# Time Delay Models in Biological Systems

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# Outline

- Time delay models in some biological systems and their analyses using robust control techniques (linear and nonlinear):
  - Neuromusculo-skeletal system
  - Gene regulatory networks
- Conclusions

# Part I
# Neuromusculo-skeletal system
# (joint work with H. Hemami)

# Neuromusculo-skeletal system

Barbara H. Connolly, “Aging in Individuals with Lifelong Disabilities”, *Physical & Occupational Therapy in Pediatrics*, Vol. 21(4) 2001.

Adequate balance during stance and gait is the result of three major factors:

1. Appropriate processing of input from the visual, vestibular, and somatosensory (primarily proprioceptive) systems that allow a person to acquire information about the body in space.
2. Central processing or the ability for the body to determine in advance, the correct appropriate sequence of responses.
3. Lastly, the body must be able to carry out the appropriate response via the effector system (strength, range of motion, flexibility, and endurance).

Central processing has been shown to be affected in older adults. Investigators have found that response times have been increased in older 79-81 adults by approximately 20 to 30 ms. This delay in response seems to contribute to instability during stance and ambulation in older persons who fall.

*Journal of Motor Behavior*, 1993, Vol. 25, No. 3, 203-216

# Is the Cerebellum a Smith Predictor?

**R. C. Miall**
**D. J. Weir**
**D. M. Wolpert**
**J. F. Stein**
Oxford University
University Laboratory of Physiology

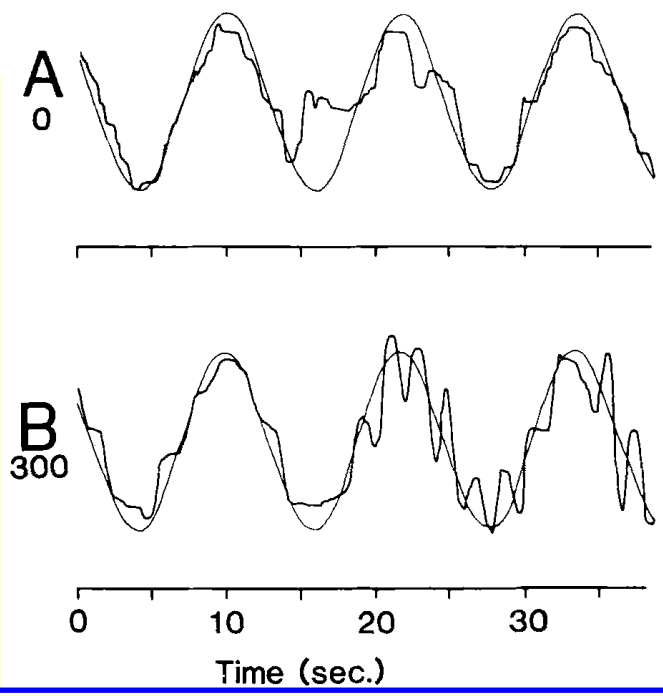
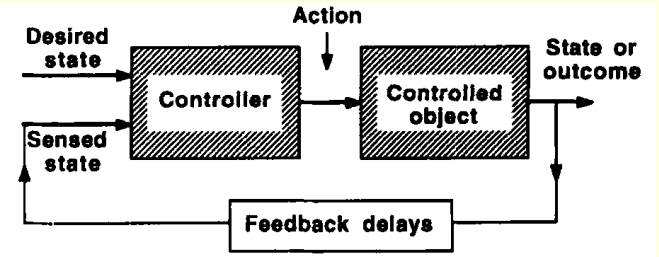
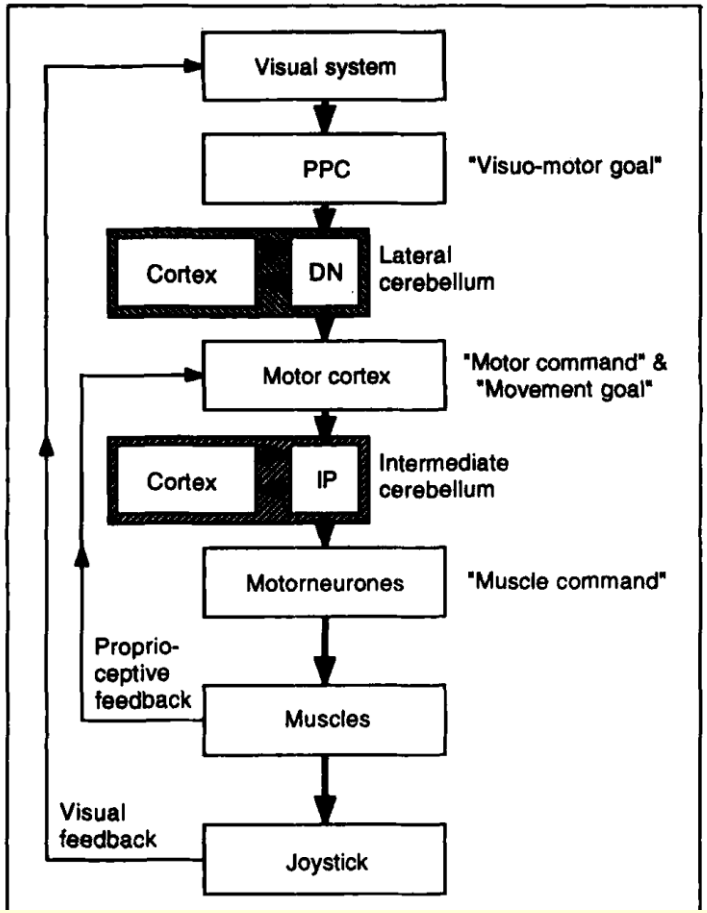
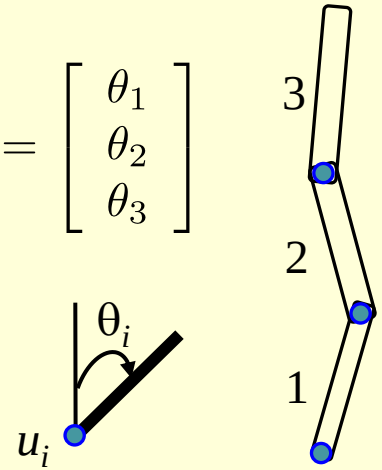



**FIGURE 5.** Tracking responses of primates. Each graph shows the position of a joystick (thick line) held by a monkey trained to follow a target (thin line) displayed on a computer screen. A. Normal responses. B. Responses when the cursor providing visual feedback was delayed by 300 ms. On the left is a period of slow, intermittent tracking; on the right, the monkey has slipped into instability. (Modified from Miall et al., 1986.)



$$\theta = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \end{bmatrix}$$




$$\mathscr{I}(\theta)\ddot{\theta} + \mathscr{B}(\theta,\dot{\theta})\dot{\theta} + g\mathscr{G}(\theta) = EU_0$$

$$\mathscr{I}(\theta) = \begin{bmatrix} I_1 + m_1k_1^2 + (m_2+m_3)\ell_1^2 & (m_2k_2+m_3\ell_2)\ell_1\cos(\theta_2-\theta_1) & m_3k_3\ell_1\cos(\theta_3-\theta_1) \\ (m_2k_2+m_3\ell_2)\ell_1\cos(\theta_2-\theta_1) & I_2 + m_2k_2^2 + m_3\ell_2^2 & m_3k_3\ell_2\cos(\theta_3-\theta_2) \\ m_3k_3\ell_1\cos(\theta_3-\theta_1) & m_3k_3\ell_2\cos(\theta_3-\theta_2) & I_3 + m_3k_3^2 \end{bmatrix}$$

$$\mathscr{B}(\theta,\dot{\theta}) = \begin{bmatrix} 0 & (m_2k_2+m_3\ell_2)\ell_1\dot{\theta}_2\sin(\theta_1-\theta_2) & m_3k_3\ell_1\dot{\theta}_3\sin(\theta_1-\theta_3) \\ (m_2k_2+m_3\ell_2)\ell_1\dot{\theta}_1\sin(\theta_2-\theta_1) & 0 & m_3k_3\ell_2\dot{\theta}_3\sin(\theta_2-\theta_3) \\ m_3k_3\ell_1\dot{\theta}_1\sin(\theta_3-\theta_1) & m_3k_3\ell_2\dot{\theta}_2\sin(\theta_3-\theta_2) & 0 \end{bmatrix}$$

$$\mathscr{G}(\theta) = \begin{bmatrix} -(m_1+m_2\ell_1+m_3\ell_1)\sin(\theta_1) \\ -(m_2k_2+m_3\ell_2)\sin(\theta_2) \\ -m_3k_3\sin(\theta_3) \end{bmatrix} \qquad E = \begin{bmatrix} 1 & -1 & 0 \\ 0 & 1 & -1 \\ 0 & 0 & 1 \end{bmatrix}$$

Equilibrium: $\theta_0 = 0,\ \dot{\theta}_0 = 0$ (stance)

