Global stability of the steady state of a cascade of biochemical reactions with time delay

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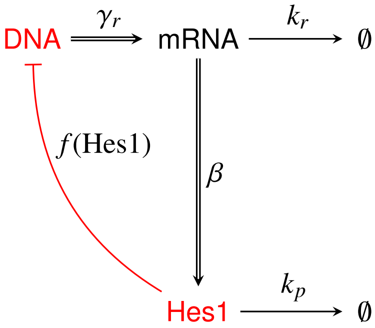
The model of Hes1 gene expression

- Protein Hes1 bounds to its own DNA blocking transcription.
- Intensity if mRNA production depends on the protein concentration — more Hes1 protein, the grater probability DNA to be blocked, thus intensity is decreasing (a negative feedback loop).
- We describe only concentrations of mRNA and protein.



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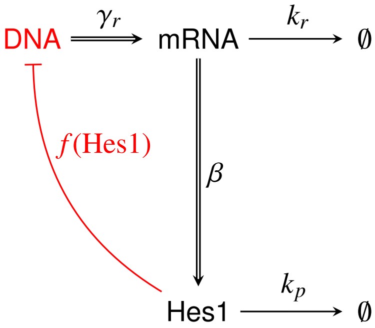

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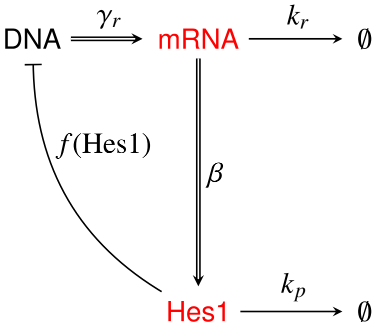

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The model of Hes1 gene expression

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

$$\dot{r}(t) = \tilde{f}(p(t-\tau_r)) - k_r r(t),$$
$$\dot{p}(t) = \beta r(t-\tau_p) - k_p p(t),$$

- $r(t)$ — mRNA concentration;
- $p(t)$ — Hes1 concentration;
- $\tilde{f}$ — decreasing function describing the influence of DNA blocking on mRNA production;
- k_r i k_p — intensities of mRNA and protein degradation;
- β — intensity of protein production (translation);
- τ_r i τ_p — times of transitions and translations;

What is known about model properties

- Non-negative solutions globally exists;
- There exist a unique positive steady stable;
- There exists an invariant compact set;
- The (local) stability of the steady state
  - (i) If $k_p k_r > |f'(1)|$, then stability for all $\tau_p, \tau_r \geq 0$.
  - (ii) If $k_p k_r < |f'(1)|$, then stability for $\tau_p + \tau_r < \tau_{\text{cr}}$, and instability for $\tau_p + \tau_r > \tau_{\text{cr}}$. At τ_{cr} the Hopf bifurcation occurs.

$$\tau_{\text{cr}} = \frac{\arccos\left(\frac{k_p k_r - \omega_0^2}{f'(1)}\right)}{\omega_0}, \omega_0 = \sqrt{\frac{1}{2}\left(-(k_p^2 + k_r^2) + \sqrt{(k_p^2 - k_r^2)^2 + 4(f'(1))^2}\right)}.$$

- 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)

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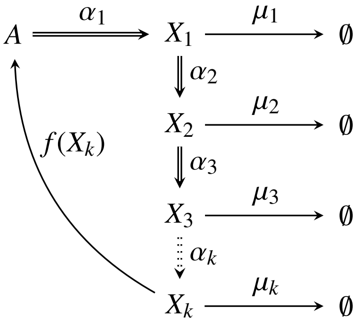
Generalisation of the model — a cascade of reactions



- α_j — production rates;
- μ_j — degradation rates;
- $\tau_j \geq 0$;
- θ_1 — a probability distribution on $[-\tau_1, 0]$;
- f_1 is a non-increasing continuous function;

The model

$$\dot{x}_1(t) = \int_{-\tau_1}^{0} \theta_1(s) f_1(x_n(t+s)) \mathrm{d}s - \mu_1 x_1(t),$$

$$\dot{x}_j(t) = \alpha_j x_{j-1}(t - \tau_j) - \mu_j x_j(t), \quad j = 2, 3, \ldots, n.$$

Global stability — the method

E. Liz, A. Ruiz-Herrera, *J. Diff. Eqs.*, **255**, 4244–4266, (2013).

Strong attractor

Let $H\colon D \to D$ be continuous on $D = (a_1, b_1) \times (a_2, b_2) \times \cdots \times (a_k, b_k)$. A point $y^* \in D$ of a discrete dynamical system

$$y(n+1) = H(y(n)), \quad n = 1, 2, 3, \ldots,$$

is called strong attractor in D if for any compact $K \subset D$ there exists a family of sets $\{I_m\}$, $m \in \mathbb{N}$, where I_m is the product of k nonempty compact intervals such that

(B1) $K \subset \mathrm{Int}(I_1) \subset D$,

(B2) $H(I_m) \subset I_{m+1} \subset \mathrm{Int}(I_m)$ for $m \in \mathbb{N}$,

(B3) $y^* \in \mathrm{Int}(I_m)$ for all $m \in \mathbb{N}$, and $\bigcap_{m=1}^{\infty} I_m = \{y^*\}$.

