth and

$$\tilde{f}(y+z) = \tilde{f}(y) + B(y)z + r(y,z),$$

where

$$\|r(y,z)\|_{\mathbb{R}^2} \le C_\varepsilon(y)\|z\|^2_{\mathbb{R}^2}, \qquad B(y) = \begin{pmatrix} 0 & \alpha_m f'(y_2)\delta^{\varepsilon}_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- $B(u^*_\varepsilon) : X^s \to X$ - bounded linear, for $s \in (0,1)$,
  $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon) \in H^1 \times H^2$
- For $s \in [5/6, 1)$: estimates uniform in ε

$$\|B(u^*_\varepsilon)z\|_X \le C\|z\|_{X^s}, \qquad \|r(u^*_\varepsilon, z)\|_X \le C\|z\|^2_{X^s}.$$

- $\Longrightarrow$ We can apply linearised stability analysis
  e.g. Henry D. Geometric Theory of Semilinear parabolic equations, 1981

Linearized stability of the steady-state solution

For $\mathcal{A}_{0,j} = (D\frac{d^2}{dx^2} - \mu_j)I$ and $\tilde{f}(u) = (\alpha_m f(p)\delta^{\varepsilon}_{x_M}(x), \alpha_p g(x)m)^T$

$$\partial_t u = \mathcal{A}_0 u + \tilde{f}(u), \qquad u = (m, p)^T$$

- $-\mathcal{A}_0$ is sectorial with $\sigma(\mathcal{A}_0) \subset (-\infty, -\mu]$, where $\mu = \min\{\mu_m, \mu_p\}$
- $X^s = ((-\mathcal{A}_0)^s)$ Hilbert subspace of $H^{2s}(0,1) \times H^{2s}(0,1)$
- $\tilde{f} : \mathbb{R}^2_+ \to \mathbb{R}^2_+$ is smooth and

$$\tilde{f}(y+z) = \tilde{f}(y) + B(y)z + r(y,z),$$

where

$$\|r(y,z)\|_{\mathbb{R}^2} \le C_\varepsilon(y)\|z\|^2_{\mathbb{R}^2}, \qquad B(y) = \begin{pmatrix} 0 & \alpha_m f'(y_2)\delta^{\varepsilon}_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- $B(u^*_\varepsilon) : X^s \to X$ - bounded linear, for $s \in (0,1)$,
  $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon) \in H^1 \times H^2$
- For $s \in [5/6, 1)$: estimates uniform in ε

$$\|B(u^*_\varepsilon)z\|_X \le C\|z\|_{X^s}, \qquad \|r(u^*_\varepsilon, z)\|_X \le C\|z\|^2_{X^s}.$$

- $\Longrightarrow$ We can apply linearised stability analysis
  e.g. Henry D. Geometric Theory of Semilinear parabolic equations, 1981

Linearized stability of the steady-state solution

For $\mathcal{A}_{0,j} = (D\frac{d^2}{dx^2} - \mu_j)I$ and $\tilde{f}(u) = (\alpha_m f(p)\delta^{\varepsilon}_{x_M}(x), \alpha_p g(x)m)^T$

$$\partial_t u = \mathcal{A}_0 u + \tilde{f}(u), \qquad u = (m,p)^T$$

- $-\mathcal{A}_0$ is sectorial with $\sigma(\mathcal{A}_0) \subset (-\infty, -\mu]$, where $\mu = \min\{\mu_m, \mu_p\}$
- $X^s = ((-\mathcal{A}_0)^s)$ Hilbert subspace of $H^{2s}(0,1) \times H^{2s}(0,1)$
- $\tilde{f} : \mathbb{R}^2_+ \to \mathbb{R}^2_+$ is smooth and

$$\tilde{f}(y+z) = \tilde{f}(y) + B(y)z + r(y,z),$$

where

$$\|r(y,z)\|_{\mathbb{R}^2} \le C_\varepsilon(y)\|z\|^2_{\mathbb{R}^2}, \qquad B(y) = \begin{pmatrix} 0 & \alpha_m f'(y_2)\delta^{\varepsilon}_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- $B(u^*_\varepsilon) : X^s \to X$ - bounded linear, for $s \in (0,1)$, $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon) \in H^1 \times H^2$
- For $s \in [5/6, 1)$: estimates uniform in ε

$$\|B(u^*_\varepsilon)z\|_X \le C\|z\|_{X^s}, \qquad \|r(u^*_\varepsilon, z)\|_X \le C\|z\|^2_{X^s}.$$

- $\Longrightarrow$ We can apply linearised stability analysis

  e.g. Henry D. Geometric Theory of Semilinear parabolic equations, 1981

Linearized stability of the steady-state solution

For $\mathcal{A}_{0,j} = (D\frac{d^2}{dx^2} - \mu_j)I$ and $\tilde{f}(u) = (\alpha_m f(p)\delta^\varepsilon_{x_M}(x), \alpha_p g(x)m)^T$

$$\partial_t u = \mathcal{A}_0 u + \tilde{f}(u), \qquad u = (m,p)^T$$

- $-\mathcal{A}_0$ is sectorial with $\sigma(\mathcal{A}_0) \subset (-\infty, -\mu]$, where $\mu = \min\{\mu_m, \mu_p\}$
- $X^s = ((-\mathcal{A}_0)^s)$ Hilbert subspace of $H^{2s}(0,1) \times H^{2s}(0,1)$
- $\tilde{f} : \mathbb{R}^2_+ \to \mathbb{R}^2_+$ is smooth and

$$\tilde{f}(y+z) = \tilde{f}(y) + B(y)z + r(y,z),$$

where

$$\|r(y,z)\|_{\mathbb{R}^2} \le C_\varepsilon(y)\|z\|^2_{\mathbb{R}^2}, \qquad B(y) = \begin{pmatrix} 0 & \alpha_m f'(y_2)\delta^\varepsilon_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- $B(u^*_\varepsilon) : X^s \to X$ - bounded linear, for $s \in (0,1)$,
  $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon) \in H^1 \times H^2$
- For $s \in [5/6, 1)$: estimates uniform in ε

$$\|B(u^*_\varepsilon)z\|_X \le C\|z\|_{X^s}, \qquad \|r(u^*_\varepsilon, z)\|_X \le C\|z\|^2_{X^s}.$$

- $\Longrightarrow$ We can apply linearised stability analysis
  e.g. Henry D. Geometric Theory of Semilinear parabolic equations, 1981

Linearized stability of the steady-state solution

For $\mathcal{A}_{0,j} = (D\frac{d^2}{dx^2} - \mu_j)I$ and $\tilde{f}(u) = (\alpha_m f(p)\delta^{\varepsilon}_{x_M}(x), \alpha_p g(x)m)^T$

$$\partial_t u = \mathcal{A}_0 u + \tilde{f}(u), \qquad u = (m,p)^T$$

- $-\mathcal{A}_0$ is sectorial with $\sigma(\mathcal{A}_0) \subset (-\infty, -\mu]$, where $\mu = \min\{\mu_m, \mu_p\}$
- $X^s = ((-\mathcal{A}_0)^s)$ Hilbert subspace of $H^{2s}(0,1) \times H^{2s}(0,1)$
- $\tilde{f} : \mathbb{R}^2_+ \to \mathbb{R}^2_+$ is smooth and

$$\tilde{f}(y+z) = \tilde{f}(y) + B(y)z + r(y,z),$$

where

$$\|r(y,z)\|_{\mathbb{R}^2} \leq C_\varepsilon(y)\|z\|^2_{\mathbb{R}^2}, \qquad B(y) = \begin{pmatrix} 0 & \alpha_m f'(y_2)\delta^{\varepsilon}_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- $B(u^*_\varepsilon) : X^s \to X$ - bounded linear, for $s \in (0,1)$,
  $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon) \in H^1 \times H^2$
- For $s \in [5/6, 1)$: estimates uniform in ε

$$\|B(u^*_\varepsilon)z\|_X \leq C\|z\|_{X^s}, \qquad \|r(u^*_\varepsilon, z)\|_X \leq C\|z\|^2_{X^s}.$$

- $\Longrightarrow$ We can apply linearised stability analysis
  e.g. Henry D. Geometric Theory of Semilinear parabolic equations, 1981

Linearized stability of the steady-state solution

For $\mathcal{A}_{0,j} = (D\frac{d^2}{dx^2} - \mu_j)I$ and $\tilde{f}(u) = (\alpha_m f(p)\delta^{\varepsilon}_{x_M}(x), \alpha_p g(x)m)^T$

$$\partial_t u = \mathcal{A}_0 u + \tilde{f}(u), \qquad u = (m,p)^T$$

- $-\mathcal{A}_0$ is sectorial with $\sigma(\mathcal{A}_0) \subset (-\infty, -\mu]$, where $\mu = \min\{\mu_m, \mu_p\}$
- $X^s = ((-\mathcal{A}_0)^s)$ Hilbert subspace of $H^{2s}(0,1) \times H^{2s}(0,1)$
- $\tilde{f} : \mathbb{R}^2_+ \to \mathbb{R}^2_+$ is smooth and

$$\tilde{f}(y+z) = \tilde{f}(y) + B(y)z + r(y,z),$$

where

$$\|r(y,z)\|_{\mathbb{R}^2} \le C_\varepsilon(y)\|z\|^2_{\mathbb{R}^2}, \qquad B(y) = \begin{pmatrix} 0 & \alpha_m f'(y_2)\delta^{\varepsilon}_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- $B(u^*_\varepsilon) : X^s \to X$ - bounded linear, for $s \in (0,1)$,
  $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon) \in H^1 \times H^2$
- For $s \in [5/6, 1)$: estimates uniform in ε

$$\|B(u^*_\varepsilon)z\|_X \le C\|z\|_{X^s}, \qquad \|r(u^*_\varepsilon, z)\|_X \le C\|z\|^2_{X^s}.$$

