Hopf Bifurcation in a Gene Regulatory Network Model:
Molecular Movement Causes Oscillations

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Talk Overview

- Gene Regulatory Networks, Transduction Factors
- Hes1 system spatial model
- Computational simulation results (PDE + stochastic PDE)
- Analysis of simplified model
- Conclusions
Transcription Factors: Gene regulatory networks

- Transcription factors are proteins that bind to specific DNA sequences
- Control flow of genetic information from DNA to RNA (transcription)
- Can either activate/promote or repress/suppress (upregulation/downregulation)
Negative feedback loops are found in a variety of signalling pathways.

Examples include Hes1, p53, NF-κB, ERK, cAMP, Heat Shock Proteins (HSP).

Experimental data reveals these pathways can give rise to oscillatory dynamics.
A generic negative feedback loop: species $x$ produces $y$ which then inhibits $x$, in turn reducing levels of $y$...
Hes1 Negative Feedback Loop
Hes1 - Experimental data: Hirata et al. (2002)
$m$ - mRNA; $p$ - protein:

\[
\begin{align*}
\frac{\partial m}{\partial t} &= \frac{\alpha_m}{1 + (p/\hat{p})^h} - \mu_m m, \\
\frac{\partial p}{\partial t} &= \alpha_p m - \mu_p p,
\end{align*}
\]

$\Rightarrow$ No oscillations
The Hes1 Transcription Factor

$m$ - mRNA; $p$ - protein:

\[
\frac{\partial m}{\partial t} = \frac{\alpha_m}{1 + (p/\hat{p})^h} - \mu_mm, \tag{1}
\]

\[
\frac{\partial p}{\partial t} = \alpha_pm - \mu_pp, \tag{2}
\]

⇒ No oscillations
The Hes1 Transcription Factor

$m$ - mRNA; $p$ - protein:

\[ \frac{\partial m}{\partial t} = \alpha_m f(p) - \mu_m m, \quad (3) \]
\[ \frac{\partial p}{\partial t} = \alpha_p m - \mu_p p, \quad (4) \]

Bendixson’s Negative Criterion $\Rightarrow$ no oscillations for any $f(p)$

\[ \frac{\partial m}{\partial t} = \alpha_m f(p - \tau) - \mu_m m, \quad (5) \]
\[ \frac{\partial p}{\partial t} = \alpha_p m - \mu_p p. \quad (6) \]
The Hes1 Transcription Factor

\( m \) - mRNA; \( p \) - protein:

\[
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\frac{\partial m}{\partial t} &= \alpha_m f(p) - \mu_m m, \\
\frac{\partial p}{\partial t} &= \alpha_p m - \mu_p p,
\end{align*}
\]

(3) \hspace{1cm} (4)

Bendixson’s Negative Criterion \( \Rightarrow \) no oscillations for any \( f(p) \)

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The Hes1 Transcription Factor

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(4)

Bendixson’s Negative Criterion $\Rightarrow$ no oscillations for any $f(p)$

$$\frac{\partial m}{\partial t} = \alpha_m f(p - \tau) - \mu_m m,$$

(5)

$$\frac{\partial p}{\partial t} = \alpha_p m - \mu_p p.$$

(6)
Hes1 Spatial Model

\[ t = D_{mn} n^2 + h_m^1 + \frac{p_n}{p}(h_m^1) + h \mu_m n \]

\[ t = D_{mc} c^2 + p_m \mu_m c \]

\[ t = D_{pn} n^2 + p_m \mu_p n \]

\[ \frac{\partial m}{\partial t} = D_m \nabla^2 m_n + \frac{a^2}{1 + \left(\frac{p_n}{p}\right)} - \mu_n m_n \]

\[ \frac{\partial p}{\partial t} = D_p \nabla^2 p_n - \mu_p p_n \]
\[
\frac{\partial [m_n]}{\partial t} = D_{m_n} \nabla^2 [m_n] + \frac{\alpha_m h}{1 + ([p_n]/\hat{p})^h} - \mu_m [m_n], \tag{7}
\]
\[
\frac{\partial [m_c]}{\partial t} = D_{m_c} \nabla^2 [m_c] - \mu_m [m_c], \tag{8}
\]
\[
\frac{\partial [p_c]}{\partial t} = D_{p_c} \nabla^2 [p_c] + \alpha_p [m_c] - \mu_p [p_c], \tag{9}
\]
\[
\frac{\partial [p_n]}{\partial t} = D_{p_n} \nabla^2 [p_n] - \mu_p [p_n]. \tag{10}
\]
Hes1 Mathematical Model: Simulation Results