Global stability — the method

Theorem (Liz, Ruiz-Herrera)

If y^* is a strong attractor for

$$y(n+1) = F(y(n)), \quad y(n) \in \mathbb{R}^k, \quad F = (F_1, \ldots, F_k),$$

in D, then y^* is global asymptotically stable for

$$\dot{x}_j(t) = -x_j(t) + F_j(x_1(t-\tau_{1j}), \ldots, x_m(t-\tau_{mj})), \quad j = 1, \ldots, k,$$

and $\tau_{ij} \geq 0$.

Remark

The above theorem works also for $\dot{x}_j = -g_j(x_j(t)) + F_j$, and the for the discrete system with the right-hand side

$$F = (g_1^{-1}(F_1), \ldots, g_k^{-1}(F_k)).$$

Why we connect delay equation with discrete one?

A simple example:

$$\dot{y}(t) = -y(t) + g\big(t, y(t), y(t-\tau)\big)$$

Rescale time $s = \dfrac{t}{\tau}$. We have than

$$\frac{1}{\tau}\dot{y}(s) + y(s) = g\big(t, y(s), y(s-1)\big).$$

Now let $\tau \to +\infty$

$$y(s) = g\big(t, y(s), y(s-1)\big).$$

Rough conclusion

Looking for the behaviour of the discrete system means looking for the behaviour of delay equation for very large delays.

The result

Equations

$$\dot{x}_1(t) = \int_{-\tau_1}^{0} \theta_1(s) f_1(x_k(t+s))\mathrm{d}s - \mu_1 x_1(t),$$

$$\dot{x}_j(t) = \alpha_j x_{j-1}(t-\tau_j) - \mu_j x_j(t), \quad j = 2, 3, \ldots, k.$$

Theorem

- θ_1 *a probability measure;*
- f_1 *Lipschitz continuous;*
- y^* *is a unique positive steady state* $(f_1(y_k^*) = \mu_1 y_1^*)$*;*
- $|f_1(x) - f(y_k^*)| < \alpha_1 |x - y_1^*|$ *for all* $x > 0$, $x \neq y_1^*$.

If $\alpha_1\alpha_2 \cdots \alpha_k \leq \mu_1\mu_2 \cdots \mu_k$, *then the steady state* y^* *is globally asymptotically stable, that is for any positive initial function* $\phi = (\phi_1, \ldots, \phi_k) \in C(\mathbb{R}^k)$ *the solution converges to* y^* *as* $t \to +\infty$.

Remarks and generalisations

Remarks

- There exists a unique positive steady state of the system;
$$f(y_n^*) = \frac{\mu_1\mu_2\cdots\mu_k}{\alpha_2\cdots\alpha_k} y_n^*$$
- If initial function are positive, solution remains positive;
- Solutions are global (exists for all $t \geq 0$);

Generalisations

- We can consider nonlinear, nondecreasing production terms f_j in equation for x_j, $j = 2, \ldots, k$ instead of linear, fulfilling
$$|f_j(x) - f_j(y_{j-1}^*)| \leq \alpha_j |x - x_j^*|;$$
- Functions f_j may depend on time, but then we need to assure the existence of the steady state;

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An idea of the proof

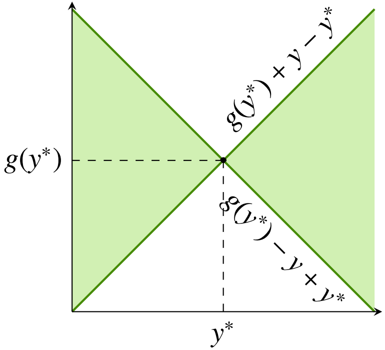
A corresponding discrete system reads

$$y_1(n+1) = \frac{1}{\mu_1} f(y_k(n)), \qquad y_j(n+1) = \frac{\alpha_j}{\mu_j} y_{j-1}(n), \quad j = 2, 3, \ldots, k.$$

We may think about the above system as for

$$y_1(n+k) = \frac{1}{\mu_1} f\left(\frac{\alpha_2 \cdots \alpha_k}{\mu_2 \cdots \alpha_k} y_1(n)\right) = g(y_1(n))$$

We need to have y^* to be a stable steady state... more: to be a little strong attractor



Strong attractor — how to construct the family $\{I_m\}$

- Move the steady state to 0;
- Assume first $\alpha_1\alpha_2\cdots\alpha_k < \mu_1\mu_2\cdots\mu_k$;
- Consider a linear discrete system

$$y_j(n+1) = \frac{\alpha_j}{\mu_j} y_{j-1}(n), \quad j = 1, 2, \ldots, k, \quad j \bmod k;$$

