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

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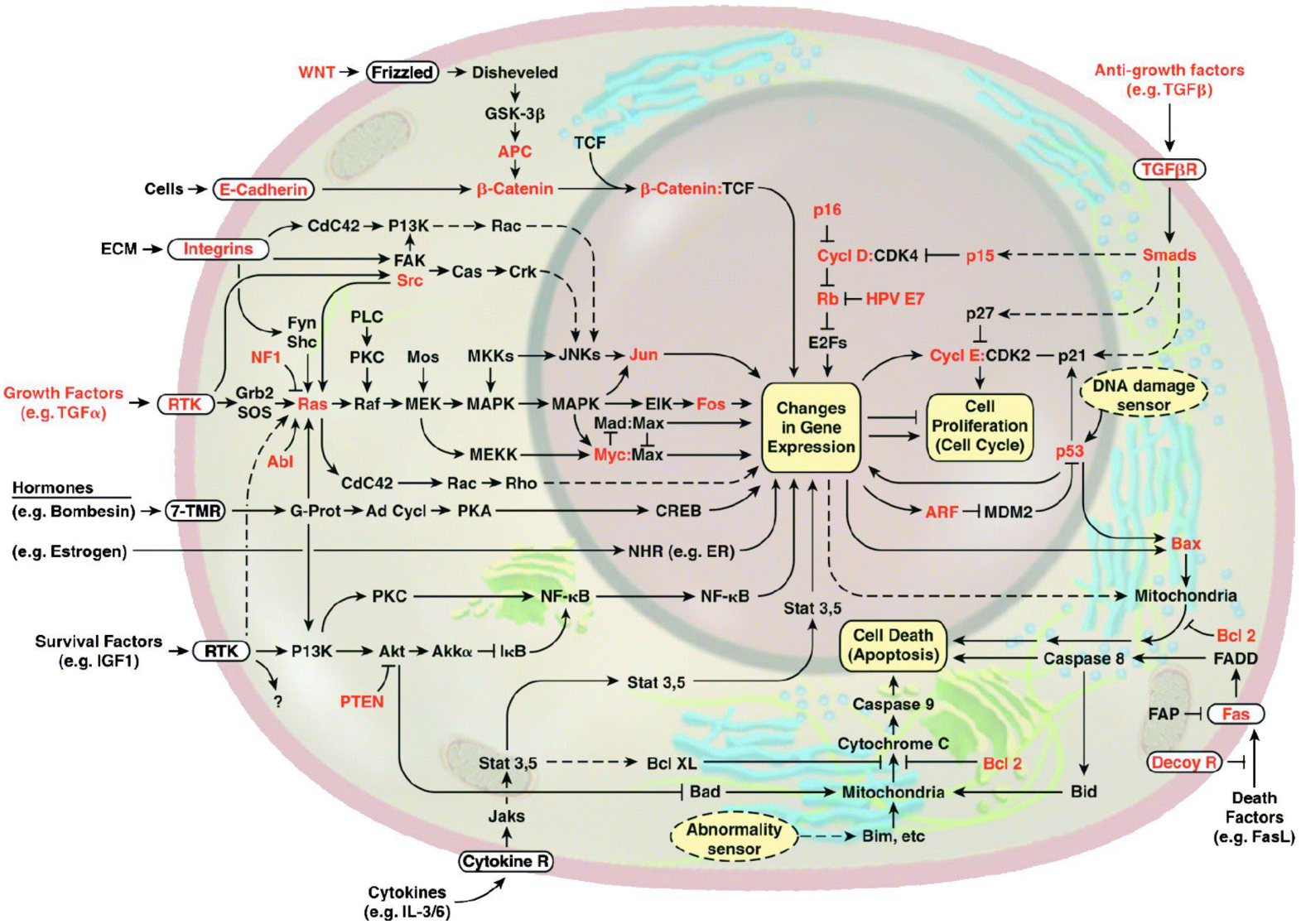
Talk Overview

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

Intracellular Pathways



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)

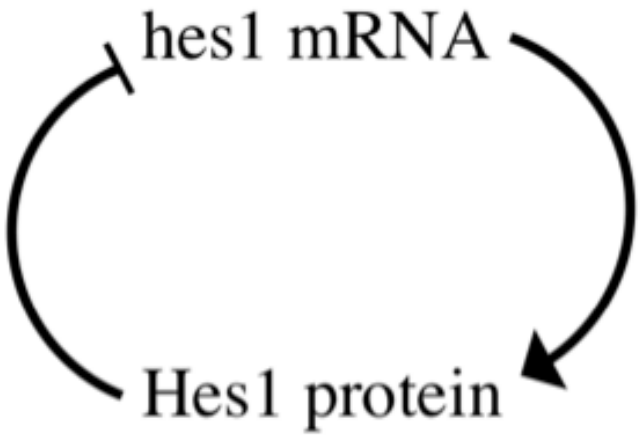
Gene regulatory networks: Negative Feedback Loops

- 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

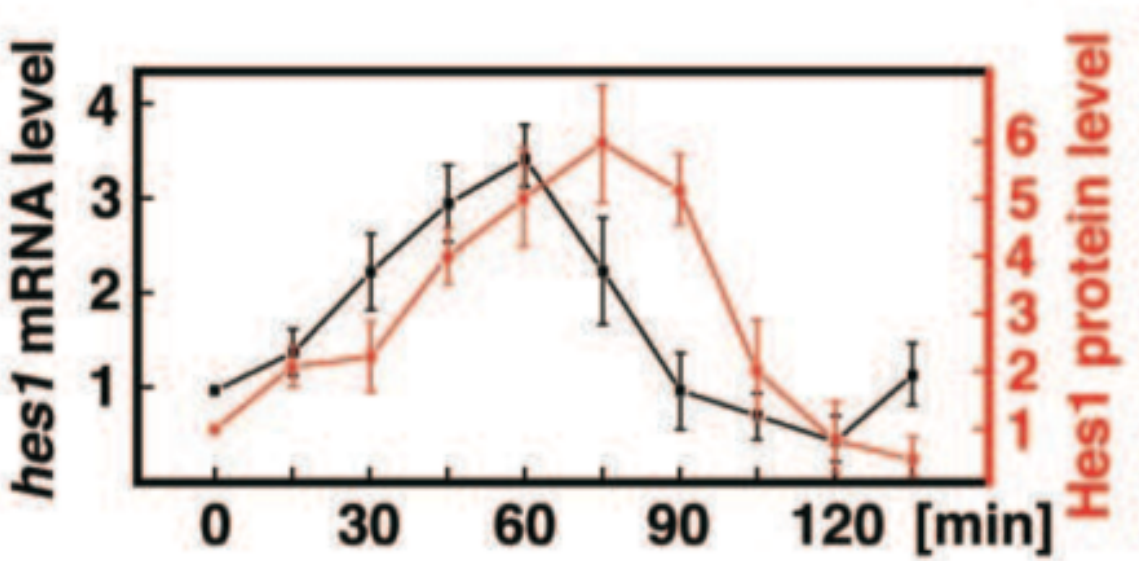
Gene regulatory networks: Negative feedback loops

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)



The Hes1 Transcription Factor

m - mRNA; p - protein:

$$\frac{\partial m}{\partial t} = \frac{\alpha_m}{1 + (p/\hat{p})^h} - \mu_m m, \quad (1)$$

$$\frac{\partial p}{\partial t} = \alpha_p m - \mu_p p, \quad (2)$$

$\Rightarrow$ No oscillations

The Hes1 Transcription Factor

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$\Rightarrow$ No oscillations