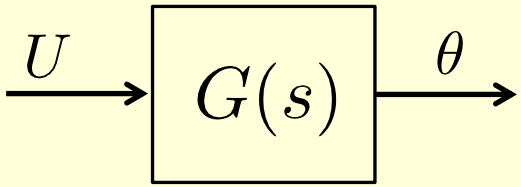
Linearization around the equilibrium:

$$J_o := \mathscr{I}(\theta_0) \qquad K = g\frac{\partial \mathscr{G}}{\partial \theta}(\theta_0)$$

Stabilizer for stance:

$$U_0 = E^{-1}\left(U - L_o\,\dot{\theta} - (K_o - K)\,\theta\right)$$

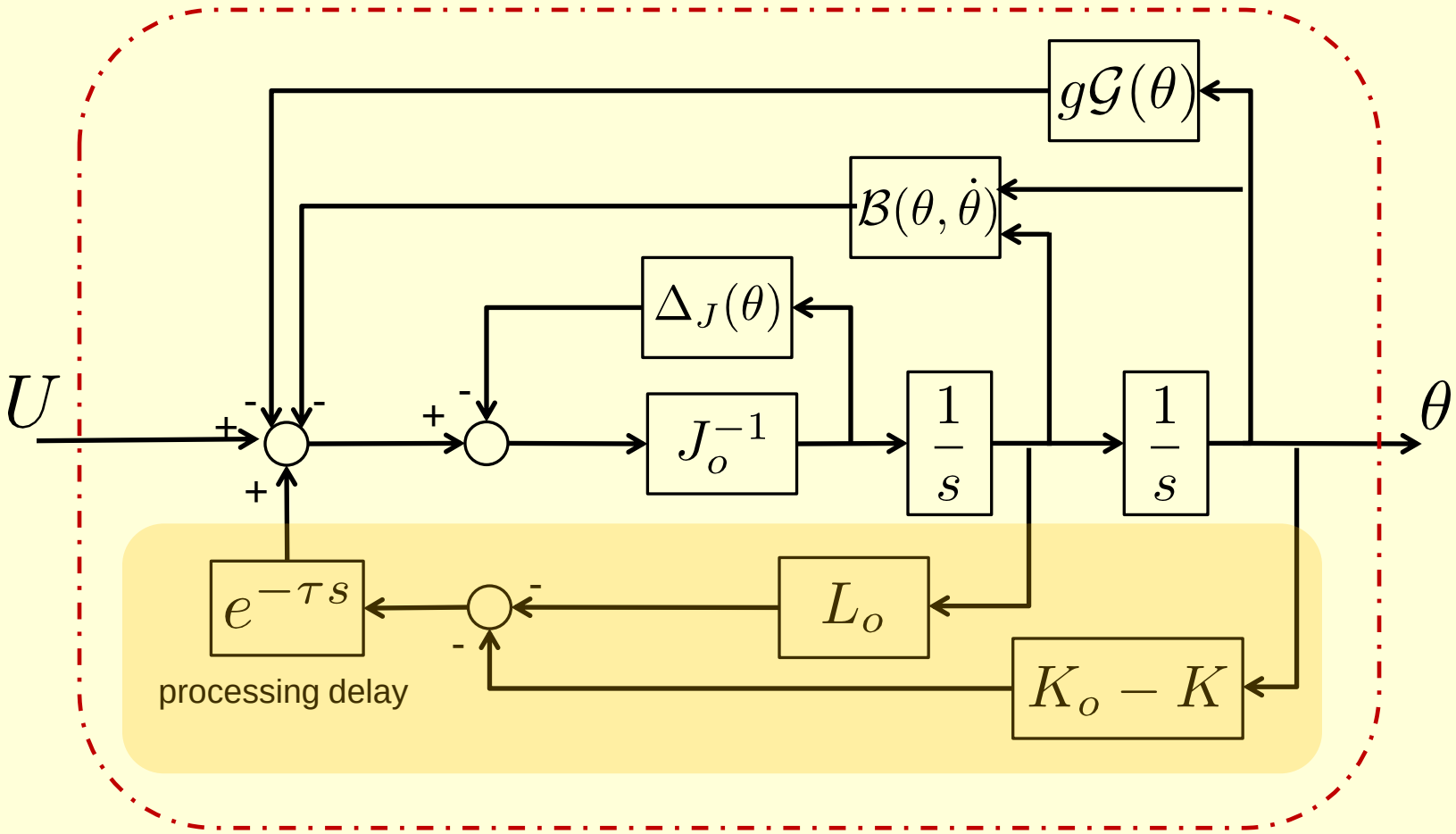
$K_o,\ L_o$ are feedback gains



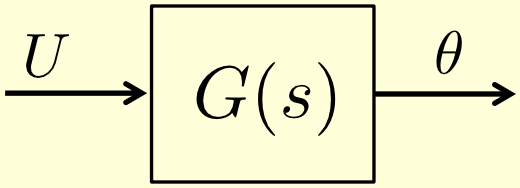

$$G(s) = (J_o s^2 + L_o s + K_o)^{-1}$$

3x3 stable transfer matrix;
minimum phase with relative degree=2

## Simulation block diagram for stance $J(\theta) = J_o + \Delta_J(\theta)$



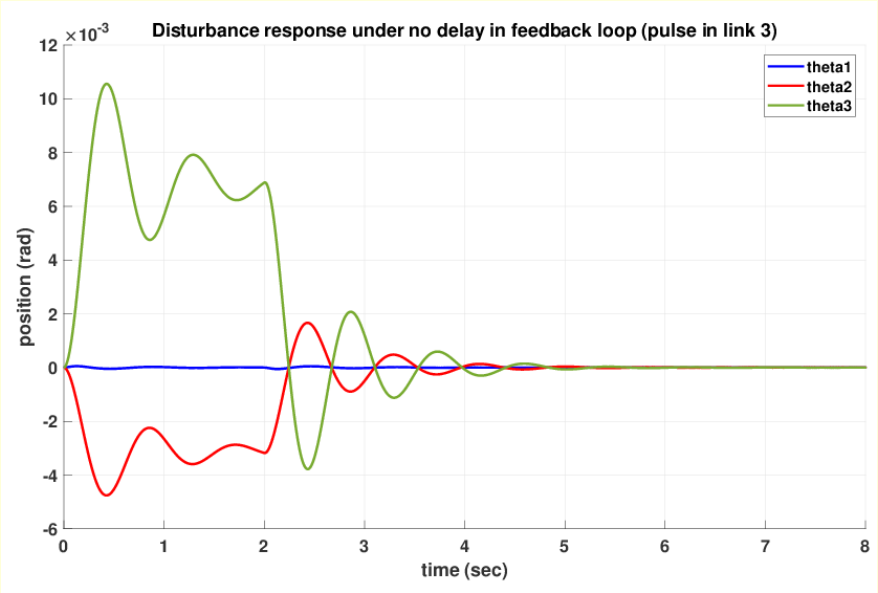

Linearized model:
for $\tau = 0$



Numerical Example:

$$I_1 = 0.17 \quad I_2 = 0.5 \quad I_3 = 2.1 \quad g = 9.81$$
$$m_1 = 5.05 \quad m_2 = 18.67 \quad m_3 = 41.87$$
$$\ell_1 = 0.401 \quad \ell_2 = 0.412 \quad \ell_3 = 0.619$$
$$k_1 = 0.21 \quad k_2 = 0.26 \quad k_3 = 0.24$$

Disturbance responses of the stabilized system for stance (nonlinear model)



