Influence of time delay on dynamic of genes expression models

Marek Bodnar

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

7. Forum Matematyków Polskich
z Udziałem Matematyków Ukraińskich

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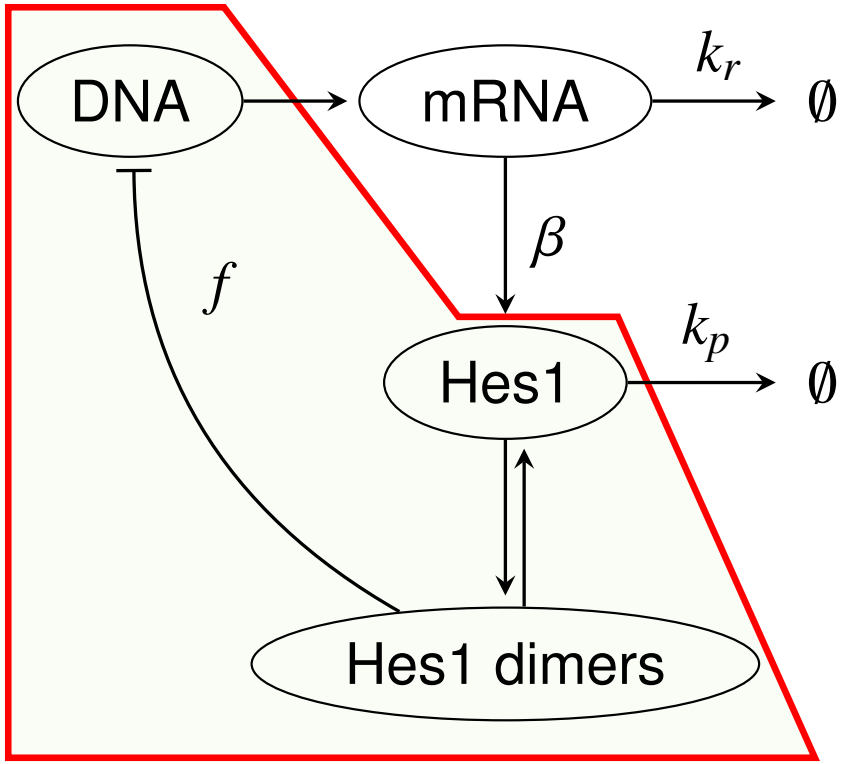
Hes1 gene expression process

- Protein Hes1 forms dimers;
- Hes1 dimers bounds to Hes1 DNA blocking transcription.
- Intensity of mRNA production depends on the protein (dimer) concentration — more Hes1 protein, the grater probability DNA to be blocked, thus intensity is decreasing (a negative feedback loop).



Classical Hes1 model describes the framed process using one variable.

Experimentally oscillations were observed

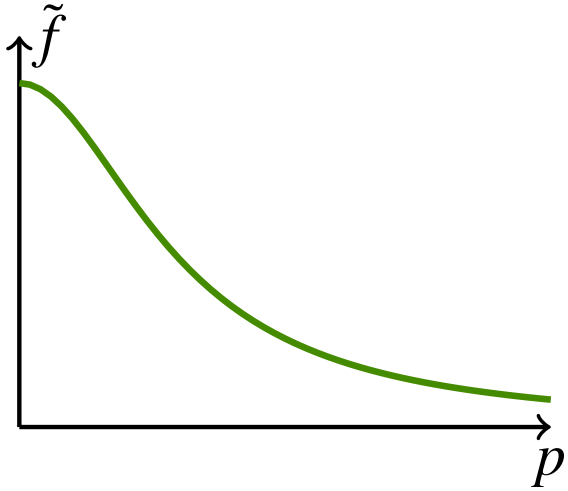
(H. Hirata i in., *Science*, **298**: 840–843, (2002))

Classical Hes1 gene expression model

Proposed in 2003. (N.A. Monk, *Curr. Biol.*, **13**: 1409–1413, (2003))

$$\begin{aligned} \dot{r}(t) &= \tilde{f}(p(t-\tau_r)) - k_r r(t)\,, \\ \dot{p}(t) &= \beta r(t-\tau_p) - k_p p(t)\,, \end{aligned} \quad \xrightarrow{\text{rescaling}} \quad \begin{aligned} \dot{x}(t) &= f(y(t-\tau_1)) - x(t)\,, \\ \dot{y}(t) &= x(t-\tau_2) - \mu y(t)\,, \end{aligned}$$

- $r(t)$ — mRNA concentration;
- $p(t)$ — Hes1 concentration;
- $\tilde{f}$ — $\searrow$ function; influence of DNA blocking on mRNA production; $f(1) = \mu$;