The Hes1 Transcription Factor

m - mRNA; p - protein:

$$\frac{\partial m}{\partial t} = \alpha_m f(p) - \mu_m m, \tag{3}$$

$$\frac{\partial p}{\partial t} = \alpha_p m - \mu_p p, \tag{4}$$

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

$$\frac{\partial m}{\partial t} = \alpha_m f(p - \tau) - \mu_m m, \tag{5}$$

$$\frac{\partial p}{\partial t} = \alpha_p m - \mu_p p. \tag{6}$$

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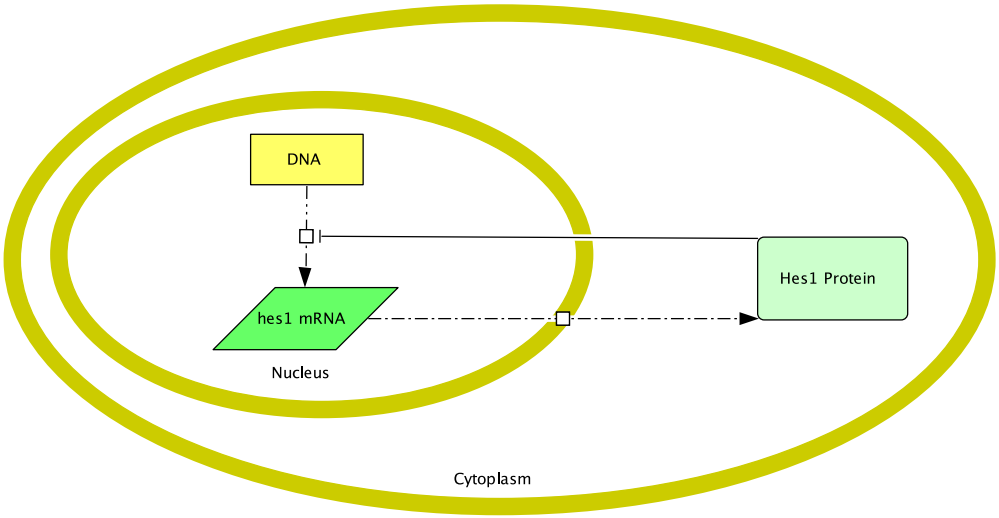
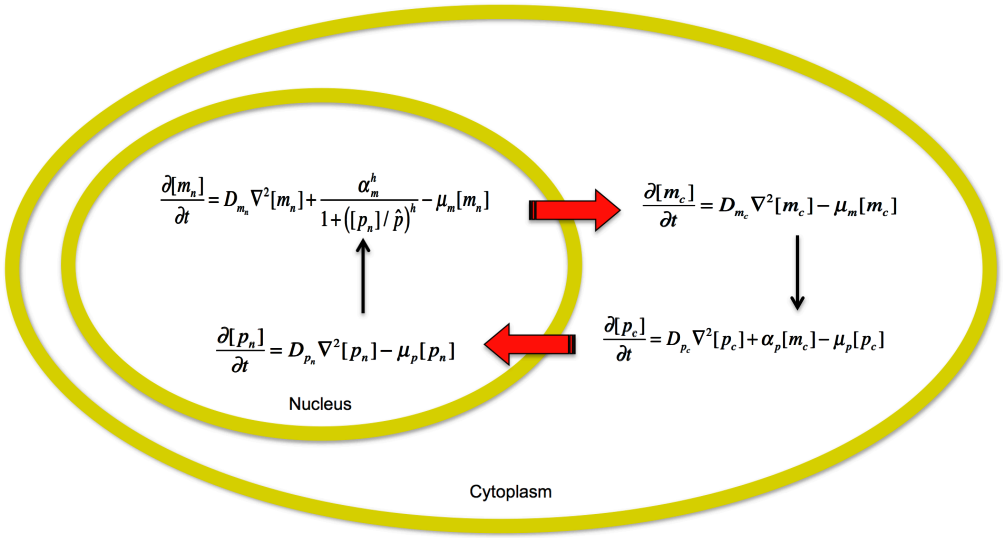
Hes1 Spatial Model





Hes1 Mathematical Model

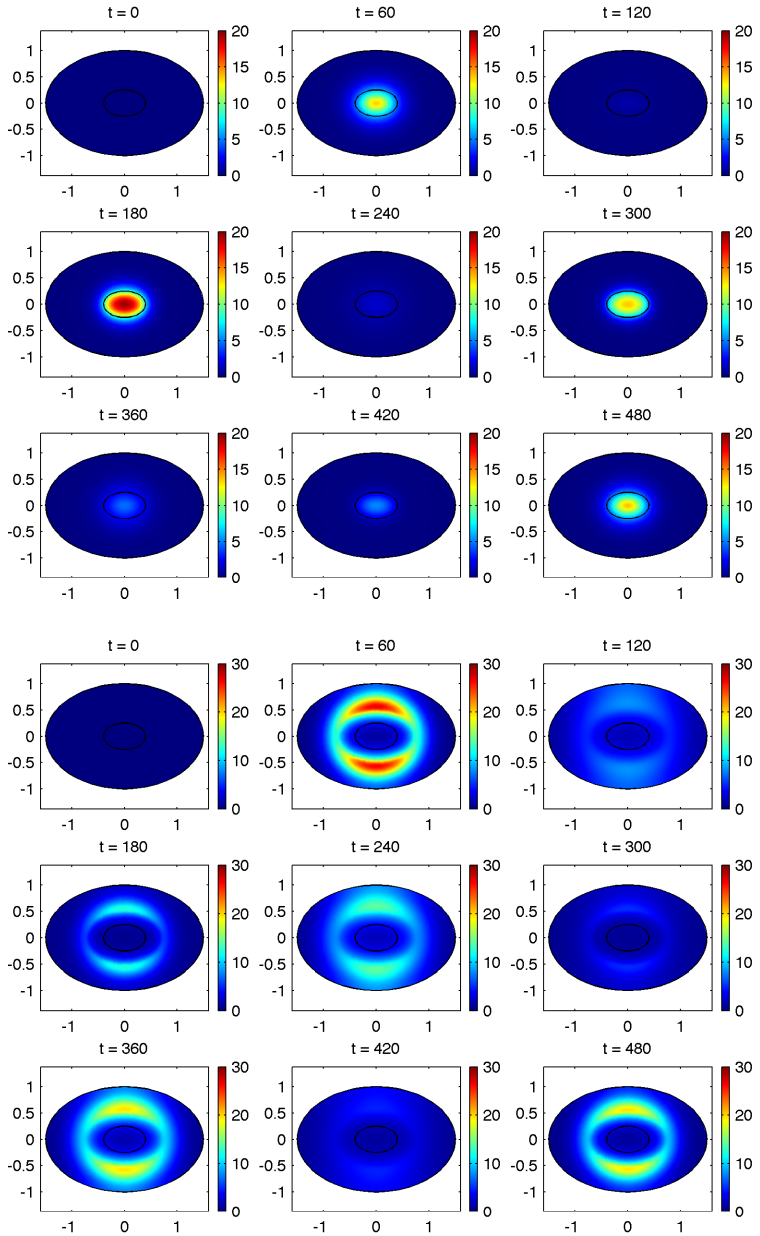
$$\frac{\partial [m_n]}{\partial t} = D_{m_n} \nabla^2 [m_n] + \frac{\alpha_m^h}{1 + ([p_n]/\hat{p})^h} - \mu_m [m_n], \tag{7}$$

