Mathematical modelling of transport and signalling processes in cells and tissues.

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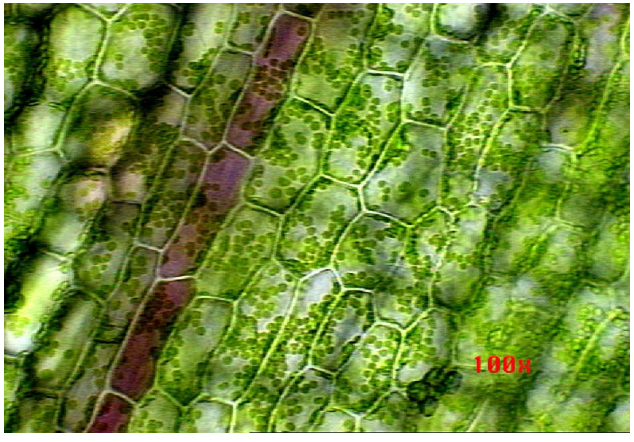
Mathematical model of a simplest gene regulatory network: canonical Hes1 GRN

Plant hormones: Modelling of Auxin signalling pathway

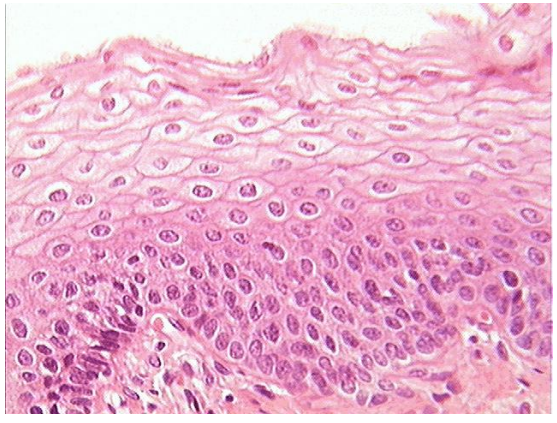
Intercellular transport of signalling molecules

The **Cell** *(from Latin cella, meaning "small room") is the basic structural, functional, and biological unit of all known living organisms. Cells are the smallest unit of life that can replicate independently, and are often called the "building blocks of life".*

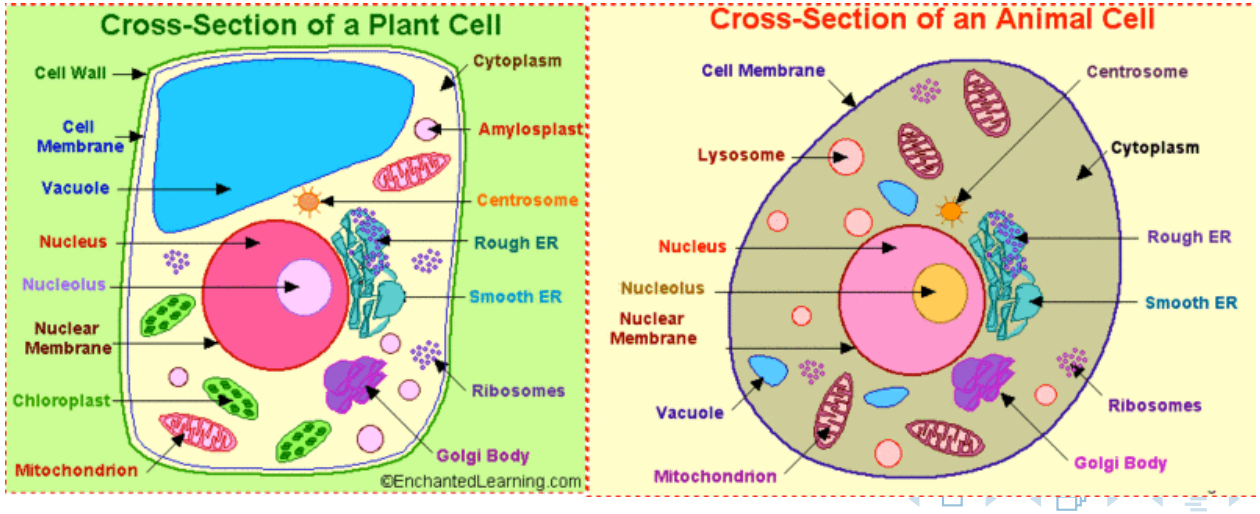
Wikipedia



Elodea leaf



Epithelial tissue



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.

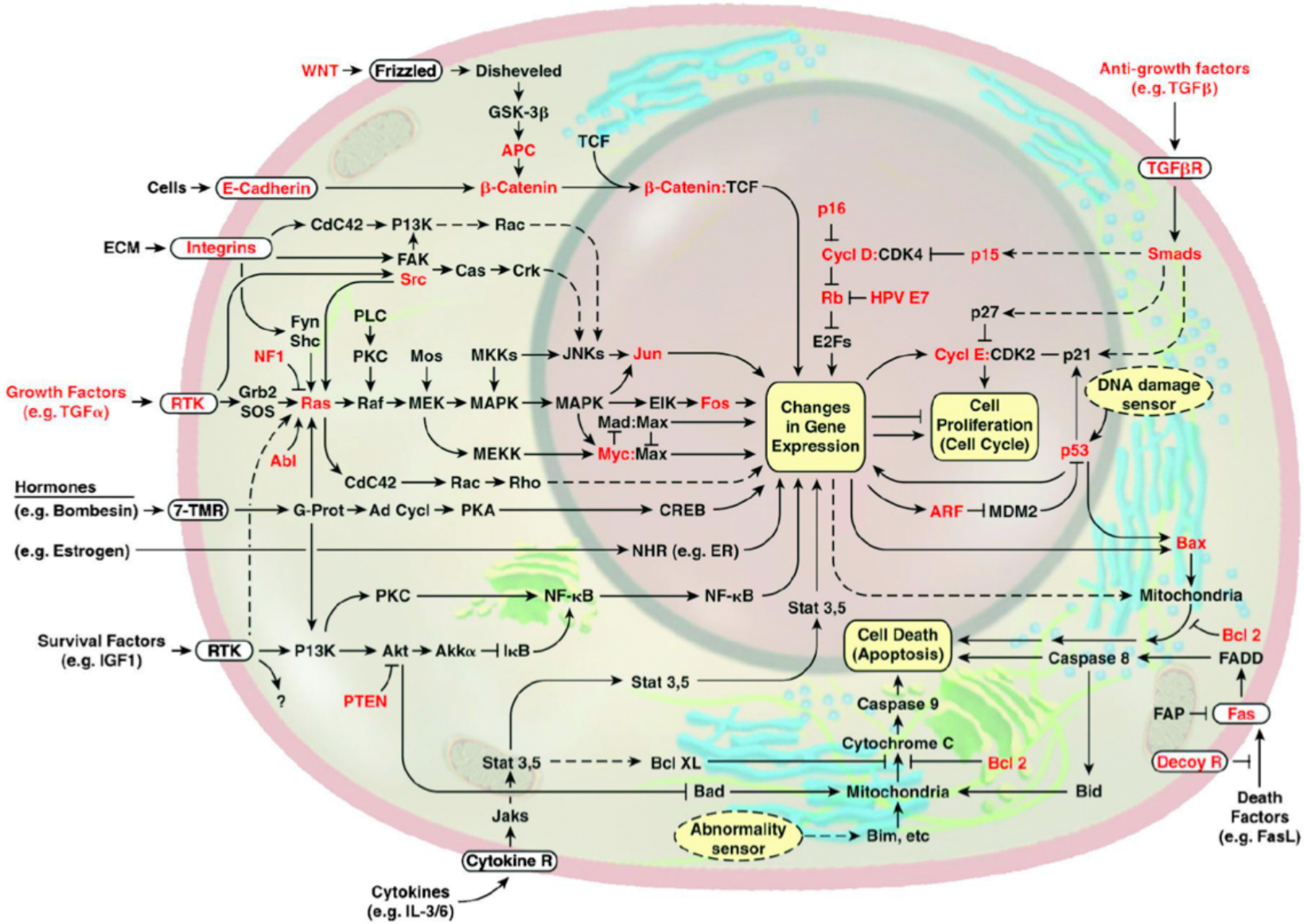
Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, abnormal growth in plants. By understanding cell signalling, diseases may be treated effectively.

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.

Modelling of Signaling Pathways and Gene Regulatory network



Modelling of signaling processes

- Logical models: the state transition from time t to time $t+1$ is defined for each x_i by a Boolean function f

$$x_i(t+1) = f_i(\mathbf{x}(t)), \qquad i = 1, \ldots, N, \quad \mathbf{x} = (x_1, \ldots, x_N)$$

- Differential equations: using the Law of Mass Action

$$\frac{d\mathbf{x}(t)}{dt} = F(t, \mathbf{x}(t))$$

- Stochastic models: chemical master equation

$$\frac{\partial P(x,t)}{\partial t} = \sum_{j=1}^{M} \left[a_j(x - \nu_j) P(x - \nu_j, t) - a_j(x) P(x,t) \right]$$

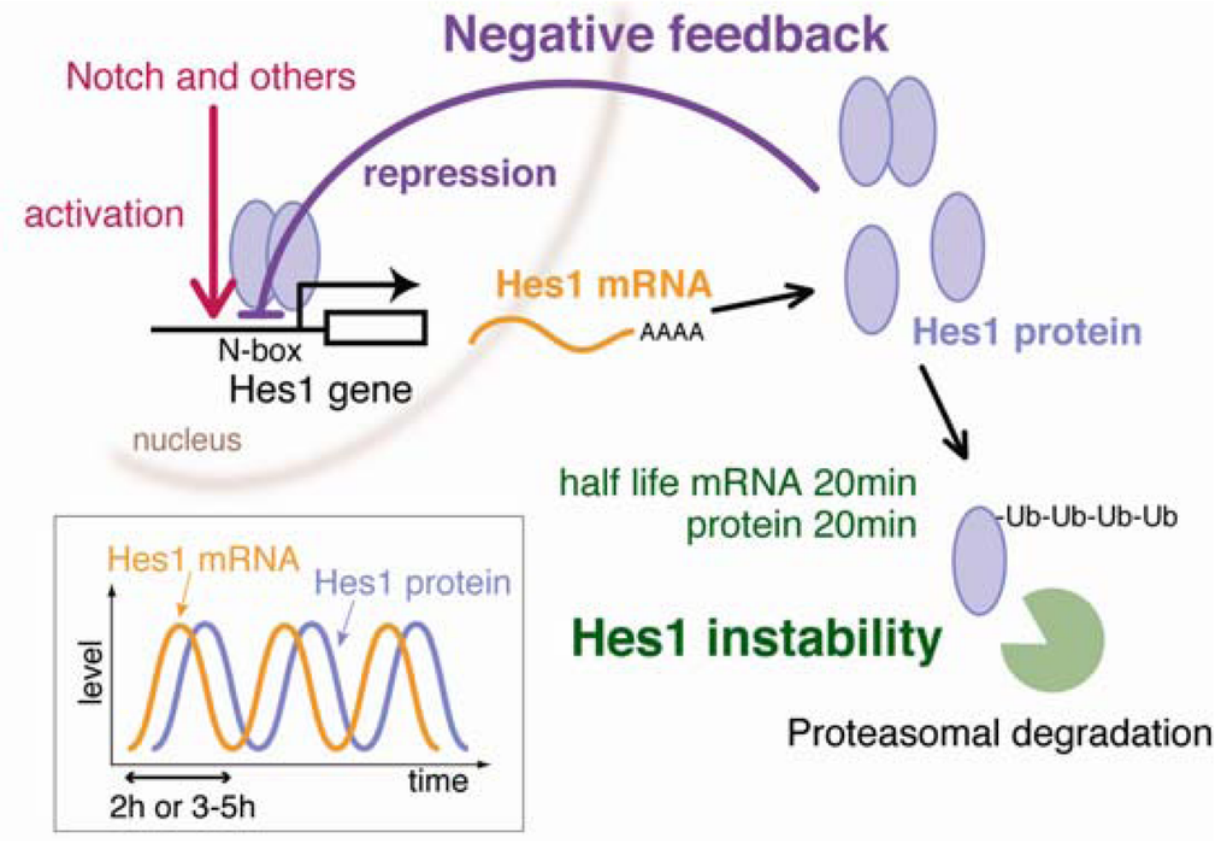
the probability of the system being in a particular state x over dt, a_j probability for a reaction to occur in the interval $[t, t+dt)$.

- Bayesian models is a probabilistic graphical model: to analyse gene expresion data.

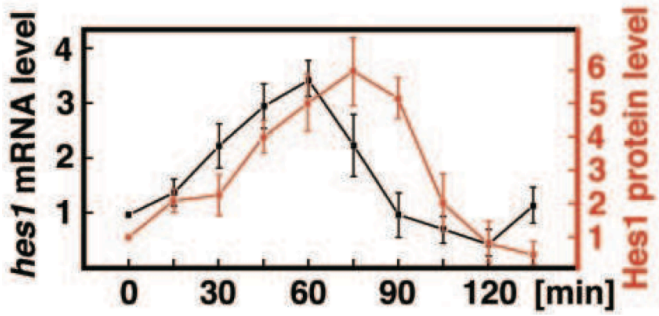
Gene Regulatory Network

- Gene regulatory network (GRN): collection of DNA segments in a cell which interact with each other to govern the gene expression levels of mRNA and proteins
- 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

Hes1 gene expression



Hes1 experimental data
Hirata et al. (2002)