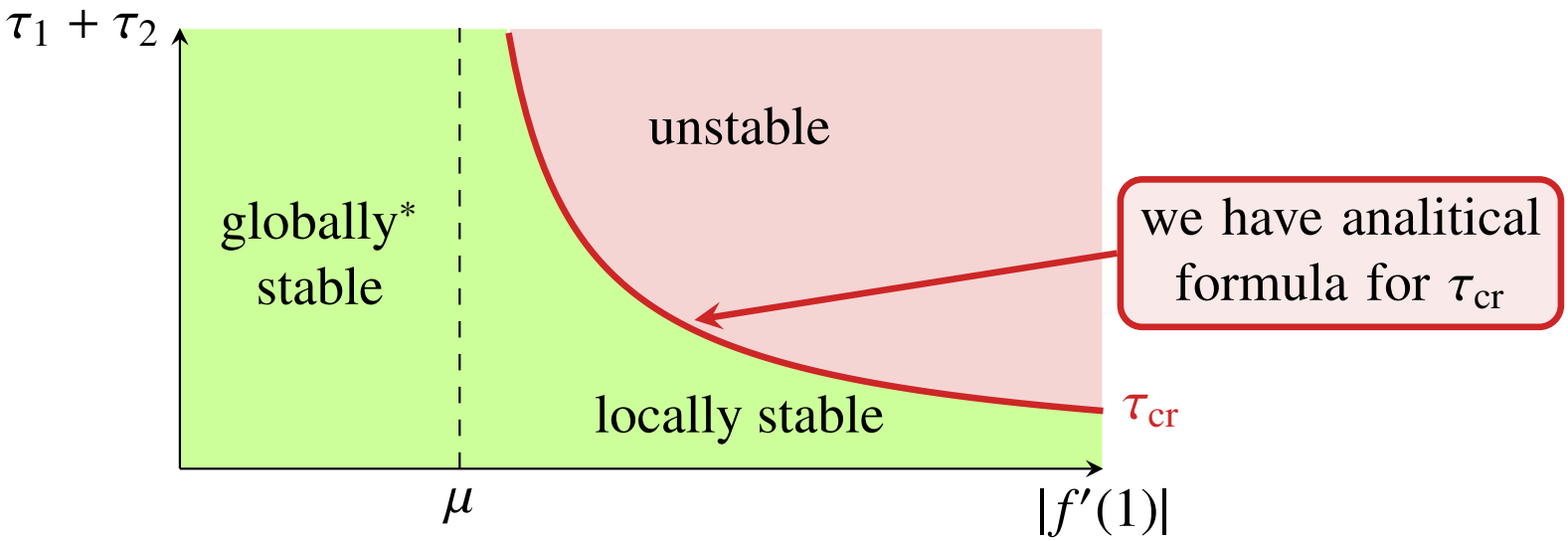


- k_r and k_p — intensities of mRNA and protein degradation;
- β — intensity of protein production (translation);
- τ_r i τ_p — times of transcriptions and translations;

What is known about model properties

✓ Non-negative, unique, bounded solution globally defined;

→ The (local) stability of the unique postive steady state



If $f'''(1) < -\alpha(f''(1))^2$, then the Hopf bifurcation is supercritical, α depends on $f'(1)$, and model parameters.

S. Bernard et al., *Phil. Trans. R. Soc. A*, **364**: 1155–1170, (2006)

M.B., A. Bartłomiejczyk, *Non. Anal. RWA*, **13**: 2228–2239, (2013)

*Global stability of the steady state is proved under additional assumptions, M.B., *J. Diff. Eqs*, **259**: 777–795, (2015)

The model with distributed delay

Question: How does distribution of delay affect the model dynamics (stability of the steady state)?

The model formulation

$$\dot{x}(t) = f\left(\int_0^\infty \theta(s)y(t-s)\right) - x(t)\,, \qquad (\star)$$
$$\dot{y}(t) = x(t) - \mu y(t)\,,$$

θ — a probabilistic measure with a finite expectation.

Assumption: $f(1) = \mu$.

A unique positive steady state: $(\mu, 1)$. Denote $d_1 = -f'(1) > 0$.

Characteristic function

$$W(\lambda) = \lambda^2 + (\mu+1)\lambda + \mu + d_1\hat{\theta}(\lambda), \quad \hat{\theta}(\lambda) = \int_0^\infty \theta(s)e^{-\lambda s}ds.$$

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Distributed delay is “more stable”

Assumption: The function θ depends on a parameter τ,

$$\hat{\theta}(\lambda,0)=\int_0^{+\infty}\theta(s;0)\mathrm{e}^{-\lambda s}\mathrm{d}s=1,\quad\text{and}\quad\tau\mapsto\hat{\theta}(\lambda;\tau)=\int_0^{+\infty}\theta(s;\tau)\mathrm{e}^{-\lambda s}\mathrm{d}s$$

is continuous in τ.

Theorem

If $\mu > d_1$ then the steady state is stable for all $\tau \geq 0$.

Proof.

- If $\tau = 0$, then $W(\lambda) = \lambda^2 + (\mu+1)\lambda + \mu + d_1$, and $\mathrm{Re}\lambda < 0$;
- Due to continuity, stability change require $W(i\omega) = 0$ for some $\omega \geq 0$ and $\tau > 0$.
- Thus, $\left|-\omega^2 + (\mu+1)\omega i\ + \mu\right|^2 = d_1^2\left|\hat{\theta}(i\omega)\right|^2$.
- Schwartz inequality $\Rightarrow \left|\int_0^{+\infty}\theta(s;\tau)\mathrm{e}^{-\lambda s}\mathrm{d}s\right| \leq 1$.
- $\omega^4 + (\mu^2+1)\omega^2 + \mu^2 - d_1^2 > 0$.