- $\Longrightarrow$ We can apply linearised stability analysis

  e.g. Henry D. Geometric Theory of Semilinear parabolic equations, 1981

Linearized stability of the steady-state solution

For $\mathcal{A}_{0,j} = (D\frac{d^2}{dx^2} - \mu_j)I$ and $\tilde{f}(u) = (\alpha_m f(p)\delta^{\varepsilon}_{x_M}(x), \alpha_p g(x) m)^T$

$$\partial_t u = \mathcal{A}_0 u + \tilde{f}(u), \qquad u = (m, p)^T$$

- $-\mathcal{A}_0$ is sectorial with $\sigma(\mathcal{A}_0) \subset (-\infty, -\mu]$, where $\mu = \min\{\mu_m, \mu_p\}$
- $X^s = ((-\mathcal{A}_0)^s)$ Hilbert subspace of $H^{2s}(0,1) \times H^{2s}(0,1)$
- $\tilde{f} : \mathbb{R}^2_+ \to \mathbb{R}^2_+$ is smooth and

$$\tilde{f}(y+z) = \tilde{f}(y) + B(y)z + r(y,z),$$

where

$$\|r(y,z)\|_{\mathbb{R}^2} \le C_\varepsilon(y)\|z\|^2_{\mathbb{R}^2}, \qquad B(y) = \begin{pmatrix} 0 & \alpha_m f'(y_2)\delta^{\varepsilon}_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- $B(u^*_\varepsilon) : X^s \to X$ - bounded linear, for $s \in (0,1)$,
  $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon) \in H^1 \times H^2$
- For $s \in [5/6, 1)$: estimates uniform in ε

$$\|B(u^*_\varepsilon)z\|_X \le C\|z\|_{X^s}, \qquad \|r(u^*_\varepsilon, z)\|_X \le C\|z\|^2_{X^s}.$$

- $\Longrightarrow$ We can apply linearised stability analysis
  e.g. Henry D. Geometric Theory of Semilinear parabolic equations, 1981

Eigenvalue problem

$$\lambda \bar{m}^\varepsilon = D\bar{m}^\varepsilon_{xx} - \mu_m \bar{m}^\varepsilon \quad + \alpha_m f'(p^*_\varepsilon(x,D))\, \delta^\varepsilon_{x_M}\, \bar{p}^\varepsilon \qquad \text{in } (0,1)$$

$$\lambda \bar{p}^\varepsilon = D\bar{p}^\varepsilon_{xx} - \mu_p \bar{p}^\varepsilon \quad + \alpha_p g(x) \bar{m}^\varepsilon \qquad \text{in } (0,1)$$

$+$ zero-flux b.c.

In operator form: $\mathcal{A}w^\varepsilon = \lambda w^\varepsilon, \quad w^\varepsilon = (\bar{m}^\varepsilon, \bar{p}^\varepsilon)^T, \quad \mathcal{A} = \mathcal{A}_0 + \mathcal{A}_1$

$$\mathcal{A}_0 = \begin{pmatrix} D\frac{d^2}{dx^2} - \mu_m & 0 \\ 0 & D\frac{d^2}{dx^2} - \mu_p \end{pmatrix}, \quad \mathcal{A}_1 = \begin{pmatrix} 0 & \alpha_m f'(p^*_\varepsilon(x,D))\, \delta^\varepsilon_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

-

Eigenvalue problem

$$\lambda \bar{m}^\varepsilon = D\bar{m}^\varepsilon_{xx} - \mu_m \bar{m}^\varepsilon \quad + \alpha_m f'(p^*_\varepsilon(x,D))\,\delta^\varepsilon_{x_M}\,\bar{p}^\varepsilon \qquad \text{in } (0,1)$$

$$\lambda \bar{p}^\varepsilon = D\bar{p}^\varepsilon_{xx} - \mu_p \bar{p}^\varepsilon \quad + \alpha_p g(x)\bar{m}^\varepsilon \qquad \text{in } (0,1)$$

$+$ zero-flux b.c.

In operator form: $\mathcal{A}w^\varepsilon = \lambda w^\varepsilon, \quad w^\varepsilon = (\bar{m}^\varepsilon, \bar{p}^\varepsilon)^T, \ \ \mathcal{A} = \mathcal{A}_0 + \mathcal{A}_1$

$$\mathcal{A}_0 = \begin{pmatrix} D\frac{d^2}{dx^2} - \mu_m & 0 \\ 0 & D\frac{d^2}{dx^2} - \mu_p \end{pmatrix}, \quad \mathcal{A}_1 = \begin{pmatrix} 0 & \alpha_m f'(p^*_\varepsilon(x,D))\,\delta^\varepsilon_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- Let T and S be operators with the same domain space $\mathcal{H}$ such that $\mathcal{D}(T) \subset \mathcal{D}(S)$ and

$$\|Su\| \leq a\|u\| + b\|Tu\|, \qquad u \in \mathcal{D}(T).$$

- Assume: T is closed and there exists a bounded T^{-1}, and S is T-bounded with a, b satisfying

$$a\|T^{-1}\| + b < 1.$$

Then, $T + S$ is a closed and bounded invertible (Kato, 1966).

Eigenvalue problem

$$\lambda\bar{m}^\varepsilon = D\bar{m}^\varepsilon_{xx} - \mu_m\bar{m}^\varepsilon \quad + \alpha_m f'(p^*_\varepsilon(x,D))\,\delta^\varepsilon_{x_M}\,\bar{p}^\varepsilon \qquad \text{in } (0,1)$$

$$\lambda\bar{p}^\varepsilon = D\bar{p}^\varepsilon_{xx} - \mu_p\bar{p}^\varepsilon \quad + \alpha_p g(x)\bar{m}^\varepsilon \qquad \text{in } (0,1)$$

$+$ zero-flux b.c.

In operator form: $\mathcal{A}w^\varepsilon = \lambda w^\varepsilon, \quad w^\varepsilon = (\bar{m}^\varepsilon, \bar{p}^\varepsilon)^T, \quad \mathcal{A} = \mathcal{A}_0 + \mathcal{A}_1$

$$\mathcal{A}_0 = \begin{pmatrix} D\frac{d^2}{dx^2} - \mu_m & 0 \\ 0 & D\frac{d^2}{dx^2} - \mu_p \end{pmatrix}, \quad \mathcal{A}_1 = \begin{pmatrix} 0 & \alpha_m f'(p^*_\varepsilon(x,D))\,\delta^\varepsilon_{x_M} \\ \alpha_p g(x) & 0 \end{pmatrix}$$

- $\mathcal{A}_0$ is self-adjoint with compact resolvent, $\mathcal{A}_1$ is bounded,

$$\|(\mathcal{A}_0 - \lambda_0 I)^{-1}\| = \frac{1}{\mathrm{dist}(\lambda_0, \sigma(\mathcal{A}_0))}$$

- The spectrum of $\mathcal{A}$ consists only of eigenvalues and

$$\|\mathcal{A}_1 u\|_X \leq \kappa\|u\|_X + 1/4\|(\mathcal{A}_0 - \lambda_0 I)u\|_X \ .$$

- $\mathcal{A}_0 + \mathcal{A}_1 - \lambda_0 I$ is bounded and invertible for all λ_0 such that $\mathcal{R}e(\lambda_0) \geq 0$ and $|\lambda_0| \geq 2\kappa$ or $|\mathcal{I}m(\lambda_0)| \geq 2\kappa$.

Existence of Hopf bifurcation

Theorem For $\varepsilon > 0$ small there exist two critical values $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$ for which a Hopf bifurcation occurs in the GRN model.

Proof: motivated by Dancer, *Methods Appl. Anal.* 1993.

Stability and instability of the steady states $(m^*_\varepsilon(x,D), p^*_\varepsilon(x,D))$

Eigenvalue problem EW_ε: For $\lambda \in \mathbb{C}$: $\mathcal{R}e(\lambda) > -\mu$ or $\mathcal{I}m(\lambda) \neq 0$:

$$\bar{m}^\varepsilon(x) = \alpha_m(\lambda I - \tilde{\mathcal{A}}_0)^{-1}\left(f'(p^*_\varepsilon)\,\bar{p}^\varepsilon(x)\,\delta^\varepsilon_{x_M}(x)\right)$$
$$\lambda\bar{p}^\varepsilon = D\frac{d^2\bar{p}^\varepsilon}{dx^2} - \mu\,\bar{p}^\varepsilon + \alpha_p\alpha_m g(x)(\lambda I - \tilde{\mathcal{A}}_0)^{-1}\left(f'(p^*_\varepsilon)\,\bar{p}^\varepsilon\,\delta^\varepsilon_{x_M}\right),$$
$$\bar{p}^\varepsilon_x(0) = \bar{p}^\varepsilon_x(1) = 0.$$

Lemma For small ε the stationary solution is stable if the limit EW_0

$$\lambda\bar{p} = D\frac{d^2\bar{p}}{dx^2} - \mu\bar{p} + \alpha_p\alpha_m g(x)G_{\lambda+\mu}(x, x_M)f'(p^*_0(x_M, D))\bar{p}(x_M)$$
$$\bar{p}_x(0) = \bar{p}_x(1) = 0$$

has no eigenvalues with $\mathcal{R}e(\lambda) \geq 0$.

Existence of Hopf bifurcation

Theorem For $\varepsilon > 0$ small there exist two critical values $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$ for which a Hopf bifurcation occurs in the GRN model.

Proof: motivated by Dancer, *Methods Appl. Anal.* 1993.