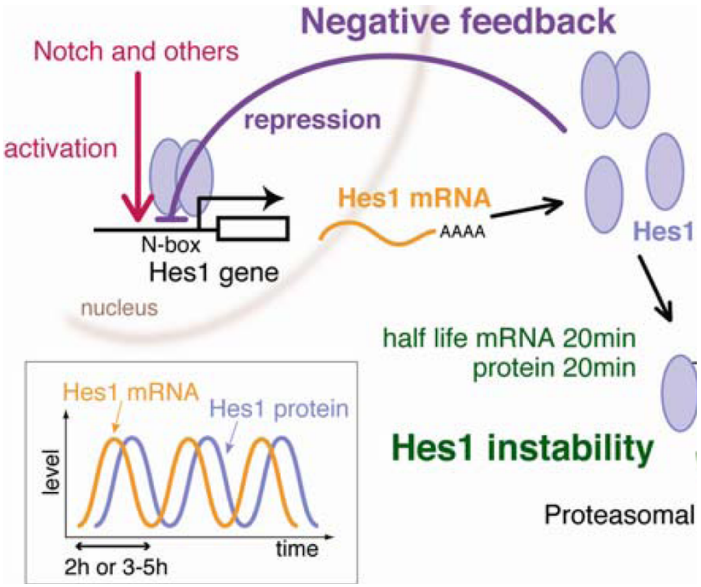


T. Kobayashi, R. Kageyama, Genes 2011

- transcription of Hes1 mRNA by a transcription factor
- translation of Hes1 protein from Hes1 mRNA
- decay of Hes1 mRNA and protein

$$\rightarrow \text{Hes1 mRNA } (m) \rightarrow \text{Hes1 protein } (p)$$

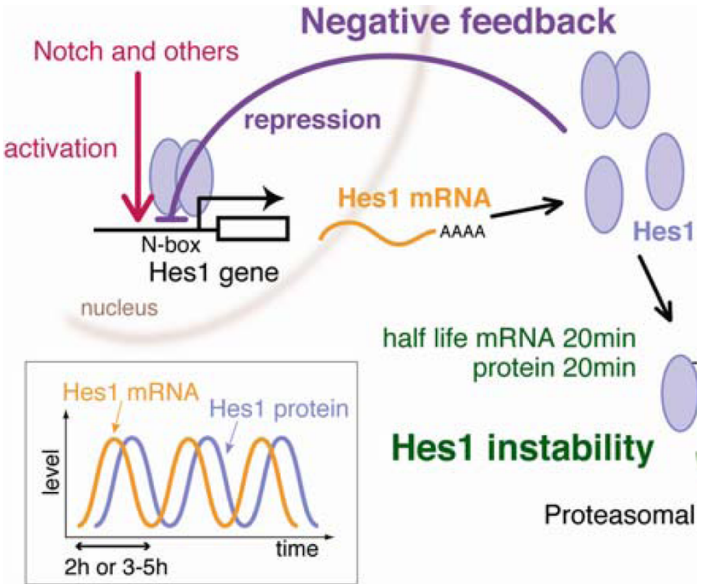
ODE model



$\rightarrow$ Hes1 mRNA $(m) \rightarrow$ Hes1 protein (p)

$$\frac{dm}{dt} = \alpha_m - \mu_m m \qquad = F(m, p)$$

ODE model



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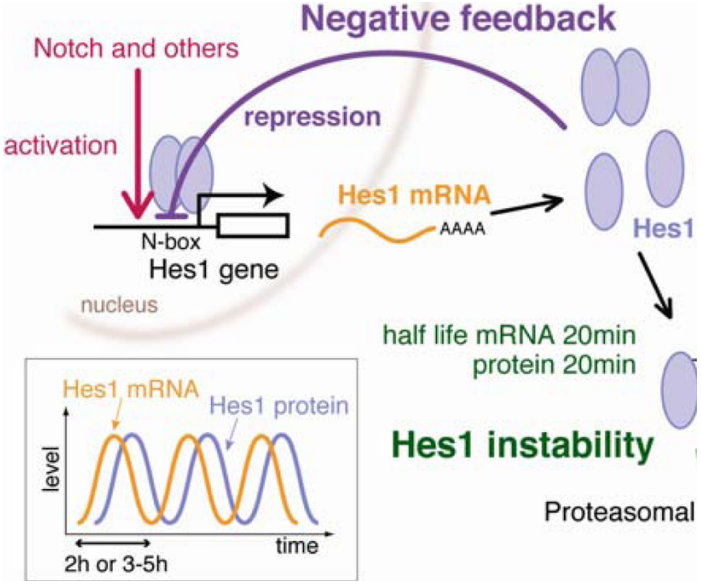
ODE model



$\rightarrow$ Hes1 mRNA $(m) \rightarrow$ Hes1 protein (p)

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$$\frac{dp}{dt} = \alpha_p\, m - \mu_p\, p \qquad = G(m,p)$$

for some $h > 1$, $\qquad f(p) = \dfrac{1}{1+[p]^h}$

ODE model

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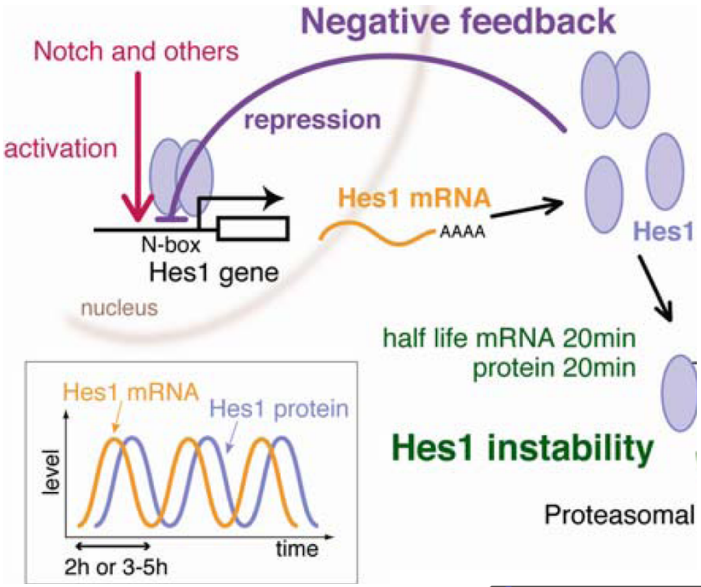

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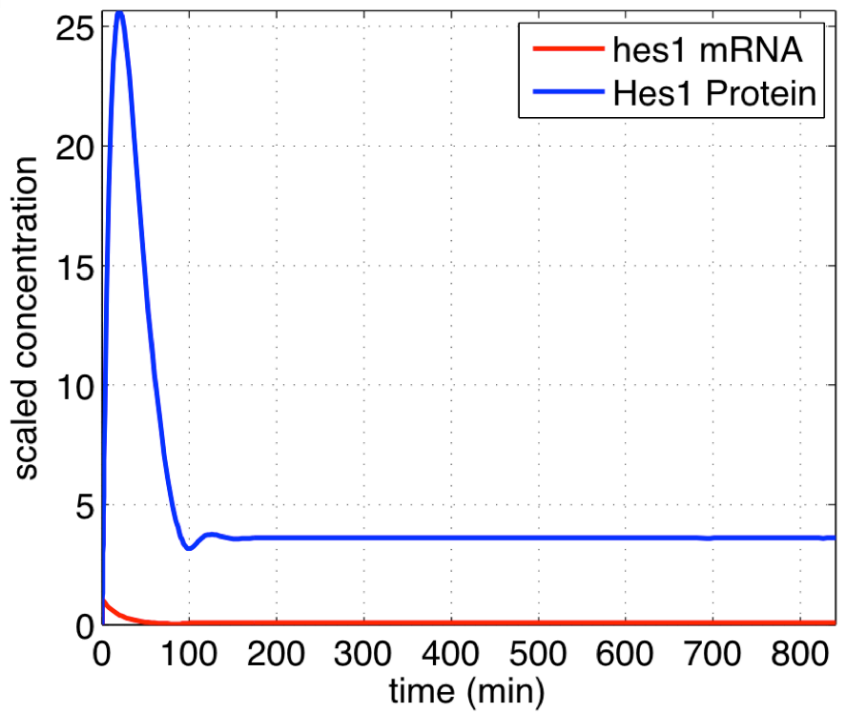

no oscillatory behaviour

Stability analysis for ODE

Steady state solutions (m^*, p^*), i.e. $\frac{dm}{dt} = 0$, $\frac{dp}{dt} = 0$,

$$G(m^*, p^*) = 0, \qquad m^* = \frac{\mu_p}{\alpha_p} p^*,$$

$$F(m^*, p^*) = 0, \qquad p^* + (p^*)^{h+1} = \frac{\alpha_m \alpha_p}{\mu_p \mu_m}, \qquad \text{choose } p^* > 0$$

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Consider small perturbations of the steady state

$$m(t) = m^* + \tilde{m}(t), \qquad p(t) = p^* + \tilde{p}(t), \qquad \text{with} \quad \|\tilde{m}\|, \|\tilde{p}\| \ll 1$$

$$\frac{d\tilde{m}}{dt} = F(m^* + \tilde{m}, p^* + \tilde{p})$$

$$\frac{d\tilde{p}}{dt} = G(m^* + \tilde{m}, p^* + \tilde{p})$$

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$$\frac{d\tilde{m}}{dt} = = F(m^*, p^*) + \frac{\partial F(m^*, p^*)}{\partial m}\tilde{m} + \frac{\partial F(m^*, p^*)}{\partial p}\tilde{p} + \dots$$

$$\frac{d\tilde{p}}{dt} = = G(m^*, p^*) + \frac{\partial G(m^*, p^*)}{\partial m}\tilde{m} + \frac{\partial G(m^*, p^*)}{\partial p}\tilde{p} + \dots$$

apply Taylor expansion about (m^*, p^*)

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$$\frac{d\tilde{m}}{dt} = = \frac{\partial F(m^*, p^*)}{\partial m}\tilde{m} + \frac{\partial F(m^*, p^*)}{\partial p}\tilde{p} + \dots$$

$$\frac{d\tilde{p}}{dt} = = \frac{\partial G(m^*, p^*)}{\partial m}\tilde{m} + \frac{\partial G(m^*, p^*)}{\partial p}\tilde{p} + \dots$$

Linearised system

$$\frac{d}{dt}\begin{pmatrix}\tilde{m}\\ \tilde{p}\end{pmatrix} = J(m^*, p^*)\begin{pmatrix}\tilde{m}\\ \tilde{p}\end{pmatrix}, \qquad J(m^*, p^*) = \begin{pmatrix} \frac{\partial F(m^*, p^*)}{\partial m} & \frac{\partial F(m^*, p^*)}{\partial p} \\ \frac{\partial G(m^*, p^*)}{\partial m} & \frac{\partial G(m^*, p^*)}{\partial p} \end{pmatrix}$$

Stability analysis for ODE

Small perturbations are solutions of the linear system

$$\frac{d}{dt}\begin{pmatrix}\tilde{m}\\ \tilde{p}\end{pmatrix} = J(m^*, p^*)\begin{pmatrix}\tilde{m}\\ \tilde{p}\end{pmatrix}$$

Consider

$$\tilde{m}(t) = e^{\lambda t}\hat{m}, \quad \tilde{p}(t) = e^{\lambda t}\hat{p}, \qquad \hat{m}, \hat{p} \in \mathbb{R}, \qquad \hat{m} \neq 0, \quad \hat{p} \neq 0$$

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Then

$$\left[J(m^*, p^*) - \lambda I\right]\begin{pmatrix}\hat{m}\\ \hat{p}\end{pmatrix} = 0 \quad \text{and} \quad \det\left(J(m^*, p^*) - \lambda I\right) = 0.$$

where $$J(m^*, p^*) = \begin{pmatrix}-\mu_p & -\alpha_m\gamma_m\\ \alpha_p & -\mu_p\end{pmatrix},$$

with $\gamma_m = -f'(p^*) = h[p^*]^{h-1}/(1 + [p^*]^h)^2$ and $\gamma_m > 0$.

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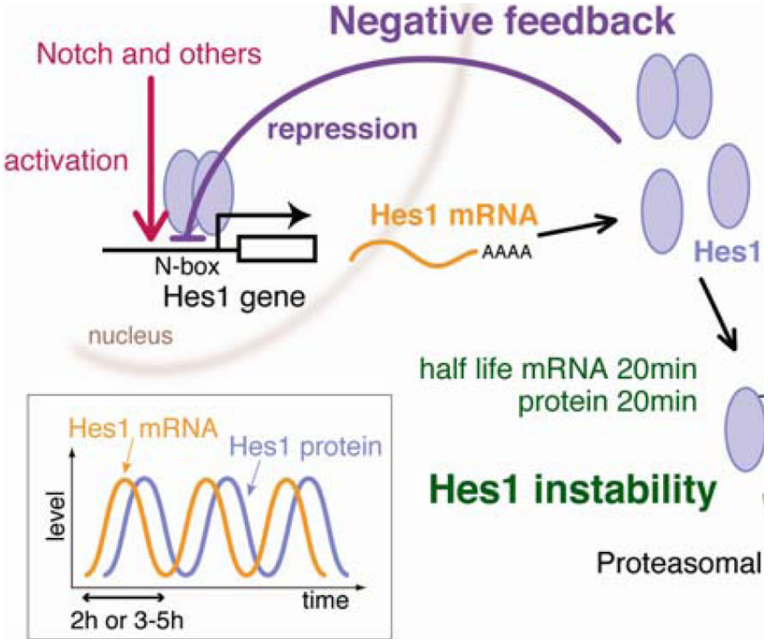
$$\det\left(J(m^*, p^*) - \lambda I\right) = \lambda^2 + (\mu_m + \mu_p)\lambda + (\alpha_m\alpha_p\gamma_m + \mu_m\mu_p) = 0$$

$$\lambda_{1,2} = \frac{1}{2}\left[-(\mu_m + \mu_p) \pm \sqrt{(\mu_m + \mu_p)^2 - 4(\alpha_m\alpha_p\gamma_m + \mu_m\mu_p)}\right]$$

$\Longrightarrow \quad \mathrm{Re}(\lambda_{1,2}) < 0 \quad \Longrightarrow \quad (m^*, p^*)$ is stable.