  We write shortly $y(n+1) = H(y(n))$.
- Choose

$$I_1 = [-q_1 a, q_1 a] \times [-q_2 a, q_2 a] \times \cdots \times [a, a]$$

  with q_j such that $H(I_1) \subset I_1$.
- Induction $\Longrightarrow I_{m+1} = H(I_m)$.
- Because $|f_1(x)| < \alpha|x|$ we have $F(I_m) \subset H(I_m)$.
- For $\alpha_1\alpha_2\cdots\alpha_k = \mu_1\mu_2\cdots\mu_k$ we need modify the above construction a little using the strict inequality on f_1;

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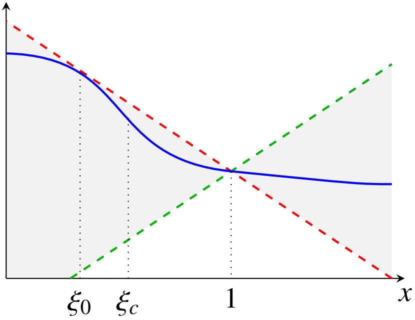
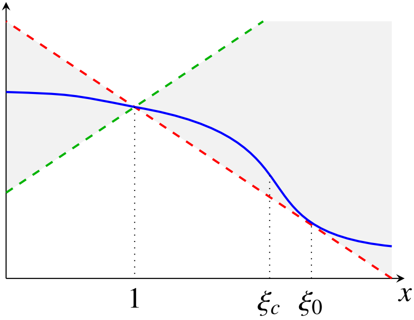
The best estimation on the function f_1

Assumption: f_1 has at most one inflection point (eg. Hill functions).

- a proper scaling $y_1^* \to 1$;
- ξ_c the inflection point of f_1;
- red line has slope $-\alpha_1$;
- green line has slope α_1;





Global stability vs local stability

Local stability for discrete delays

- $|f_1'(1)|\alpha_2 \cdots \alpha_k < \mu_1 \cdots \mu_k \implies$ stable independently on time delay (also for distributed delay);
- $|f_1'(1)|\alpha_2 \cdots \alpha_k > \mu_1 \cdots \mu_k$ and $f'(1) < 0 \implies$ stable for small $\tau_1 + \cdots \tau_k$ and unstable for large. The Hopf bifurcation occurs;
- $|f_1'(1)|\alpha_2 \cdots \alpha_k > \mu_1 \cdots \mu_k$ and $f'(1) > 0 \implies$ unstable;

Global stability

- Condition: $\alpha_1\alpha_2 \cdots \alpha_k \le \mu_1 \cdots \mu_k$, with $\alpha_1 \ge |f_1'(1)|$;
- If f_1 has an inflection point at $y_1^* = 1$, then $\alpha_1 = |f_1'(1)|$;
- If inflection point is different from 1, $\alpha_1 > |f_1'(1)|$;
- The method obviously does not work if stability depends on time delay.

Application to a classic Hes1 model

- f_1 is a Hill function;
- discrete delay;

$$\dot r(t) = \frac{\alpha k^h}{k^h + (p(t-\tau_r))^h} - k_r r(t)\,,$$
$$\dot p(t) = \beta r(t-\tau_p) - k_p p(t)\,,$$

The result

Let $\bar b$ be a unique positive solution to $\dfrac{(b^h+1)h(\xi_0(b))^{h-1}}{b^h + (\xi_0(b))^h} = 1$,

where $\xi_0(b)$ is a positive solution to

$$\xi^{2h} + \xi^h\Big(b^h - 1 - h(b^h+1)\Big) + \xi^{h-1}h(b^h+1) - b^h = 0,$$

such that $\xi_0(b) \neq 1$ unless 1 is a triple root. Then

$$\frac{\bar b^{h+1}}{\bar b^h + 1} < \frac{k\,k_p k_r}{\alpha\beta}, \implies \text{global stability.}$$

Global stability of the steady state

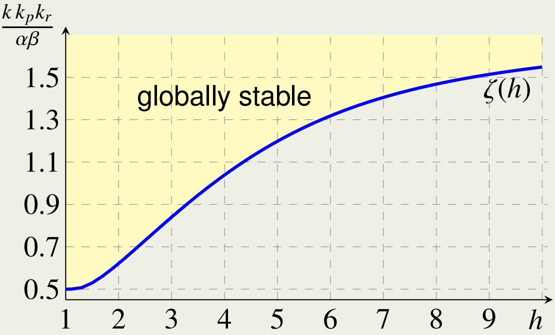
The case $h = 2$

$$\frac{k\,k_p k_r}{\alpha\beta} \geq \frac{5\sqrt{5}}{18} \approx 0.6211,$$

The case $h \to 1$

$$\frac{k\,k_p k_r}{\alpha\beta} \geq \zeta(h) \to \frac{1}{2}$$

Dependence on Hill coefficient



Conclusions

- We presented a generalisation of Hes1 gene expression model;
- We proved condition guaranteeing global stability of the positive steady state;
- The general result was applied to the classical Hes1 model;

More details:

M.B., General model of a cascade of reactions with time delays: Global stability analysis
J. Diff. Eqs, **259**: 777–795, (2015), doi: 10.1016/j.jde.2015.02.024.

Thank you for your attention!

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