Stability and instability of the steady states $(m^*_\varepsilon(x,D), p^*_\varepsilon(x,D))$

Eigenvalue problem EW_ε: For $\lambda \in \mathbb{C}$: $\mathcal{R}e(\lambda) > -\mu$ or $\mathcal{I}m(\lambda) \neq 0$:

$$\bar{m}^\varepsilon(x) = \alpha_m(\lambda I - \tilde{A}_0)^{-1}\left(f'(p^*_\varepsilon)\,\bar{p}^\varepsilon(x)\,\delta^\varepsilon_{x_M}(x)\right)$$

$$\lambda\bar{p}^\varepsilon = D\frac{d^2\bar{p}^\varepsilon}{dx^2} - \mu\,\bar{p}^\varepsilon + \alpha_p\alpha_m g(x)(\lambda I - \tilde{A}_0)^{-1}\left(f'(p^*_\varepsilon)\,\bar{p}^\varepsilon\,\delta^\varepsilon_{x_M}\right),$$

$$\bar{p}^\varepsilon_x(0) = \bar{p}^\varepsilon_x(1) = 0.$$

Lemma For small ε the stationary solution is stable if the limit EW_0

$$\lambda\bar{p} = D\frac{d^2\bar{p}}{dx^2} - \mu\bar{p} + \alpha_p\alpha_m g(x)G_{\lambda+\mu}(x,x_M)f'(p^*_0(x_M,D))\bar{p}(x_M)$$

$$\bar{p}_x(0) = \bar{p}_x(1) = 0$$

has no eigenvalues with $\mathcal{R}e(\lambda) \geq 0$.

Existence of Hopf bifurcation

Theorem For $\varepsilon > 0$ small there exist two critical values $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$ for which a Hopf bifurcation occurs in the GRN model.

Proof: motivated by Dancer, *Methods Appl. Anal.* 1993.

Stability and instability of the steady states $(m^*_\varepsilon(x,D), p^*_\varepsilon(x,D))$

Eigenvalue problem EW_ε: For $\lambda \in \mathbb{C}$: $\mathcal{R}e(\lambda) > -\mu$ or $\mathcal{I}m(\lambda) \neq 0$:

$$\bar{m}^\varepsilon(x) = \alpha_m(\lambda I - \tilde{\mathcal{A}}_0)^{-1}\left(f'(p^*_\varepsilon)\,\bar{p}^\varepsilon(x)\,\delta^\varepsilon_{x_M}(x)\right)$$

$$\lambda\bar{p}^\varepsilon = D\frac{d^2\bar{p}^\varepsilon}{dx^2} - \mu\,\bar{p}^\varepsilon + \alpha_p\alpha_m g(x)(\lambda I - \tilde{\mathcal{A}}_0)^{-1}\left(f'(p^*_\varepsilon)\,\bar{p}^\varepsilon\,\delta^\varepsilon_{x_M}\right),$$

$$\bar{p}^\varepsilon_x(0) = \bar{p}^\varepsilon_x(1) = 0.$$

Lemma For small ε the stationary solution is stable if the limit EW_0

$$\lambda\bar{p} = D\frac{d^2\bar{p}}{dx^2} - \mu\bar{p} + \alpha_p\alpha_m g(x) G_{\lambda+\mu}(x,x_M) f'(p^*_0(x_M,D))\bar{p}(x_M)$$

$$\bar{p}_x(0) = \bar{p}_x(1) = 0$$

has no eigenvalues with $\mathcal{R}e(\lambda) \geq 0$.

Existence of Hopf bifurcation

Theorem For $\varepsilon > 0$ small there exist two critical values $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$ for which a Hopf bifurcation occurs in the GRN model.

Proof: motivated by Dancer, *Methods Appl. Anal.* 1993.

Stability and instability of the steady states $(m^*_\varepsilon(x, D), p^*_\varepsilon(x, D))$

Eigenvalue problem EW_ε: For $\lambda \in \mathbb{C}$: $\mathcal{R}e(\lambda) > -\mu$ or $\mathcal{I}m(\lambda) \neq 0$:

$$\bar{m}^\varepsilon(x) = \alpha_m(\lambda I - \tilde{\mathcal{A}}_0)^{-1} \left(f'(p^*_\varepsilon)\, \bar{p}^\varepsilon(x)\, \delta^\varepsilon_{x_M}(x)\right)$$

$$\lambda \bar{p}^\varepsilon = D\frac{d^2\bar{p}^\varepsilon}{dx^2} - \mu\, \bar{p}^\varepsilon + \alpha_p\alpha_m g(x)(\lambda I - \tilde{\mathcal{A}}_0)^{-1} \left(f'(p^*_\varepsilon)\, \bar{p}^\varepsilon\, \delta^\varepsilon_{x_M}\right),$$

$$\bar{p}^\varepsilon_x(0) = \bar{p}^\varepsilon_x(1) = 0.$$

Lemma For small ε the stationary solution is stable if the limit EW_0

$$\lambda \bar{p} = D\frac{d^2\bar{p}}{dx^2} - \mu\bar{p} + \alpha_p\alpha_m g(x) G_{\lambda+\mu}(x, x_M) f'(p^*_0(x_M, D))\bar{p}(x_M)$$

$$\bar{p}_x(0) = \bar{p}_x(1) = 0$$

has no eigenvalues with $\mathcal{R}e(\lambda) \geq 0$.

Stability of steady states: Proof of Lemma

- The spectrum of $\mathcal{A}$ is bounded from above: for $\mathcal{R}e(\lambda_{\varepsilon_j}) \geq 0$

$$\lambda_{\varepsilon_j} \to \tilde{\lambda} \quad \text{with} \quad \mathcal{R}e(\tilde{\lambda}) \geq 0, \text{ as } \varepsilon_j \to 0,\ j \to \infty$$

- $\bar{m}^\varepsilon \rightharpoonup \bar{m}$ weakly in $H^1(0,1)$ and strongly in $C([0,1])$ and $\bar{p}^\varepsilon \rightharpoonup \bar{p}$ weakly in $H^2(0,1)$ and strongly in $C^1([0,1])$.
- For λ with $\mathcal{R}e(\lambda) \geq 0$, taking $\mathcal{R}e(\bar{m}^\varepsilon) - i\mathcal{I}m(\bar{m}^\varepsilon)$

$$\|\bar{m}^\varepsilon\|_{L^\infty(0,1)} \leq C\|\bar{p}^\varepsilon\|_{L^\infty(0,1)} \ .$$

- For λ with $\mathcal{R}e(\lambda) \geq 0$: $\quad \lambda \notin \sigma(\tilde{\mathcal{A}}_0)$
  $\implies |\bar{p}^\varepsilon(x)| > 0$ in $(x_M - \varepsilon, x_M + \varepsilon)$.
- Strong convergence of $\bar{p}^{\varepsilon_j}$ in $C^1([0,1])$ $\implies \bar{p}(x_M) \neq 0$, otherwise $\bar{p}(x) = 0$ for all $x \in [0,1]$ and contradicts the normalisation $\|\bar{m}\|_{L^2(0,1)} + \|\bar{p}\|_{L^2(0,1)} = 1$.
- $\implies \bar{p}(x) \neq 0$ in $(0,1)$ and EW_0 has nontrivial solution for $\tilde{\lambda}$ with $\mathcal{R}e(\tilde{\lambda}) \geq 0$.

Hopf bifurcation for EW_ε: ε small

EW_ε

$$\bar{m}^\varepsilon(x) = \alpha_m(\lambda I - \tilde{\mathcal{A}}_0)^{-1}\left(f'(p^*_\varepsilon)\,\bar{p}^\varepsilon(x)\,\delta^\varepsilon_{x_M}(x)\right)$$

$$\lambda\bar{p}^\varepsilon = D\frac{d^2\bar{p}^\varepsilon}{dx^2} - \mu\,\bar{p}^\varepsilon + \alpha_p\alpha_m g(x)(\lambda I - \tilde{\mathcal{A}}_0)^{-1}\left(f'(p^*_\varepsilon)\,\bar{p}^\varepsilon\,\delta^\varepsilon_{x_M}\right),$$

$$\bar{p}^\varepsilon_x(0) = \bar{p}^\varepsilon_x(1) = 0.$$

EW_0

$$\lambda\bar{p} = D\frac{d^2\bar{p}}{dx^2} - \mu\bar{p} + \alpha_p\alpha_m g(x) G_{\lambda+\mu}(x, x_M) f'(p^*_0(x_M, D))\bar{p}(x_M)$$

$$\bar{p}_x(0) = \bar{p}_x(1) = 0$$

Theorem For small $\varepsilon > 0$ we have that :
If $\tilde{\lambda}$ is an eigenvalue of EW_0 with $\mathcal{R}e(\tilde{\lambda}) > -\mu$,
then there is an eigenvalue λ_ε of EW_ε, with λ_ε near $\tilde{\lambda}$ and $\lambda_\varepsilon \to \tilde{\lambda}$ as $\varepsilon \to 0$.

The same result holds for $\mathcal{R}e(\tilde{\lambda}) \leq -\mu$ with $\mathcal{I}m(\tilde{\lambda}) \neq 0$.

Proof In a manner similar to (Dancer 1993)

Hopf bifurcation for EW_ε: ε small

EW_ε

$$\bar{m}^\varepsilon(x) = \alpha_m(\lambda I - \tilde{\mathcal{A}}_0)^{-1}\left(f'(p_\varepsilon^*)\,\bar{p}^\varepsilon(x)\,\delta_{x_M}^\varepsilon(x)\right)$$

$$\lambda\bar{p}^\varepsilon = D\frac{d^2\bar{p}^\varepsilon}{dx^2} - \mu\,\bar{p}^\varepsilon + \alpha_p\alpha_m g(x)(\lambda I - \tilde{\mathcal{A}}_0)^{-1}\left(f'(p_\varepsilon^*)\,\bar{p}^\varepsilon\,\delta_{x_M}^\varepsilon\right),$$

$$\bar{p}_x^\varepsilon(0) = \bar{p}_x^\varepsilon(1) = 0.$$

EW_0

$$\lambda\bar{p} = D\frac{d^2\bar{p}}{dx^2} - \mu\bar{p} + \alpha_p\alpha_m g(x)G_{\lambda+\mu}(x, x_M)f'(p_0^*(x_M, D))\bar{p}(x_M)$$

$$\bar{p}_x(0) = \bar{p}_x(1) = 0$$

Theorem For small $\varepsilon > 0$ we have that :

If $\tilde{\lambda}$ is an eigenvalue of EW_0 with $\mathcal{R}e(\tilde{\lambda}) > -\mu$,
then there is an eigenvalue λ_ε of EW_ε, with λ_ε near $\tilde{\lambda}$ and $\lambda_\varepsilon \to \tilde{\lambda}$ as $\varepsilon \to 0$.