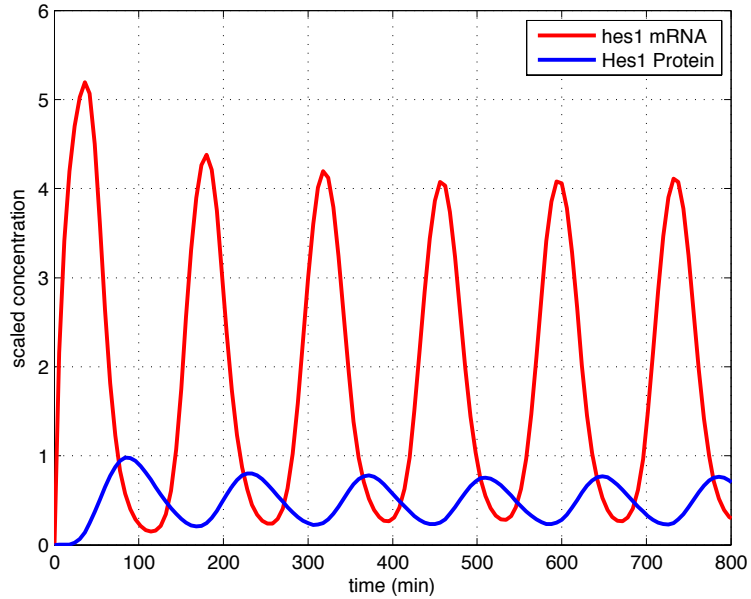
$$\frac{\partial [m_c]}{\partial t} = D_{m_c} \nabla^2 [m_c] - \mu_m [m_c], \tag{8}$$

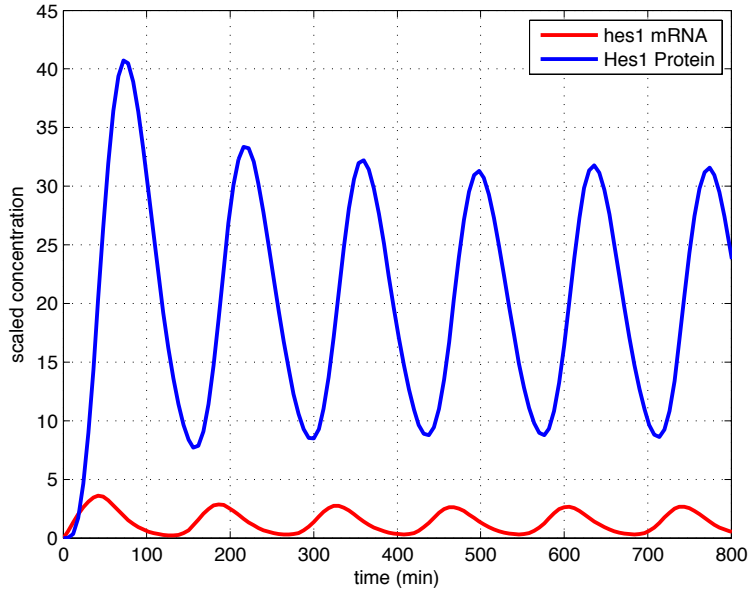
$$\frac{\partial [p_c]}{\partial t} = D_{p_c} \nabla^2 [p_c] + \alpha_p [m_c] - \mu_p [p_c], \tag{9}$$

$$\frac{\partial [p_n]}{\partial t} = D_{p_n} \nabla^2 [p_n] - \mu_p [p_n]. \tag{10}$$

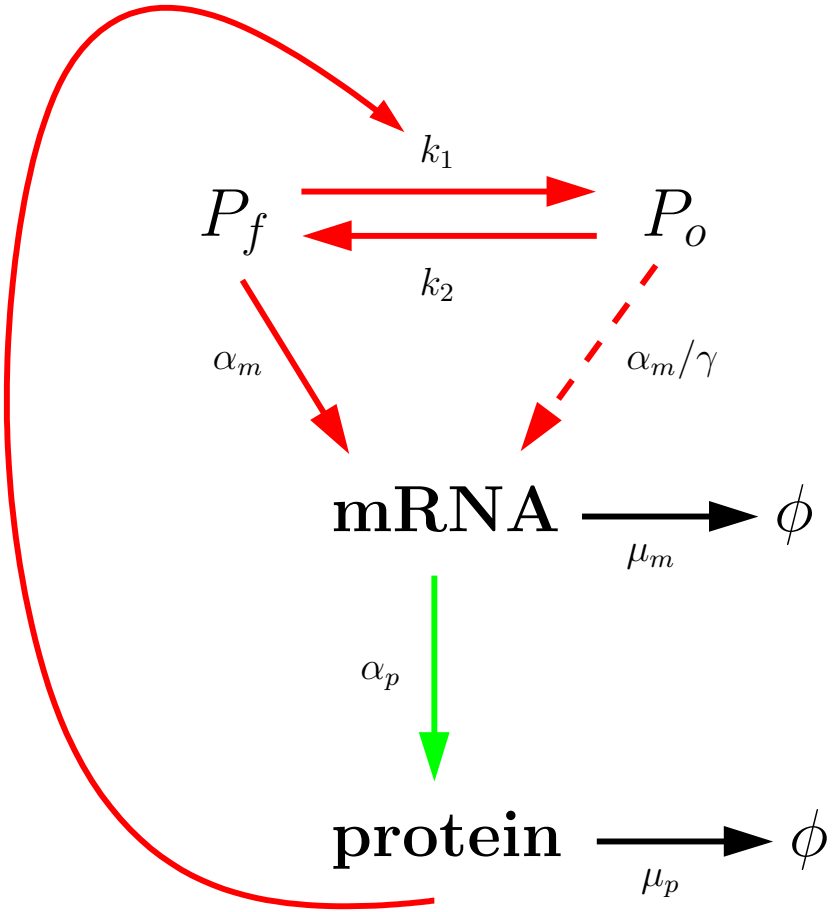
Hes1 Mathematical Model: Simulation Results