DDE model - Monk (Current Biology 2003)



$$\frac{dm(t)}{dt} = \frac{\alpha_m}{1+[p(t)]^h} - \mu_m m(t)$$

$$\frac{dp(t)}{dt} = \alpha_p m(t) - \mu_p p(t)$$

no oscillatory behaviour

stable steady state

Adding delay produces oscillatory dynamics

$$\frac{dm(t)}{dt} = \frac{\alpha_m}{1+\left[p(t-\tau_m)\right]^h} - \mu_m m(t), \qquad h > 1$$

$$\frac{dp(t)}{dt} = \alpha_p m(t-\tau_p) - \mu_p p(t)$$

$$m(t) = m_0(t) \quad t \in [-\tau_m, 0], \quad p(t) = p_0(t) \quad t \in [-\tau_p, 0]$$

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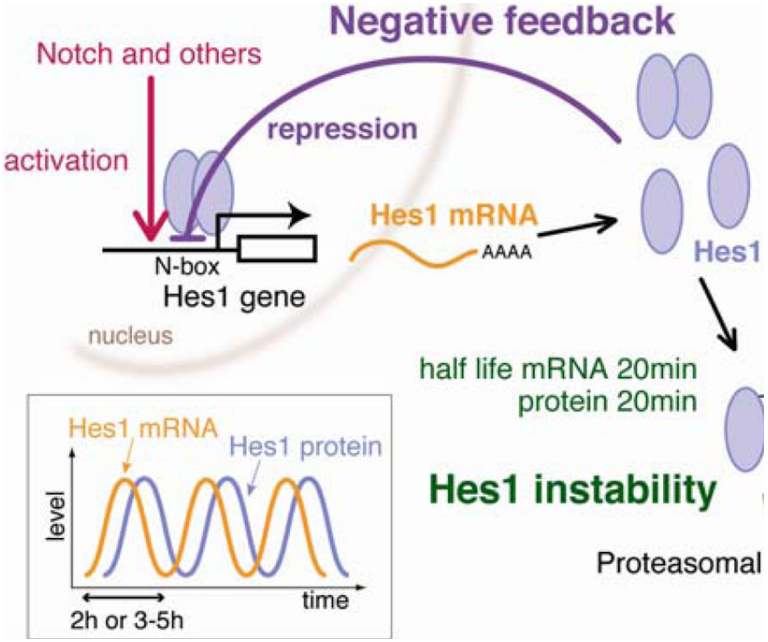

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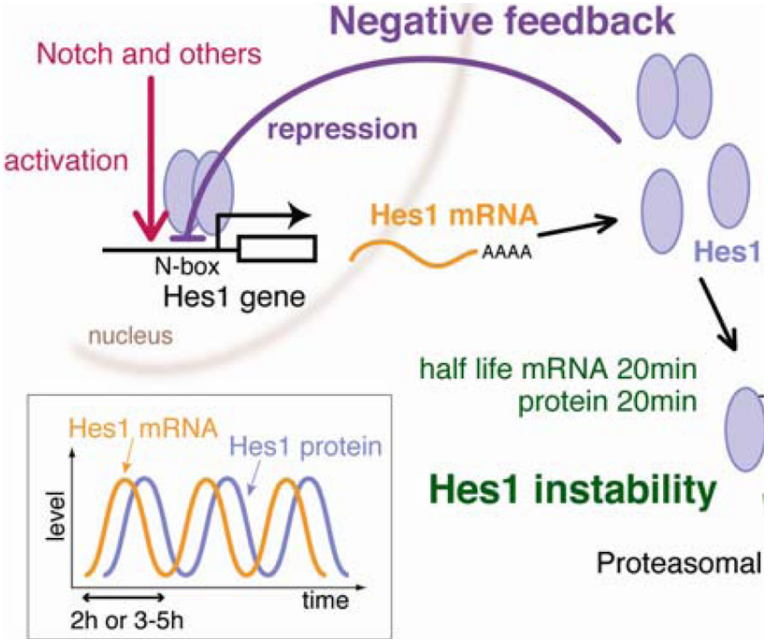

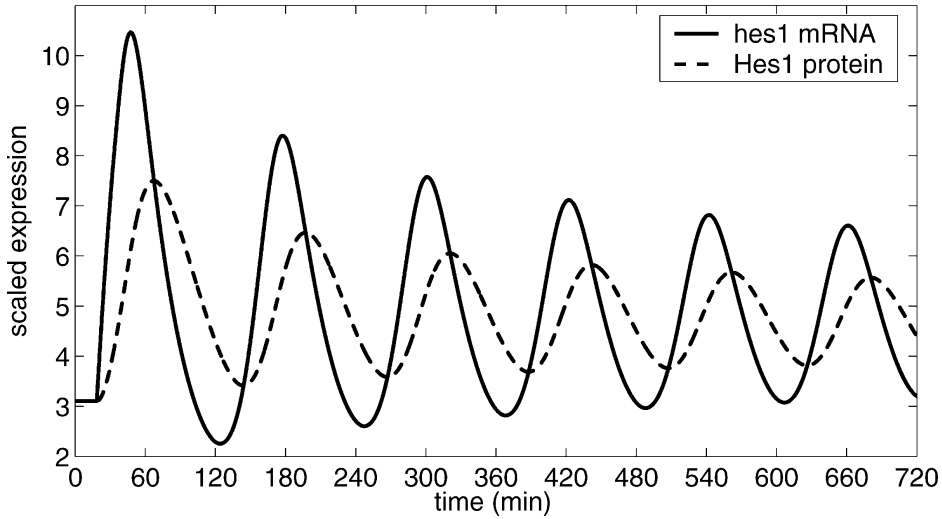

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Stability analysis of delay differential equations

Small perturbations $m(t) = m^* + \tilde{m}(t), \quad p(t) = p^* + \tilde{p}(t)$:

$$\frac{d\tilde{m}(t)}{dt} = -\alpha_m \gamma_m \tilde{p}(t - \tau_m) - \mu_m \tilde{m}(t)$$

$$\frac{d\tilde{p}(t)}{dt} = \alpha_p \tilde{m}(t - \tau_p) - \mu_p \tilde{p}(t)$$

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Consider $\tilde{m}(t) = e^{\lambda t}\hat{m}$ and $\tilde{p}(t) = e^{\lambda t}\hat{p}$ and obtain

$$\det \begin{pmatrix} -\mu_m - \lambda & -\gamma_m \alpha_m e^{-\lambda \tau_m} \\ \alpha_p e^{-\lambda \tau_p} & -\mu_p - \lambda \end{pmatrix} = 0$$

$\Longleftrightarrow$

$$\lambda^2 + (\mu_m + \mu_p)\lambda + \mu_m \mu_p + \gamma_m \alpha_m \alpha_p e^{-\lambda \tau} = 0, \qquad \tau = \tau_m + \tau_p$$

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For $\gamma_m \alpha_m \alpha_p > \mu_m \mu_p$ there exist $\omega_0 > 0$ such that

$\lambda = \pm i\omega_0$ single pair of pure imaginary eigenvalues

for $\tau_j = \frac{1}{\omega_0}\left[\sin^{-1}\left(\frac{\mu_m + \mu_p}{\alpha_p \alpha_m \gamma_m}\omega_0\right) + 2\pi j\right], \qquad j = 0, 1, 2, \ldots$

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$$\tilde{m}(t) = e^{\lambda t}\hat{m}, \quad \tilde{p}(t) = e^{\lambda t}\hat{p}, \quad e^{i\omega_0 t} = \cos(\omega_0 t) + i \sin(\omega_0 t)$$

Stability analysis of delay differential equations

$$\lambda^2 + (\mu_m + \mu_p)\lambda + \mu_m\mu_p + \gamma_m\alpha_m\alpha_p e^{-\lambda\tau} = 0$$

Considering the eigenvalues $\lambda = \lambda(\tau)$ as functions of τ we have

$$\frac{d}{d\tau}(\operatorname{Re}\lambda)(\tau_j) > 0, \quad j = 0, 1, 2, \ldots \Longrightarrow (m^*, p^*) \text{ unstable for all } \tau \geq \tau_0$$

Stability analysis of delay differential equations

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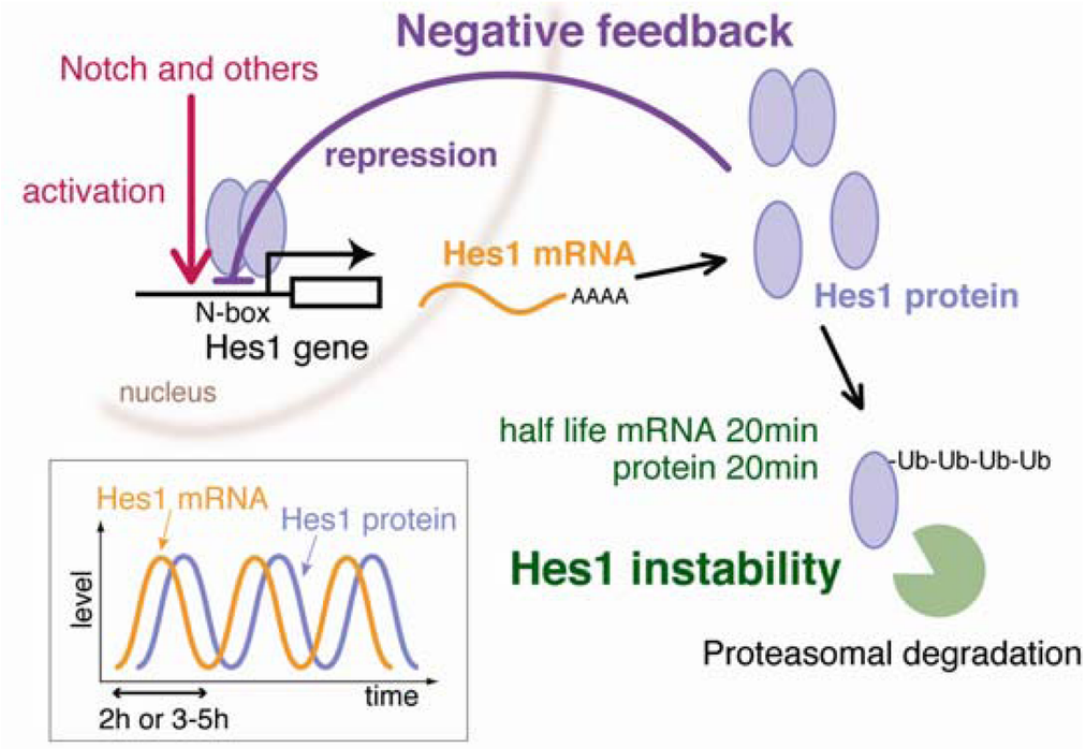
Theorem (Hopf Bifurcation)

- (F, G) is continuously differentiable in (m, p) and τ.
- $(m^*(\tau), p^*(\tau))$ isolate stationary solution for $\tau \geq 0$
- for $\tau = \tau_j$ there exists a simple pair of pure imaginary eigenvalues $\lambda = \pm i\omega_0$ with $\omega_0 \neq 0$
- for all $n \in \mathbb{Z} \setminus \{1, -1\}$, $\pm i\, n\, \omega_0$ are not eigenvalue
- near τ_j we have the eigenvalues $\lambda = r(\tau) \pm i\omega(\tau)$, with r and ω are continuous and $r(\tau_j) = 0, \quad \omega(\tau_j) = \omega_0$
- transversality condition: $\dfrac{d}{d\tau}(\mathrm{Re}\lambda)(\tau_j) = \dfrac{dr}{d\tau}(\tau_j) \neq 0$

Then the system has periodic solutions in a neighborhood of τ_j, bifurcating from the stationary solution.

Hes1 gene expression oscillation



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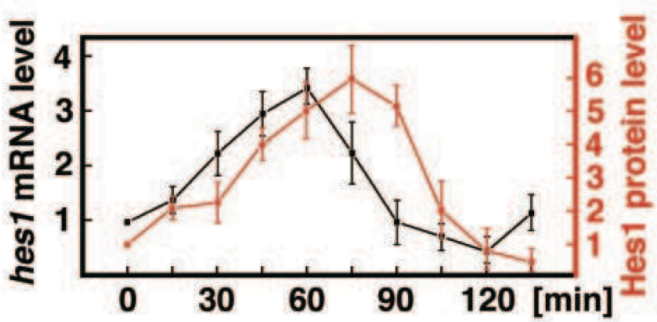
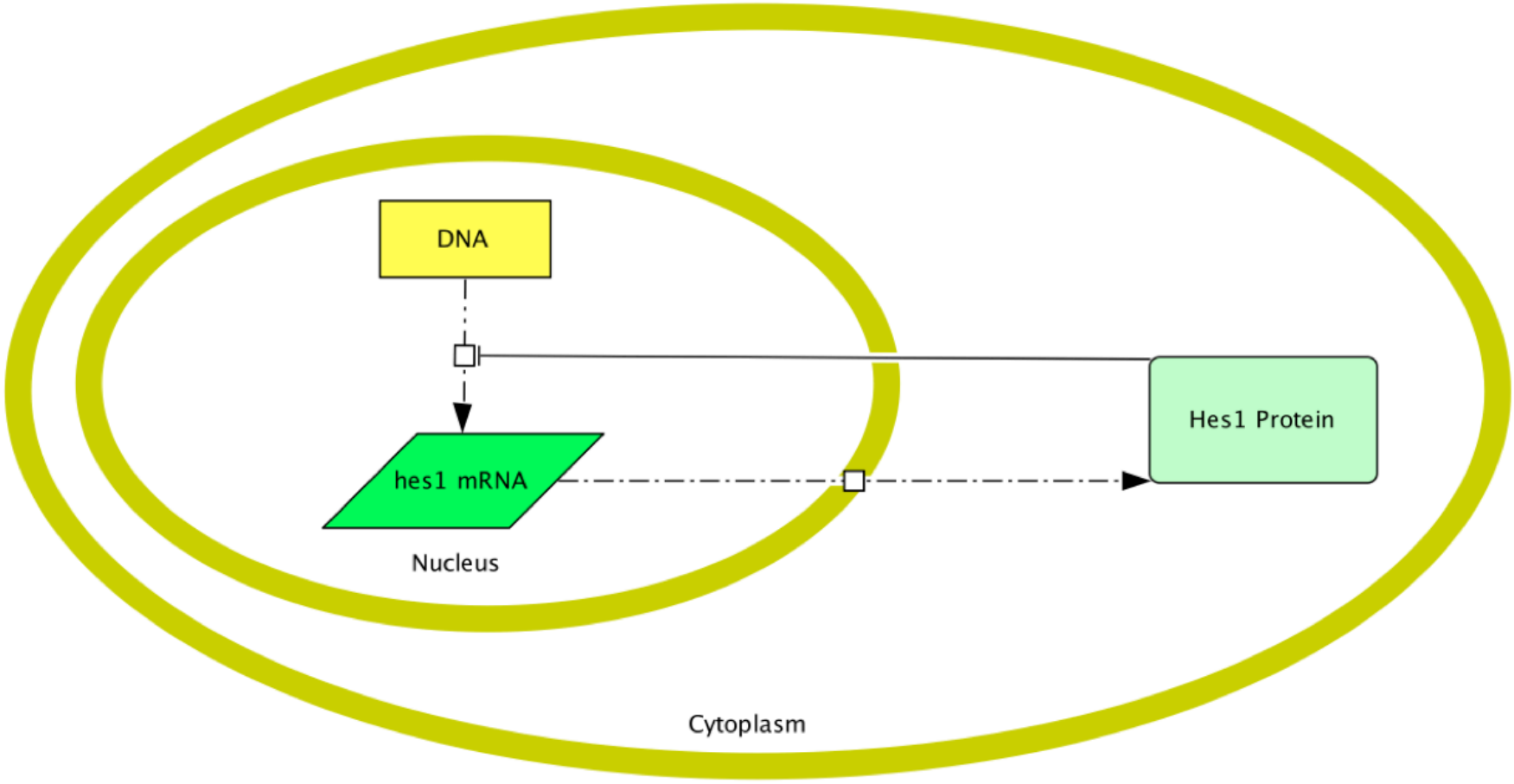


T. Kobayashi, R. Kageyama, Genes 2011

Interaction between cell nucleus and cell cytoplasm:

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

Model Schematic

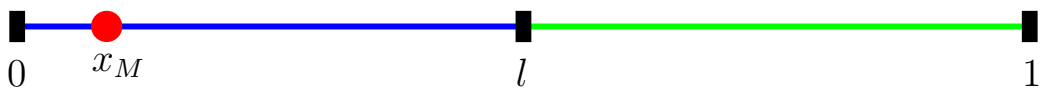


Mathematical Model GRN: spatial movement

$$\frac{\partial m}{\partial t} = + \frac{\alpha_m}{1+p^h} - \mu\, m \qquad \text{in } (0,T)\times(0,1)$$

$$\frac{\partial p}{\partial t} = + \alpha_p\, m - \mu\, p \qquad \text{in } (0,T)\times(0,1),$$

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



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

Mathematical Model GRN: spatial movement

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

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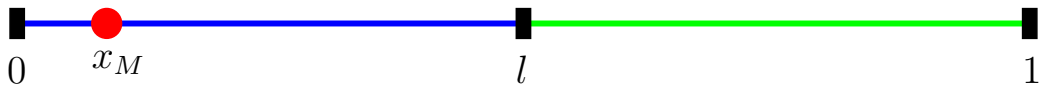
$$m(0) = m_0, \quad p(0) = p_0 \qquad \text{in } (0,1),$$

$\delta^{\varepsilon}_{x_M}$ – Dirac sequence,

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



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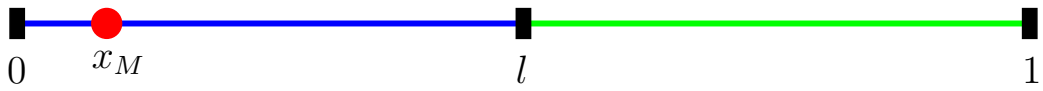

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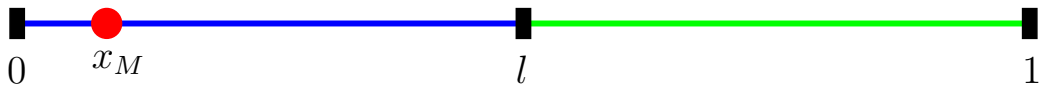
$$m(0) = m_0, \quad p(0) = p_0 \qquad \text{in } (0,1),$$

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

$\delta^{\varepsilon}_{x_M}$ – Dirac sequence,

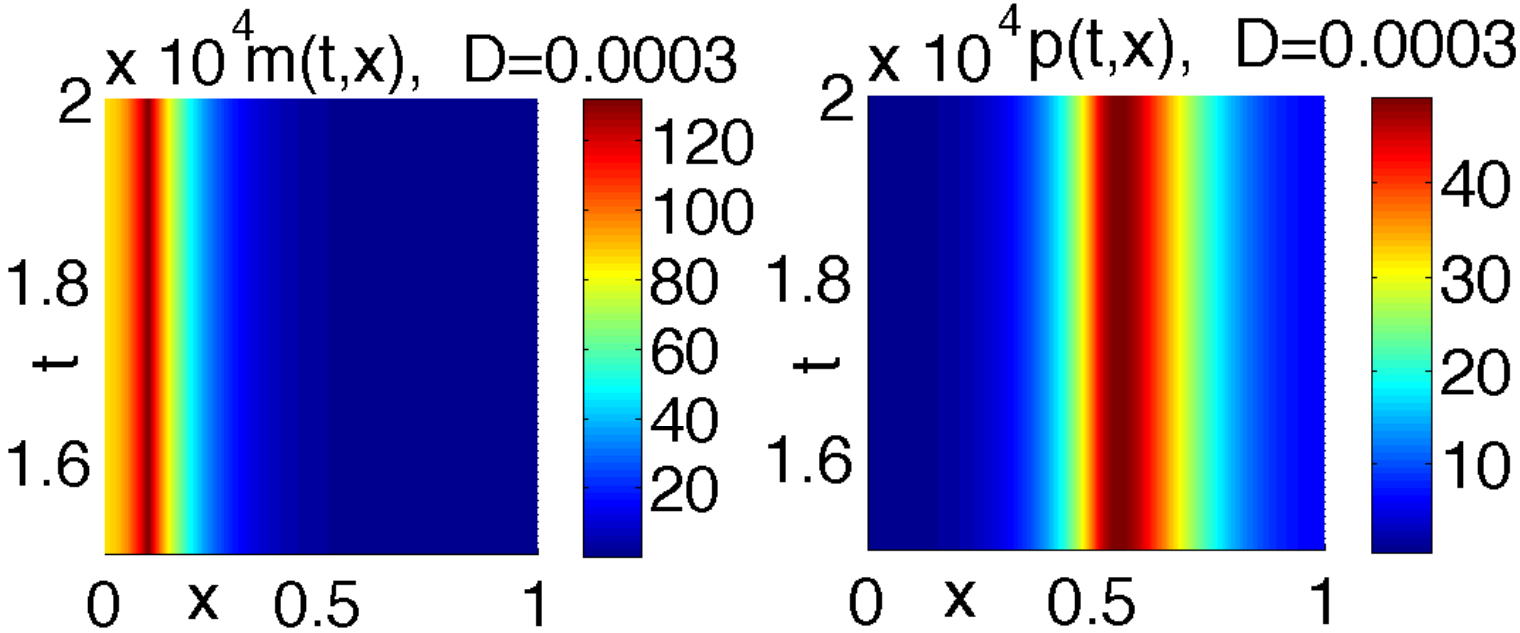
$$g(x) = \begin{cases} 0, & \text{if } x < l \\ 1, & \text{if } x \geq l \end{cases}$$