The same result holds for $\mathcal{R}e(\tilde{\lambda}) \leq -\mu$ with $\mathcal{I}m(\tilde{\lambda}) \neq 0$.

Proof In a manner similar to (Dancer 1993)

Hopf bifurcation for original GRN model

Hopf Bifurcation Theorem

- For $p \geq -\theta$, with $0 < \theta < 1$, f is a smooth function in p

$$\partial_t \tilde{u} = \mathcal{A}\, \tilde{u} + F(\tilde{u}, D),$$

where $\tilde{u} = (\tilde{m}, \tilde{p})^T$ with $\tilde{m} = m - m^*_\varepsilon$, $\tilde{p} = p - p^*_\varepsilon$, and $F(\tilde{u}, D) = \alpha_m((f(\tilde{p} + p^*_\varepsilon) - f(p^*_\varepsilon) - f'(p^*_\varepsilon)\tilde{p})\delta^\varepsilon_{x_M}(x), 0)^T$.

- $\mathcal{A} = \mathcal{A}(D)$ is linear in D
- $p^*_\varepsilon = p^*_\varepsilon(D)$ is smooth function for $D > 0$, we have $F \in C^2(U \times (\underline{D}, \overline{D}))$, for $U \subset \mathbb{R} \times (-1, \infty)$, such that $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon)^T \in U$, and some $0 < \underline{D} < d_1$ and $\overline{D} > d_2$.
- $F(0, D) = 0$, $\partial_{\tilde{m}} F(0, D) = 0$, and $\partial_{\tilde{p}} F(0, D) = 0$ for $D \in (\underline{D}, \overline{D})$.
- $-\mathcal{A}$ is the infinitesimal generator of a strongly continuous analytic semigroup and $(\lambda I - \mathcal{A})^{-1}$ is compact for λ in the resolvent set of $\mathcal{A}$ for all values of $D \in (\underline{D}, \overline{D})$.

Hopf bifurcation for original GRN model

Hopf Bifurcation Theorem

- For $p \geq -\theta$, with $0 < \theta < 1$, f is a smooth function in p

$$\partial_t \tilde{u} = \mathcal{A}\,\tilde{u} + F(\tilde{u}, D),$$

where $\tilde{u} = (\tilde{m}, \tilde{p})^T$ with $\tilde{m} = m - m_\varepsilon^*$, $\tilde{p} = p - p_\varepsilon^*$, and $F(\tilde{u}, D) = \alpha_m((f(\tilde{p} + p_\varepsilon^*) - f(p_\varepsilon^*) - f'(p_\varepsilon^*)\tilde{p})\delta_{x_M}^\varepsilon(x), 0)^T$.

- $\mathcal{A} = \mathcal{A}(D)$ is linear in D
- $p_\varepsilon^* = p_\varepsilon^*(D)$ is smooth function for $D > 0$, we have $F \in C^2(U \times (\underline{D}, \overline{D}))$, for $U \subset \mathbb{R} \times (-1, \infty)$, such that $u_\varepsilon^* = (m_\varepsilon^*, p_\varepsilon^*)^T \in U$, and some $0 < \underline{D} < d_1$ and $\overline{D} > d_2$.
- $F(0, D) = 0$, $\partial_{\tilde{m}} F(0, D) = 0$, and $\partial_{\tilde{p}} F(0, D) = 0$ for $D \in (\underline{D}, \overline{D})$.
- $-\mathcal{A}$ is the infinitesimal generator of a strongly continuous analytic semigroup and $(\lambda I - \mathcal{A})^{-1}$ is compact for λ in the resolvent set of $\mathcal{A}$ for all values of $D \in (\underline{D}, \overline{D})$.

Hopf bifurcation for original GRN model

Hopf Bifurcation Theorem

- For $p \geq -\theta$, with $0 < \theta < 1$, f is a smooth function in p

$$\partial_t \tilde{u} = \mathcal{A}\, \tilde{u} + F(\tilde{u}, D),$$

where $\tilde{u} = (\tilde{m}, \tilde{p})^T$ with $\tilde{m} = m - m_\varepsilon^*$, $\tilde{p} = p - p_\varepsilon^*$, and $F(\tilde{u}, D) = \alpha_m((f(\tilde{p} + p_\varepsilon^*) - f(p_\varepsilon^*) - f'(p_\varepsilon^*)\tilde{p})\delta_{x_M}^\varepsilon(x), 0)^T$.

- $\mathcal{A} = \mathcal{A}(D)$ is linear in D
- $p_\varepsilon^* = p_\varepsilon^*(D)$ is smooth function for $D > 0$, we have $F \in C^2(U \times (\underline{D}, \overline{D}))$, for $U \subset \mathbb{R} \times (-1, \infty)$, such that $u_\varepsilon^* = (m_\varepsilon^*, p_\varepsilon^*)^T \in U$, and some $0 < \underline{D} < d_1$ and $\overline{D} > d_2$.
- $F(0, D) = 0$, $\partial_{\tilde{m}} F(0, D) = 0$, and $\partial_{\tilde{p}} F(0, D) = 0$ for $D \in (\underline{D}, \overline{D})$.
- $-\mathcal{A}$ is the infinitesimal generator of a strongly continuous analytic semigroup and $(\lambda I - \mathcal{A})^{-1}$ is compact for λ in the resolvent set of $\mathcal{A}$ for all values of $D \in (\underline{D}, \overline{D})$.

Hopf bifurcation for original GRN model

Hopf Bifurcation Theorem

- For $p \geq -\theta$, with $0 < \theta < 1$, f is a smooth function in p

$$\partial_t \tilde{u} = \mathcal{A}\, \tilde{u} + F(\tilde{u}, D),$$

  where $\tilde{u} = (\tilde{m}, \tilde{p})^T$ with $\tilde{m} = m - m_\varepsilon^*$, $\tilde{p} = p - p_\varepsilon^*$, and $F(\tilde{u}, D) = \alpha_m((f(\tilde{p} + p_\varepsilon^*) - f(p_\varepsilon^*) - f'(p_\varepsilon^*)\tilde{p})\delta_{x_M}^\varepsilon(x), 0)^T$.
- $\mathcal{A} = \mathcal{A}(D)$ is linear in D
- $p_\varepsilon^* = p_\varepsilon^*(D)$ is smooth function for $D > 0$, we have $F \in C^2(U \times (\underline{D}, \overline{D}))$, for $U \subset \mathbb{R} \times (-1, \infty)$, such that $u_\varepsilon^* = (m_\varepsilon^*, p_\varepsilon^*)^T \in U$, and some $0 < \underline{D} < d_1$ and $\overline{D} > d_2$.
- $F(0, D) = 0$, $\partial_{\tilde{m}} F(0, D) = 0$, and $\partial_{\tilde{p}} F(0, D) = 0$ for $D \in (\underline{D}, \overline{D})$.
- $-\mathcal{A}$ is the infinitesimal generator of a strongly continuous analytic semigroup and $(\lambda I - \mathcal{A})^{-1}$ is compact for λ in the resolvent set of $\mathcal{A}$ for all values of $D \in (\underline{D}, \overline{D})$.

Hopf bifurcation for original GRN model

Hopf Bifurcation Theorem

- For $p \geq -\theta$, with $0 < \theta < 1$, f is a smooth function in p

$$\partial_t \tilde{u} = \mathcal{A}\, \tilde{u} + F(\tilde{u}, D),$$

  where $\tilde{u} = (\tilde{m}, \tilde{p})^T$ with $\tilde{m} = m - m^*_\varepsilon$, $\tilde{p} = p - p^*_\varepsilon$, and $F(\tilde{u}, D) = \alpha_m((f(\tilde{p} + p^*_\varepsilon) - f(p^*_\varepsilon) - f'(p^*_\varepsilon)\tilde{p})\delta^\varepsilon_{x_M}(x), 0)^T$.
- $\mathcal{A} = \mathcal{A}(D)$ is linear in D
- $p^*_\varepsilon = p^*_\varepsilon(D)$ is smooth function for $D > 0$, we have $F \in C^2(U \times (\underline{D}, \overline{D}))$, for $U \subset \mathbb{R} \times (-1, \infty)$, such that $u^*_\varepsilon = (m^*_\varepsilon, p^*_\varepsilon)^T \in U$, and some $0 < \underline{D} < d_1$ and $\overline{D} > d_2$.
- $F(0, D) = 0$, $\partial_{\tilde{m}} F(0, D) = 0$, and $\partial_{\tilde{p}} F(0, D) = 0$ for $D \in (\underline{D}, \overline{D})$.
- $-\mathcal{A}$ is the infinitesimal generator of a strongly continuous analytic semigroup and $(\lambda I - \mathcal{A})^{-1}$ is compact for λ in the resolvent set of $\mathcal{A}$ for all values of $D \in (\underline{D}, \overline{D})$.

Analysis of the spectrum of EW_0

$$\lambda\bar{p} = D\frac{d^2\bar{p}}{dx^2} - \mu\bar{p} + \alpha_p\alpha_m g(x) G_{\lambda+\mu}(x, x_M) f'(p_0^*(x_M, D))\bar{p}(x_M)$$

- Limit eigenvalue problem: $\lambda \notin \sigma(\tilde{\mathcal{A}}_0)$

$$\bar{p}(x) = \alpha_p\alpha_m f'(p_0^*(x_M, D))\bar{p}(x_M) \int_0^1 g(y)\, G_{\lambda+\mu}(x, y) G_{\lambda+\mu}(y, x_M) dy$$

- Nonlinear equation for eigenvalues λ $\quad$ ($\bar{p}(x_M) \neq 0$)

$$\begin{aligned} R(\lambda) \quad = \quad & \frac{\alpha_p\alpha_m}{4} f'(p_0^*(x_M, D))\cosh^2(\theta_\lambda\, x_M)\left[\theta_\lambda + \sinh(\theta_\lambda)\right] \\ & -\theta_\lambda\, D(\mu + \lambda)\, \sinh^2(\theta_\lambda) = 0 \end{aligned}$$

- Simplicity of eigenvalues $D_1^c \approx 3.117 \times 10^{-4}$, $D_2^c \approx 7.885 \times 10^{-3}$, $\lambda_1^c \approx 17.641 \times 10^{-3}\, i$, $\lambda_2^c \approx 51.235 \times 10^{-3}\, i$

$$R'(\lambda_1^c) \approx -3.347 \times 10^6 + 9.901 \times 10^5 i, \quad R'(\lambda_2^c) \approx 1.848 + 0.647i$$

- Transversality condition : $\mathcal{R}e\left(\frac{d\lambda}{dD}|_{D_j^c, \lambda_j^c}\right) \neq 0$

$\Longrightarrow$ $(\lambda_j^c(D), \overline{\lambda_j^c}(D))$ cross the imaginary axes with non-zero speed.