Mark Chaplain
GRN Modelling
Będlewo 12th June 2015
Hes1 Spatial Stochastic Model

URDME [ Unstructured-mesh, Reaction-Diffusion Master Equation ]
spatial Gillespie algorithm
Hes1 Spatial Stochastic Model

\[
\begin{align*}
P_f + \text{protein} & \xrightarrow{k_1} \frac{1}{k_2} P_o, \quad \text{(promoter, } x_m, \text{ nucleus)} \\
P_f & \xrightarrow{\alpha_m} mRNA, \quad \text{(promoter, } x_m, \text{ nucleus)} \\
P_o & \xrightarrow{\alpha_m/\gamma} mRNA, \quad \text{(promoter, } x_m, \text{ nucleus)} \\
mRNA & \xrightarrow{\alpha_p} mRNA + \text{protein}, \quad \text{(cytoplasm, } \Omega_c) \\
mRNA & \xrightarrow{\mu_m} \phi, \quad \text{(entire cell, } \Omega) \\
\text{protein} & \xrightarrow{\mu_p} \phi, \quad \text{(entire cell, } \Omega) \\
\text{protein}_i & \xrightarrow{D/h^2} \text{protein}_{i+1}, \quad \text{(entire cell, } \Omega) \\
mRNA_i & \xrightarrow{D/h^2} mRNA_{i+1}, \quad \text{(entire cell, } \Omega) \\
\text{protein}_i & \xrightarrow{D/h^2} \text{protein}_{i-1}, \quad \text{(entire cell, } \Omega) \\
mRNA_i & \xrightarrow{D/h^2} mRNA_{i-1}, \quad \text{(entire cell, } \Omega)
\end{align*}
\]
Experimental data from Kobayashi et al.\textsuperscript{1} showing Hes1 protein levels in murine embryonic stem cells.

\textsuperscript{1}Kobayashi et al. (2009) The cyclic gene Hes1 contributes to diverse differentiation responses of embryonic stem cells \textit{Genes Dev.} \textbf{23}, 1870 - 1875
Corresponding simulation results from the spatial stochastic model\textsuperscript{1}.

Computational Results: Summary

- Spatial model(s) generate oscillatory dynamics without the need for a delay
- Simulations indicate that spatial movement of molecules is important - no oscillations if diffusion too small or too large
Simplified Hes1 Model
Simplified Hes1 Model

\[
\frac{\partial m}{\partial t} = D \frac{\partial^2 m}{\partial x^2} + \alpha_m f(p) \delta_{x_M}^{\varepsilon}(x) - \mu_m m \quad \text{in} \; (0, T) \times (0, 1),
\]

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

\[
\frac{\partial m(t, 0)}{\partial x} = \frac{\partial m(t, 1)}{\partial x} = 0, \quad \frac{\partial p(t, 0)}{\partial x} = \frac{\partial p(t, 1)}{\partial x} = 0 \quad \text{in} \; (0, T),
\]

\[
m(0, x) = m_0(x), \quad p(0, x) = p_0(x) \quad \text{in} \; (0, 1),
\]
Simplified Model

\[ f(p) = \frac{1}{1 + p^h}, \text{ with } h \geq 2 \]

\[ \delta_{x_M}^\varepsilon \] denotes the Dirac approximation of the \( \delta \)-distribution located at \( x_M \), with \( \varepsilon > 0 \) a small parameter and \( \delta_{x_M}^\varepsilon \) has compact support i.e. \[ \delta_{x_M}^\varepsilon (x) = \frac{1}{2\varepsilon} (1 + \cos(\pi (x - x_M)/\varepsilon)) \text{ for } |x - x_M| < \varepsilon \text{ and } \delta_{x_M}^\varepsilon (x) = 0 \text{ for } |x - x_M| \geq \varepsilon \]

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

![Graphs showing computational results](image-url)
There is a stationary solution, stable for small values of the diffusion coefficient $D$, which becomes unstable for $D \geq D_{1,\epsilon}^c$, with $D_{1,\epsilon}^c \approx 3.117 \times 10^{-4}$, and again stable for $D > D_{2,\epsilon}^c$, where $D_{2,\epsilon}^c \approx 7.885 \times 10^{-3}$. For diffusion coefficients between the two critical values, i.e. $D \in [D_{1,\epsilon}^c, D_{2,\epsilon}^c]$, numerical simulations show the existence of stable periodic solutions.
First we examine the stationary solutions \( u_\varepsilon^* = (m_\varepsilon^*, p_\varepsilon^*)^T \) of the system satisfying the following one-dimensional boundary-value problem:

\[
\begin{align*}
D \frac{d^2 m_\varepsilon^*}{dx^2} - \mu_m m_\varepsilon^* + \alpha_m f(p_\varepsilon^*) \delta_{x_M}^\varepsilon(x) &= 0 & \text{in } (0, 1), \\
D \frac{d^2 p_\varepsilon^*}{dx^2} - \mu_p p_\varepsilon^* + \alpha_p g(x) m_\varepsilon^* &= 0 & \text{in } (0, 1), \\
\frac{dm_\varepsilon^*(0)}{dx} &= \frac{dm_\varepsilon^*(1)}{dx} = 0, & \frac{dp_\varepsilon^*(0)}{dx} &= \frac{dp_\varepsilon^*(1)}{dx} = 0.
\end{align*}
\]
For very small diffusion coefficients $D \ll 1$, in the zero-order approximation we obtain:

$$
0 = \alpha_m f(p^*_\varepsilon)\delta_{x_m}(x) - \mu_m m^*_\varepsilon, \quad 0 = \alpha_p g(x)m^*_\varepsilon - \mu_p p^*_\varepsilon \quad \text{in } (0, 1).
$$