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The Erlang distribution

It is a Gamma distribution with the shape parameter being a natural number.

$$\theta(s) = \begin{cases} 0 & s < \tau_m \\ \dfrac{a^m}{(m-1)!}(s-\tau_m)^{m-1}\mathrm{e}^{-a(s-\tau_m)} & s \geq \tau_m \end{cases}$$

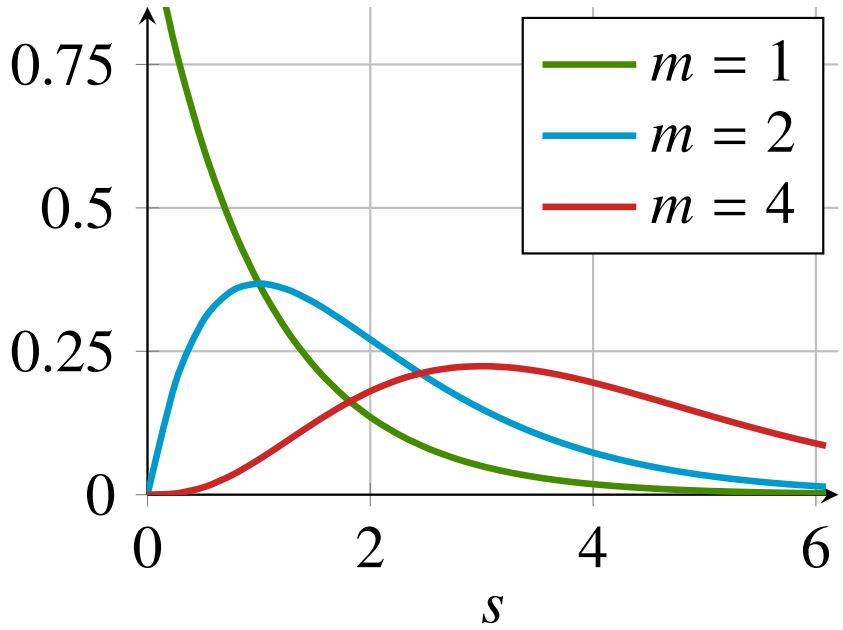
Notation: $\tau_m = 0$ — non-shifted, $\tau_m > 0$ — shifted;

Distribution parameters

- average delay $\tau = \tau_m + \dfrac{m}{a}$.
- variance of delay: $\dfrac{m}{a^2}$;

The Laplace transform

$$\hat{\theta}(\lambda) = \frac{a^m}{(a+\lambda)^m}\mathrm{e}^{-\lambda\tau_m}.$$



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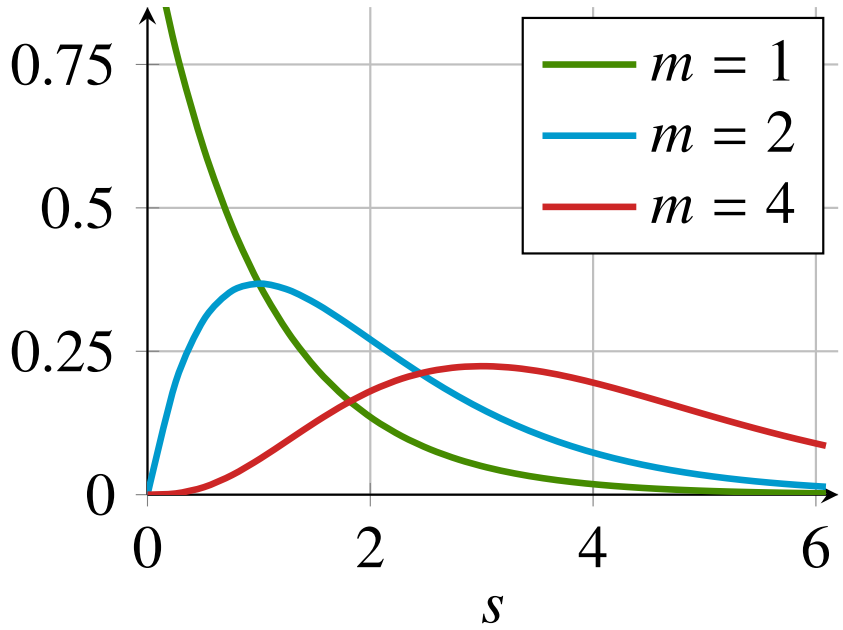

A general result for shifted distributions

Theorem

Assumptions:

1. $\mu < d_1$ *(for* $\mu \geq d_1$ *the steady state is always locally stable).*
2. *the steady state is locally stable for* $\tau_m = 0$.

Then there exists τ_c *such that*

- *the steady state is stable for* $0 \leq \tau_m < \tau_c$;
- *the steady state is unstable for* $\tau_m > \tau_c$;
- *at* $\tau_m = \tau_c$ *the Hopf bifurcation occurs.*

Proof.

- Eigenvalues: $(a+\lambda)^m(\lambda^2+(\mu+1)\lambda+\mu) = -a^m d_1 \mathrm{e}^{-\lambda\tau_m}$.
- Stability change occurs for $\omega > 0$ such that

$$F(\omega) = (a^2+\omega^2)^m(\omega^4+(\mu^2+1)\omega^2+\mu^2) - d_1^2 a^{2m}.$$

- The Descart's Rule of Signs + Cooke, Driessche (1996). ∎

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The case $m = 1$

Theorem

For $m = 1$ *and* $\tau_m = 0$*:*

1. $d_1 < (\mu_1 + 1)\left(1 + \sqrt{\mu}\right)^2 \Longrightarrow$ *steady state is stable for all* $\tau = 1/a$*;*
2. $d_1 > (\mu_1 + 1)\left(1 + \sqrt{\mu}\right)^2 \Longrightarrow$ *there exists* $0 < \tau_1 < \tau_2$
   1. *steady state is stable for* $1/a = \tau < \tau_1$ *and* $1/a = \tau > \tau_2$*;*
   2. *steady state is unstable for* $\tau_1 < \tau < \tau_2$*.*

Proof.