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

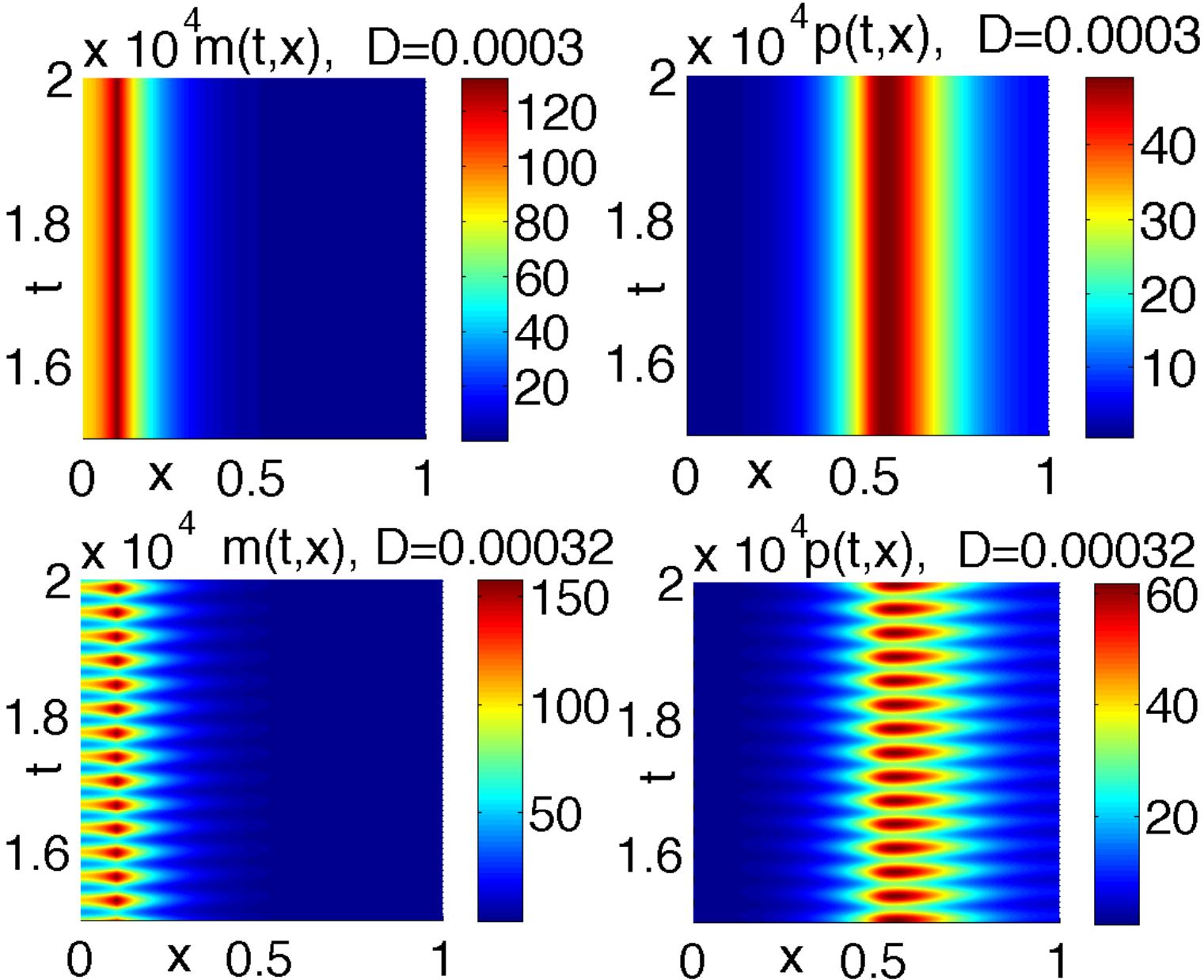
Numerical simulations for

$$D = 3 \cdot 10^{-4}$$

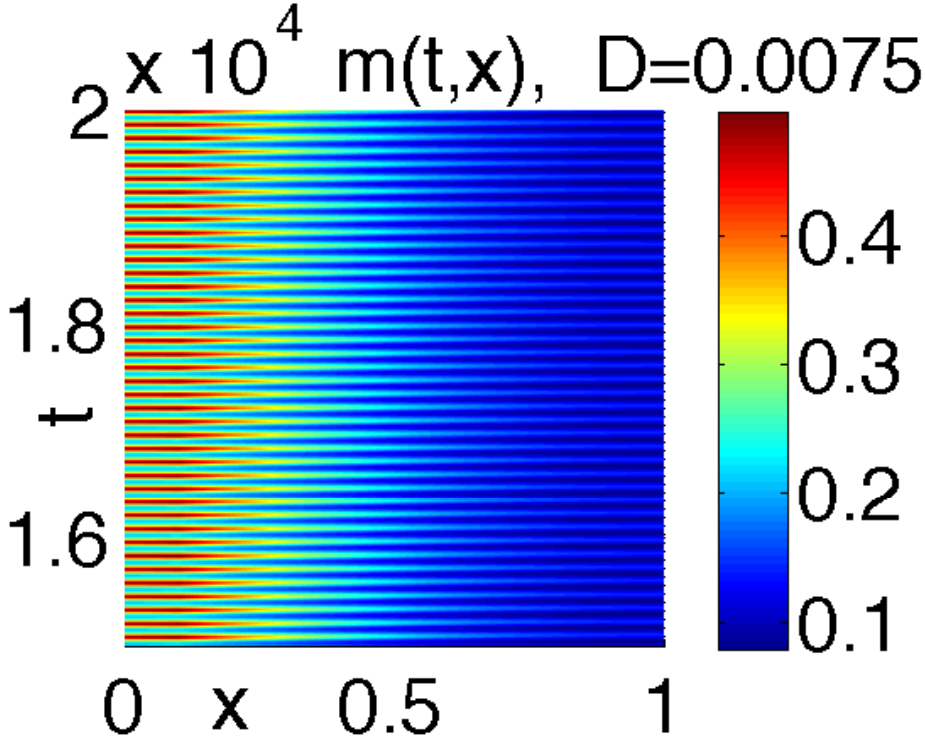


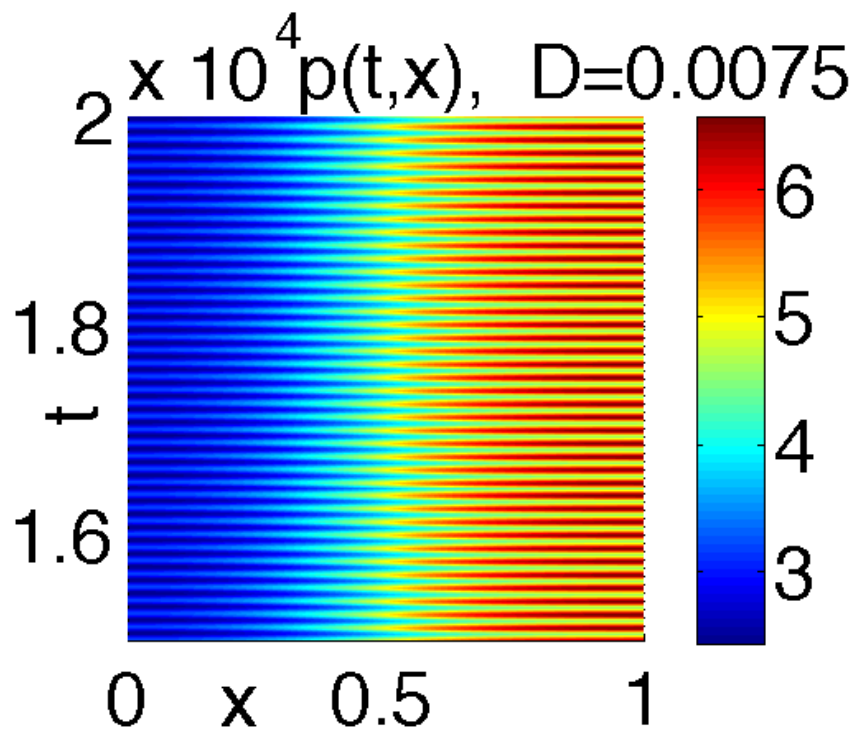
Numerical simulations for

$D = 3 \cdot 10^{-4}$ **and** $D = 3.2 \cdot 10^{-4}$

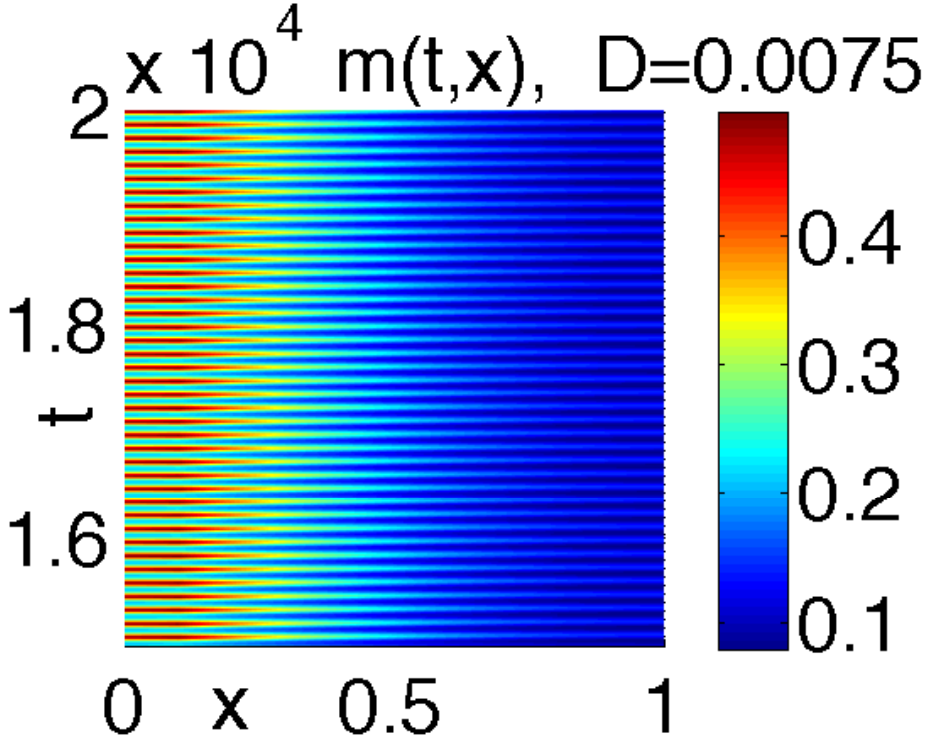


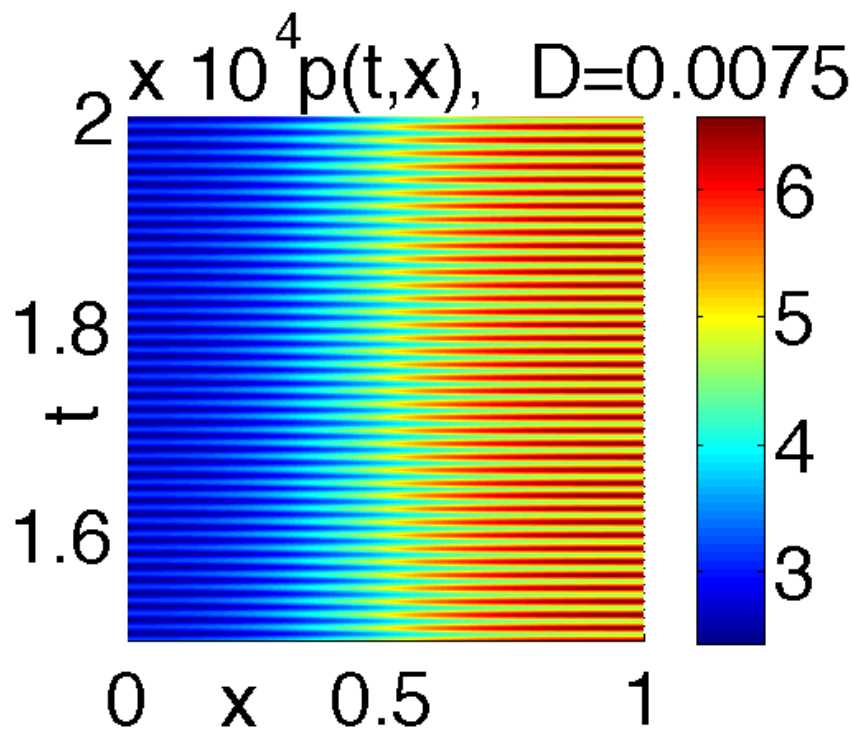
Numerical simulations $D = 7.5 \cdot 10^{-3}$,

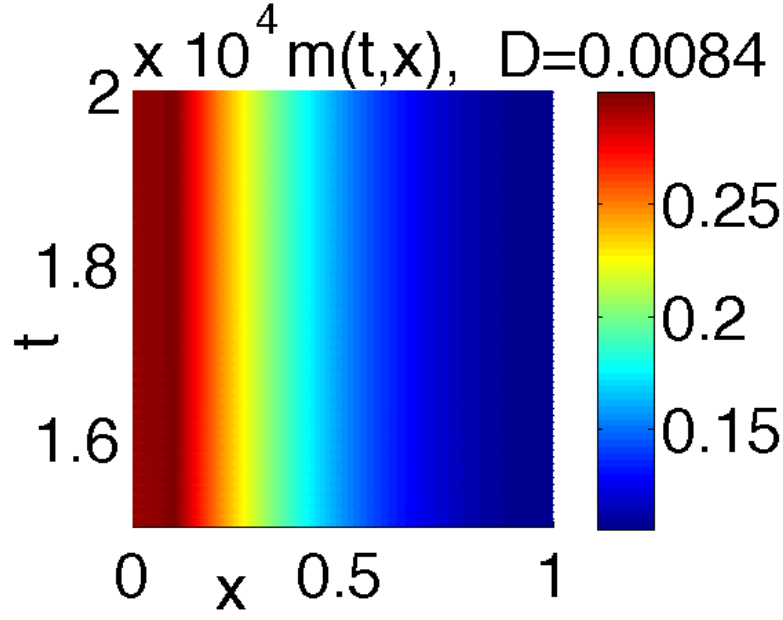


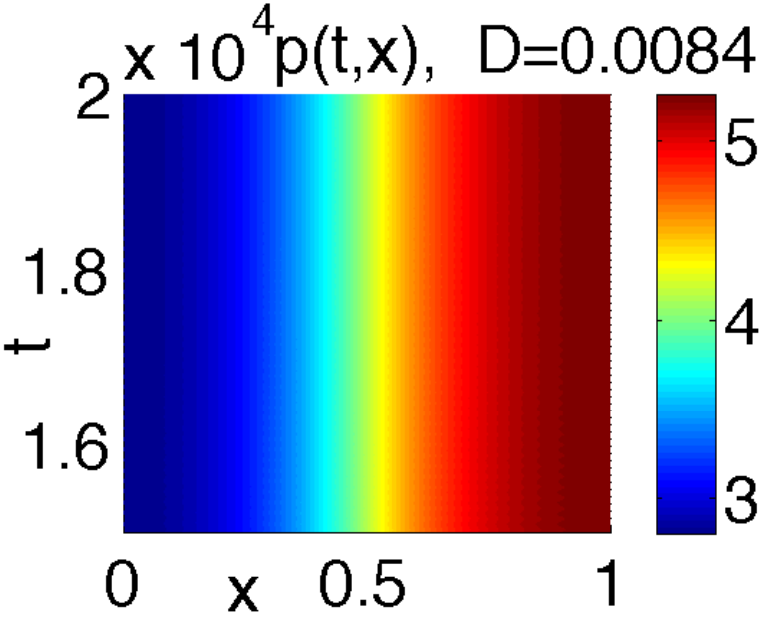


Numerical simulations $D = 7.5 \cdot 10^{-3}$, $D = 8.4 \cdot 10^{-3}$









Hopf Bifurcation for GRN

Eigenvalue problem

$$\begin{aligned}
\lambda \bar{m}^\varepsilon &= D\bar{m}^\varepsilon_{xx} - \mu \bar{m}^\varepsilon \quad + \alpha_m f'(p^*_\varepsilon(x,D))\,\delta^\varepsilon_{x_M}\,\bar{p}^\varepsilon \quad \text{in } (0,1)\\
\lambda \bar{p}^\varepsilon &= D\bar{p}^\varepsilon_{xx} - \mu \bar{p}^\varepsilon \quad + \alpha_p g(x)\bar{m}^\varepsilon \quad \text{in } (0,1)\\
&+ \text{ zero-flux b.c.}
\end{aligned}$$

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

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

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

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

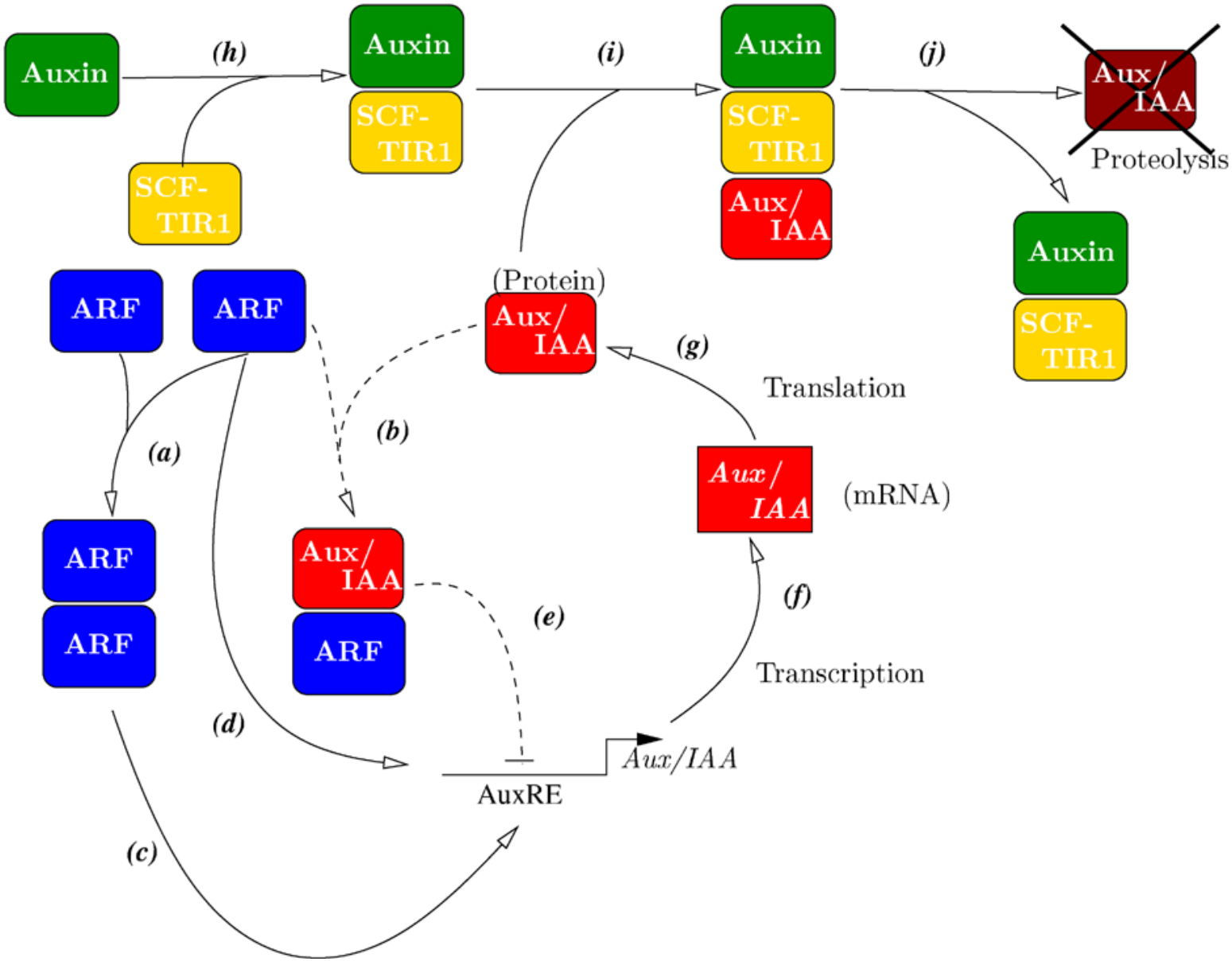
where $\mathcal{A}_0 = (D\frac{d^2}{dx^2} - \mu)$.

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 canonical Hes1 GRN model.

A bit more complicated network: Auxin signalling

- Auxins belong to the most important plant hormones and play a central role in growth and development regulation.
  (direction of growth, changes in shoot and root branching and changes in vascular differentiation).
- Transcription factor ARF (auxin response factor) activates Aux/IAA gene and the transcription of Aux/IAA mRNA
- The accumulation of Aux/IAA protein stimulates the formation of ARF:Aux/IAA protein complexes, which repress Aux/IAA genes and inhibits the production of Aux/IAA mRNA.
- When the levels of Aux/IAA proteins fall, the concentration of free ARFs increases, enhancing Aux/IAA transcription and translation.
- Auxin functions by mediating the activation of the Aux/IAA family of genes by auxin mediating turnover of Aux/IAA proteins (ubiquitination)
- The instability of Aux/IAA proteins is required for normal auxin signalling.

Auxin signalling



Middletona, King, Bennett, Owena, *Bull.Math.Biol.* 2010

Vernoux et al. *Molecular Systems Biol.* 2011

Auxin (A) binds to its receptor TIR1 (r_f) forming Aux:TIR1 complex (r_b)

$$\mathrm{Aux} + \mathrm{TIR1} \underset{\gamma_A}{\overset{\beta_A}{\rightleftharpoons}} \mathrm{Aux:TIR1}$$

Aux:TIR1 (r_b) targets Aux/IAA protein (p) by forming Aux:TIR1:IAA (p_b) whose dissociation results in the ubiquitin-tagged protein Aux/IAA* (p_u)

$$\mathrm{Aux:TIR1} + \mathrm{IAA} \underset{\gamma_r}{\overset{\beta_r}{\rightleftharpoons}} \mathrm{Aux:TIR1:IAA} \overset{\beta_{pb}}{\rightarrow} \mathrm{Aux:TIR1} + \mathrm{IAA}^*$$

Auxin synthesised and degrade at the constant rates α_A and μ_A

$$\overset{\alpha_A}{\rightarrow} \mathrm{Aux} \overset{\mu_A}{\rightarrow} \emptyset, \qquad \mathrm{IAA}^* \overset{\mu_u}{\rightarrow} \emptyset$$

ARF monomer (R) can homodimerise or bind Aux/IAA protein (p)

$$\mathrm{ARF} + \mathrm{ARF} \underset{\gamma_R}{\overset{\beta_R}{\rightleftharpoons}} \mathrm{ARF}_2, \qquad \mathrm{IAA} + \mathrm{ARF} \underset{\gamma_p}{\overset{\beta_p}{\rightleftharpoons}} \mathrm{ARF:IAA}$$

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Auxin Signalling Network: Law of Mass Action

$$\frac{dA}{dt} = \alpha_A - \mu_A A - \beta_A A r_f + \gamma_A r_b$$

$$\overset{A}{\mathrm{Aux}} + \overset{r_f}{\mathrm{TIR1}} \underset{\gamma_A}{\overset{\beta_A}{\rightleftharpoons}} \overset{r_b}{\mathrm{Aux:TIR1}}$$

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$$\overset{A}{\text{Aux}} + \overset{r_f}{\text{TIR1}} \underset{\gamma_A}{\overset{\beta_A}{\rightleftharpoons}} \text{Aux} : \overset{r_b}{\text{TIR1}}$$

$$\left.\begin{aligned}
\frac{dr_f}{dt} &= -\beta_A A r_f + \gamma_A r_b \\
\frac{dr_b}{dt} &= \beta_A A r_f - \gamma_A r_b - \beta_r r_b p + (\gamma_r + \beta_{pb}) p_b \\
\frac{dp_b}{dt} &= \beta_r r_b p - (\gamma_r + \beta_{pb}) p_b
\end{aligned}\right\}$$

$$\begin{array}{l}
\overset{r_b}{\text{Aux}} : \text{TIR1} + \overset{p}{\text{IAA}} \\
\quad \overset{\beta_r}{\underset{\gamma_r}{\rightleftharpoons}} \quad \text{Aux} : \overset{p_b}{\text{TIR1}} : \text{IAA} \\
\quad \overset{\beta_{pb}}{\rightarrow} \quad \overset{r_b}{\text{Aux}} : \text{TIR1} + \overset{p_u}{\text{IAA}}{}^*
\end{array}$$