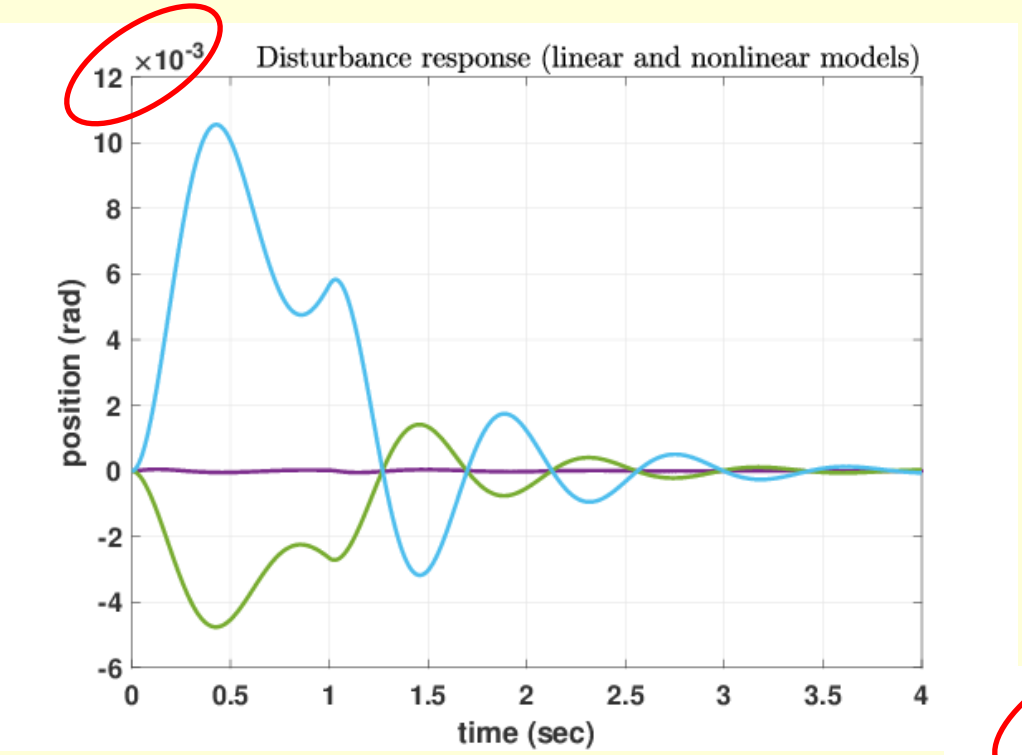

$\tau = 0$

$\tau = 0.025$

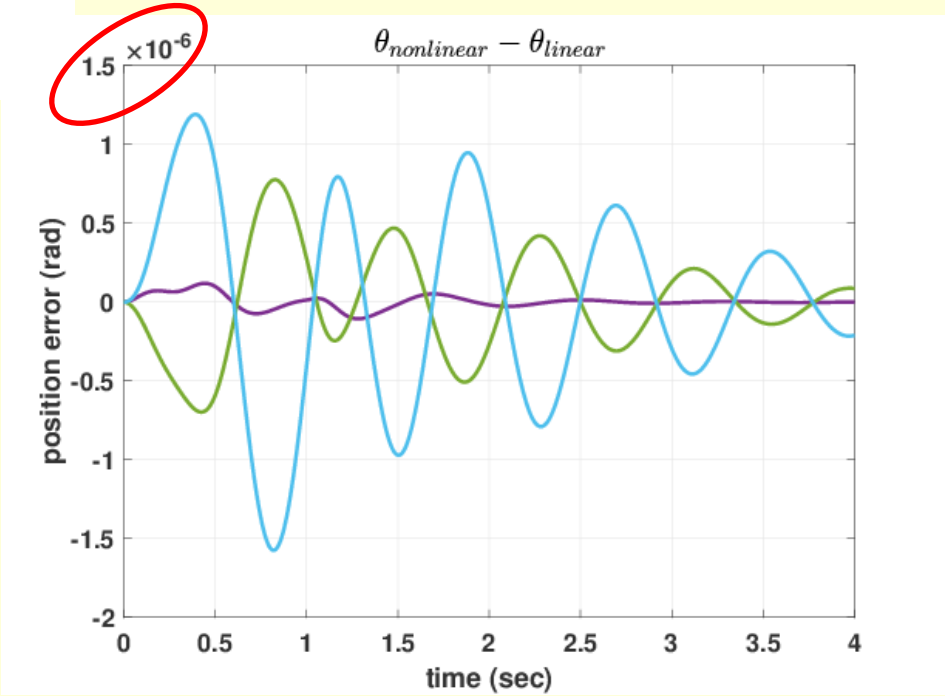
Stabilizer for stance with delay in the loop:

$$U_0 = E^{-1}\left(U - L_o\,\dot{\theta}(t-\tau) - (K_o - K)\,\theta(t-\tau)\right)$$

# Nonlinear versus Linear Model

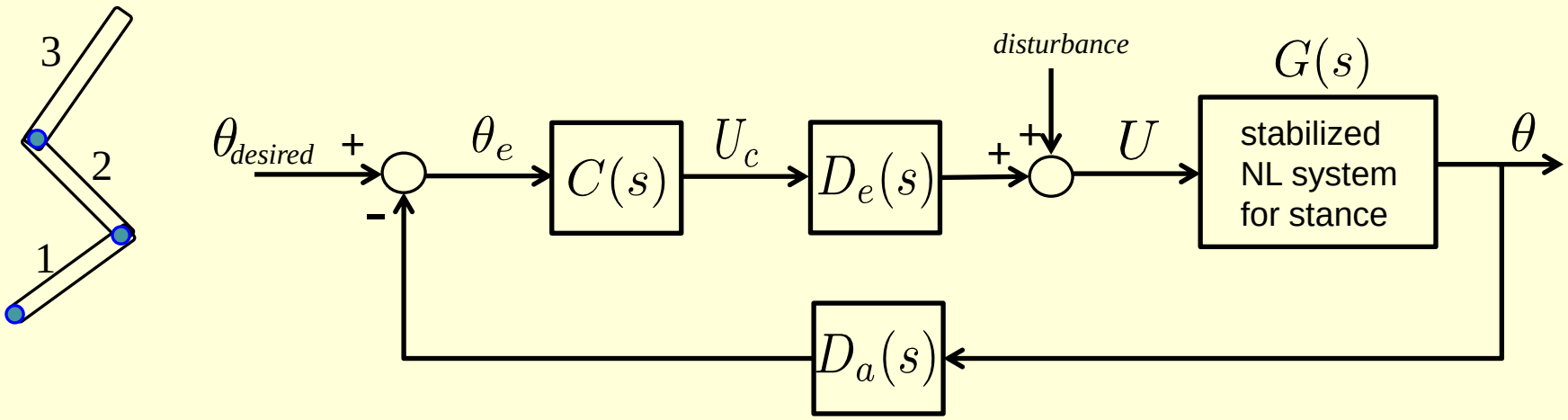



relative error is in the order of $10^{-3}$

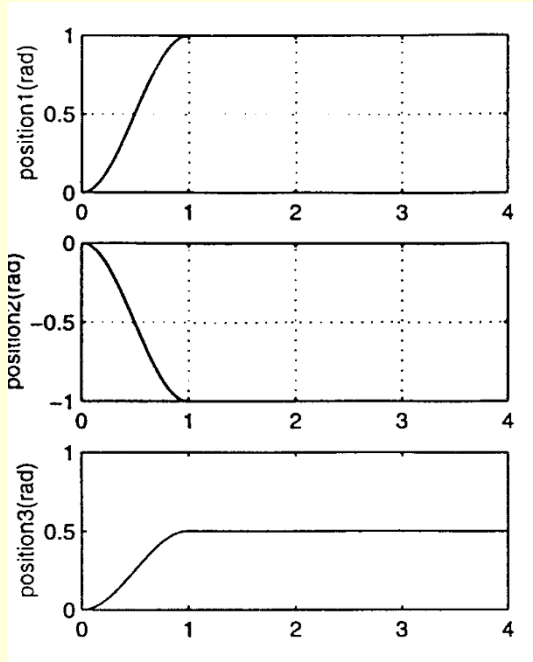



$$\tau = 0$$

# Feedback mechanism for squatting maneuver




$\theta_{desired}$




$C(s)$ Controller (CNS)

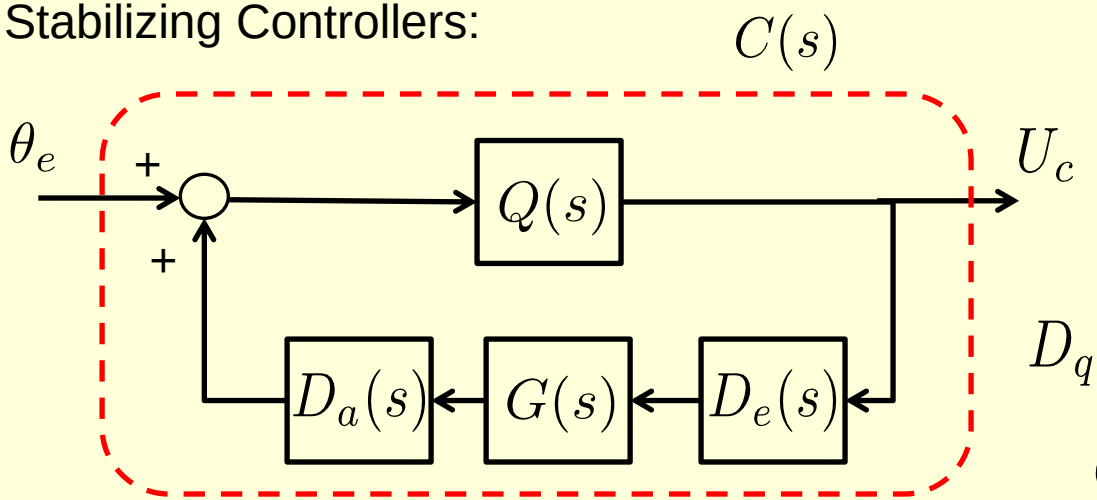
$D_e(s)$, $D_a(s)$ efferent and afferent delays (diagonal blocks)

$T(s)$ closed loop map from $\theta_{desired}$ to $\theta$

assuming nonlinear system is linearized

Desired form of the closed loop map: $T(s) = G_d(s)D_d(s)$

Stabilizing Controllers:




$$\underbrace{\begin{aligned} Q(s) &= D_q(s)G^{-1}(s)G_d(s) \\ D_q(s)D_e(s) &= D_d(s) = e^{-hs}\mathrm{I}_{3\times 3} \\ G_d(s) &= \frac{1}{(\tau_d s+1)^2}\,\mathrm{I}_{3\times 3} \end{aligned}}$$