- Eigenvalues are zeros of the polynomial

$$(a + \lambda)(\lambda^2 + (\mu + 1)\lambda + \mu) + ad_1.$$

- The Rout-Hurwitz criterion implies a condition

$$w_{RH}(a) = a^2(\mu + 1) + a\left((\mu + 1)^2 - d_1\right) + \mu(\mu + 1) > 0.$$

- $d_1 < (1 + \mu)^2 \Longrightarrow w_{RH}(a) > 0$ for $a > 0$.

Proof — continuation

$$w_{RH}(a) = a^2(\mu+1) + a\Big((\mu+1)^2 - d_1\Big) + \mu(\mu+1) > 0.$$

- for $d_1 > (1+\mu)^2$ we calculate discriminant of w_{RH}
$$\Delta_{RH} = d_1^2 - 2(1+\mu)^2 d_1 + (1+\mu)^2(1-\mu)^2$$
- Δ_{RH} is a quadratic polynomial in d_1. Discriminant is
$$\Delta_{d_1} = 16\mu(\mu+1)^2 > 0$$
and Δ_{RH} is negative for
$$(\mu+1)^2 - 2\sqrt{\mu}(\mu+1) < d_1 < (\mu+1)^2 + 2\sqrt{\mu}(\mu+1)$$
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- Thus for $d_1 < (\mu+1)\Big(1+\sqrt{\mu}\Big)^2$ we have $w_{RH}(a) > 0$, for all a;
for $d_1 > (\mu+1)\Big(1+\sqrt{\mu}\Big)^2$ inequality $w_{RH}(a) > 0$ holds for small and large a.

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The case $m = 2$, $\tau_m = 0$

The situation is more complex. The characteristic function is a polynomial of degree 4

$$(a + \lambda)^2(\lambda^2 + (\mu + 1)\lambda + \mu) + a^2 d_1.$$

The Rout-Hurwitz criterion implies a condition

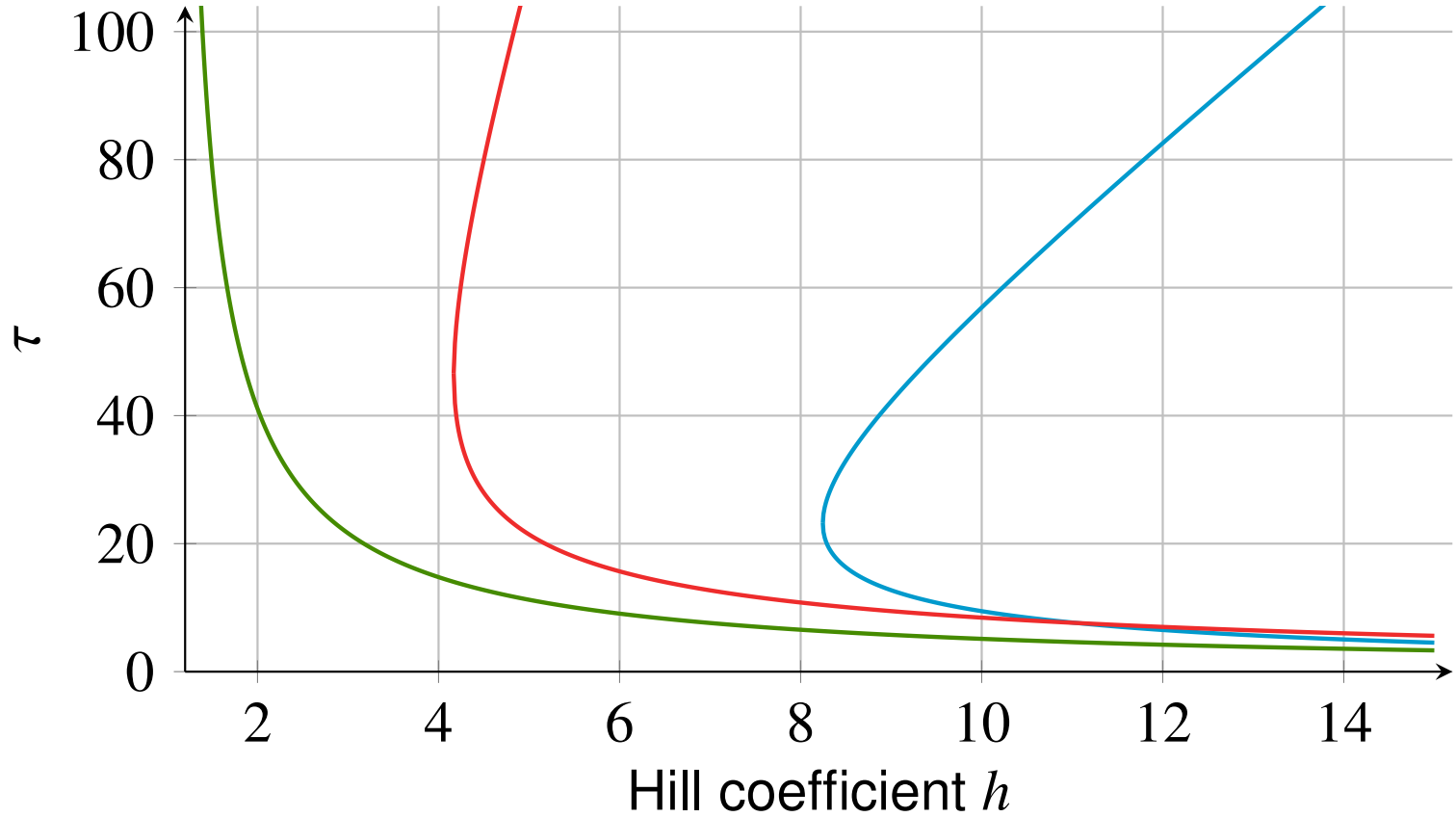
$$a^4 + 2\left(\mu + 1 - \frac{d_1}{\mu + 1}\right)a^3 + \left(\mu(\mu+4) + 1 - 2d_1\right)a^2 + \frac{(\mu + 1)(4\mu - d_1)}{2}\, a + \mu^2 > 0$$