Auxin Signalling Network: Law of Mass Action

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\end{aligned}\right\}$$

$$\left.\begin{aligned}
&\overset{r_b}{\text{Aux : TIR1}} + \overset{p}{\text{IAA}} \\
&\underset{\gamma_r}{\overset{\beta_r}{\rightleftharpoons}} \overset{p_b}{\text{Aux : TIR1 : IAA}} \\
&\xrightarrow{\beta_{pb}} \overset{r_b}{\text{Aux : TIR1}} + \overset{p_u}{\text{IAA}^*}
\end{aligned}\right\}$$

$$\frac{dm}{dt} = f(R, R_p, R_2) - \mu_m m$$

mRNA (m) production by ARF, ARF_2

inhibition by ARF:IAA (R_p)

$$\frac{dp}{dt} = \alpha_p m - \beta_r r_b p + \gamma_r p_b - \beta_p p R + \gamma_p R_p$$

$$\text{ARF} + \text{ARF} \underset{\gamma_R}{\overset{\beta_R}{\rightleftharpoons}} \text{ARF}_2,$$

$$\text{IAA} + \text{ARF} \underset{\gamma_p}{\overset{\beta_p}{\rightleftharpoons}} \text{ARF : IAA}$$

Auxin Signalling Network: Law of Mass Action

$$\frac{dA}{dt} = \alpha_A - \mu_A A - \beta_A A r_f + \gamma_A r_b$$

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$$\left.\begin{aligned}
\frac{dR}{dt} &= -2\beta_R R^2 + 2\gamma_R R_2 - \beta_p p R + \gamma_p R_p \\
\frac{dR_p}{dt} &= \beta_p p R - \gamma_p R_p \\
\frac{dR_2}{dt} &= \beta_R R^2 - \gamma_R R_2
\end{aligned}\right\}$$

$$\left.\begin{aligned}
&\mathrm{ARF} + \mathrm{ARF} \underset{\gamma_R}{\overset{\beta_R}{\rightleftharpoons}} \mathrm{ARF_2}, \\
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Auxin Signalling Network: Law of Mass Action

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$$\frac{dm}{dt} = f(R, R_p, R_2) - \mu_m m$$

mRNA (m) production by ARF, ARF_2

inhibition by ARF:IAA (R_p)

$$\frac{dp}{dt} = \alpha_p m - \beta_r r_b p + \gamma_r p_b - \beta_p p R + \gamma_p R_p$$

$$\left.\begin{aligned} \frac{dR}{dt} &= -2\beta_R R^2 + 2\gamma_R R_2 - \beta_p p R + \gamma_p R_p \\ \frac{dR_p}{dt} &= \beta_p p R - \gamma_p R_p \\ \frac{dR_2}{dt} &= \beta_R R^2 - \gamma_R R_2 \end{aligned}\right\} \frac{dR}{dt} + \frac{dR_p}{dt} + 2\frac{dR_2}{dt} = 0$$

where $f(R, R_p, R_2) = (\alpha_m R + 2\beta_m R_2 + \gamma_m R^2)/(1 + \kappa_m R_p + \zeta_m p R)$

Auxin Signalling Network

Assume that total concentrations of TIR1 (r_f) and ARF (T) are constant:

$$p_b + r_f + r_b = r_{f,\mathrm{int}}, \quad R + R_p + 2R_2 = R_{\mathrm{int}}.$$

$$\frac{dA}{dt} = -\beta_A\, A\, r_f + \gamma_A\, r_b + \alpha_A - \mu_A\, A,$$

$$\frac{dr_f}{dt} = -\beta_A\, A r_f + \gamma_A r_b$$

$$\frac{dr_b}{dt} = \beta_A\, A\, r_f - \gamma_A\, r_b - \beta_r\, r_b\, p + (\gamma_r + \beta_{pb})(r_{f,\mathrm{int}} - r_b - r_f)$$

$$\frac{dm}{dt} = F(R, R_p, R_{\mathrm{int}}) - \mu_m\, m,$$

$$\frac{dp}{dt} = \alpha_p m - \beta_r\, r_b\, p + \gamma_r(r_{f,int} - r_b - r_f) - \beta_p\, p\, R + \gamma_p\, R_p,$$

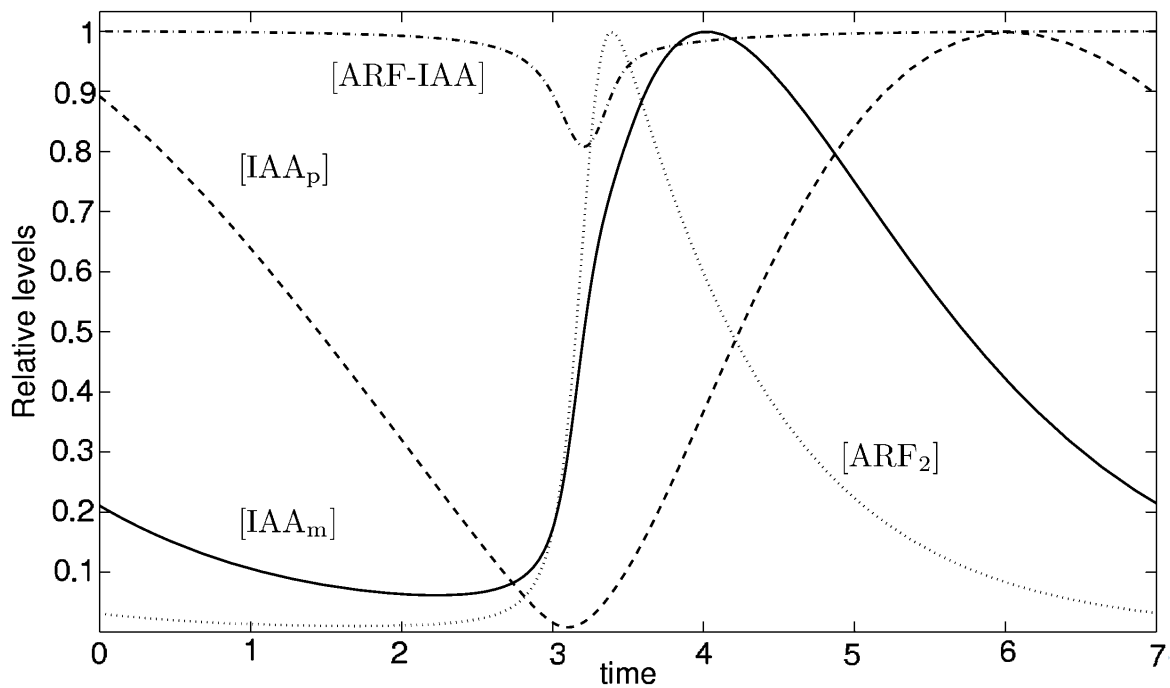
$$\frac{dR}{dt} = -2\beta_R\, R^2 + \gamma_R(R_{\mathrm{int}} - R_p - R) - \beta_p\, p\, R + \gamma_p\, R_p$$

$$\frac{dR_p}{dt} = \beta_p\, p\, R - \gamma_p\, R_p$$

$$\frac{dp_u}{dt} = \beta_{pb}\,(r_{f,\mathrm{int}} - r_b - r_f) - \mu_u\, p_u,$$

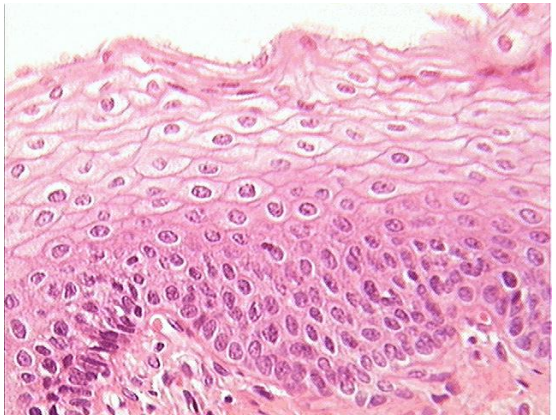
$$F(R, R_p, R_{\mathrm{int}}) = (\alpha_m R + \beta_m(R_{\mathrm{int}} - R_p - R) + \gamma_m R^2)/(1 + \kappa_m R_p + \zeta_m\, p\, R)$$

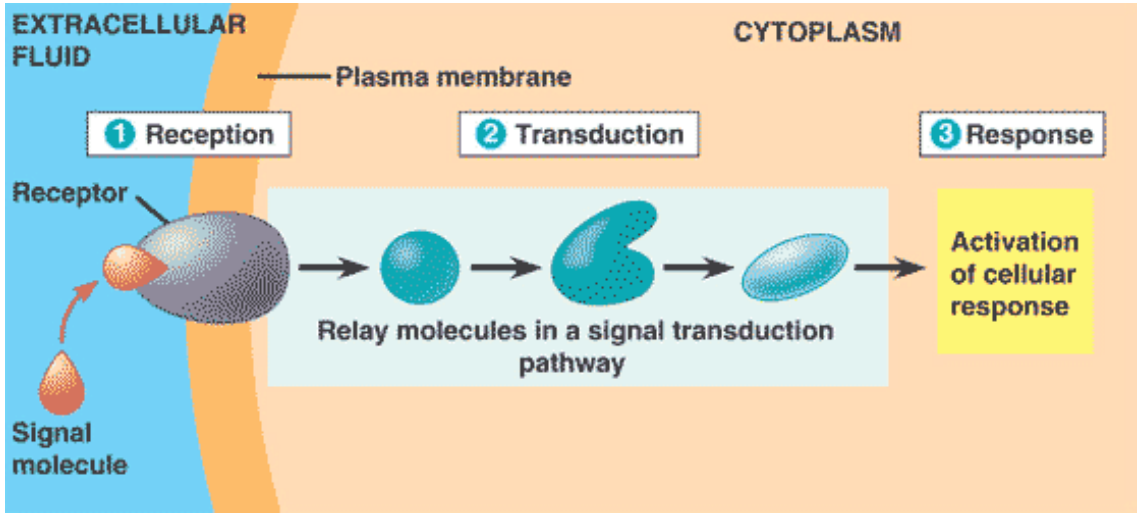
- Non-dimesionalization: rates of formation and dissociation of ARF_2 and the effective rate of Aux/IAA translation (translation rate/ production of ubiquitin-tagged protein) are key parameters
- Long time behaviour: exists a single steady-state.
- Stability analysis: three parameter regimes
  - mono-stable: steady-state is stable or it is unstable and there exists a stable limit-cycle (slow formation and dissociation of ARF_2 and large effective rate of translation)
  - bi-stable: steady-state is stable and there exist a stable and an unstable limit-cycles



Middletona, King, Bennett, Owena, *Bull.Math.Biol.* 2010

Intercellular transport of signalling molecules



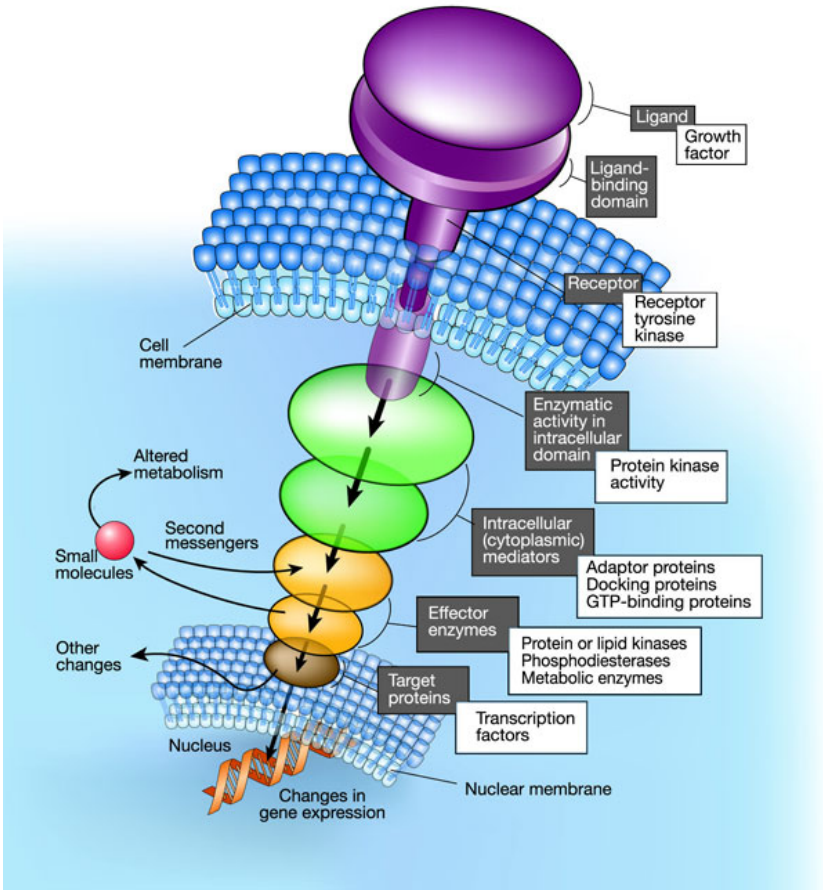


http://www.quia.com/jg/1225839list.html

Signalling 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

Intercellular transport of signalling molecules



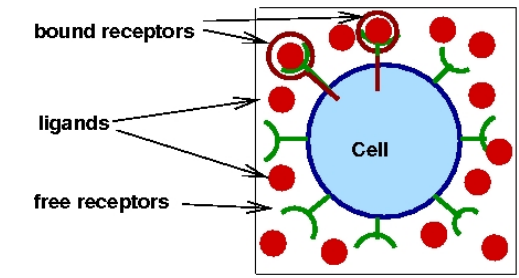
J. Downward, *Nature* 2001

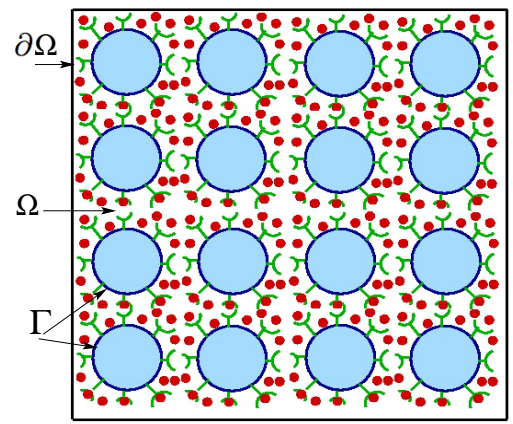
- Consider signalling molecules (ligands) l in the intercellular space and receptors on the cell membrane
- Free and bound receptors r_f and r_b
- Cells produce new receptors r_f and signalling molecules (ligands) l
- Ligands l diffuse in the intercellular space and bind to the receptors on the membrane
- Bound receptors r_b dissociate back to free receptors and ligands
- All the considered molecules undergo natural decay

Mathematical model

- Diffusion, production and decay of signalling molecules (ligands) in the intercellular space

$$\frac{\partial}{\partial t} l = \nabla \cdot (D \nabla l) + p_l(l) - \mu_l \, l$$





- Binding on the cell surfaces

$$D \, \nabla l \cdot \nu = -b \, l \, r_f + d \, r_b \qquad \text{on} \quad \Gamma$$

l	density of ligands	μ_l	rate of decay of ligands,
p_l	production of ligands,	D	diffusion coefficient.