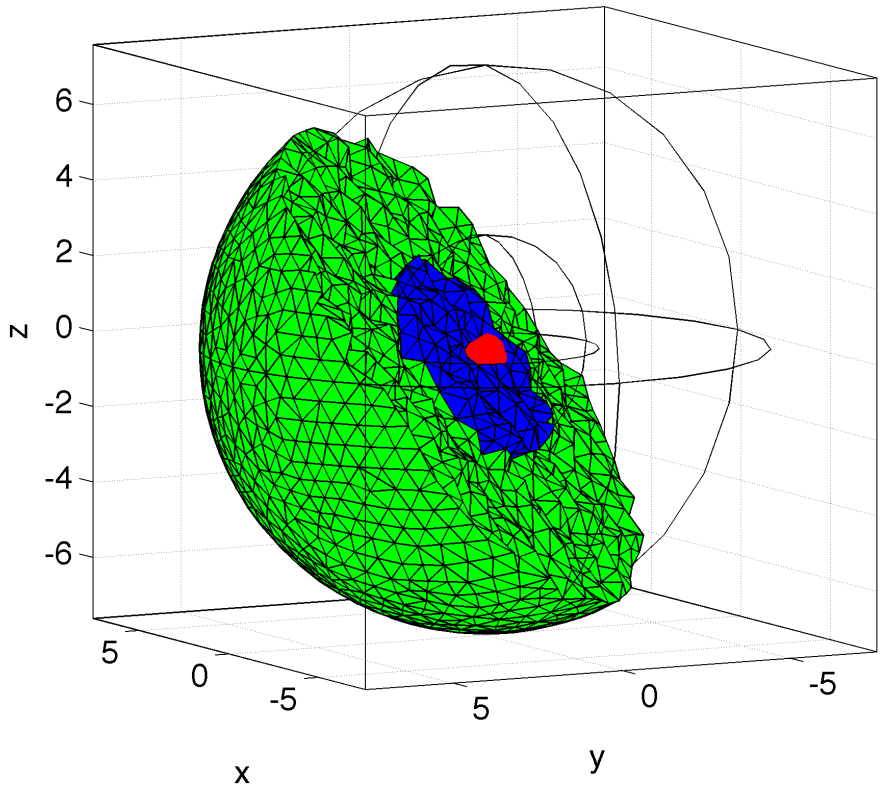






Hes1 Spatial Stochastic Model



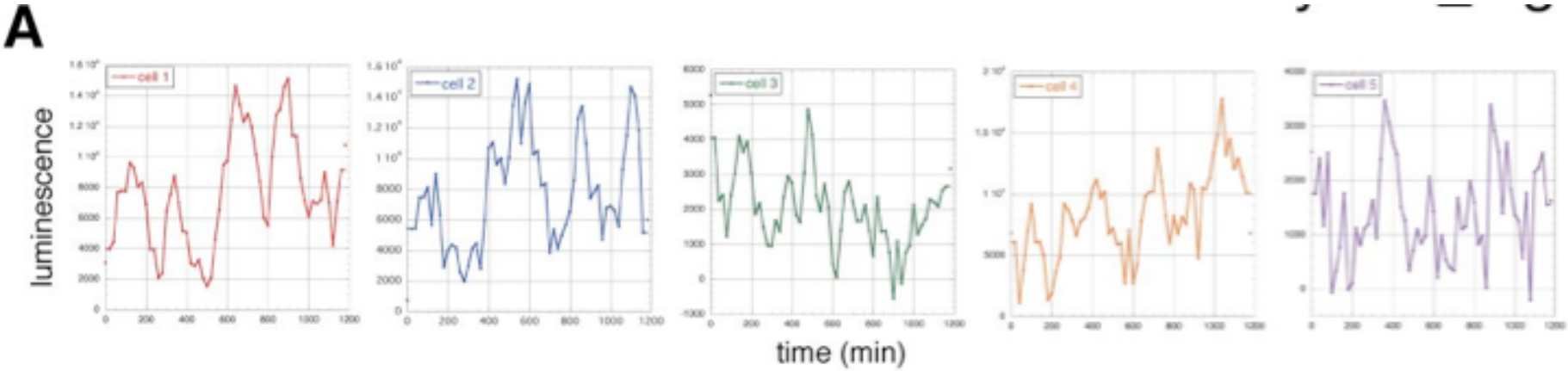


URDME [Unstructured-mesh, Reaction-Diffusion Master Equation]
spatial Gillespie algorithm

Hes1 Spatial Stochastic Model

$$
\begin{aligned}
P_f + protein &\underset{k_2}{\overset{k_1}{\rightleftharpoons}} P_o, && (\textbf{promoter}, x_m, \textbf{nucleus}) \\
P_f &\xrightarrow{\alpha_m} mRNA, && (\textbf{promoter}, x_m, \textbf{nucleus}) \\
P_o &\xrightarrow{\alpha_m/\gamma} mRNA, && (\textbf{promoter}, x_m, \textbf{nucleus}) \\
mRNA &\xrightarrow{\alpha_p} mRNA + protein, && (\textbf{cytoplasm}, \Omega_c) \\
mRNA &\xrightarrow{\mu_m} \phi, && (\textbf{entire cell}, \Omega) \\
protein &\xrightarrow{\mu_p} \phi, && (\textbf{entire cell}, \Omega) \\
protein_i &\xrightarrow{D/h^2} protein_{i+1}, && (\textbf{entire cell}, \Omega) \\
mRNA_i &\xrightarrow{D/h^2} mRNA_{i+1}, && (\textbf{entire cell}, \Omega) \\
protein_i &\xrightarrow{D/h^2} protein_{i-1}, && (\textbf{entire cell}, \Omega) \\
mRNA_i &\xrightarrow{D/h^2} mRNA_{i-1}, && (\textbf{entire cell}, \Omega)
\end{aligned}
$$

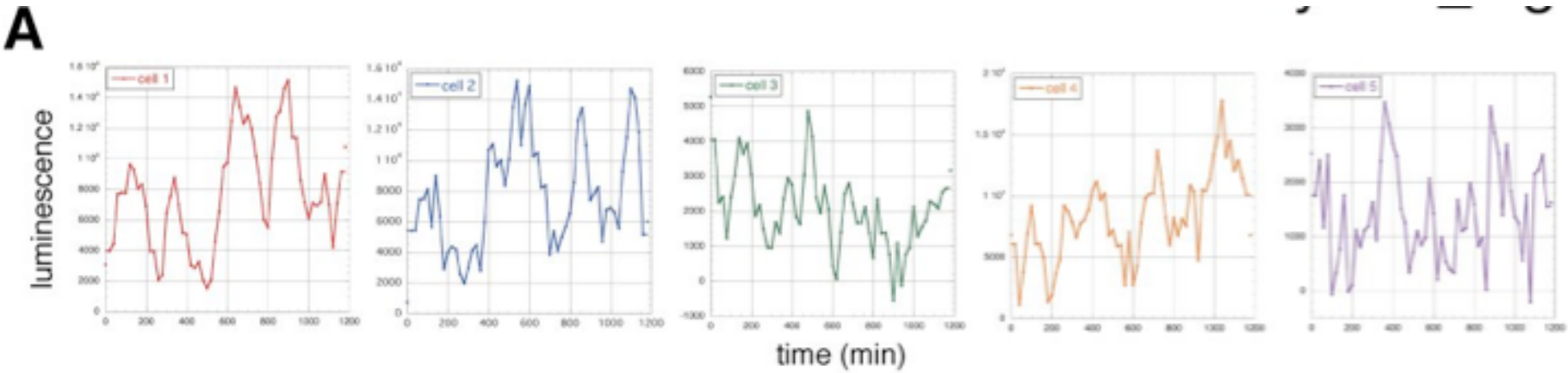
Hes1: Experimental Data/Simulation Results

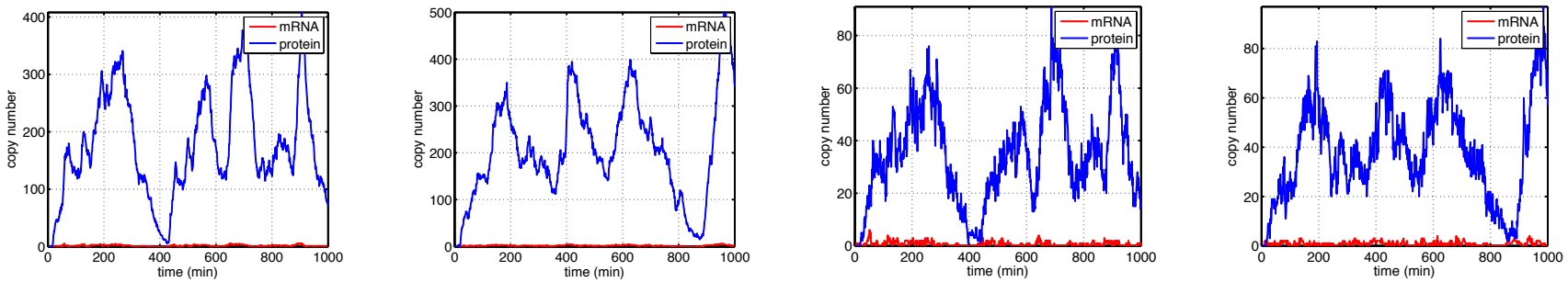


Experimental data from Kobayashi et al.[1] showing Hes1 protein levels in murine embryonic stem cells.

[1] Kobayashi et al. (2009) The cyclic gene Hes1 contributes to diverse differentiation responses of embryonic stem cells *Genes Dev.* **23**, 1870 - 1875

Hes1: Experimental Data/Simulation Results





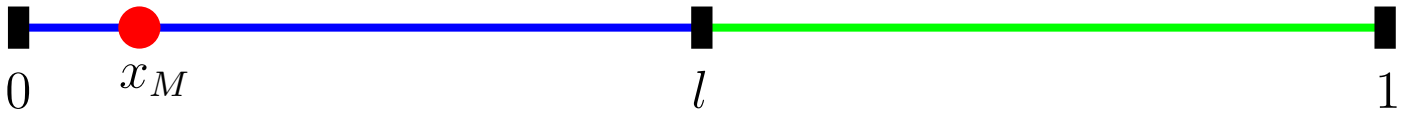
Corresponding simulation results from the spatial stochastic model[1].