Observations

- $\mu < d_1 < 2\mu$ the steady state is stable for all $\tau = 2/a$;
- if d_1 is large the steady state is stable only for small and large τ;

Numerical results

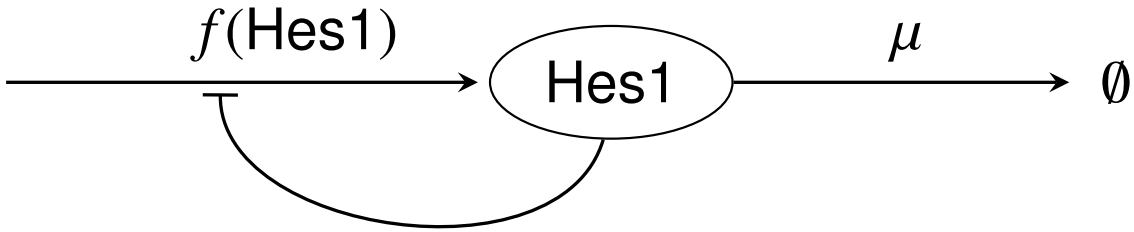
Parameters as in N.A. Monk, *Curr. Biol.*, **13**: 1409–1413, (2003)



- Green line — critical τ for the discrete delay;
- Blue line — critical τ for the Erlang distribution, $m = 1$;
- Red line — critical τ for the Erlang distribution, $m = 2$;

Model simplification

Why do we need to consider mRNA? Consider only the protein concentration.



Simplified model

$$\dot{x} = f\Big(x(t-\tau)\Big) - \mu x(t),$$

where

- $x(t)$ — protein concentration;
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- μ — intensity of protein degradation;
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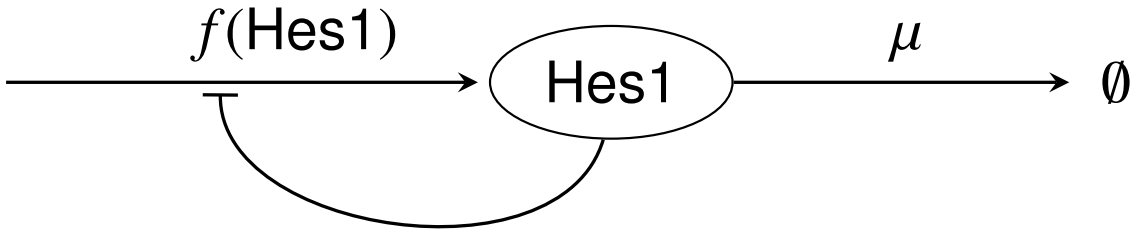

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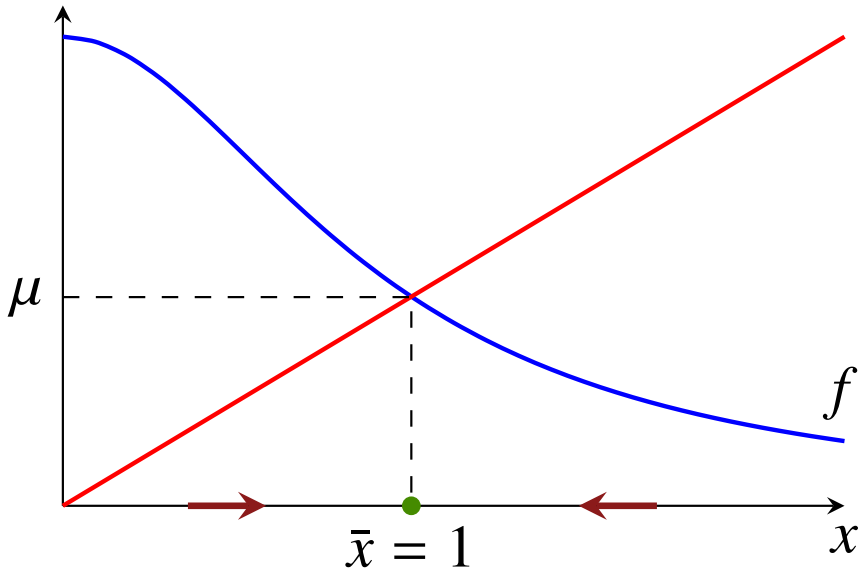
Properties of the simplified model

The case without delay



Steady state $\bar{x} = 1$ is globally stable.