Mathematical model

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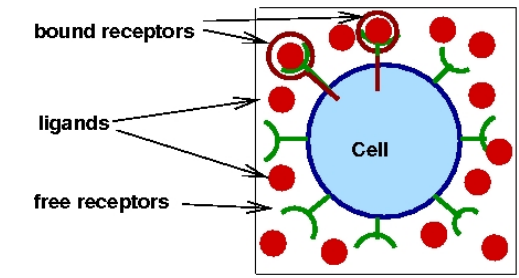

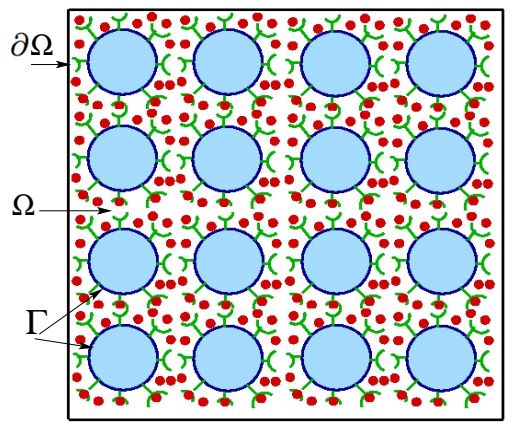

- Interaction between a signalling molecule L and a free receptor R_f results into a bound receptor R_b

$$L + R_f \underset{d}{\overset{b}{\rightleftharpoons}} R_b$$

binding process is governed by the Law of Mass Action

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- Diffusion, production and decay of signalling molecules (ligands) in the intercellular space

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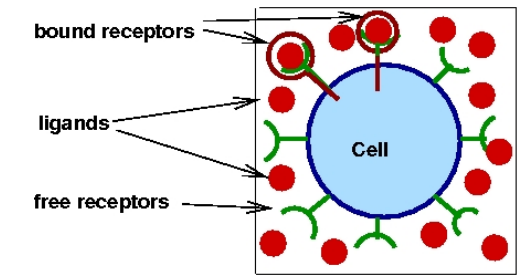

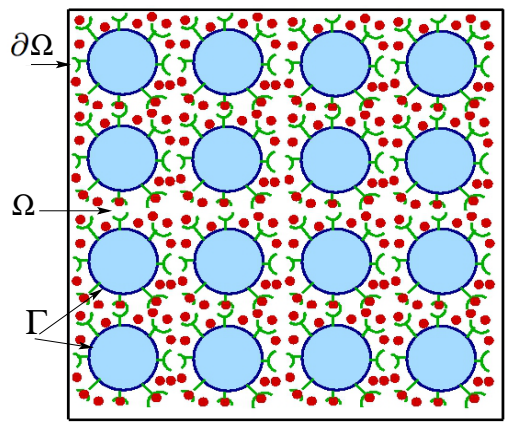

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- Binding on the cell surfaces

$$D \, \nabla l \cdot \nu = -b \, l \, r_f + d \, r_b \qquad \text{on} \quad \Gamma$$

l density of ligands $\quad \mu_l$ rate of decay of ligands,
p_l production of ligands, $\quad D$ diffusion coefficient.

Mathematical modelling of signalling processes

- Reaction equations for the receptors on the cell surface Γ

$$\frac{\partial}{\partial t} r_f = -b\, r_f\, l + d\, r_b - \mu_f\, r_f \qquad \text{on } \Gamma,\ t > 0$$

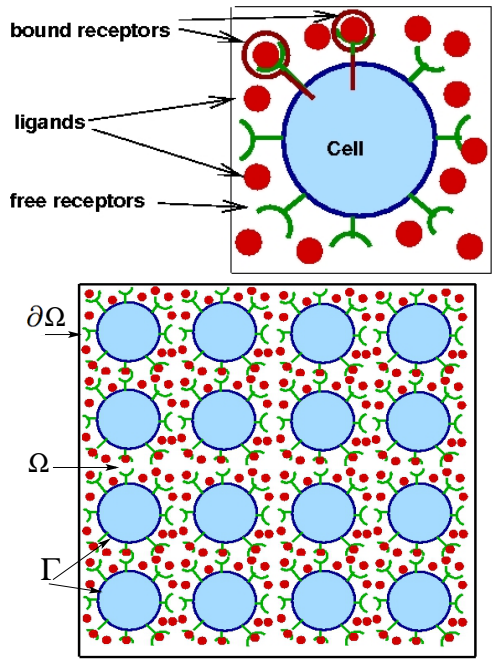
$$\frac{\partial}{\partial t} r_b = b\, r_f\, l - d\, r_b - \mu_b r_b \qquad \text{on } \Gamma,\ t > 0$$

with initial conditions

$$r_f(0, x) = r_{f,\text{int}}(x) \qquad \text{on } \Gamma$$

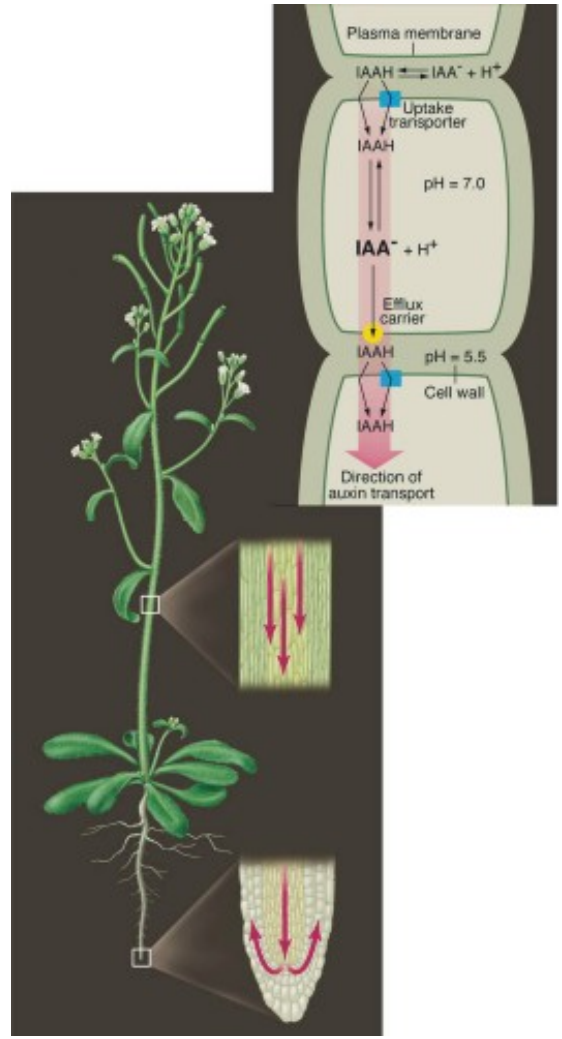
$$r_b(0, x) = r_{b,\text{int}}(x) \qquad \text{on } \Gamma$$

r_f,	r_b	density of free and bound receptors
μ_f,	μ_b	rates of decay of free and bound receptors
d		rate of dissociation of bound receptors
b		rate of binding of ligands and free receptors



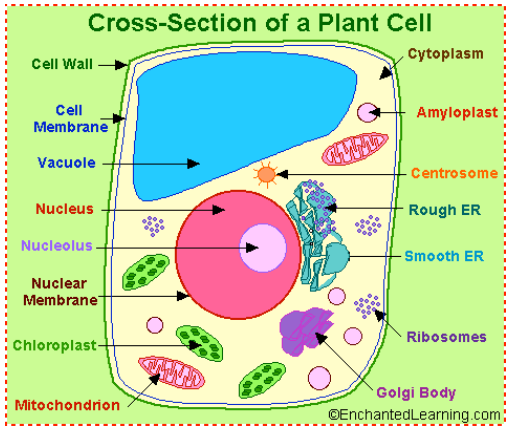
Cell to cell transport of plant hormones
Polar transport of auxin

- Auxin (IAA) is mostly produced in the plant shoot and is transported polar from cell to cell through the shoot and stem towards the roots.
- Plant hormones (signalling molecules) regulate plant growth, determine the formation of flowers, stems, leaves, the shedding of leaves, and the development and ripening of fruit
- Aim: To determine the distribution and the transport velocity of the auxin



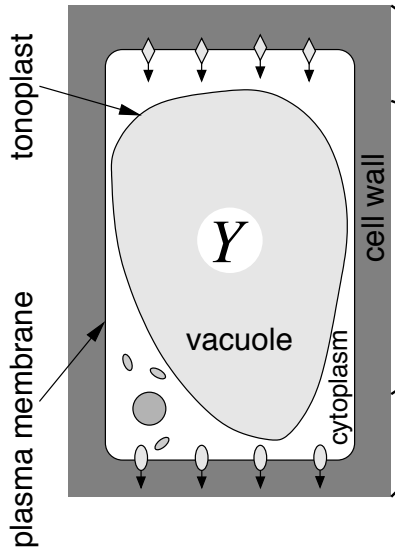
Auxin (IAA) is a weak acid which dissociates into ions

$$\mathrm{IAAH} \underset{r_r}{\overset{r_d}{\rightleftharpoons}} \mathrm{IAA}^- + \mathrm{H}^+$$



r_d and r_r are dissociation and recombination rates.

- IAAH predominates in cell wall due to acidic pH
- IAA^- predominates in cytoplasm due to neutral pH
- IAAH is uncharged and can diffuse through membrane
- membrane is impermeable to IAA^- due to charge
- influx protein AUX1 transports IAA^- into cytoplasm
- efflux PIN proteins transport IAA^- out of cell



Due to the negative charge, the electric potential differences across the plasma membrane and tonoplast produce an additional flux of IAA^-.

(membrane potential acts on changed IAA^-: ca. $-120\ mV$ between cell wall and cytoplasm and 50 mV between cytoplasm and vacuole).

Mathematical model

$$\mathrm{IAAH} \underset{r_r}{\overset{r_d}{\rightleftharpoons}} \mathrm{IAA}^- + \mathrm{H}^+ ,$$

- u the concentrations of the auxin ions IAA^-
- v the concentrations of the protonated auxin IAAH

- The mobility of the ions is given by the permeability P
- ϕ is the electric field, assume ϕ cell is independent of u (concentration of other ions is much larger as of u).
- $P\,\phi\,u$ is the electric flux.
- Initial and boundary conditions

Mathematical model

$$\mathrm{IAAH} \underset{r_r}{\overset{r_d}{\rightleftharpoons}} \mathrm{IAA^-} + \mathrm{H^+},$$

- u the concentrations of the auxin ions $\mathrm{IAA^-}$
- v the concentrations of the protonated auxin IAAH

$$\begin{aligned} \partial_t u &= r_d\, v - r_r\, u \\ \partial_t v &= -r_d\, v + r_r\, u \end{aligned}$$

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- v the concentrations of the protonated auxin IAAH

$$\begin{aligned} \partial_t u &= \nabla \cdot (D_u \nabla u) &&+ r_d\, v - r_r\, u \\ \partial_t v &= \nabla \cdot (D_v \nabla v) &&- r_d\, v + r_r\, u \end{aligned}$$

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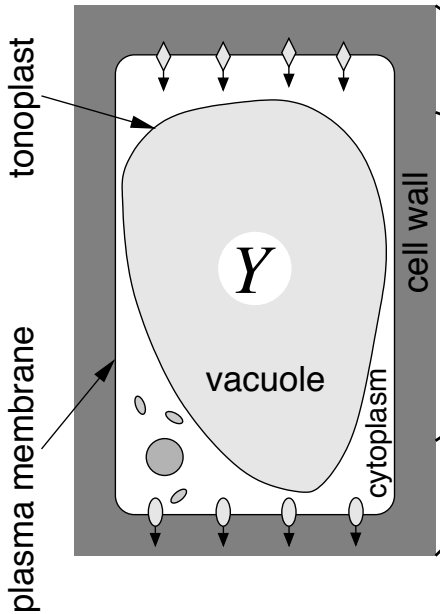
- The mobility of the ions is given by the permeability P
- ϕ is the electric field, assume ϕ cell is independent of u (concentration of other ions is much larger as of u).
- $P \phi u$ is the electric flux.
- Initial and boundary conditions

Model parameters and scaling

- $D\,\nabla u_0 \approx 16\,u_0$ in wall
  $\approx 240\,u_0$ in cytoplasm
  $\approx 10^{-9} u_0$ in plasma membranes
- $P\,\phi\,u_0 \approx 0.3\,u_0 \sim 30\,u_0$
  in plasma membrane.
- Reaction rates:
  $r_d \approx 5{\cdot}10^9\,h^{-1}$ and $r_r \approx 5{\cdot}10^6 \sim 5{\cdot}10^8\,h^{-1}$.



Time scale in the model is the characteristic reaction time the flux terms have to be scaled by $\varepsilon = 10^{-3}$.