[1] Sturrock, Hellander, Matzavinos, Chaplain (2013) Spatial stochastic modelling of the Hes1 gene regulatory network: intrinsic noise can explain heterogeneity in embryonic stem cell differentiation. *J. R. Soc. Interface* **10**, 20120988

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

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

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

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

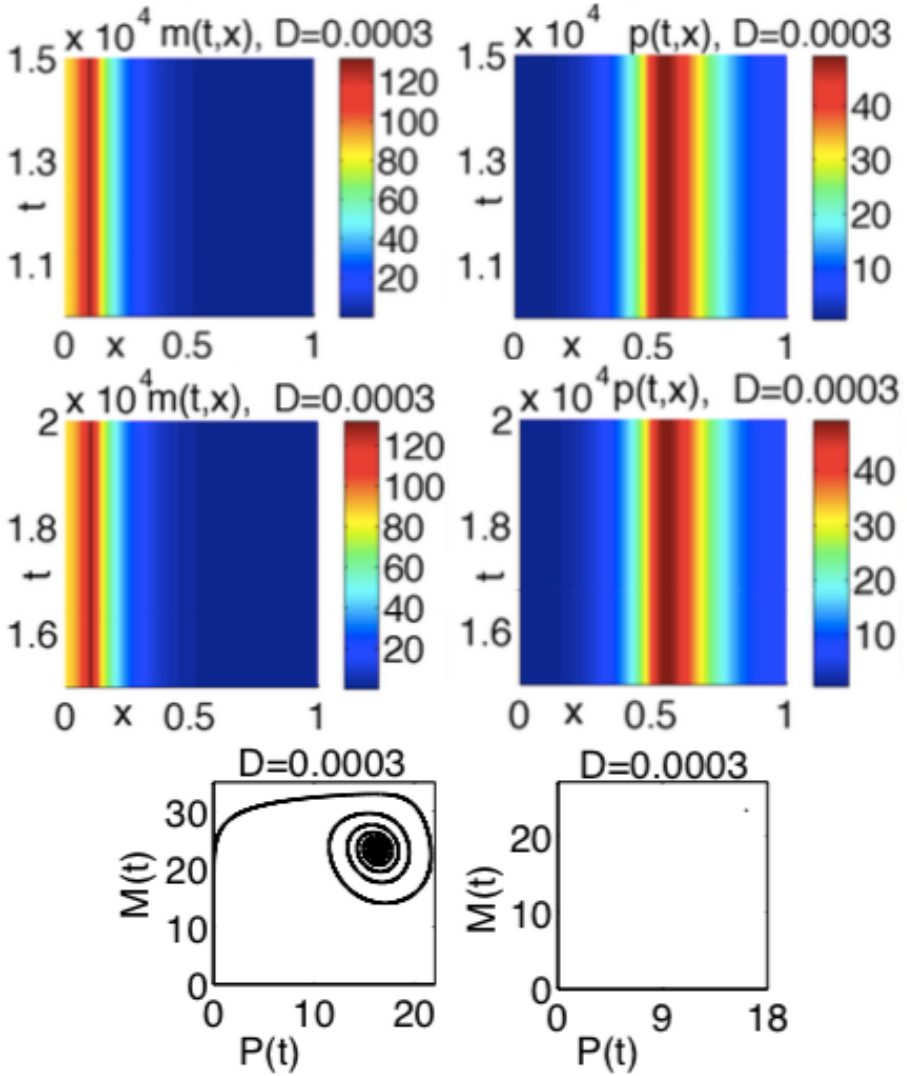
Simplified Model

$f(p) = 1/(1+p^h)$, with $h \geq 2$

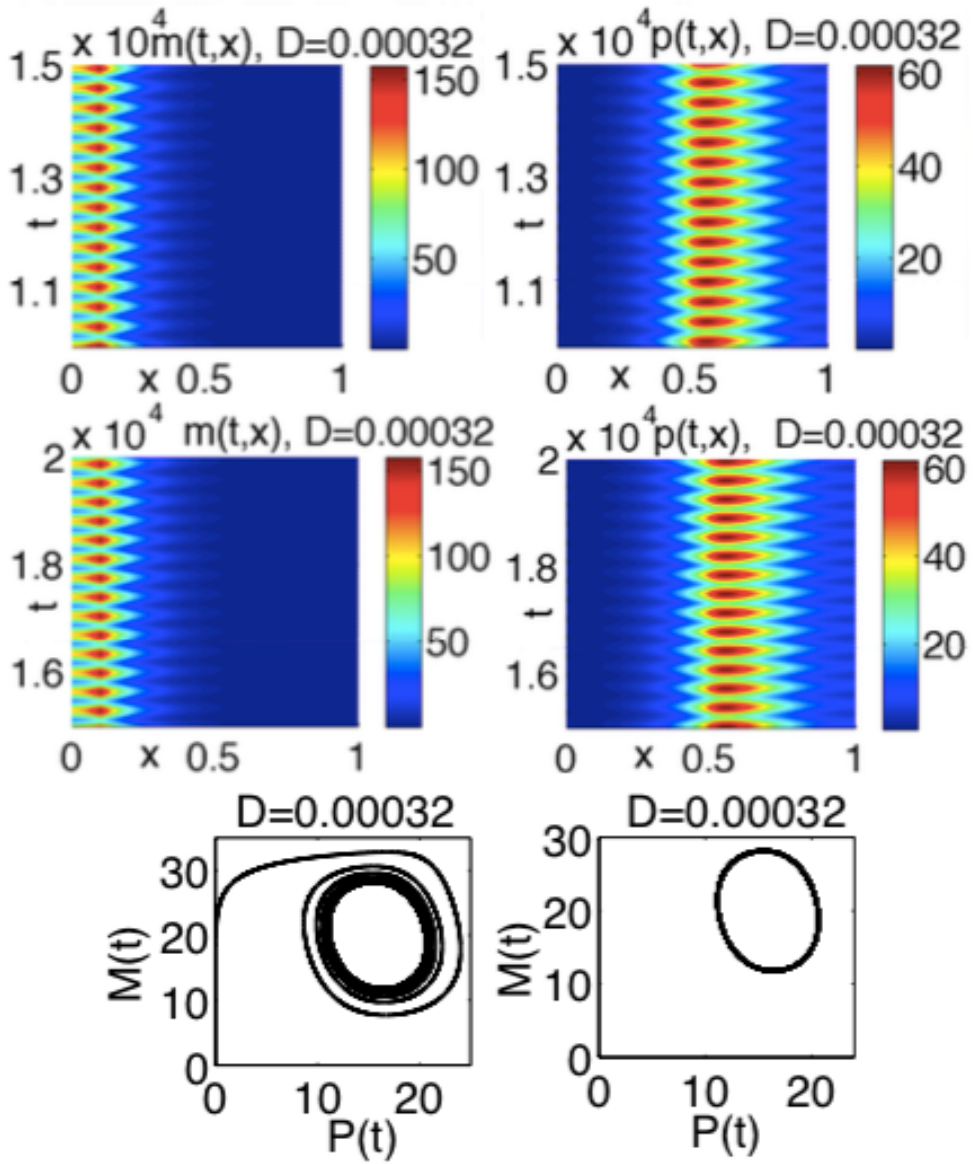
$\delta^{\varepsilon}_{x_M}$ denotes the Dirac approximation of the δ-distribution located at x_M, with $\varepsilon > 0$ a small parameter and $\delta^{\varepsilon}_{x_M}$ has compact support i.e. $\delta^{\varepsilon}_{x_M}(x) = \frac{1}{2\varepsilon}(1+\cos(\pi(x-x_M)/\varepsilon))$ for $|x-x_M| 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