The case with delay

Linearisation around $\bar{x} = 1$ gives

$$\dot{x}(t) \approx -\mu x(t) - \left|f'(1)\right| x(t-\tau).$$

Standard theory of delay differential equation

$$\Downarrow$$

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Conclusion

There is no large difference in models behaviours.

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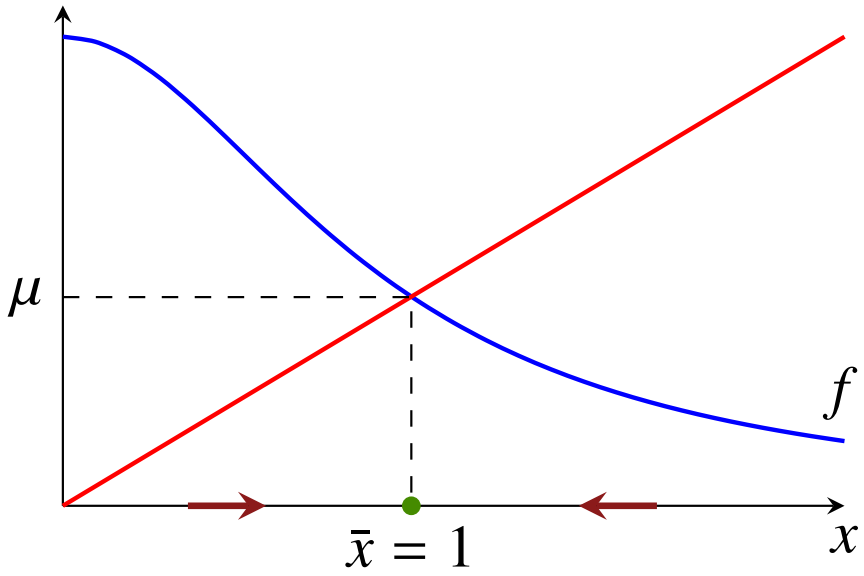

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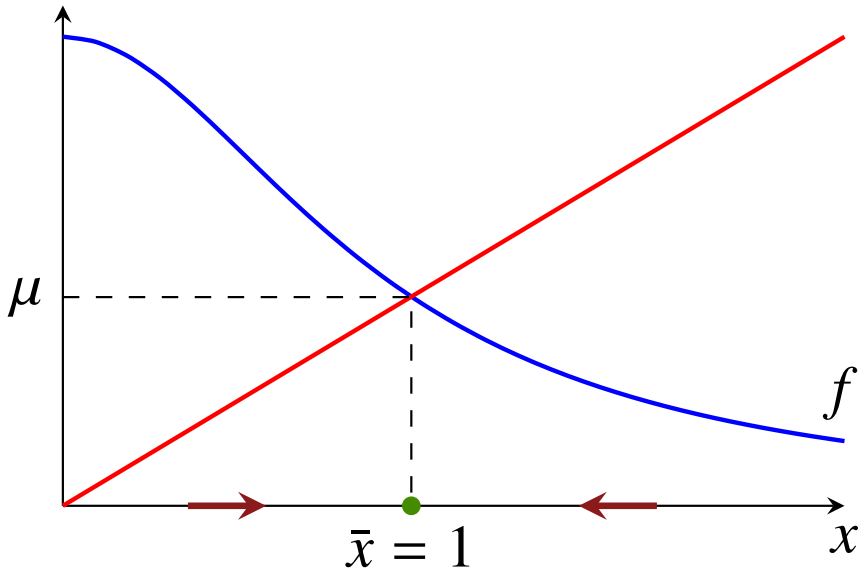

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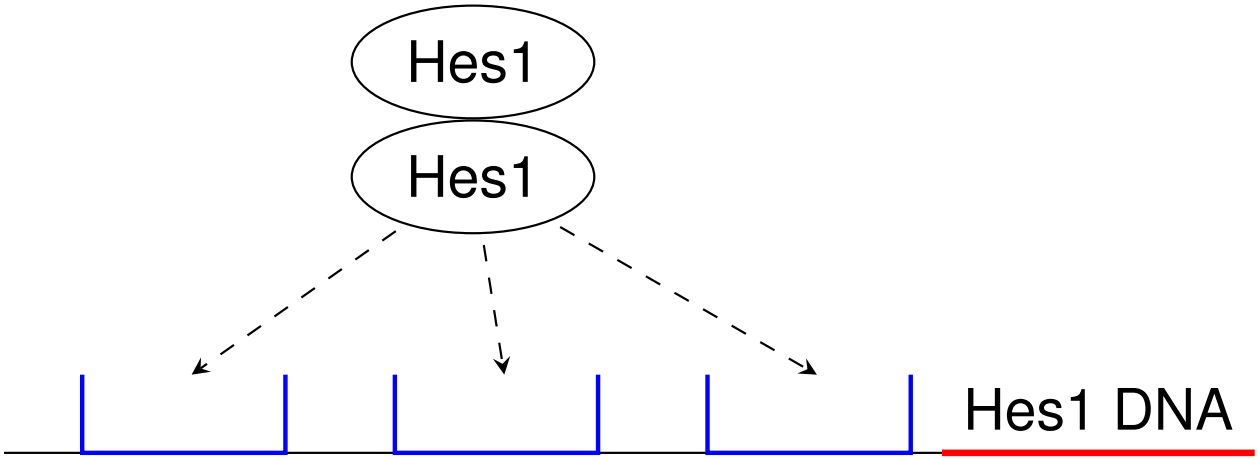
More complex models — assumptions