Since $g(x) = 0$ for $x \in [0, l)$, the second equation yields that $p^*_\varepsilon(x, D) = 0$ in $[0, l)$ and thus $m^*_\varepsilon(x, D) = \frac{\alpha_m}{\mu_m} \delta_{x_m}(x)$ in $[0, 1]$. Using the fact that $x_M \in (0, l)$ we obtain for sufficiently small $\varepsilon > 0$ that $m^*_\varepsilon(x, D) = 0$ for $x \in [l, 1]$ and thus $p^*_\varepsilon(x, D) = 0$ in $[0, 1]$.

Therefore for very small $D$ we have localisation of mRNA concentration around $x_M$, whereas the concentration of protein is approximately zero everywhere in $[0, 1]$. 
For large diffusion coefficients, i.e. $D \gg 1$ and therefore $1/D \ll 1$, we have

$$0 = \frac{d^2 m^*_\epsilon}{dx^2} + \frac{1}{D} \left( \alpha_m f(p^*_\epsilon) \delta^\epsilon \delta^\epsilon_M(x) - \mu_m m^*_\epsilon \right) \quad \text{in} \ (0, 1),$$

$$0 = \frac{d^2 p^*_\epsilon}{dx^2} + \frac{1}{D} \left( \alpha_p g(x) m^*_\epsilon - \mu_p p^*_\epsilon \right) \quad \text{in} \ (0, 1),$$

$$\frac{dm^*_\epsilon}{dx}(0) = \frac{dm^*_\epsilon}{dx}(1) = 0, \quad \frac{dp^*_\epsilon}{dx}(0) = \frac{dp^*_\epsilon}{dx}(1) = 0.$$

Thus $m^*_\epsilon(x, D) \approx \text{constant}$ and $p^*_\epsilon(x, D) \approx \text{constant}$. 
Simplified Model: Steady States
Simplified Model: Steady States

\[ m_\varepsilon^*(x, D) = \alpha_m \int_0^1 G_{\mu_m}(x, y) f(p_\varepsilon^*(y, D)) \delta_{x_M}(y) \, dy , \]

\[ p_\varepsilon^*(x, D) = \alpha_m \alpha_p \int_0^1 g(z) G_{\mu_p}(x, z) \int_0^1 G_{\mu_m}(z, y) f(p_\varepsilon^*(y, D)) \delta_{x_M}(y) \, dy \, dz , \]
Simplified Model: Steady States

\[ G_{\mu_j}(y, x) = \begin{cases} 
\frac{1}{(\mu_j D)^{1/2} \sinh(\theta_j)} \cosh(\theta_j y) \cosh(\theta_j (1 - x)), & 0 < y < x < 1 \\
\frac{1}{(\mu_j D)^{1/2} \sinh(\theta_j)} \cosh(\theta_j (1 - y)) \cosh(\theta_j x), & 0 < x < y < 1
\end{cases} \]

with \( \theta_j = (\mu_j / D)^{1/2} \), for \( j = m, p \), the Green’s function satisfying the boundary-value problem

\[ DG_{yy} - \mu_j G = -\delta_x \quad \text{in} \ (0, 1), \quad G_y(0, x) = G_y(1, x) = 0. \]
Simplified Model: Steady States

\[ m_0^*(x, D) = \alpha_m G_{\mu m}(x, x_M) f(p_0^*(x_M, D)), \]

\[ p_0^*(x, D) = \alpha_m \alpha_p f(p_0^*(x_M, D)) \int_0^1 g(y) G_{\mu p}(x, y) G_{\mu m}(y, x_M) \, dy, \]

Since \( x_M < l \) and \( g(y) = 0 \) for \( 0 \leq y < l \), we have

\[ G_{\mu m}(y, x_M) = \frac{1}{(\mu_m D)^{1/2} \sinh(\theta_m)} \cosh(\theta_m (1 - y)) \cosh(\theta_m x_M), \]