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

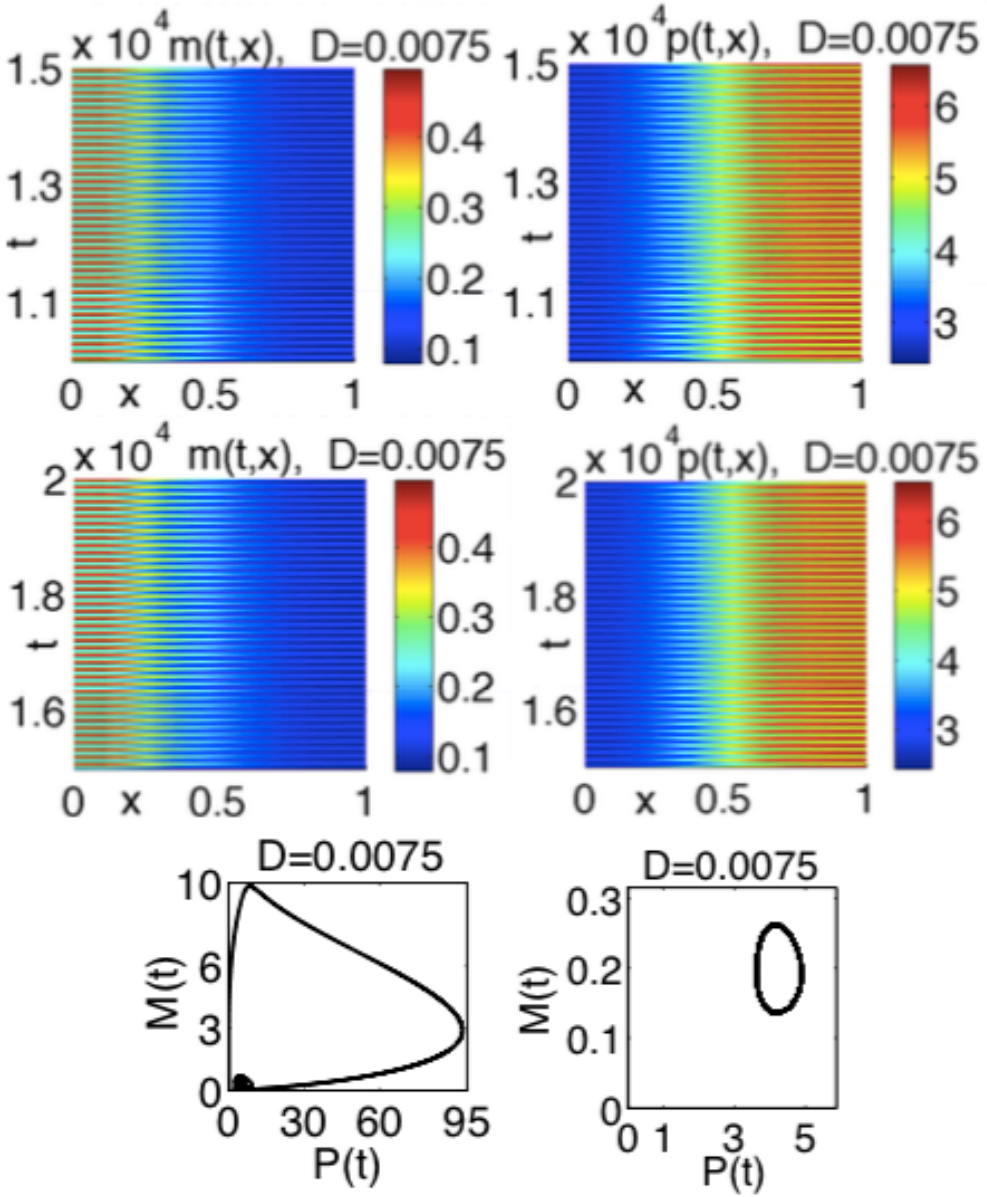
Computational Results



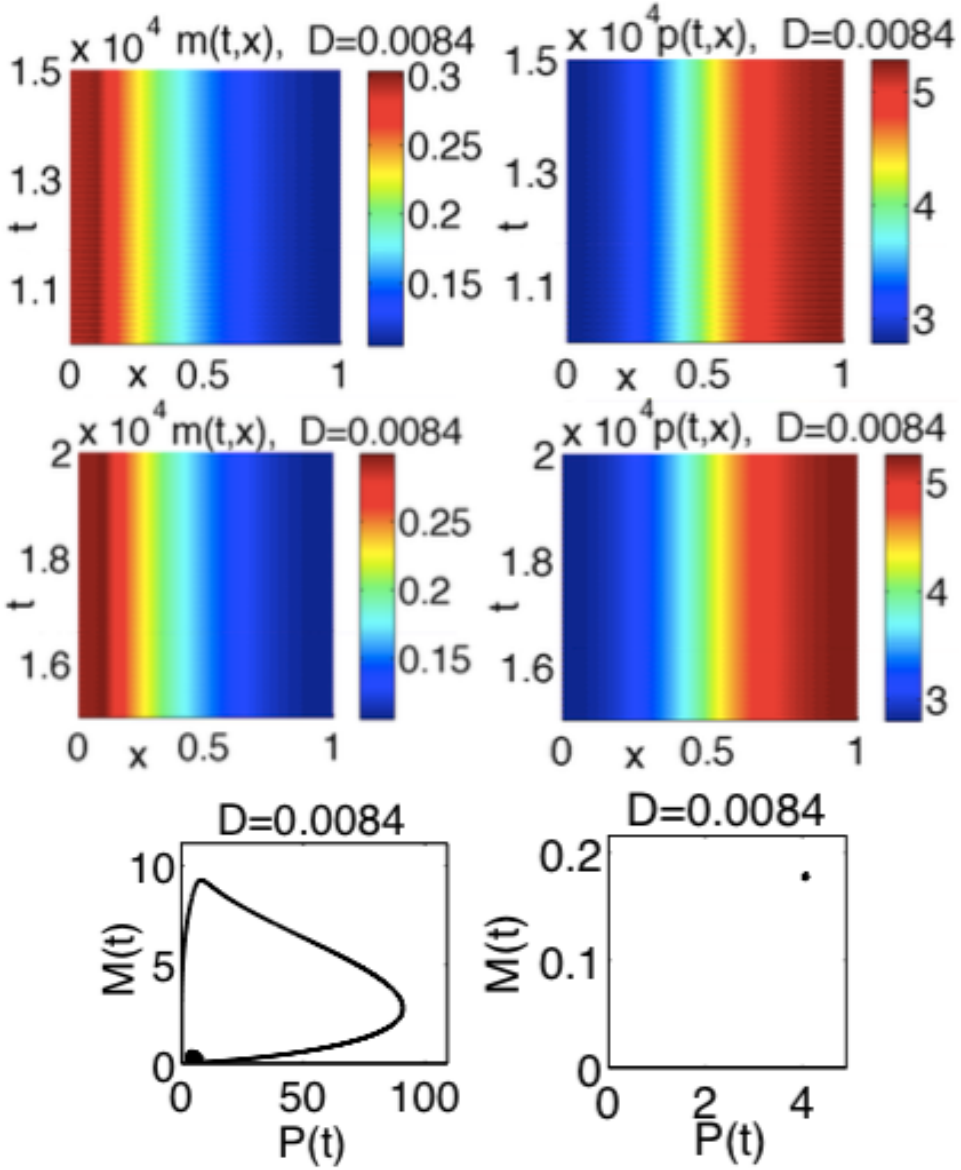
Computational Results



Computational Results



Computational Results



Computational Results: Summary

There is a stationary solution, stable for small values of the diffusion coefficient D, which becomes unstable for $D \geq D^c_{1,\varepsilon}$, with $D^c_{1,\varepsilon} \approx 3.117 \times 10^{-4}$, and again stable for $D > D^c_{2,\varepsilon}$, where $D^c_{2,\varepsilon} \approx 7.885 \times 10^{-3}$. For diffusion coefficients between the two critical values, i.e. $D \in [D^c_{1,\varepsilon}, D^c_{2,\varepsilon}]$, numerical simulations show the existence of stable periodic solutions.