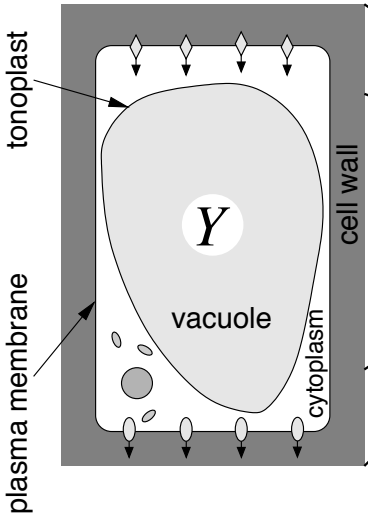
$$\begin{aligned} \partial_t u &= \varepsilon\,\nabla\cdot(D_u\,\nabla u) - \varepsilon\,\nabla\cdot(P\,\phi\,u) + R_d\,v - R_r\,u, \\ \partial_t v &= \varepsilon\,\mathrm{div}\,(D_v\,\nabla v) \qquad\qquad\qquad\qquad - R_d\,v + R_r\,u \end{aligned}$$

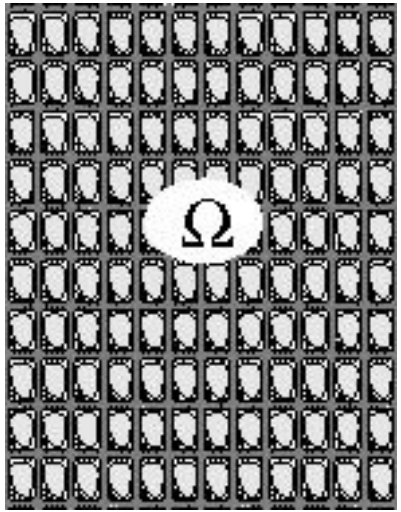
where $R_d = \varepsilon\,r_d, \quad R_r = \varepsilon\,r_r$

Microscopic structure

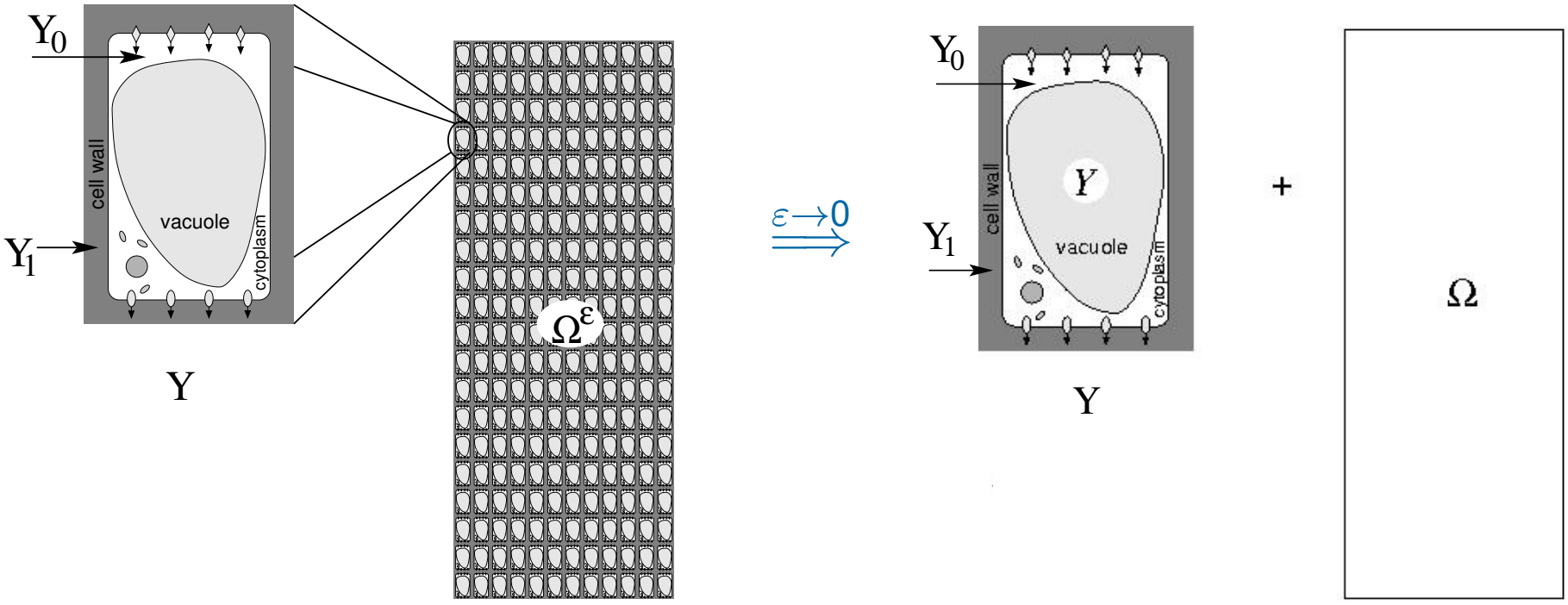
$$D_u = \begin{cases} 0.0016 & \text{in cell wall,} \\ 3.6 \cdot 10^{-12} & \text{in plasma membrane,} \\ 0.024 & \text{in cytoplasm,} \\ 3.6 \cdot 10^{-12} & \text{in tonoplast,} \\ 0.024 & \text{in vacuole} \end{cases} \qquad D_v = \begin{cases} 0.0016 & \text{in cell wall,} \\ 2 \cdot 10^{-7} & \text{in plasma membrane,} \\ 0.024 & \text{in cytoplasm,} \\ 2 \cdot 10^{-7} & \text{in tonoplast,} \\ 0.024 & \text{in vacuole} \end{cases}$$

$$P = \begin{cases} 0 & \text{in cell wall,} \\ 0.1 & \text{in plasma membrane,} \\ 0 & \text{in cytoplasm,} \\ 0.2 & \text{in tonoplast,} \\ 0 & \text{in vacuole} \end{cases} \qquad \phi = \begin{cases} 0 & \text{in cell wall,} \\ 120 \cdot 10^3 & \text{in plasma membrane,} \\ 0 & \text{in cytoplasm,} \\ 50 \cdot 10^3 & \text{in tonoplast,} \\ 0 & \text{in vacuole} \end{cases}$$



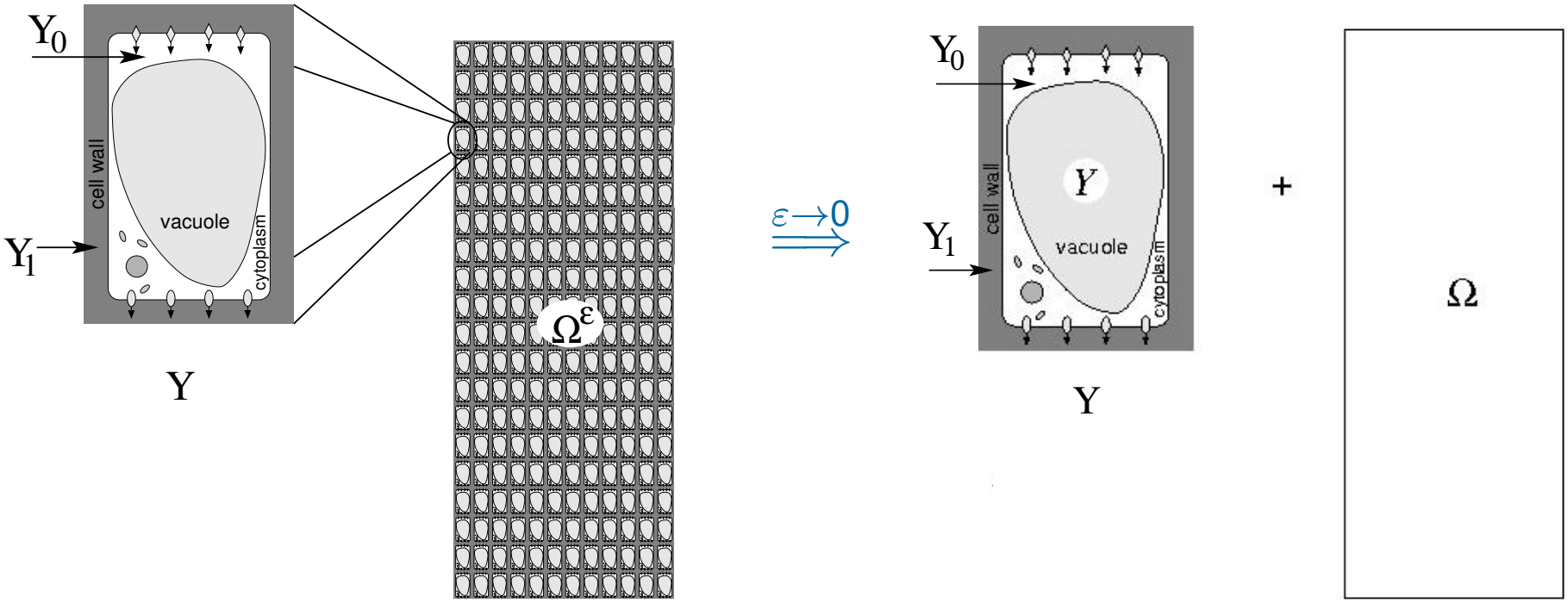


Homogenization



- The aim of homogenization is to give the macroscopic properties by taking the properties of the microscopic structure into account.
- To link macroscopic parameters with microscopic properties of the system.
- Derivation of macroscopic models simplifies numerical simulation.

Homogenization



- The aim of homogenization is to give the macroscopic properties by taking the properties of the microscopic structure into account.
- To link macroscopic parameters with microscopic properties of the system.
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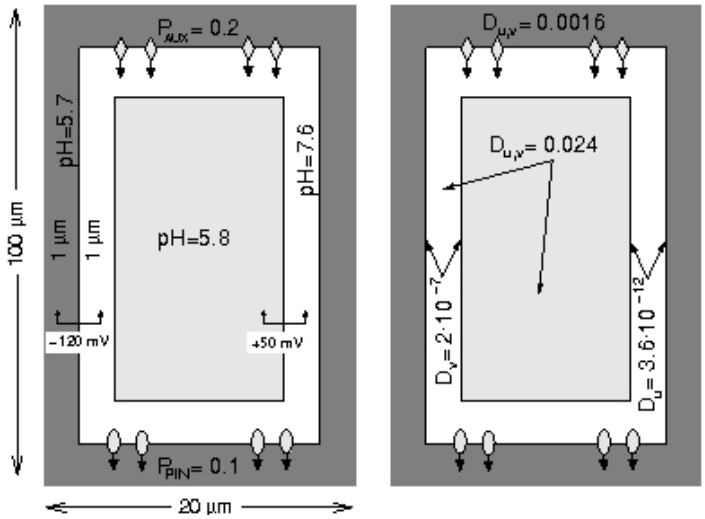
Solve cell problems

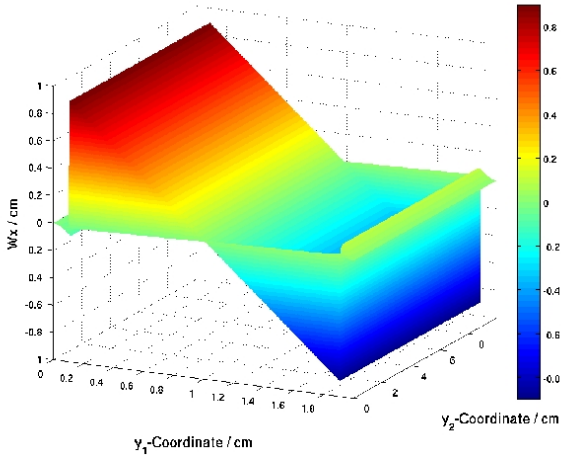
and calculate effective coefficients using physiological data

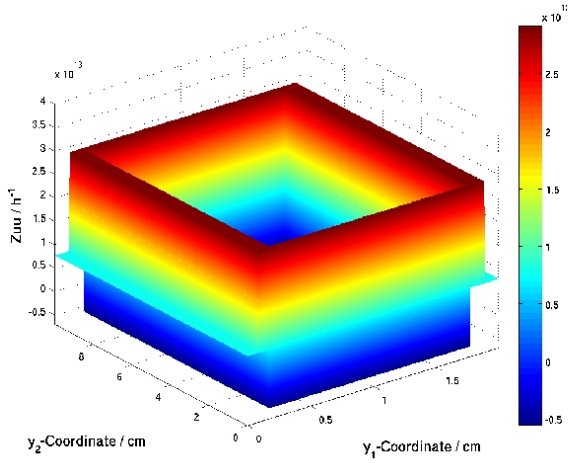


- $Y = (0, 20\mu m) \times (0, 100\mu m)$
- Cell wall and cytoplasm are $1\mu m$
- AUX1: $\{y \in Y | y_2 = 1,\ 1 \leq y_1 \leq 19\}\mu m$ with permeability 0.2cm h^{-1}
- PIN: $\{y \in Y | y_2 = 99,\ 1 \leq y_1 \leq 19\}\mu m$ with permeability 0.1 cmh^{-1}.

- Permeability of tonoplast transport protein: 0.2 cmh^{-1}
- Scalar diffusivity: cytoplasm and vacuole: $D_w = 0.024$ cm^2s^{-1}; cell wall: $D_w/15$; membrane: $2 \cdot 10^{-7}$ cm^2s^{-1} for IAAH and $3.6 \cdot 10^{-12} cm^2s^{-1}$ for IAA^-.
- Cell wall $pH = 5.8$, vacuole $pH = 5.7$ cytoplasm $pH = 7.6 \Rightarrow$ $R_r^{\varepsilon} = R_d\, 10^{pKa - pH^{\varepsilon}}$, where $R_d = 5 \cdot 10^9\ h^{-1} = \text{const}$.
- The constant approximation for the electric field: membrane potential: $-120mV$; tonoplast potential: $50mV$

Numerical results: Auxin transport velocity





Solutions of the cell problems: w_x (diffusion), Z_{uu} (transport).

$$\frac{\mathcal{A}_u}{D_w} = \begin{pmatrix} 1.37 & \mathcal{O}(10^{-12}) \\ \mathcal{O}(10^{-12}) & 6.7 \end{pmatrix} \cdot 10^{-3}, \quad \frac{\mathcal{A}_v}{D_w} = \begin{pmatrix} 2.85 & \mathcal{O}(10^{-11}) \\ \mathcal{O}(10^{-11}) & 21.6 \end{pmatrix} \cdot 10^{-3}.$$

$$\mathcal{V}_{uu} = \begin{pmatrix} \mathcal{O}(10^{-4}) \\ 0.638 \end{pmatrix} \; cm\, h^{-1} \quad , \quad \mathcal{V}_{uv} = \begin{pmatrix} \mathcal{O}(10^{-11}) \\ \mathcal{O}(10^{-7}) \end{pmatrix} \; cm\, h^{-1},$$

$$\mathcal{V}_{vu} = \begin{pmatrix} \mathcal{O}(10^{-11}) \\ \mathcal{O}(10^{-7}) \end{pmatrix} \; cm\, h^{-1} \quad , \quad \mathcal{V}_{vv} = \begin{pmatrix} \mathcal{O}(10^{-8}) \\ \mathcal{O}(10^{-4}) \end{pmatrix} \; cm\, h^{-1}.$$

Value $\mathcal{V}_{uu} \approx 0.6$ cm h^{-1} near published experimental value.
(measurements of pulses of radioactivelly labeled auxin: $1.2 \backsim 1.5\, cm h^{-1}$).

Conclusion

- Different modelling approaches can explain oscillatory behaviour of gene regulatory networks with negative feedback
- Spatial models on the scale of a single cell are considered to describe the intercellular transport of signalling molecules in a plant tissue

Thank you very much for your attention