Hopf bifurcation

$$R(\lambda) = \frac{\alpha_p \alpha_m}{4} f'(p_0^*(x_M, D)) \cosh^2(\theta_\lambda x_M)\left[\theta_\lambda + \sinh(\theta_\lambda)\right] - \theta_\lambda D(\mu+\lambda) \sinh^2(\theta_\lambda) = 0$$

- Consider $\tilde{R}(\tilde{\lambda}) = R(r + ib + \tilde{\lambda}), \quad \tilde{R}(\tilde{\lambda}) : B_r(0) \to \mathbb{C}$, where $B_r(0) = \{z \in \mathbb{C} : |z| \leq r\}$, $\lambda = r + ib + \tilde{\lambda}$ and
- We show that for some $D > 0$ the winding number of $\Phi(t) = \tilde{R}(re^{it}) = R(r + ib + re^{it})$ for $t \in [0, 2\pi]$ is non-zero:

$$W(\Phi) = \frac{1}{2\pi i} \int_0^{2\pi} \frac{\Phi'(t)}{\Phi(t)} dt = 2.$$

- For all λ_ε: $\mathcal{R}e(\lambda_\varepsilon) < 0$ for $D < D^c_{1,\varepsilon}$ and $D > D^c_{2,\varepsilon}$
- There exist $\tilde{\lambda}_\varepsilon$: $\mathcal{R}e(\tilde{\lambda}_\varepsilon) > 0$ for $D^c_{1,\varepsilon} < D < D^c_{2,\varepsilon}$ and $0 \notin \sigma(\mathcal{A})$.
- There are two critical values of D, i.e $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$ for which $\mathcal{A}$ has a pair of purely imaginary eigenvalues
- The fact that $\lambda_{j,\varepsilon}(D)$ are zeros of an analytic function with respect to D and $\lambda_{j,\varepsilon}$ and not identical zero
  $\Longrightarrow \lambda_{j,\varepsilon}(D)$ are isolated
  $\Longrightarrow \lambda^c_{j,\varepsilon}(D)$ and $\overline{\lambda^c_{j,\varepsilon}}(D)$ cross the real line with non-zero speed as the bifurcation parameter D increases, $j = 1, 2$.

Hopf bifurcation

$$R(\lambda) = \frac{\alpha_p \alpha_m}{4} f'(p_0^*(x_M, D)) \cosh^2(\theta_\lambda x_M) \left[\theta_\lambda + \sinh(\theta_\lambda)\right] - \theta_\lambda D(\mu+\lambda) \sinh^2(\theta_\lambda) = 0$$

- Consider $\tilde{R}(\tilde{\lambda}) = R(r + ib + \tilde{\lambda})$, $\quad \tilde{R}(\tilde{\lambda}) : B_r(0) \to \mathbb{C}$, where $B_r(0) = \{z \in \mathbb{C} : |z| \leq r\}$, $\lambda = r + ib + \tilde{\lambda}$ and
- We show that for some $D > 0$ the winding number of $\Phi(t) = \tilde{R}(re^{it}) = R(r + ib + re^{it})$ for $t \in [0, 2\pi]$ is non-zero:

$$W(\Phi) = \frac{1}{2\pi i} \int_0^{2\pi} \frac{\Phi'(t)}{\Phi(t)} dt = 2.$$

- For all λ_ε: $\mathcal{R}e(\lambda_\varepsilon) < 0$ for $D < D^c_{1,\varepsilon}$ and $D > D^c_{2,\varepsilon}$
- There exist $\tilde{\lambda}_\varepsilon$: $\mathcal{R}e(\tilde{\lambda}_\varepsilon) > 0$ for $D^c_{1,\varepsilon} < D < D^c_{2,\varepsilon}$ and $0 \notin \sigma(\mathcal{A})$.
- There are two critical values of D, i.e $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$ for which $\mathcal{A}$ has a pair of purely imaginary eigenvalues
- The fact that $\lambda_{j,\varepsilon}(D)$ are zeros of an analytic function with respect to D and $\lambda_{j,\varepsilon}$ and not identical zero
  $\implies \lambda_{j,\varepsilon}(D)$ are isolated
  $\implies \lambda^c_{j,\varepsilon}(D)$ and $\overline{\lambda^c_{j,\varepsilon}}(D)$ cross the real line with non-zero speed as the bifurcation parameter D increases, $j = 1, 2$.

Hopf bifurcation

$$R(\lambda) = \frac{\alpha_p \alpha_m}{4} f'(p_0^*(x_M, D))\cosh^2(\theta_\lambda\, x_M)\left[\theta_\lambda + \sinh(\theta_\lambda)\right] - \theta_\lambda\, D(\mu+\lambda)\, \sinh^2(\theta_\lambda) = 0$$

- Consider $\tilde{R}(\tilde{\lambda}) = R(r + ib + \tilde{\lambda})$, $\quad \tilde{R}(\tilde{\lambda}) : B_r(0) \to \mathbb{C}$, where $B_r(0) = \{z \in \mathbb{C} : |z| \leq r\}$, $\lambda = r + ib + \tilde{\lambda}$ and
- We show that for some $D > 0$ the winding number of $\Phi(t) = \tilde{R}(re^{it}) = R(r + ib + re^{it})$ for $t \in [0, 2\pi]$ is non-zero:

$$W(\Phi) = \frac{1}{2\pi i} \int_0^{2\pi} \frac{\Phi'(t)}{\Phi(t)} dt = 2.$$

- For all λ_ε: $\mathcal{R}e(\lambda_\varepsilon) < 0$ for $D < D^c_{1,\varepsilon}$ and $D > D^c_{2,\varepsilon}$
- There exist $\tilde{\lambda}_\varepsilon$: $\mathcal{R}e(\tilde{\lambda}_\varepsilon) > 0$ for $D^c_{1,\varepsilon} < D < D^c_{2,\varepsilon}$ and $0 \notin \sigma(\mathcal{A})$.
- There are two critical values of D, i.e $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$ for which $\mathcal{A}$ has a pair of purely imaginary eigenvalues
- The fact that $\lambda_{j,\varepsilon}(D)$ are zeros of an analytic function with respect to D and $\lambda_{j,\varepsilon}$ and not identical zero
  $\Longrightarrow$ $\lambda_{j,\varepsilon}(D)$ are isolated
  $\Longrightarrow$ $\lambda^c_{j,\varepsilon}(D)$ and $\overline{\lambda^c_{j,\varepsilon}}(D)$ cross the real line with non-zero speed as the bifurcation parameter D increases, $j = 1, 2$.

Hopf bifurcation

$$R(\lambda)=\frac{\alpha_p\alpha_m}{4}f'(p_0^*(x_M,D))\cosh^2(\theta_\lambda\, x_M)\left[\theta_\lambda+\sinh(\theta_\lambda)\right]-\theta_\lambda\, D(\mu+\lambda)\,\sinh^2(\theta_\lambda)=0$$

- Consider $\tilde{R}(\tilde{\lambda})=R(r+ib+\tilde{\lambda})$, $\quad \tilde{R}(\tilde{\lambda}):B_r(0)\to\mathbb{C}$, where $B_r(0)=\{z\in\mathbb{C}:|z|\le r\}$, $\lambda=r+ib+\tilde{\lambda}$ and
- We show that for some $D>0$ the winding number of $\Phi(t)=\tilde{R}(re^{it})=R(r+ib+re^{it})$ for $t\in[0,2\pi]$ is non-zero:

$$W(\Phi)=\frac{1}{2\pi i}\int_0^{2\pi}\frac{\Phi'(t)}{\Phi(t)}dt=2.$$

- For all λ_ε: $\mathcal{R}e(\lambda_\varepsilon)<0$ for $D<D^c_{1,\varepsilon}$ and $D>D^c_{2,\varepsilon}$
- There exist $\tilde{\lambda}_\varepsilon$: $\mathcal{R}e(\tilde{\lambda}_\varepsilon)>0$ for $D^c_{1,\varepsilon}<D<D^c_{2,\varepsilon}$ and $0\notin\sigma(\mathcal{A})$.
- There are two critical values of D, i.e $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$ for which $\mathcal{A}$ has a pair of purely imaginary eigenvalues
- The fact that $\lambda_{j,\varepsilon}(D)$ are zeros of an analytic function with respect to D and $\lambda_{j,\varepsilon}$ and not identical zero
  $\Longrightarrow$ $\lambda_{j,\varepsilon}(D)$ are isolated
  $\Longrightarrow$ $\lambda^c_{j,\varepsilon}(D)$ and $\overline{\lambda^c_{j,\varepsilon}}(D)$ cross the real line with non-zero speed as the bifurcation parameter D increases, $j=1,2$.