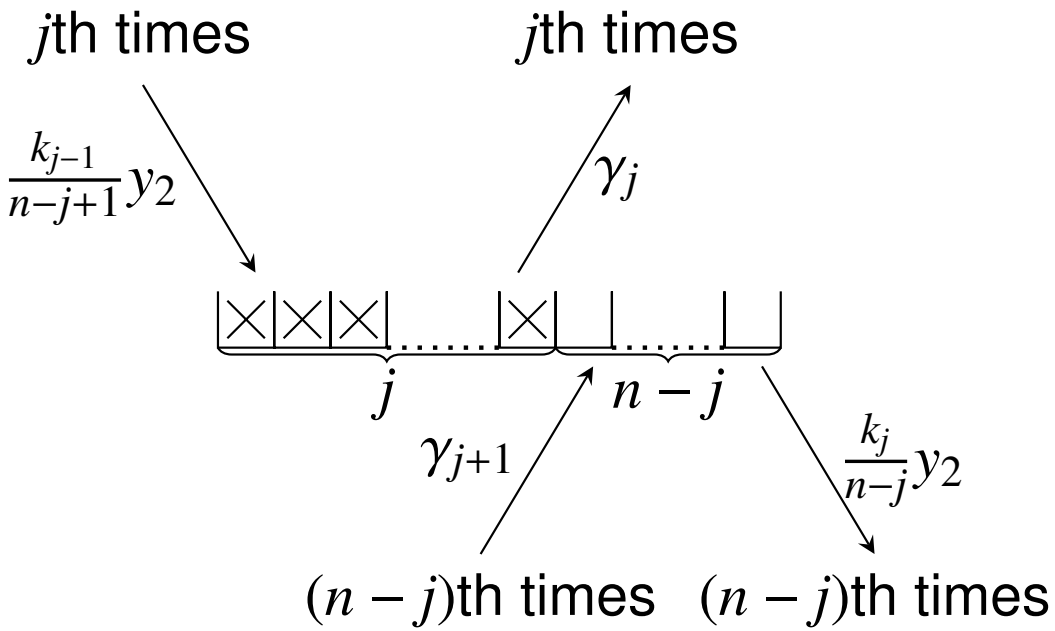


1. Two proteins need bound one to other creating dimer.
2. Hes1 promoter has at least three bounding sites.
3. Dimer bounded to the promoter blocks transcriptions.

The reaction scheme

The change of the probability is due to one of the following actions:

- the Hes1 dimer may bound to one of $n - j$ free sites, to each with probability $\frac{k_j}{n-j} y_2$;
- one of j bounded dimers may dissolve, each with intensity γ_j.



Equations part I (for free/occupied sites)

Equations for probabilities that DNA has $0, 1, \ldots n$ binding sites occupied have the following form

$$
\begin{aligned}
x_0' &= \gamma_1 x_1 - k_0 y_2 x_0, \\
x_j' &= k_{j-1} x_{j-1} y_2 + (j+1)\gamma_{j+1} x_{j+1} - (k_j y_2 + j\gamma_j) x_j, \quad 1 \le j \le n-1, \\
x_n' &= k_{n-1} y_2 x_{n-1} - n\gamma_n x_n,
\end{aligned}
$$

- x_0 – probability that all binding sites is free,
- x_j – probability that jth of binding sites are occupied,
- x_n – probability that all binding sites are occupied,
- y_2 – concentration of Hes1 dimers.

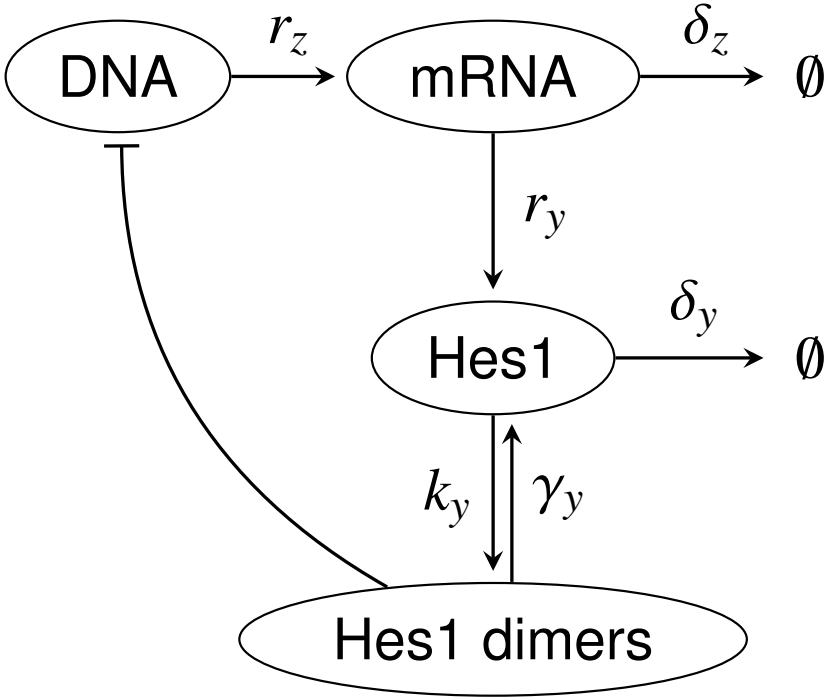
Moreover, $x_0 + x_1 + \ldots + x_n = 1$.