\( x_M < y < 1 \), where \( \theta_m = (\mu_m / D)^{1/2} \)
\[ p_0^*(x_M, D) = f(p_0^*(x_M, D)) \frac{\alpha_p \alpha_m}{2} \frac{\cosh(\theta_m x_M) \cosh(\theta_p x_M)}{\sqrt{\mu_m \mu_p} D \sinh(\theta_m) \sinh(\theta_p)} \]

\[ \times \left[ \frac{\sinh((\theta_p + \theta_m)(1 - l))}{\theta_p + \theta_m} + \frac{\sinh((\theta_p - \theta_m)(1 - l))}{\theta_p - \theta_m} \right] \]

for \( \theta_m \neq \theta_p \), and for \( \theta_m = \theta_p (= \theta) \)

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

\[ \times \left[ 2\theta(1 - l) + \sinh(2\theta(1 - l)) \right] \]
Simplified Model: Steady States

→ only one positive solution for all values of $D \in [d_1, d_2]$.

Thus, since $m_0^*(x, D)$ and $p_0^*(x, D)$ are uniquely defined by $p_0^*(x_M, D)$, for every $D \in [d_1, d_2]$ we have a unique positive solution of the stationary problem with $\varepsilon = 0$. Then the strong convergence of $m_\varepsilon^* \to m_0^*$, $p_\varepsilon^* \to p_0^*$ as $\varepsilon \to 0$ in $C([0, 1])$ and the fact that nonnegative steady states $(m_\varepsilon^*, p_\varepsilon^*)^T$ are isolated imply the uniqueness of the positive steady state of the time-dependent problem for small $\varepsilon > 0$. 
\[ \frac{\partial m}{\partial t} = D \frac{\partial^2 m}{\partial x^2} + \alpha_m f(p) \delta^\varepsilon_x (x) - \mu_m m \quad \text{in} \ (0, T) \times (0, 1), \]

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

\[ \frac{\partial m(t, 0)}{\partial x} = \frac{\partial m(t, 1)}{\partial x} = 0, \quad \frac{\partial p(t, 0)}{\partial x} = \frac{\partial p(t, 1)}{\partial x} = 0 \quad \text{in} \ (0, T), \]

\[ m(0, x) = m_0(x), \quad p(0, x) = p_0(x) \quad \text{in} \ (0, 1), \]
Linearised Stability Analysis

\[ m = m^* + \epsilon \bar{m}^\varepsilon \]

\[ p = p^* + \epsilon \bar{p}^\varepsilon \]
Linearised Stability Analysis

\[ \lambda \bar{m}^\varepsilon = D \bar{m}_{xx}^\varepsilon + \alpha_m f'(p_\varepsilon^*(x, D)) \delta_{x_M}^\varepsilon (x) \bar{p}^\varepsilon - \mu_m \bar{m}^\varepsilon \quad \text{in} \ (0, 1), \]

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

\[ \bar{m}_x^\varepsilon (0) = \bar{m}_x^\varepsilon (1) = 0, \quad \bar{p}_x^\varepsilon (0) = \bar{p}_x^\varepsilon (1) = 0, \]

or in operator form

\[ \mathbf{A} w^\varepsilon = \lambda w^\varepsilon, \]

where \( w^\varepsilon = (\bar{m}^\varepsilon, \bar{p}^\varepsilon)^T \) and \( \mathbf{A} = \mathbf{A}_0 + \mathbf{A}_1 \)
Linearised Stability Analysis

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

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

Now examine the eigenvalues of \( \mathcal{A} \ldots \)
Hopf Bifurcation

**Theorem**

For $\varepsilon > 0$ small there exist two critical values of the parameter $D$, i.e. $D_{1,\varepsilon}^c$ and $D_{2,\varepsilon}^c$, for which a Hopf bifurcation occurs in the model.


(+ Dr. Mariya Ptashnyk)
Hopf Bifurcation

Theorem

At both critical values of the bifurcation parameter, $D_{1,\epsilon}^c$ and $D_{2,\epsilon}^c$, a supercritical Hopf bifurcation occurs in the system and the family of periodic orbits bifurcating from the stationary solution at each Hopf bifurcation point is stable.

(techniques from weakly nonlinear analysis and the central manifold theory)
spatial movement of the molecules alone is sufficient to cause the oscillations\textsuperscript{2}

\[ \Rightarrow \text{importance of modelling transcription factor systems where negative feedback loops are involved using explicitly spatial models} \]
spatial movement of the molecules alone is sufficient to cause the oscillations\(^2\)

⇒ importance of modelling transcription factor systems where negative feedback loops are involved using explicitly spatial models

Future Work

Experimental data from Lahav et al.\textsuperscript{3}
showing p53 and Mdm2 protein levels in individual cells.

\textsuperscript{3}Lahav et al. (2004) Dynamics of the p53-Mdm2 feedback loop in individual cells. 
\textit{Nature Genetics} 36, 147 - 150
Future Work

Corresponding simulation results from a spatial stochastic p53 model.
Thanks

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