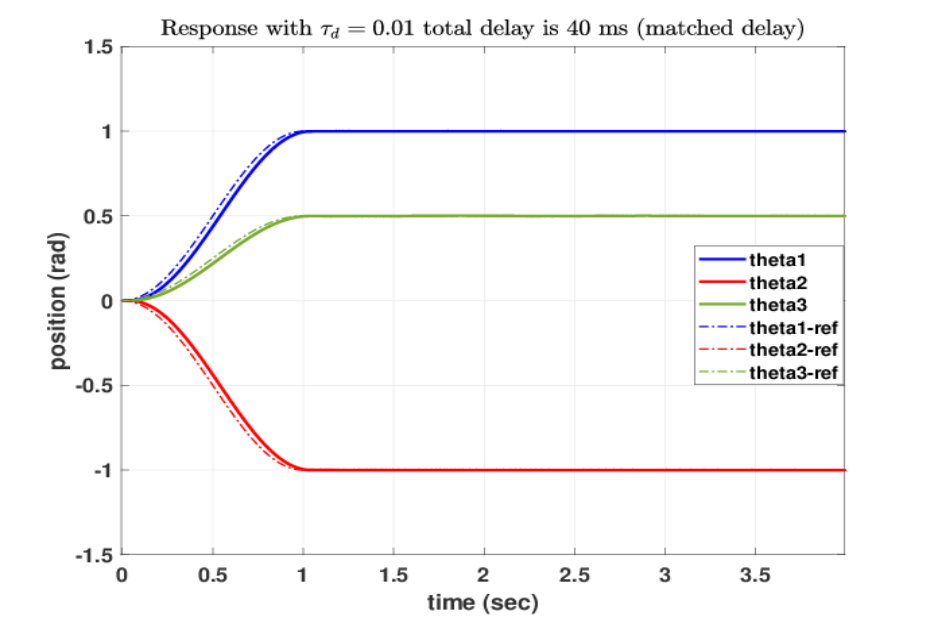
$$T(s) = \frac{e^{-hs}}{(\tau_d s+1)^2}\mathrm{I}_{3\times 3}$$

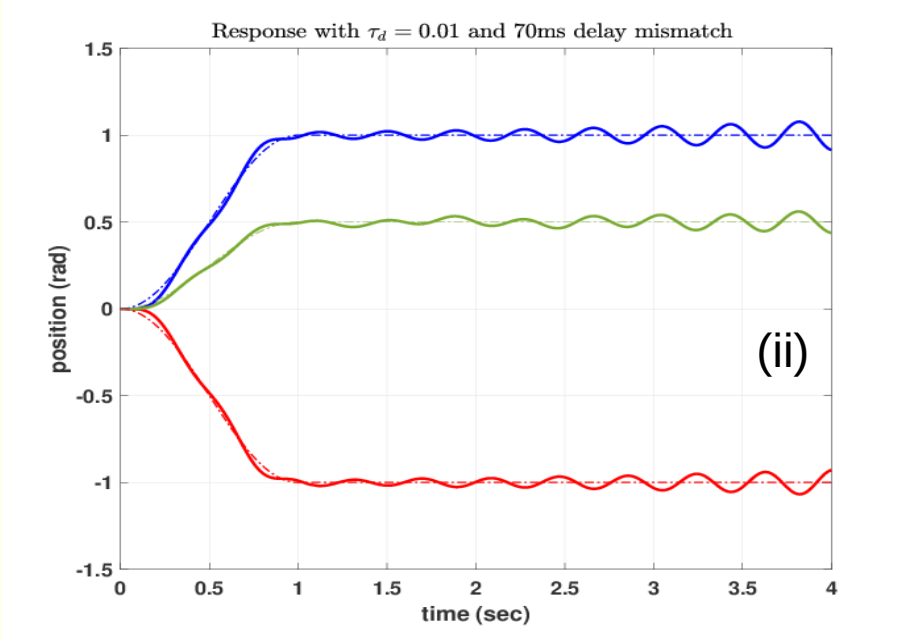
(all three links are synchronized)

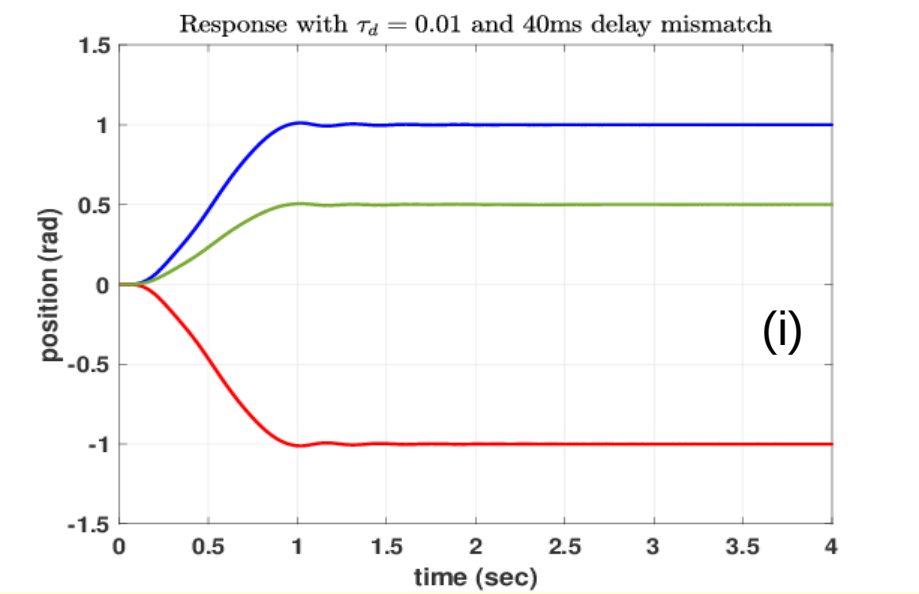
- CNS has copies of system dynamics for stance and time delays.
- Mismatch happens with aging or health problems.
- Robustness to mismatch in delays and parameters of the system dynamics as well as using linear model versus nonlinear model are analyzed in the literature (e.g Hemami and Ö., 2000).

efferent and afferent delays = 20ms (40ms total delay)
controller uses correct values of the delays

$\tau_d = 0.01$ in all cases




controller uses 40ms total delay but actual total delay is

(i) 80ms (delay mismatch is 40ms)
(ii) 110ms (delay mismatch is 70ms)

Conclusion: additional 20ms delays in afferent and efferent paths are OK but if these increase to 35 ms the result is instability. These results depend on $\tau_d$.

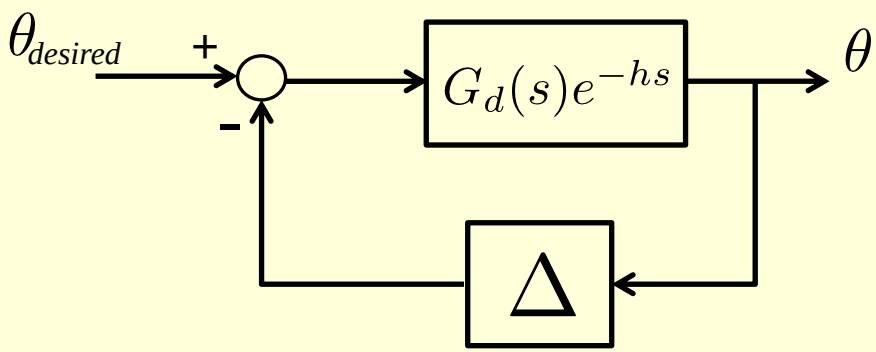
**"Response times have been increased in older 79-81 adults by approximately 20 to 30 ms. This delay in response seems to contribute to instability during stance and ambulation in older persons who fall."**

## Further Research Questions:

- What are the feedback gains for stance in real biological system? How can we set-up an experiment to measure these gains?

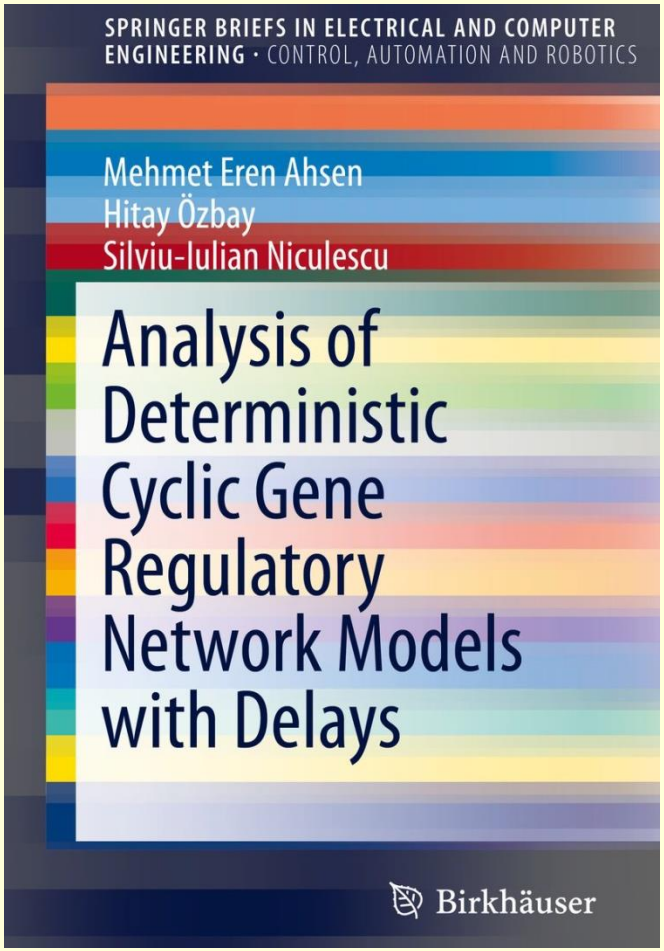
- Can an adaptation be made with aging, e.g. adjusting the gains or updating the system model in the controller with changing delays?