Simplified Model: Steady States

First we examine the stationary solutions $u_\varepsilon^* = (m_\varepsilon^*, p_\varepsilon^*)^T$ of the system satisfying the following one-dimensional boundary-value problem:

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

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

$$\frac{dm_\varepsilon^*(0)}{dx} = \frac{dm_\varepsilon^*(1)}{dx} = 0, \qquad \frac{dp_\varepsilon^*(0)}{dx} = \frac{dp_\varepsilon^*(1)}{dx} = 0\ .$$

Simplified Model: Steady States

For very small diffusion coefficients $D \ll 1$, in the zero-order approximation we obtain:

$$0 = \alpha_m \, f(p^*_\varepsilon)\delta^\varepsilon_{x_M}(x) - \mu_m \, m^*_\varepsilon \, , \qquad 0 = \alpha_p \, g(x) \, m^*_\varepsilon - \mu_p \, p^*_\varepsilon \qquad \text{in } (0,1) \, .$$

Since $g(x) = 0$ for $x \in [0, l)$, the second equation yields that $p^*_\varepsilon(x, D) = 0$ in $[0, l)$ and thus $m^*_\varepsilon(x, D) = \frac{\alpha_m}{\mu_m}\delta^\varepsilon_{x_M}(x)$ 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 $[0, 1]$.

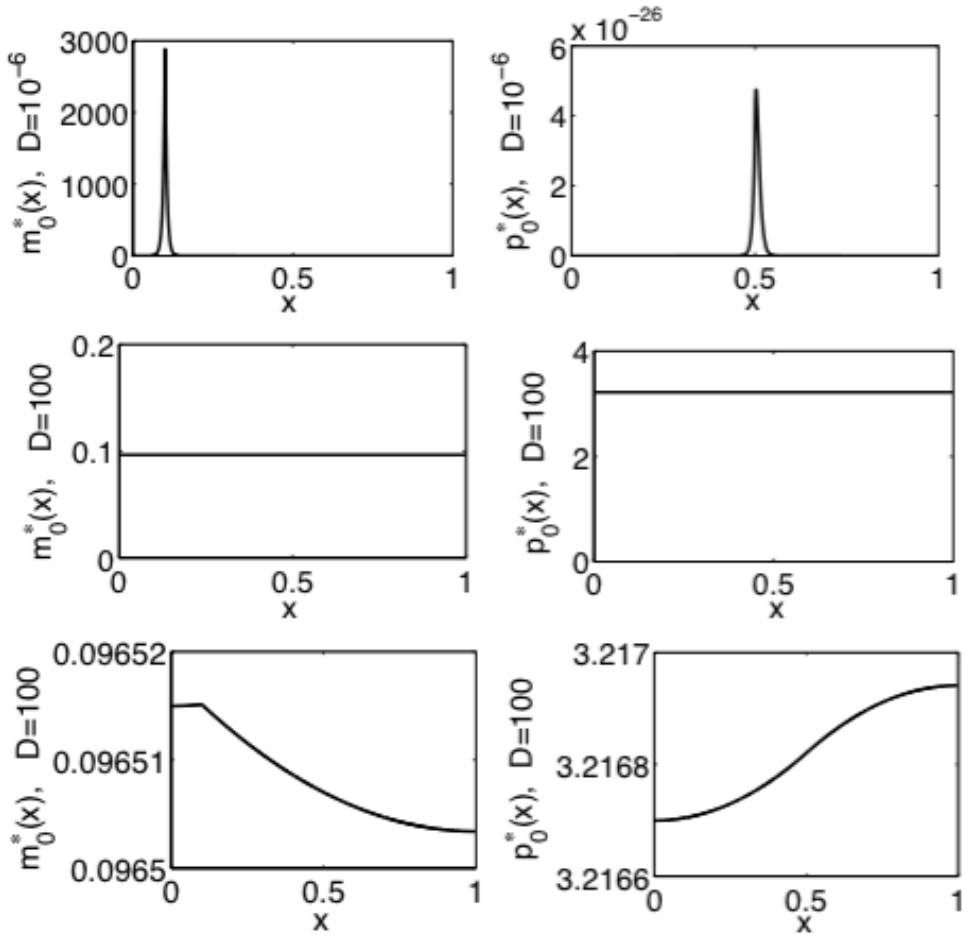
Simplified Model: Steady States

For large diffusion coefficients, i.e. $D \gg 1$ and therefore $1/D \ll 1$, we have

$$
\begin{aligned}
0 &= \frac{d^2 m_\varepsilon^*}{dx^2} + \frac{1}{D}\left(\alpha_m \, f(p_\varepsilon^*)\delta_{x_M}^\varepsilon(x) - \mu_m \, m_\varepsilon^*\right) \qquad \text{in } (0,1)\,, \\
0 &= \frac{d^2 p_\varepsilon^*}{dx^2} + \frac{1}{D}\left(\alpha_p \, g(x) \, m_\varepsilon^* - \mu_p \, p_\varepsilon^*\right) \qquad \text{in } (0,1)\,, \\
&\frac{dm_\varepsilon^*}{dx}(0) = \frac{dm_\varepsilon^*}{dx}(1) = 0, \qquad \frac{dp_\varepsilon^*}{dx}(0) = \frac{dp_\varepsilon^*}{dx}(1) = 0\,.
\end{aligned}
$$

Thus $m_\varepsilon^*(x, D) \approx$ constant and $p_\varepsilon^*(x, D) \approx$ constant.

Simplified Model: Steady States



Simplified Model: Steady States

$$m^*_\varepsilon(x,D) = \alpha_m \int_0^1 G_{\mu_m}(x,y) f(p^*_\varepsilon(y,D)) \delta^\varepsilon_{x_M}(y)\, dy \ ,$$

$$p^*_\varepsilon(x,D) = \alpha_m \alpha_p \int_0^1 g(z) G_{\mu_p}(x,z) \int_0^1 G_{\mu_m}(z,y) f(p^*_\varepsilon(y,D)) \delta^\varepsilon_{x_M}(y)\, dy\, dz,$$

Simplified Model: Steady States

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

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

$$DG_{yy} - \mu_j G = -\delta_x \quad \text{in } (0,1), \qquad G_y(0,x) = G_y(1,x) = 0.$$

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 $\theta_m = (\mu_m / D)^{1/2}$

Simplified Model: Steady States

$$p_0^*(x_M, D) = f(p_0^*(x_M, D)) \frac{\alpha_p \alpha_m}{2} \frac{\cosh(\theta_m\, x_M) \cosh(\theta_p\, x_M)}{\sqrt{\mu_m \mu_p}\, D\, \sinh(\theta_m) \sinh(\theta_p)}$$
$$\times \left[\frac{\sinh((\theta_p + \theta_m)(1-l))}{\theta_p + \theta_m} + \frac{\sinh((\theta_p - \theta_m)(1-l))}{\theta_p - \theta_m} \right]$$

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

$\rightarrow$ 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 $m_\varepsilon^* \rightarrow m_0^*$, $p_\varepsilon^* \rightarrow p_0^*$ as $\varepsilon \rightarrow 0$ 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 $\varepsilon > 0$.

Linearised Stability Analysis

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

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

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

Linearised Stability Analysis

$$m = m^*_\varepsilon + \epsilon \bar{m}^\varepsilon$$

$$p = p^*_\varepsilon + \epsilon \bar{p}^\varepsilon$$

Linearised Stability Analysis

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

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

or in operator form

$$\mathcal{A}w^\varepsilon = \lambda w^\varepsilon,$$

where $w^\varepsilon = (\bar{m}^\varepsilon, \bar{p}^\varepsilon)^T$ and $\mathcal{A} = \mathcal{A}_0 + \mathcal{A}_1$

Linearised Stability Analysis

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

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

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. $D^c_{1,\varepsilon}$ and $D^c_{2,\varepsilon}$, for which a Hopf bifurcation occurs in the model.