Hopf bifurcation

$$R(\lambda) = \frac{\alpha_p \alpha_m}{4} f'(p_0^*(x_M, D)) \cosh^2(\theta_\lambda\, x_M) \left[\theta_\lambda + \sinh(\theta_\lambda)\right] - \theta_\lambda\, D(\mu+\lambda)\, \sinh^2(\theta_\lambda) = 0$$

- Consider $\tilde{R}(\tilde{\lambda}) = R(r + ib + \tilde{\lambda})$, $\quad \tilde{R}(\tilde{\lambda}) : B_r(0) \to \mathbb{C}$, where $B_r(0) = \{z \in \mathbb{C} : |z| \leq r\}$, $\lambda = r + ib + \tilde{\lambda}$ and
- We show that for some $D > 0$ the winding number of $\Phi(t) = \tilde{R}(re^{it}) = R(r + ib + re^{it})$ for $t \in [0, 2\pi]$ is non-zero:

$$W(\Phi) = \frac{1}{2\pi i} \int_0^{2\pi} \frac{\Phi'(t)}{\Phi(t)} dt = 2.$$

- For all λ_ε: $\mathcal{R}e(\lambda_\varepsilon) < 0$ for $D < D^c_{1,\varepsilon}$ and $D > D^c_{2,\varepsilon}$
- There exist $\tilde{\lambda}_\varepsilon$: $\mathcal{R}e(\tilde{\lambda}_\varepsilon) > 0$ for $D^c_{1,\varepsilon} < D < D^c_{2,\varepsilon}$ and $0 \notin \sigma(\mathcal{A})$.
- There are two critical values of D, i.e $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$ for which $\mathcal{A}$ has a pair of purely imaginary eigenvalues
- The fact that $\lambda_{j,\varepsilon}(D)$ are zeros of an analytic function with respect to D and $\lambda_{j,\varepsilon}$ and not identical zero
  $\Longrightarrow$ $\lambda_{j,\varepsilon}(D)$ are isolated
  $\Longrightarrow$ $\lambda^c_{j,\varepsilon}(D)$ and $\overline{\lambda^c_{j,\varepsilon}}(D)$ cross the real line with non-zero speed as the bifurcation parameter D increases, $j = 1, 2$.

Stability of the Hopf Bifurcation

Theorem At both critical values of the bifurcation parameter, $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$, a supercritical Hopf bifurcation occurs and the family of periodic orbits bifurcating from the stationary solution is stable.

1. Weakly nonlinear analysis: $D = D^c_{j,\varepsilon} + \delta^2\nu + \cdots, \qquad \nu = \pm 1,$

   $\lambda_{j,\varepsilon}(D) = \lambda^c_{j,\varepsilon} + \dfrac{\partial \lambda_{j,\varepsilon}}{\partial D}\delta^2\nu + \cdots$, where $\delta > 0$ and $j = 1, 2$.

$$m(t, T, x) = m^*_\varepsilon(x, D) + \delta m_1(t, T, x) + \delta^2 m_2(t, T, x) + \delta^3 m_3(t, T, x) + O(\delta^4)$$
$$p(t, T, x) = p^*_\varepsilon(x, D) + \delta p_1(t, T, x) + \delta^2 p_2(t, T, x) + \delta^3 p_3(t, T, x) + O(\delta^4)$$

2. Equations reduced to the central manifold in the normal form

$$\frac{dA}{dt} = \lambda^c_{j,\varepsilon}\, A + a_{j,\varepsilon}\, \tilde{D}\, A + b_{j,\varepsilon}\, A\, |A|^2 + O(|A|(|\tilde{D}| + |A|^2)^2),$$

   where $\tilde{D} = D - D^c_{j,\varepsilon}$. The solutions on the centre manifold

$$u = A\xi + \overline{A\xi} + \Phi(A, \bar{A}, \tilde{D}), \qquad A \in \mathbb{C},$$

   where $\xi = (\xi_1, \xi_2)$ is an eigenvector for the eigenvalue $\lambda^c_{j,\varepsilon}$

Stability: Central manifold and Normal form

- $\tilde{D} = D - D^c_{j,\varepsilon}$ and $\tilde{m} = m - m^*_\varepsilon(x, D)$, $\tilde{p} = p - p^*_\varepsilon(x, D)$, where $m^*_\varepsilon(x, D)$ and $p^*_\varepsilon(x, D)$ are the stationary solutions.
- For $u(t,x) = (\tilde{m}(t,x), \tilde{p}(t,x))$ we have

$$\partial_t u = \mathcal{A}_{D^c_{j,\varepsilon}} u + \tilde{F}(u, \tilde{D}),$$

with

$$\mathcal{A}_{D^c_{j,\varepsilon}} = \begin{pmatrix} D^c_{j,\varepsilon} \dfrac{\partial^2}{\partial x^2} - \mu & \alpha_m f'(p^*_\varepsilon(x, D^c_{j,\varepsilon}))\delta^\varepsilon_{x_M}(x) \\ \alpha_p\, g(x) & D^c_{j,\varepsilon} \dfrac{\partial^2}{\partial x^2} - \mu \end{pmatrix}$$

and

$$\tilde{F}(u, \tilde{D}) = \begin{pmatrix} \alpha_m \left[f(\tilde{p} + p^*_\varepsilon(\tilde{D})) - f(p^*_\varepsilon(\tilde{D})) - f'(p^*_\varepsilon(D^c_{j,\varepsilon}))\, \tilde{p} \right] \delta^\varepsilon_{x_M} + \tilde{D}\partial^2_x \tilde{m} \\ \tilde{D}\partial^2_x \tilde{p} \end{pmatrix}$$

Central manifold theory and Normal Form

For Φ a polynomial ansatz can be made:

$$\Phi(A, \bar{A}, \tilde{D}) = \sum_{r,s,q} \Phi_{rsq} A^r \bar{A}^s \tilde{D}^q \ ,$$

with $\Phi_{100} = 0$, $\Phi_{010} = 0$ and $\Phi_{rsq} = \overline{\Phi}_{srq}$.

Considering orders of $\tilde{D}A$, A^2, $A\bar{A}$, $A^2\bar{A}$, implies the equations:

$$\begin{aligned}
-\mathcal{A}_{D^c_{j,\varepsilon}} \Phi_{001} &= \partial_{\tilde{D}} \tilde{F}(0,0), \\
a_{j,\varepsilon}\xi + (\lambda^c_{j,\varepsilon} - \mathcal{A}_{D^c_{j,\varepsilon}})\Phi_{101} &= \partial_u \partial_{\tilde{D}} \tilde{F}(0,0)\xi + \partial_u^2 \tilde{F}(0,0)(\xi, \Phi_{001}), \\
(2\lambda^c_{j,\varepsilon} - \mathcal{A}_{D^c_{j,\varepsilon}})\Phi_{200} &= \frac{1}{2}\partial_u^2 \tilde{F}(0,0)(\xi,\xi), \\
-\mathcal{A}_{D^c_{j,\varepsilon}} \Phi_{110} &= \partial_u^2 \tilde{F}(0,0)(\xi,\bar{\xi}), \\
b_{j,\varepsilon}\xi + (\lambda^c_{j,\varepsilon} - \mathcal{A}_{D^c_{j,\varepsilon}})\Phi_{210} &= \partial_u^2 \tilde{F}(0,0)(\bar{\xi}, \Phi_{200}) + \partial_u^2 \tilde{F}(0,0)(\xi, \Phi_{110}) \\
&\quad + \frac{1}{2}\partial_u^3 \tilde{F}(0,0)(\xi,\xi,\bar{\xi}).
\end{aligned}$$

Normal form and weakly-nonlinear analysis

Taking

$$\tilde{m}(t,x) = m(t,x) - m^*_\varepsilon(x,D) \approx \delta$$

$$\tilde{p}(t,x) = p(t,x) - p^*_\varepsilon(x,D) \approx \delta$$

$$\tilde{D} \approx \delta^2 \nu \quad \text{and} \quad T = t/\delta^2$$

into normal form implies

$$\delta \frac{dA}{dt} + \delta^3 \frac{dA}{dT} = \lambda^c_{j,\varepsilon} \delta A + a_{j,\varepsilon} \delta^3 \nu A + \delta^3 b_{j,\varepsilon} A|A|^2 + \delta^5 O(|A|(|\nu| + |A|^2)^2).$$

Then for the terms of orders δ and δ^3, we obtain the equations derived using weakly-nonlinear analysis, i.e.

$$\frac{dA}{dt} = \lambda^c_{j,\varepsilon} A \quad \text{and} \quad \frac{dA}{dT} = a_{j,\varepsilon}\, \nu\, A + b_{j,\varepsilon}\, A|A|^2 \,.$$

Thank you very much for your attention

Chaplain, Ptashnyk, Sturrock (2015) *Hopf bifurcation in a gene regulatory network model: molecular movement causes oscillations*, M3AS.

Relations between eigenvalue problems EW_ε and EW_0

- For $h \in E = C([0,1])$

$$W_\varepsilon(\lambda)h = \alpha_p \alpha_m g(x) \int_0^1 G_{\lambda+\mu}(x,y) f'(p^*_\varepsilon) \delta^\varepsilon_{x_M}(y) h(y) dy - \lambda h$$

- For $\lambda \in T = \{\lambda \in \mathbb{C}, \mathcal{R}e(\lambda) \geq -\mu + \vartheta, |\lambda| \leq \Theta\}$, for some $\Theta \geq 2\kappa$, $0 < \vartheta < \mu/2$

  $(-\tilde{A}_0)^{-1} W_\varepsilon(\lambda)$ is a collectively compact on E and converges pointwise to $(-\tilde{A}_0)^{-1} W_0(\lambda)$ as $\varepsilon \to 0$

$$W_0(\lambda)h = \alpha_p \alpha_m g(x) G_{\lambda+\mu}(x, x_M) f'(p^*_0(x_M, D)) h(x_M) - \lambda h$$

  and $\tilde{A}_0 = D\frac{d^2}{dx^2} - \mu$

- $$\|W_\varepsilon(\lambda)h\|_E \leq C\|h\|_E \qquad \text{for all } \lambda \in T,$$

  $(-\tilde{A}_0)^{-1}$- compact $\implies$ $(-\tilde{A}_0)^{-1} W_\varepsilon(\lambda)$ for $\lambda \in T$ collective compact.

- $W_\varepsilon(\lambda)$ and $W_0(\lambda)$, for $\mathcal{R}e(\tilde{\lambda}) > -\mu$ or $\mathcal{I}m(\tilde{\lambda}) \neq 0$, depend analytically on λ.