- What is the delay margin for this particular nonlinear system? For the linearized model it is relatively easy to compute the DM.




$\Delta$ : captures delay mismatch and other linear/nonlinear neglected dynamics

# Part II
# Analysis of Gene Regulatory Networks (with M. E. Ahsen and S-I. Niculescu)

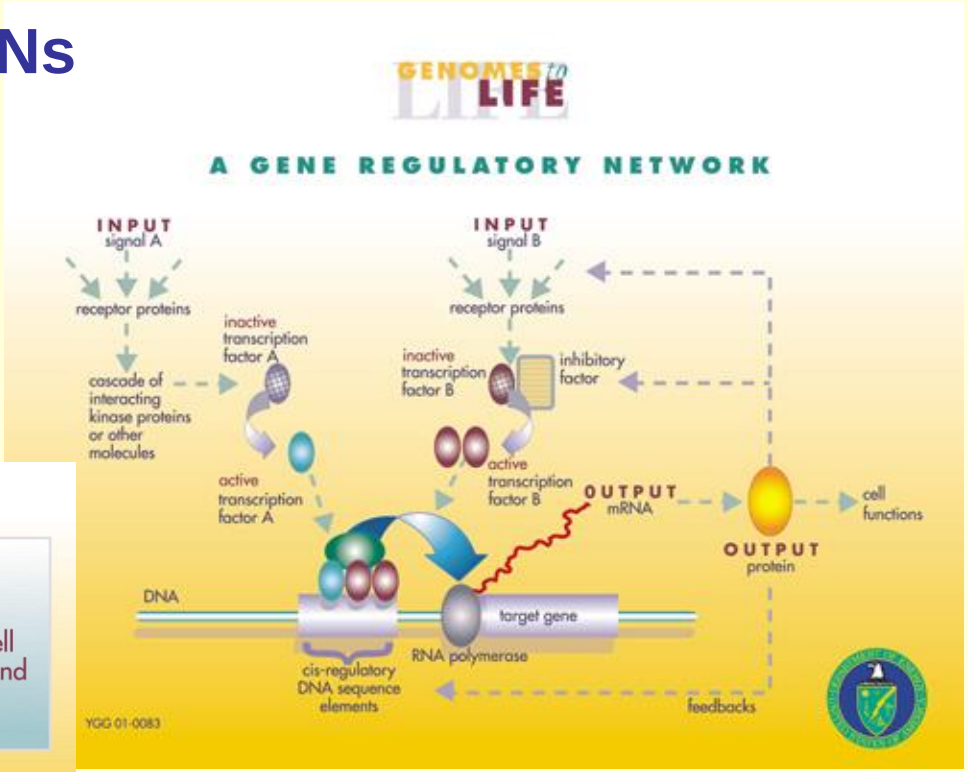


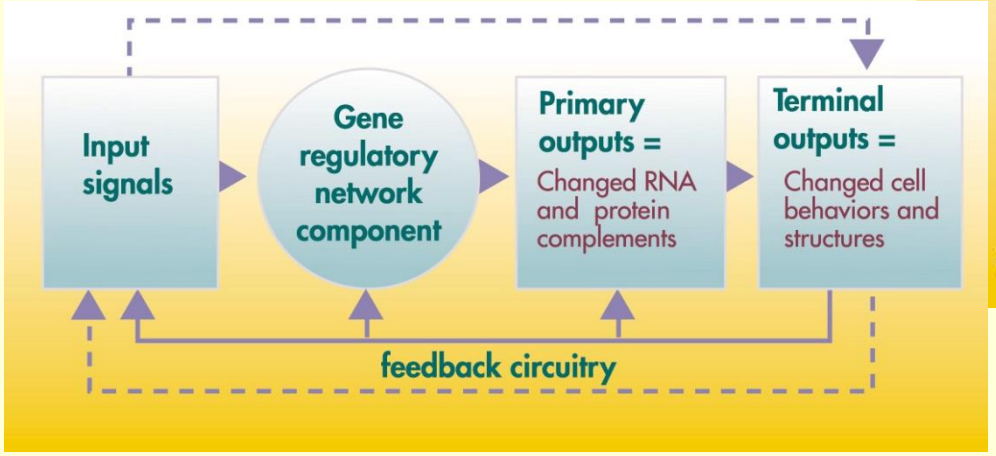
# Analysis of Gene Regulatory Networks

Definition of a GRN (Wikipedia): A **gene regulatory network** or **genetic regulatory network (GRN)** is a collection of DNA segments in a cell which interact with each other indirectly (through their RNA and protein expression products) and with other substances in the cell, thereby governing the expression levels of mRNA and proteins.

## Mathematical Models of GRNs

- Coupled ODEs
- Boolean Networks
- Stochastic Simulators



# Coupled ODEs

Guy Karlebach and Ron Shamir,
"Modelling and analysis of gene regulatory networks"
***Nature Reviews Molecular Cell Biology,*** 9, 770-780 (October 2008)

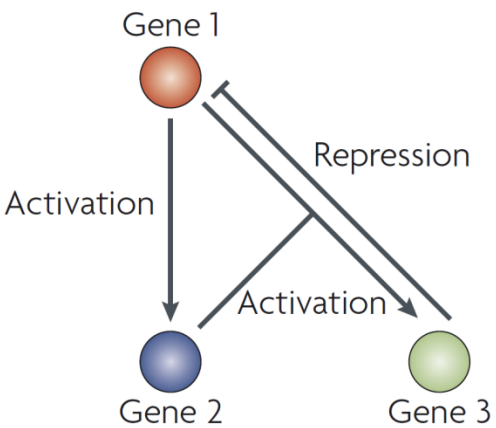
**a**

$$\frac{d(gene_1)}{dt} = k_{1,s} \cdot \frac{1}{1 + k_{1,3} \cdot gene_3} - k_{1,d} \cdot gene_1$$

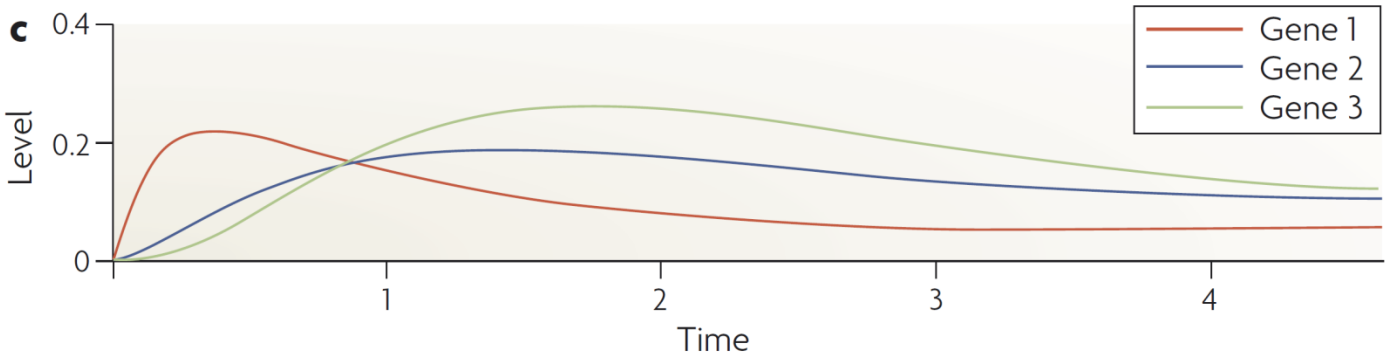
$$\frac{d(gene_2)}{dt} = k_{2,s} \cdot \frac{k_{2,1} \cdot gene_1}{1 + k_{2,1} \cdot gene_1} - k_{2,d} \cdot gene_2$$

$$\frac{d(gene_3)}{dt} = k_{3,s} \cdot \frac{k_{3,1} \cdot gene_1 \cdot k_{3,2} \cdot gene_2}{(1 + k_{3,1} \cdot gene_1) \cdot (1 + k_{3,2} \cdot gene_2)} - k_{3,d} \cdot gene_3$$