Equations part II (for mRNA, protein and dimers)

$$y_1' = 2\gamma_y y_2 - 2k_y\, y_1^2 + r_y z - \delta_y\, y_1,$$

$$y_2' = -\sum_{j=0}^{n-1} k_j x_j y_2 + \sum_{j=1}^{n} j\gamma_j\, x_j - \gamma_y y_2 + k_y\, y_1^2,$$

$$z' = r_z x_0 - \delta_z\, z,$$



- γ_y – intensity of dissolving a Hes1 dimers
- k_y – intensity of a formation of Hes1 dimers

Reduction

- The full model is complex enough (even without delay) to investigate first simpler system.
- We assume that dynamic of binding to/dissolving from DNA promoter is much faster.
- We use quasi-stationary approximation (Tikhonov theorem).

After some algebra we get, for a fixed y_2

$$x_0 = f(y_2),$$
$$x_j = \frac{1}{j!}\frac{k_0 \dots k_{j-1}}{\gamma_1 \dots \gamma_j} y_2^j f(y_2), \quad 1 \le j \le n,$$

where

$$f(y_2) = \frac{1}{1 + \sum_{j=1}^{n} \frac{1}{j!}\frac{k_0 \dots k_{j-1}}{\gamma_1 \dots \gamma_j} y_2^j}.$$

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Model with dimers

$$
\begin{aligned}
y_1' &= 2\gamma_y y_2 - 2k_y\, y_1^2 + r_y z - \delta_y\, y_1,\\
y_2' &= -\gamma_y y_2 + k_y\, y_1^2,\\
z' &= r_z f(y_2) - \delta_z\, z,
\end{aligned}
\qquad
f(y_2) = \frac{1}{1 + \sum_{j=1}^{n} \frac{1}{j!} \frac{k_0 \ldots k_{j-1}}{\gamma_1 \ldots \gamma_j} y_2^j}.
$$

where

- y_1 – concentration of the Hes1 protein,
- y_2 – concentration of Hes1 dimers,
- z – concentration of hes1 mRNA,
- γ_y – intensity of dissolving a Hes1 dimer,
- k_y – intensity of a formation of Hes1 dimers,
- r_y i r_z – production rates of Hes1 and its mRNA, respectively,
- δ_y i δ_z degradation rates of Hes1 and its mRNA, respectively.

Stability of the steady state

Theorem

If

$$\left|f'(\bar{y}_2)\right| < \frac{\left(4k_y\bar{y}_1 + \delta_y + \gamma_y\right)\left((4k_y\bar{y}_1 + \delta_y + \delta_z)\delta_z + (\delta_y + \delta_z)\gamma_y\right)}{2k_y r_y r_z \bar{y}_1}$$

then the positive steady state of the system with dimers is locally asymptotically stable.

Theorem

If the function f *is given by* $f(y_2) = \dfrac{1}{1 + a_1 y_2 + \cdots + a_n y_2^n}$ *then*

1. *for* $n \leq 4$ *the steady state is locally asymptotically stable,*
2. *for* $n \geq 5$ *there exists set of parameters as well as the function* f *such that the steady state is unstable.*

Model with dimers and time delay

Time delay in transcription

$$
\begin{aligned}
y_1'(t) &= 2\gamma_y y_2 - 2k_y\, y_1^2(t) + r_y z(t) - \delta_y\, y_1(t),\\
y_2'(t) &= -\gamma_y y_2(t) + k_y\, y_1^2(t),\\
z'(t) &= r_z f\big(y_2(t-\tau)\big) - \delta_z\, z(t),
\end{aligned}
$$

If the steady state is stable for $\tau = 0$

$$
\left|f'(\bar{y}_2)\right| < \frac{\Big(4k_y\bar{y}_1 + \delta_y + \gamma_y\Big)\Big((4k_y\bar{y}_1 + \delta_y + \delta_z)\delta_z + (\delta_y + \delta_z)\gamma_y\Big)}{2k_y r_y r_z \bar{y}_1}
$$

then

- if $\left|f'(\bar{y}_2)\right| < \dfrac{\gamma_y\delta_y\delta_z}{2k_y r_y r_z \bar{y}_1}$ then it is stable for all $\tau \geq 0$.
- if $\left|f'(\bar{y}_2)\right| > \dfrac{\gamma_y\delta_y\delta_z}{2k_y r_y r_z \bar{y}_1}$ then it is stable for all $0 \leq \tau \leq \tau_{\mathrm{cr}}$ and it is unstable for larger τ. At τ_{cr} the Hopf bifurcation occurs.

Summary and conclusions

Are oscillation possible?

model	without delay	discrete delay	distributed delay
only protein	no	no	no
classical	no	Yes, $h > 1 + \varepsilon$	Yes, $h > 1 + \varepsilon$
with dimers	Yes, $h \geq 5$	Yes	?Yes,?
full model	probably yes	probably yes	probably yes

Conclusions

- We compared different “levels” of the same model of gene expression with a negative feedback loop.
- In the simplest model oscillation are impossible, even after introducing time delay.
- Taking into account more details of the process, oscillation are possible for the model without time delay.

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Thank you for your attention!
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