Relations between eigenvalue problems EW_ε and EW_0

- For $h \in E = C([0,1])$

$$W_\varepsilon(\lambda)h = \alpha_p\alpha_m g(x)\int_0^1 G_{\lambda+\mu}(x,y)f'(p_\varepsilon^*)\delta_{x_M}^\varepsilon(y)h(y)dy - \lambda h$$

- For $\lambda \in T = \{\lambda \in \mathbb{C},\ \mathcal{R}e(\lambda) \geq -\mu + \vartheta,\ |\lambda| \leq \Theta\}$, for some $\Theta \geq 2\kappa$, $0 < \vartheta < \mu/2$

  $(-\tilde{A}_0)^{-1}W_\varepsilon(\lambda)$ is a collectively compact on E and converges pointwise to $(-\tilde{A}_0)^{-1}W_0(\lambda)$ as $\varepsilon \to 0$

$$W_0(\lambda)h = \alpha_p\alpha_m g(x)G_{\lambda+\mu}(x,x_M)f'(p_0^*(x_M,D))h(x_M) - \lambda h$$

  and $\tilde{A}_0 = D\frac{d^2}{dx^2} - \mu$

-

$$\|W_\varepsilon(\lambda)h\|_E \leq C\|h\|_E \qquad \text{for all} \quad \lambda \in T,$$

  $(-\tilde{A}_0)^{-1}$- compact $\Longrightarrow$ $(-\tilde{A}_0)^{-1}W_\varepsilon(\lambda)$ for $\lambda \in T$ collective compact.

- $W_\varepsilon(\lambda)$ and $W_0(\lambda)$, for $\mathcal{R}e(\tilde{\lambda}) > -\mu$ or $\mathcal{I}m(\tilde{\lambda}) \neq 0$, depend analytically on λ.

Relations between eigenvalue problems EW_ε and EW_0

- For $h \in E = C([0,1])$

$$W_\varepsilon(\lambda)h = \alpha_p \alpha_m g(x) \int_0^1 G_{\lambda+\mu}(x,y) f'(p_\varepsilon^*) \delta_{x_M}^\varepsilon(y) h(y) dy - \lambda h$$

- For $\lambda \in T = \{\lambda \in \mathbb{C}, \mathcal{R}e(\lambda) \geq -\mu + \vartheta, |\lambda| \leq \Theta\}$, for some $\Theta \geq 2\kappa$, $0 < \vartheta < \mu/2$

  $(-\tilde{A}_0)^{-1} W_\varepsilon(\lambda)$ is a collectively compact on E and converges pointwise to $(-\tilde{A}_0)^{-1} W_0(\lambda)$ as $\varepsilon \to 0$

$$W_0(\lambda)h = \alpha_p \alpha_m g(x) G_{\lambda+\mu}(x, x_M) f'(p_0^*(x_M, D)) h(x_M) - \lambda h$$

  and $\tilde{A}_0 = D \frac{d^2}{dx^2} - \mu$

- $$\|W_\varepsilon(\lambda)h\|_E \leq C\|h\|_E \qquad \text{for all } \lambda \in T,$$

  $(-\tilde{A}_0)^{-1}$- compact $\implies$ $(-\tilde{A}_0)^{-1} W_\varepsilon(\lambda)$ for $\lambda \in T$ collective compact.

- $W_\varepsilon(\lambda)$ and $W_0(\lambda)$, for $\mathcal{R}e(\tilde{\lambda}) > -\mu$ or $\mathcal{I}m(\tilde{\lambda}) \neq 0$, depend analytically on λ.

Relations between eigenvalue problems EW_ε and EW_0

- For $h \in E = C([0,1])$

$$W_\varepsilon(\lambda)h = \alpha_p \alpha_m g(x) \int_0^1 G_{\lambda+\mu}(x,y) f'(p_\varepsilon^*) \delta_{x_M}^\varepsilon(y) h(y) dy - \lambda h$$

- For $\lambda \in T = \{\lambda \in \mathbb{C},\ \mathcal{R}e(\lambda) \geq -\mu + \vartheta,\ |\lambda| \leq \Theta\}$, for some $\Theta \geq 2\kappa$, $0 < \vartheta < \mu/2$

  $(-\tilde{A}_0)^{-1} W_\varepsilon(\lambda)$ is a collectively compact on E and converges pointwise to $(-\tilde{A}_0)^{-1} W_0(\lambda)$ as $\varepsilon \to 0$

$$W_0(\lambda)h = \alpha_p \alpha_m g(x) G_{\lambda+\mu}(x, x_M) f'(p_0^*(x_M, D)) h(x_M) - \lambda h$$

  and $\tilde{A}_0 = D \frac{d^2}{dx^2} - \mu$

- $$\|W_\varepsilon(\lambda)h\|_E \leq C \|h\|_E \qquad \text{for all } \lambda \in T,$$

  $(-\tilde{A}_0)^{-1}$- compact $\implies$ $(-\tilde{A}_0)^{-1} W_\varepsilon(\lambda)$ for $\lambda \in T$ collective compact.

- $W_\varepsilon(\lambda)$ and $W_0(\lambda)$, for $\mathcal{R}e(\tilde{\lambda}) > -\mu$ or $\mathcal{I}m(\tilde{\lambda}) \neq 0$, depend analytically on λ.

- $I - (-\tilde{\mathcal{A}}_0)^{-1} W_0(\lambda)$ is a Fredholm operator with index zero
- $\tilde{\lambda} : \; I - (-\tilde{\mathcal{A}}_0)^{-1} W_0(\tilde{\lambda})$ is not invertible
- $E = \mathcal{N} \oplus M$ and $E = \mathcal{R} \oplus Y$, where $\mathcal{N} = \mathcal{N}(I - (-\tilde{\mathcal{A}}_0)^{-1} W_0(\tilde{\lambda}))$, $\mathcal{R} = \mathcal{R}(I - (-\tilde{\mathcal{A}}_0)^{-1} W_0(\tilde{\lambda}))$
- $Q : E \to \mathcal{R}$ be the projection onto $\mathcal{R}$ parallel to Y.
- $Q(I - (-\tilde{\mathcal{A}}_0)^{-1} W_\varepsilon(\lambda)) : M \to \mathcal{R}$ is invertible with uniformly bounded inverse, for λ near $\tilde{\lambda}$ and ε is small.
- For $\bar{p}^\varepsilon = m + k \in E$ with $k \in \mathcal{N}$ and $m \in M$

$$EW_\varepsilon : \qquad (I - (-\tilde{\mathcal{A}}_0)^{-1} W_{\varepsilon_j}(\lambda))(m + k) = 0$$

$$Q(I - (-\tilde{\mathcal{A}}_0)^{-1} W_{\varepsilon_j}(\lambda))m = -Q(I - (-\tilde{\mathcal{A}}_0)^{-1} W_{\varepsilon_j}(\lambda))k$$

- The invertibility of $\left(Q(I - (-\tilde{\mathcal{A}}_0)^{-1} W_{\varepsilon_j}(\lambda))\right)$ on M implies

$$m = -\left[Q(I - (-\tilde{\mathcal{A}}_0)^{-1} W_{\varepsilon_j}(\lambda))\right]^{-1} \left(Q(I - (-\tilde{\mathcal{A}}_0)^{-1} W_{\varepsilon_j}(\lambda))k\right) = S_{\varepsilon_j}(\lambda)k.$$

- $S_{\varepsilon_j}(\lambda_{\varepsilon_j})k \to S_0(\tilde{\lambda})k$ if $\lambda_{\varepsilon_j} \to \tilde{\lambda}$ and $\varepsilon_j \to 0$ as $j \to \infty$.

- $I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\lambda)$ is a Fredholm operator with index zero
- $\tilde{\lambda}:\ I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\tilde{\lambda})$ is not invertible
- $E=\mathcal{N}\oplus M$ and $E=\mathcal{R}\oplus Y$, where $\mathcal{N}=\mathcal{N}(I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\tilde{\lambda}))$, $\mathcal{R}=\mathcal{R}(I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\tilde{\lambda}))$
- $Q:E\to\mathcal{R}$ be the projection onto $\mathcal{R}$ parallel to Y.
- $Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_\varepsilon(\lambda)):M\to\mathcal{R}$ is invertible with uniformly bounded inverse, for λ near $\tilde{\lambda}$ and ε is small.
- For $\bar{p}^\varepsilon=m+k\in E$ with $k\in\mathcal{N}$ and $m\in M$

$$EW_\varepsilon: \qquad (I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))(m+k)=0$$

$$Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))m=-Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))k$$

- The invertibility of $\left(Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))\right)$ on M implies

$$m=-\left[Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))\right]^{-1}\left(Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))k\right)=S_{\varepsilon_j}(\lambda)k.$$

- $S_{\varepsilon_j}(\lambda_{\varepsilon_j})k\to S_0(\tilde{\lambda})k$ if $\lambda_{\varepsilon_j}\to\tilde{\lambda}$ and $\varepsilon_j\to 0$ as $j\to\infty$.

- $I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\lambda)$ is a Fredholm operator with index zero
- $\tilde{\lambda}:\ I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\tilde{\lambda})$ is not invertible
- $E=\mathcal{N}\oplus M$ and $E=\mathcal{R}\oplus Y$, where
  $\mathcal{N}=\mathcal{N}(I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\tilde{\lambda}))$, $\mathcal{R}=\mathcal{R}(I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\tilde{\lambda}))$
- $Q:E\to\mathcal{R}$ be the projection onto $\mathcal{R}$ parallel to Y.
- $Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_\varepsilon(\lambda)):M\to\mathcal{R}$ is invertible with uniformly bounded inverse, for λ near $\tilde{\lambda}$ and ε is small.
- For $\bar{p}^\varepsilon=m+k\in E$ with $k\in\mathcal{N}$ and $m\in M$

$$EW_\varepsilon:\qquad (I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))(m+k)=0$$

$$Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))m=-Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))k$$

- The invertibility of $\left(Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))\right)$ on M implies

$$m=-\left[Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))\right]^{-1}\left(Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))k\right)=S_{\varepsilon_j}(\lambda)k.$$

- $S_{\varepsilon_j}(\lambda_{\varepsilon_j})k\to S_0(\tilde{\lambda})k$ if $\lambda_{\varepsilon_j}\to\tilde{\lambda}$ and $\varepsilon_j\to 0$ as $j\to\infty$.