**b**




**c**



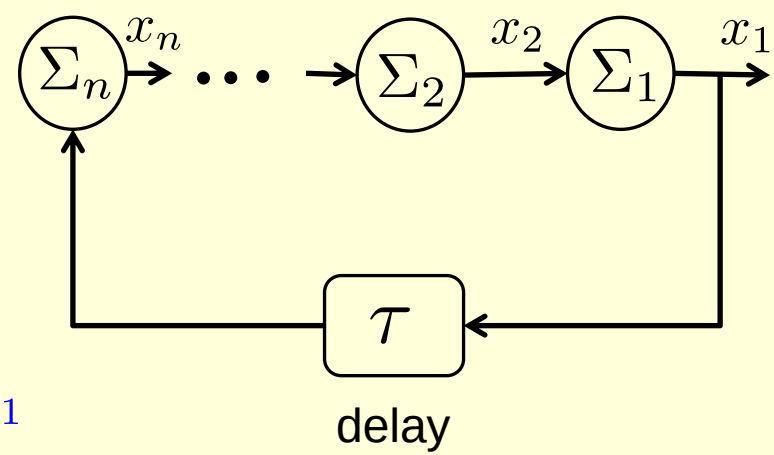
# Simplified Model with Time Delay

$$\left.\begin{array}{lrcl}
\Sigma_1\} & \dot{x}_1(t) & = & -\lambda_1 x_1(t) + g_1(x_2(t)) \\
\Sigma_2\} & \dot{x}_2(t) & = & -\lambda_2 x_2(t) + g_2(x_3(t)) \\
 & & \vdots & \\
\Sigma_n\} & \dot{x}_n(t) & = & -\lambda_n x_n(t) + g_n(x_1(t-\tau))
\end{array}\right\} \Sigma$$

$$\frac{d(gene_1)}{dt} = k_{1,s} \cdot \frac{1}{1 + k_{1,3} \cdot gene_3} - k_{1,d} \cdot gene_1 \quad x_3$$

$$\frac{d(gene_2)}{dt} = k_{2,s} \cdot \frac{k_{2,1} \cdot gene_1}{1 + k_{2,1} \cdot gene_1} - k_{2,d} \cdot gene_2 \quad x_2$$

$$\frac{d(gene_3)}{dt} = k_{3,s} \cdot \frac{k_{3,1} \cdot \cancelto{c}{gene_1} \cdot k_{3,2} \cdot gene_2}{(1 + k_{3,1} \cdot \cancelto{c}{gene_1}) \cdot (1 + k_{3,2} \cdot gene_2)} - k_{3,d} \cdot gene_3 \quad x_1$$




System Theoretic Questions:

1. How many *equilibrium points* do we have?
2. Are these *stable* equilibrium points?

## Definitions

$$f^m = \underbrace{f \circ \cdots \circ f}_{m \text{ compositions}}$$

*Fixed point*: $f(x) = x$

First, second and third derivatives: $f', f'', f'''$

Three times differentiable functions on positive real axis: $\mathcal{D}^3(\mathbb{R}_+)$

*Schwarzian derivative*:

$$Sf(x) = \begin{cases} -\infty & \text{if } f'(x) = 0 \\ \dfrac{f'''(x)}{f'(x)} - \dfrac{3}{2}\left(\dfrac{f''(x)}{f'(x)}\right)^2 & \text{if } f'(x) \neq 0 \end{cases}$$

# Assumptions on $\Sigma$

*Assumption 1* For all $i = 1, 2, ..., n$, we have $\lambda_i > 0$ .
*Assumption 2* For all $i = 1, 2, ..., n$, the nonlinearity functions $g_i$ satisfy:
*(i)* $g_i(x)$ is a bounded function defined on $\mathbb{R}_+$;
*(ii)* we have either $g_i'(x) < 0$ or $g_i'(x) > 0$ $\forall x \in (0, \infty)$.
*(iii)* Each function $g_i$ has $Sg_i(x) < 0$ $\forall x \in (0, \infty)$.

Definition:
The gene regulatory network is under *negative (resp. positive) feedback* if

$$g'(x) < 0 \qquad \forall x \in (0, \infty)$$

respectively

$$g'(x) > 0 \qquad \forall x \in (0, \infty)$$

where

$$g = (\frac{1}{\lambda_1} g_1) \circ (\frac{1}{\lambda_2} g_2) \circ ... \circ (\frac{1}{\lambda_n} g_n).$$

# GRNs under Negative Feedback

$$\left.\begin{array}{rcl} \dot{x}_1(t) & = & -\lambda_1 x_1(t) + g_1(x_2(t)) \\ \dot{x}_2(t) & = & -\lambda_2 x_2(t) + g_2(x_3(t)) \\ & \vdots & \\ \dot{x}_n(t) & = & -\lambda_n x_n(t) + g_n(x_1(t-\tau)) \end{array}\right\} \Sigma$$

Let $g_1, \ldots, g_n$, satisfy *Assumption 2* and consider the system under negative feedback, i.e.,

$$g = (\frac{1}{\lambda_1} g_1) \circ (\frac{1}{\lambda_2} g_2) \circ \ldots \circ (\frac{1}{\lambda_n} g_n) \qquad g'(x) < 0 \ \forall x \in (0, \infty)$$

In this case, $g$ has a unique fixed point and hence $\Sigma$ has a unique equilibrium point ; $x_{eq} = (x_1, \ldots, x_n)$.

For the system $\Sigma$, $\mathbb{R}^n_+$ is a positively invariant set. Moreover, $x(t)$ remains bounded for any $x(0) \in \mathbb{R}^n_+$.

## Global Stability Results (Delay Independent and Delay Dependent):

The system has a unique equilibrium point given by $x_{eq} = [x_1, ..., x_n]^{\mathtt{T}}$, where $x_1$ is the unique fixed point of the function $g$. Moreover, if

$$|g'(x_1)| < 1,$$

then for any nonnegative initial condition the solution satisfies

$$\lim_{t\to\infty} x(t) = x_{eq}.$$

If we have

$$|g'(x_1)| > 1, \qquad (\star)$$

then stability of the equilibrium point depends on the value of the time delay. Even if the equilibrium is locally unstable, the solution $x(t)$ is bounded: under$(\star)$ the function $g \circ g$ has exactly three distinct fixed points

$$y_1 < x_1 < y_2.$$

Then, for any positive initial condition, we have

$$y_1 < \lim_{t\to\infty} \underline{x_i(t)} \leq \lim_{t\to\infty} \overline{x_i(t)} < y_2 \qquad \forall i = 1, 2, ..., n.$$

# Homogenous GRNs Under Negative Feedback

$$\begin{cases} \dot{x}_i(t) &= -x_i(t) + f(x_{i+1}(t)) \qquad i = 1, 2, ..., n-1 \\ \dot{x}_n(t) &= -x_n(t) + f(x_1(t-\tau)) \end{cases}$$

$$f(x) = \frac{a}{b + x^m}, \qquad a, b > 0, \quad m \in \{1,\ 2,\ 3, \ldots\}.$$

Since $g = f^n$ and

$$f'(x) < 0, \qquad \forall x \in (0, \infty).$$

the system is under negative feedback if and only if *n* is odd.

$f$ has unique fixed point satisfying

$$f(x_0) = \frac{a}{b + x_0^m} = x_0$$

$$|g'(x_0)| < 1 \quad \Leftrightarrow \quad (|f'(x_0)|)^n < 1 \quad \Leftrightarrow \quad \frac{(m-1)a}{mb} < x_0$$

$$\Longleftrightarrow \quad \boxed{\left(\frac{a}{m}\right)^m < \left(\frac{b}{m-1}\right)^{m+1}} \qquad m = 2,\ 3,\ \ldots$$

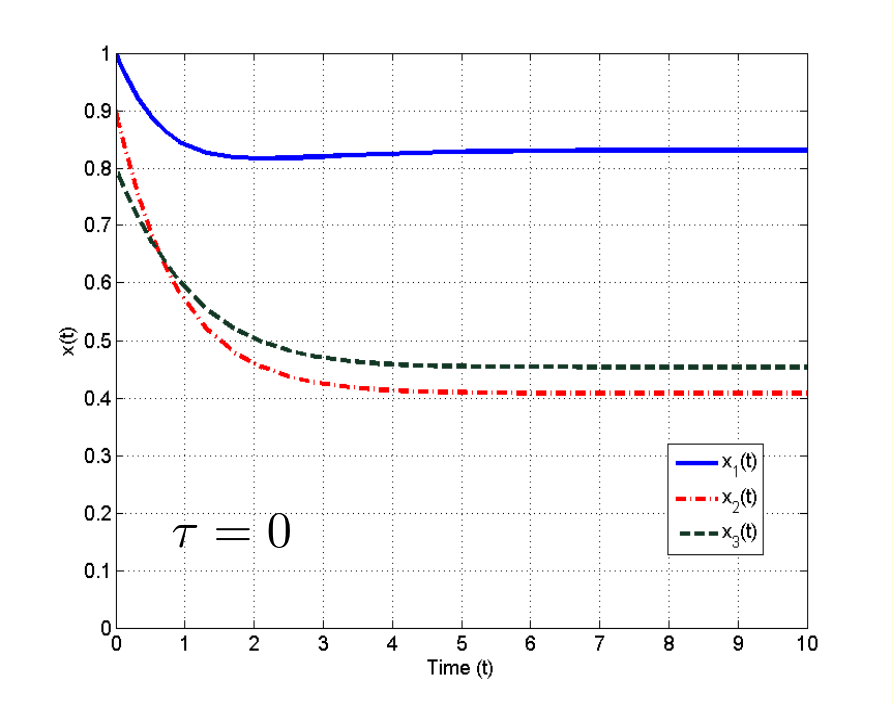
If this condition is satisfied the equilibrium point $x_{eq} = [x_0 \ \cdots \ x_0]^{\mathrm{T}}$ is globally stable independent of delay.