Dancer, E. N. (1993) On uniqueness and stability for solutions of singularly perturbed predator-prey type equations with diffusion.
J. Diff. Equations **102**, 1-32.
(+ Dr. Mariya Ptashnyk)

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 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)

Conclusion

spatial movement of the molecules alone
is sufficient to cause the oscillations[2]

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

[2]Chaplain, M.A.J., Ptashnyk, M., Sturrock, M. (2015) Hopf Bifurcation in a Gene Regulatory Network Model: Molecular Movement Causes Oscillations. *Math. Mod. Meth. Appl. Sci.* **25**, 1179-1215. (Open Access)
`http://www.worldscientific.com/doi/pdf/10.1142/S021820251550030X`

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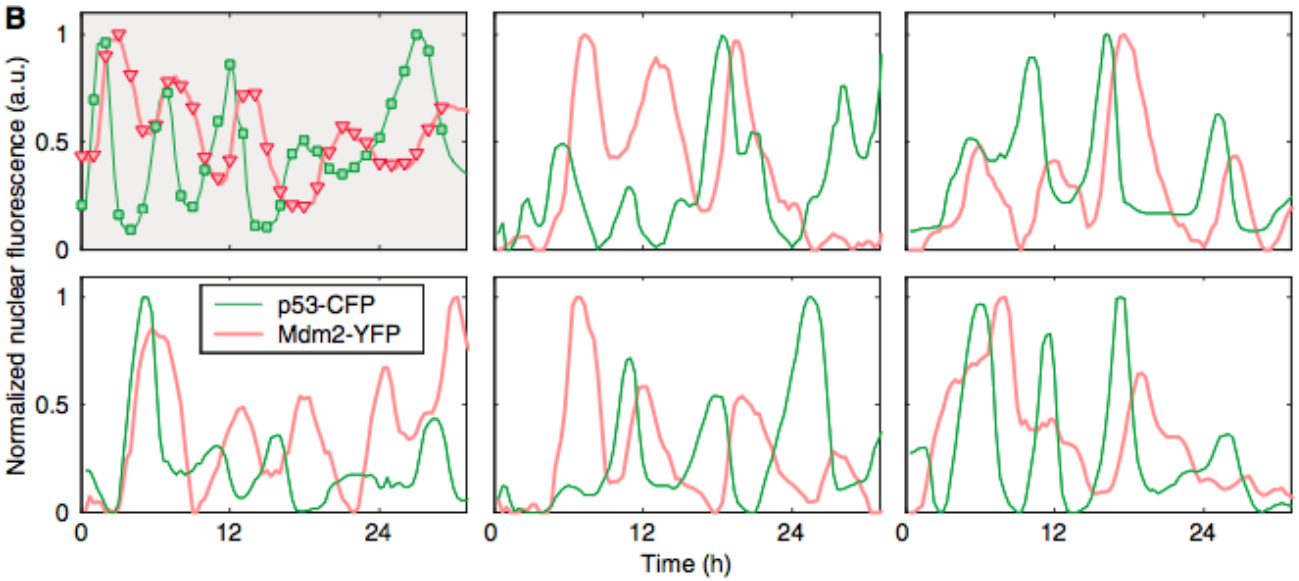
where negative feedback loops are involved
using explicitly spatial models

[2]Chaplain, M.A.J., Ptashnyk, M., Sturrock, M. (2015) Hopf Bifurcation in a Gene Regulatory Network Model: Molecular Movement Causes Oscillations. *Math. Mod. Meth. Appl. Sci.* **25**, 1179-1215. (Open Access)
`http://www.worldscientific.com/doi/pdf/10.1142/S021820251550030X`

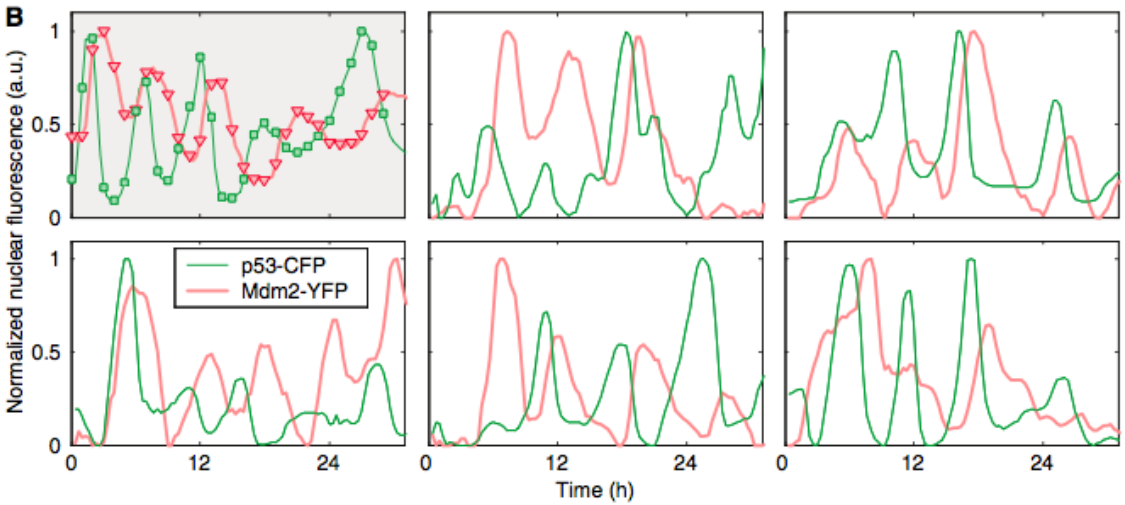
Future Work

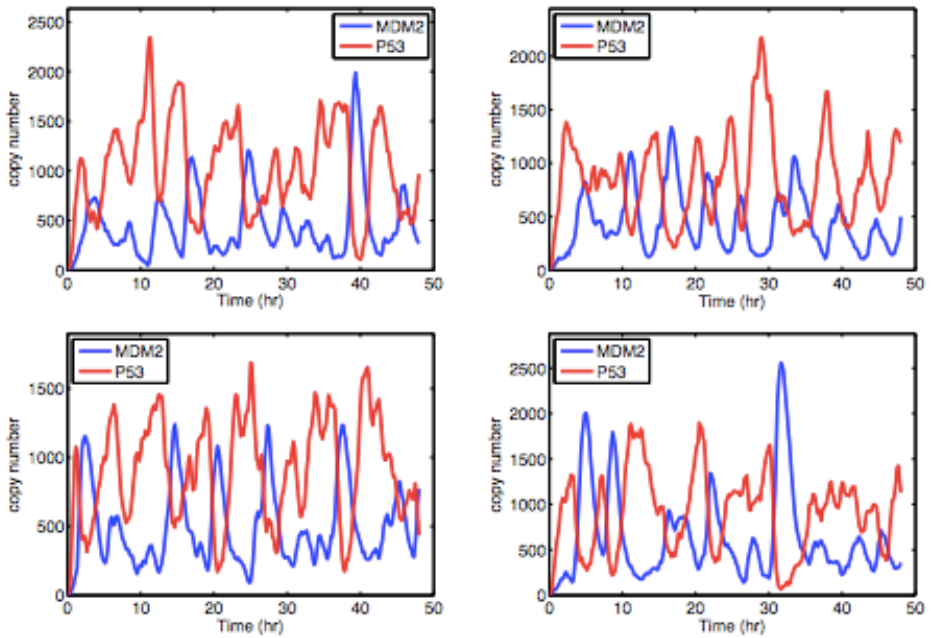


Experimental data from Lahav et al.[3]
showing p53 and Mdm2 protein levels in individual cells.

[3] Lahav et al. (2004) Dynamics of the p53-Mdm2 feedback loop in individual cells. *Nature Genetics* **36**, 147 - 150

Future Work





Corresponding simulation results from a spatial stochastic p53 model.

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