- $I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\lambda)$ is a Fredholm operator with index zero
- $\tilde{\lambda}$: $I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\tilde{\lambda})$ is not invertible
- $E=\mathcal{N}\oplus M$ and $E=\mathcal{R}\oplus Y$, where $\mathcal{N}=\mathcal{N}(I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\tilde{\lambda}))$, $\mathcal{R}=\mathcal{R}(I-(-\tilde{\mathcal{A}}_0)^{-1}W_0(\tilde{\lambda}))$
- $Q:E\to\mathcal{R}$ be the projection onto $\mathcal{R}$ parallel to Y.
- $Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_\varepsilon(\lambda)):M\to\mathcal{R}$ is invertible with uniformly bounded inverse, for λ near $\tilde{\lambda}$ and ε is small.
- For $\bar{p}^\varepsilon=m+k\in E$ with $k\in\mathcal{N}$ and $m\in M$

$$EW_\varepsilon: \qquad (I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))(m+k)=0$$

$$Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))m=-Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))k$$

- The invertibility of $\left(Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))\right)$ on M implies

$$m=-\left[Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))\right]^{-1}\left(Q(I-(-\tilde{\mathcal{A}}_0)^{-1}W_{\varepsilon_j}(\lambda))k\right)$$
$$=S_{\varepsilon_j}(\lambda)k.$$

- $S_{\varepsilon_j}(\lambda_{\varepsilon_j})k\to S_0(\tilde{\lambda})k$ if $\lambda_{\varepsilon_j}\to\tilde{\lambda}$ and $\varepsilon_j\to 0$ as $j\to\infty$.

- $I - (-\tilde{A}_0)^{-1} W_0(\lambda)$ is a Fredholm operator with index zero
- $\tilde{\lambda}: \; I - (-\tilde{A}_0)^{-1} W_0(\tilde{\lambda})$ is not invertible
- $E = \mathcal{N} \oplus M$ and $E = \mathcal{R} \oplus Y$, where
  $\mathcal{N} = \mathcal{N}(I - (-\tilde{A}_0)^{-1} W_0(\tilde{\lambda}))$, $\mathcal{R} = \mathcal{R}(I - (-\tilde{A}_0)^{-1} W_0(\tilde{\lambda}))$
- $Q: E \to \mathcal{R}$ be the projection onto $\mathcal{R}$ parallel to Y.
- $Q(I - (-\tilde{A}_0)^{-1} W_\varepsilon(\lambda)) : M \to \mathcal{R}$ is invertible with uniformly bounded inverse, for λ near $\tilde{\lambda}$ and ε is small.
- For $\bar{p}^\varepsilon = m + k \in E$ with $k \in \mathcal{N}$ and $m \in M$

$$EW_\varepsilon : \qquad (I - (-\tilde{A}_0)^{-1} W_{\varepsilon_j}(\lambda))(m + k) = 0$$

$$Q(I - (-\tilde{A}_0)^{-1} W_{\varepsilon_j}(\lambda))m = -Q(I - (-\tilde{A}_0)^{-1} W_{\varepsilon_j}(\lambda))k$$

- The invertibility of $\left(Q(I - (-\tilde{A}_0)^{-1} W_{\varepsilon_j}(\lambda))\right)$ on M implies

$$m = -\left[Q(I - (-\tilde{A}_0)^{-1} W_{\varepsilon_j}(\lambda))\right]^{-1} \left(Q(I - (-\tilde{A}_0)^{-1} W_{\varepsilon_j}(\lambda))k\right) = S_{\varepsilon_j}(\lambda)k.$$

- $S_{\varepsilon_j}(\lambda_{\varepsilon_j})k \to S_0(\tilde{\lambda})k$ if $\lambda_{\varepsilon_j} \to \tilde{\lambda}$ and $\varepsilon_j \to 0$ as $j \to \infty$.

- EW_ε is reduced to

$$Z_{\varepsilon_j}(\lambda)k = 0 \text{ for } k \in \mathcal{N},$$

where $Z_\varepsilon(\lambda) = (I - Q)\left(I - (-\tilde{A}_0)^{-1}W_\varepsilon(\lambda)\left(I + S_\varepsilon(\lambda)\right)\right)$.

- $Z_{\varepsilon_j}(\lambda_{\varepsilon_j})k \to Z_0(\lambda)k$
  for $\lambda_{\varepsilon_j} \to \lambda, \varepsilon_j \to 0$ as $j \to \infty$ for each fixed $k \in \mathcal{N}$

$$\|Z_{\varepsilon_j}(\lambda_{\varepsilon_j}) - Z_0(\lambda)\| \to 0 \qquad \text{as} \quad j \to \infty\,.$$

- $W_0(\lambda)$ analytic $\Longrightarrow$ $Z_0(\lambda)$ analytic in λ.
- $\tilde{\mathcal{A}}$ has compact resolvent $\Longrightarrow$ spectrum of $\tilde{\mathcal{A}}$ is discrete and consists of eigenvalues.
- $Z_0(\lambda)$ is invertible for some $\lambda \in T$ $\Longrightarrow$ $\det Z_0(\lambda)$ does not vanish identically on T and its zeros are isolated
  $\Longrightarrow$ the topological degree of $\det Z_0(\lambda)$ is positive in the neighbourhood of $\tilde{\lambda}$.
- Homotopy invariance of the topological degree $\Longrightarrow$ the degree of $\det Z_{\varepsilon_j}(\lambda_{\varepsilon_j})$ is equal to the degree of $\det Z_0(\lambda)$ and is positive in the neighbourhood of $\tilde{\lambda}$ and small ε_j.
- $\det Z_\varepsilon(\lambda_\varepsilon)$ has a solution $\Longrightarrow$ $\mathcal{A}$ has an eigenvalue near $\tilde{\lambda}$.

- EW_ε is reduced to

$$Z_{\varepsilon_j}(\lambda)k = 0 \text{ for } k \in \mathcal{N},$$

where $Z_\varepsilon(\lambda) = (I - Q)\left(I - (-\tilde{\mathcal{A}}_0)^{-1} W_\varepsilon(\lambda)\left(I + S_\varepsilon(\lambda)\right)\right)$.

- $Z_{\varepsilon_j}(\lambda_{\varepsilon_j})k \to Z_0(\lambda)k$
  for $\lambda_{\varepsilon_j} \to \lambda, \varepsilon_j \to 0$ as $j \to \infty$ for each fixed $k \in \mathcal{N}$

$$\|Z_{\varepsilon_j}(\lambda_{\varepsilon_j}) - Z_0(\lambda)\| \to 0 \qquad \text{as} \quad j \to \infty .$$

- $W_0(\lambda)$ analytic $\Longrightarrow$ $Z_0(\lambda)$ analytic in λ.
- $\tilde{\mathcal{A}}$ has compact resolvent $\Longrightarrow$ spectrum of $\tilde{\mathcal{A}}$ is discrete and consists of eigenvalues.
- $Z_0(\lambda)$ is invertible for some $\lambda \in T$ $\Longrightarrow$ $\det Z_0(\lambda)$ does not vanish identically on T and its zeros are isolated

  $\Longrightarrow$ the topological degree of $\det Z_0(\lambda)$ is positive in the neighbourhood of $\tilde{\lambda}$.
- Homotopy invariance of the topological degree $\Longrightarrow$ the degree of $\det Z_{\varepsilon_j}(\lambda_{\varepsilon_j})$ is equal to the degree of $\det Z_0(\lambda)$ and is positive in the neighbourhood of $\tilde{\lambda}$ and small ε_j.
- $\det Z_\varepsilon(\lambda_\varepsilon)$ has a solution $\Longrightarrow$ $\mathcal{A}$ has an eigenvalue near $\tilde{\lambda}$.

- EW_ε is reduced to

$$Z_{\varepsilon_j}(\lambda)k = 0 \text{ for } k \in \mathcal{N},$$

where $Z_\varepsilon(\lambda) = (I - Q)\left(I - (-\tilde{\mathcal{A}}_0)^{-1} W_\varepsilon(\lambda)\,(I + S_\varepsilon(\lambda))\right).$

- $Z_{\varepsilon_j}(\lambda_{\varepsilon_j})k \to Z_0(\lambda)k$
  for $\lambda_{\varepsilon_j} \to \lambda, \varepsilon_j \to 0$ as $j \to \infty$ for each fixed $k \in \mathcal{N}$

$$\|Z_{\varepsilon_j}(\lambda_{\varepsilon_j}) - Z_0(\lambda)\| \to 0 \qquad \text{as} \quad j \to \infty\,.$$

- $W_0(\lambda)$ analytic $\Longrightarrow$ $Z_0(\lambda)$ analytic in λ.
- $\tilde{\mathcal{A}}$ has compact resolvent $\Longrightarrow$ spectrum of $\tilde{\mathcal{A}}$ is discrete and consists of eigenvalues.
- $Z_0(\lambda)$ is invertible for some $\lambda \in T$ $\Longrightarrow$ $\det Z_0(\lambda)$ does not vanish identically on T and its zeros are isolated
  $\Longrightarrow$ the topological degree of $\det Z_0(\lambda)$ is positive in the neighbourhood of $\tilde{\lambda}$.
- Homotopy invariance of the topological degree $\Longrightarrow$ the degree of $\det Z_{\varepsilon_j}(\lambda_{\varepsilon_j})$ is equal to the degree of $\det Z_0(\lambda)$ and is positive in the neighbourhood of $\tilde{\lambda}$ and small ε_j.
- $\det Z_\varepsilon(\lambda_\varepsilon)$ has a solution $\Longrightarrow$ $\mathcal{A}$ has an eigenvalue near $\tilde{\lambda}$.