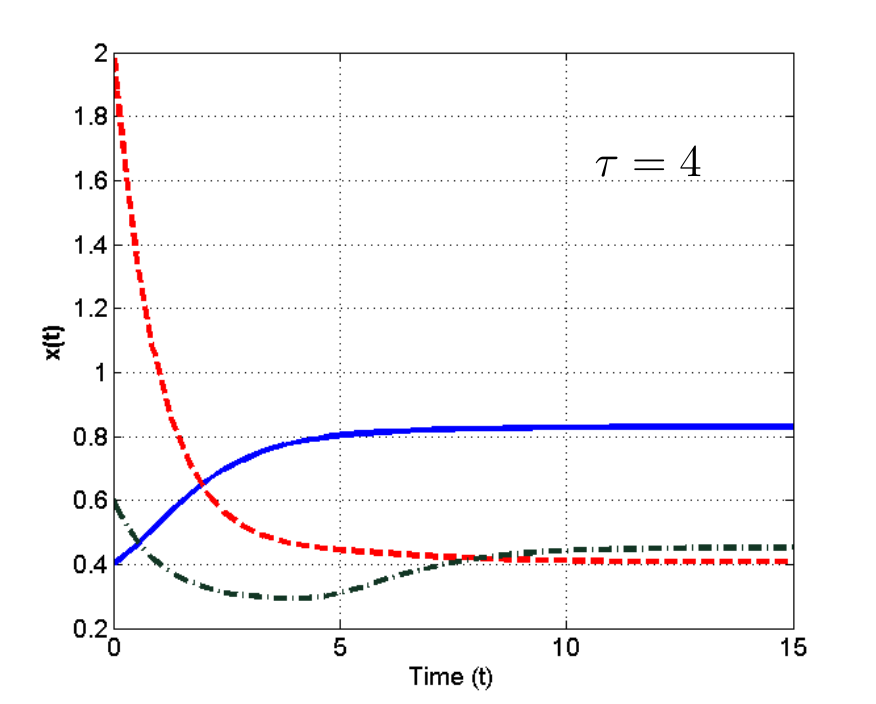
# Examples

$$n = 3,\ \lambda_1 = \lambda_2 = \lambda_3 = 1$$

$$g_1(x) = \frac{1}{1+x} \qquad g_2(x) = \frac{2}{2+x} \qquad g_3(x) = \frac{1}{3+x}.$$

$$x_{eq} = (0.83, 0.4, 0.45) \qquad |g'(0.83)| = 0.0173 < 1$$



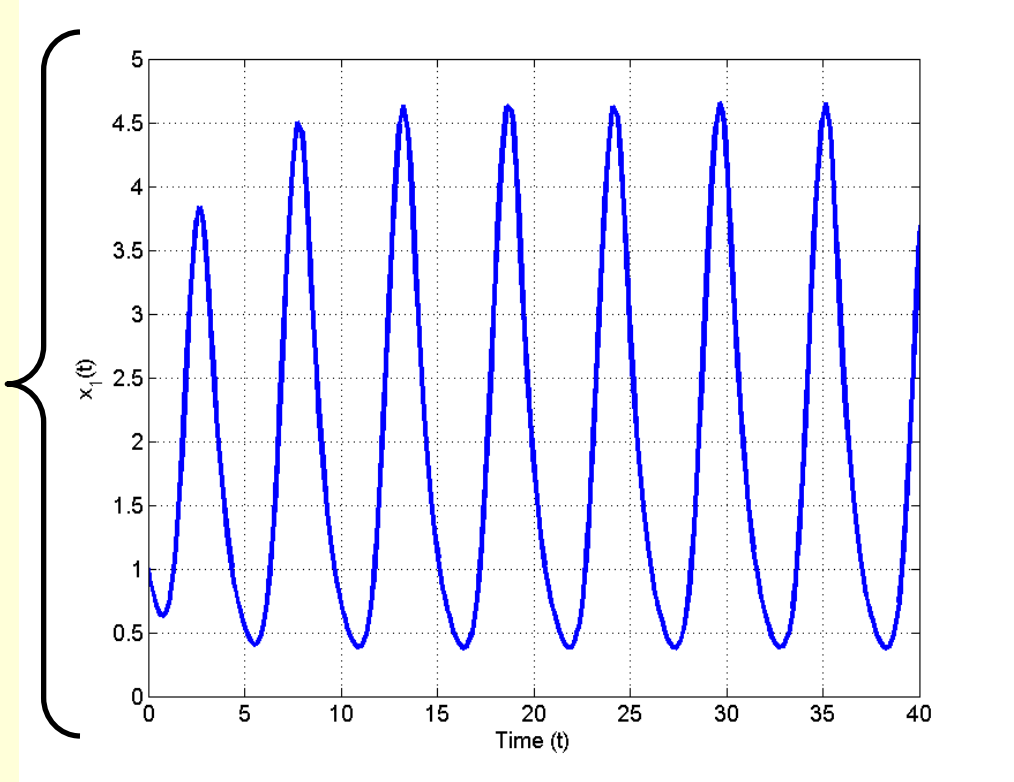
Homogenous GRN with $a = 2,\ b = 0.25,\ m = 3,\ n = 3$ $\quad f(x) = \dfrac{2}{0.25 + x^3}$

$$\left(\frac{a}{m}\right)^m = 0.2963 > \left(\frac{b}{m-1}\right)^{m+1} = 0.00024$$

$g = f \circ f$ has three fixed points :

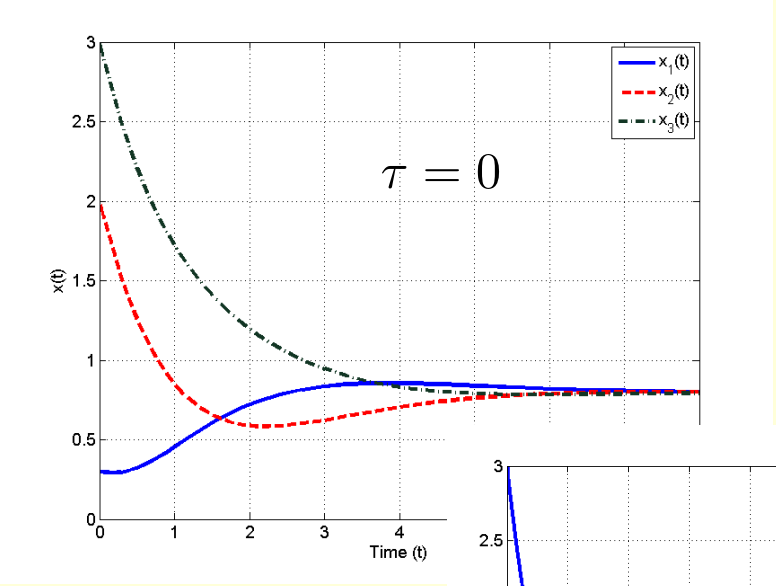
$0.0039,\ 1.1442$ and $8.0000$

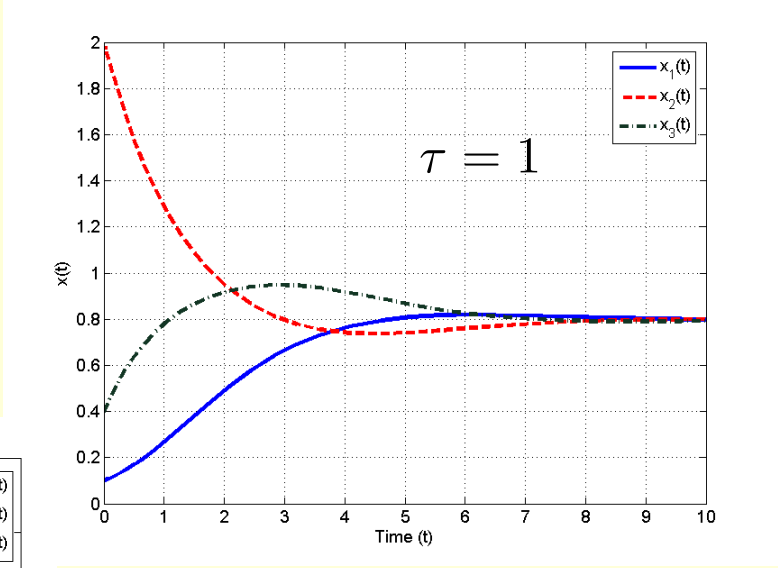
stays within these bounds

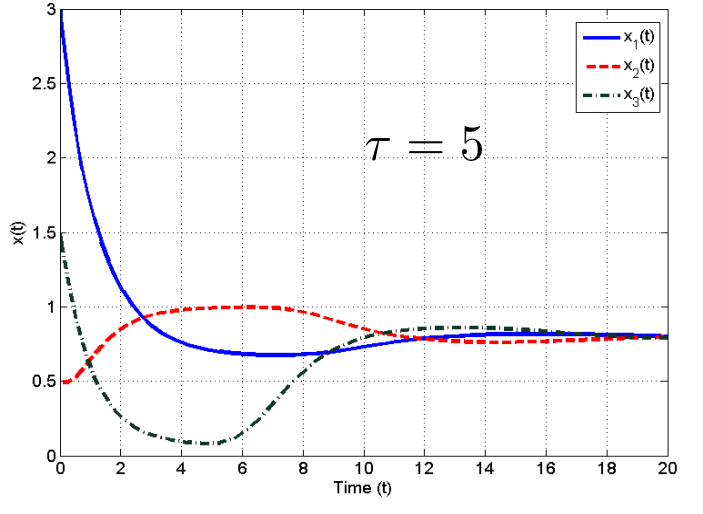


Homogenous GRN with $a = 2,\ b = 2,\ m = 2,\ n = 3 \qquad f(x) = \dfrac{2}{2 + x^2}$

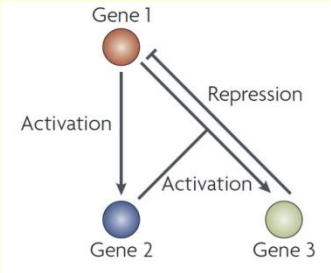
$$\left(\frac{a}{m}\right)^m = 1 < \left(\frac{b}{m-1}\right)^{m+1} = 8 \qquad x_{eq} = (0.7709, 0.7709, 0.7709).$$

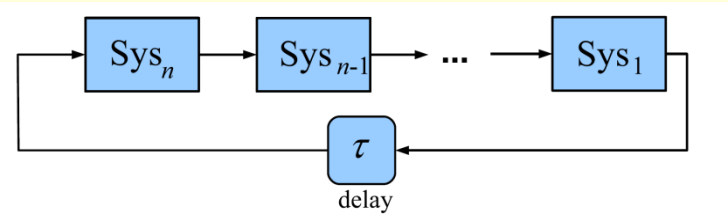


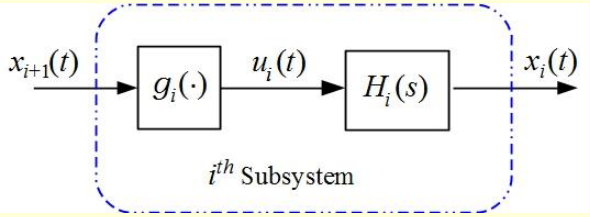



# Delay dependent local stability condition for the case $|g'(x_1)| > 1$




Linearization around an equilibrium point $x = [x_1 \ \cdots \ x_n]^{\mathrm{T}}$

$$\dot{z}(t) = A_0 z(t) + A_1 z(t-\tau)$$

$$A_0 = \begin{bmatrix} -\lambda_1 & g_1'(x_2) & 0 & \cdots & 0 \\ 0 & -\lambda_2 & g_2'(x_3) & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & -\lambda_{n-1} & g_{n-1}'(x_n) \\ 0 & 0 & \cdots & 0 & -\lambda_n \end{bmatrix}, \quad A_1 = \begin{bmatrix} 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & \cdots & 0 \\ g_n'(x_1) & 0 & \cdots & 0 \end{bmatrix}$$

$\rho_i := g_i'(x_{i+1}),\ i = 1, \ldots, n,$ with $x_{n+1} = x_1.$

# The Secant Condition for Time Delay Systems

Linearized system model for the GRN:

$$\dot{z}_i(t) = -\lambda_i \; z_i(t) + \rho_i \; z_{i+1}(t) \qquad i = 1, \ldots, n$$

with delayed feedback $z_{n+1}(t) = z_1(t - \tau)$

Characteristic equation:

$$\chi(s) := \prod_{i=1}^{n} \left( \frac{s}{\lambda_i} + 1 \right) + k e^{-\tau s} = 0 \qquad \text{where} \qquad k := -\prod_{i=1}^{n} \frac{\rho_i}{\lambda_i} > 0$$

In fact, $k = g'(x_1)$

A sufficient condition for stability from the small gain theorem: $k \leq 1$

Another simple sufficient condition will be given for the case where $k > 1$

The secant condition when $\tau = 0$ (a sufficient condition for stability) :

$$k \leq \left(\sec \frac{\pi}{n}\right)^n \qquad \text{equivalently} \qquad \frac{\pi}{n} > \arccos\left(\sqrt[n]{1/k}\right)$$

When delay is non-zero we need an extra small-delay condition: $\tau < \max\{\tau_m, \widetilde{\tau}_m\}$ where

$$\tau_m := \frac{\pi - n \arccos\left(\sqrt[n]{1/k}\right)}{\lambda \sqrt{k^{2/n} - 1}}$$

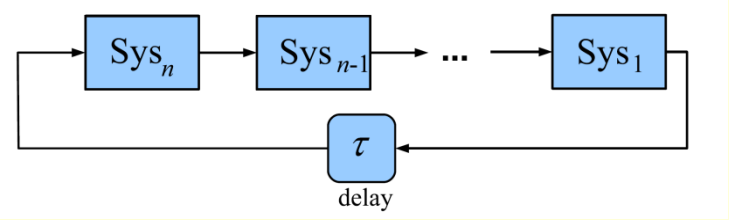
$$\widetilde{\tau}_m := \frac{\pi - n \arccos\left(\sqrt[n]{1/k}\right)}{\widetilde{\lambda} \sqrt[2n]{k^2 - 1}},$$

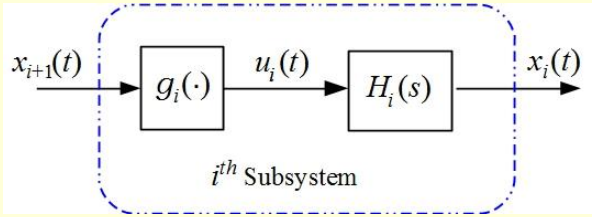
$$\lambda := \max_i \lambda_i \text{ and } \widetilde{\lambda} := \left(\prod_{i=1}^n \lambda_i\right)^{1/n}$$

When all $\lambda_i$ are equal (homogenous case) we have $\tau_m \geq \widetilde{\tau}_m$ and a necessary and sufficient condition for local stability is

$$k \leq \left(\sec \frac{\pi}{n}\right)^n \quad \text{and} \quad \tau < \tau_m$$

**Example:** Repressilator is a special kind of homogenous GRN with $n = 3$

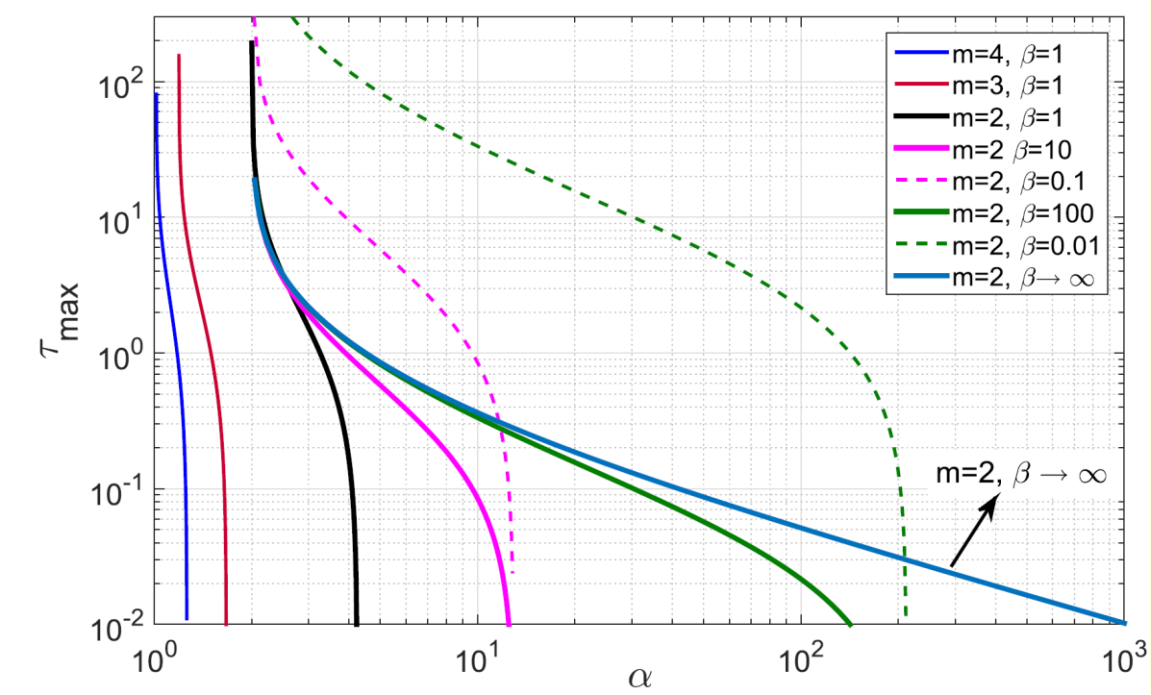



$$g_i(x) = \frac{\alpha}{1 + x^m} \qquad H_i(s) = \frac{1}{(s+1)(s/\beta + 1)}$$

$\beta \to \infty$ corresponds to the case we have considered

Maximum allowable time delay for local stability :



# Conclusions

- Many biological system models involve time delays.
- Effects of time delays are analyzed and delay margins are determined for linearized models around the equilibrium.
- Experimental validation and parameter estimation for these models are important missing links at this point. Strong multidisciplinary collaborations are needed with experts from biology and medicine.