# BME233--Dynamic Systems in Biology and Medicine

## Course Roadmap

| | |
|---|---|
| Week 1-2 | Introduction ◇ Basic definitions: system, system variables (inputs, outputs, states, parameters), and models ◇ Taxonomy of systems and models ◇ Input-output and state-space models ◇ Order of a dynamic system |
| Week 3-4½<br>Linear Systems | Canonical linear time-invariant (LTI) systems ◇ Impulse response ◇ Convolution ◇ Laplace Transform ◇ The Convolution Theorem ◇ Transfer function ◇ Poles ◇ Equilibrium ◇ Stability ◇ Frequency response ◇ Bode plot ◇ Feedback and Control ◇ Midterm exam (take-home) |
| Week 4½ -10<br>Nonlinear Systems | Equilibrium states ◇ Phase portraits ◇ Linearization ◇ Stability ◇ Attractors ◇ Isoclines ◇ Periodic orbits ◇ Elementary index theory ◇ Gradient systems ◇ Guest lecture ◇ Poincaré-Bendixson Theorem ◇ Elementary bifurcation theory ◇ Elementary chaos theory (time permitting) ◇ Final exam (take-home) |

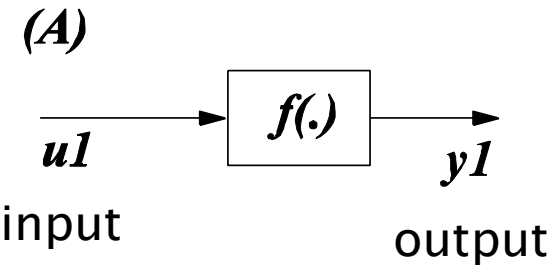
**Q**: What is the central topic of BME233?

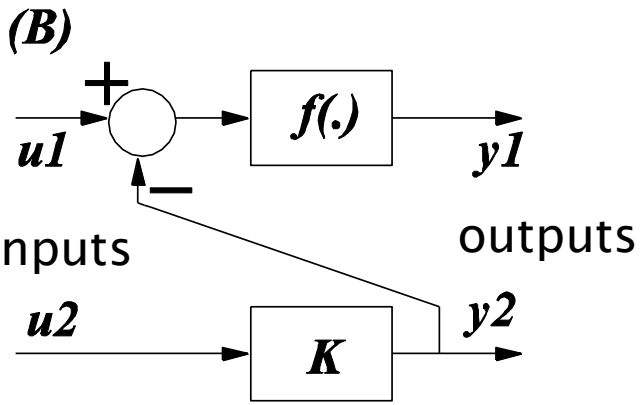
**A**: To apply dynamic system theory (modeling, analysis, control) to biomedical and biological systems.

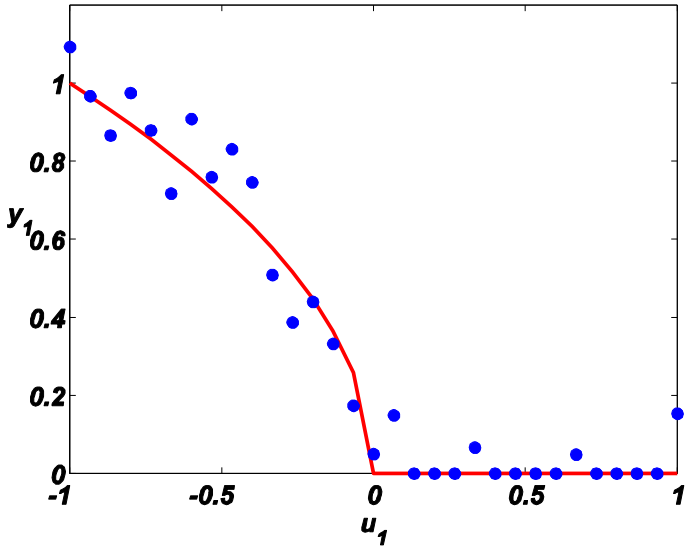
## Purpose of System Theory in Biology and Medicine

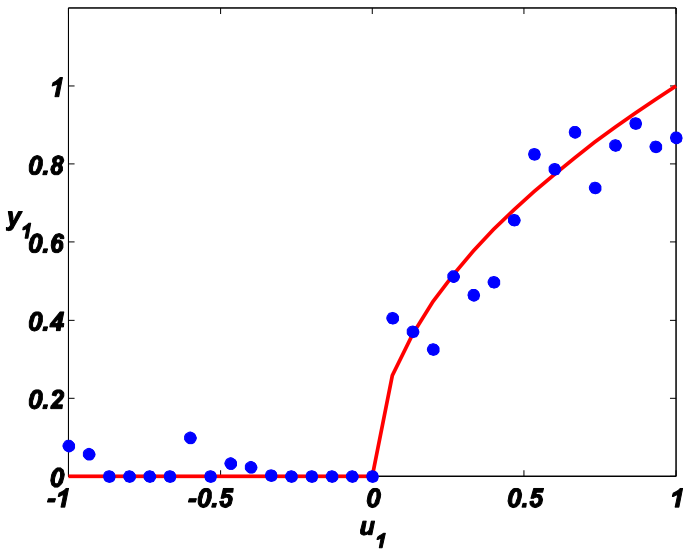
- Experimental science (e.g. biology) largely reductionist.
- Problems broken down into simpler sub-problems and studied one piece at a time.
- Complex systems involve complex interactions among basic units.
- Mathematical models allow the examination of interactions that *cannot* be studied by the reductionist approach.
- Mathematical models can make forecasts that *cannot* be extrapolated from data (measurements).

Example: *[Pitfalls of Reductionism]*



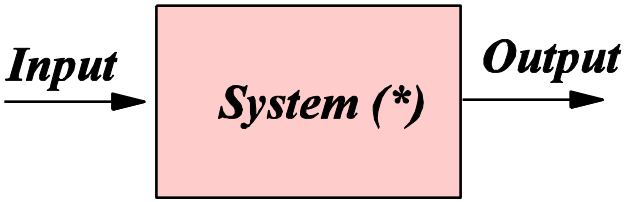




$$y_1 = f(u_1) = \begin{cases} \sqrt{|u_1|}, & u_1 < 0 \\ 0, & u_1 \geq 0 \end{cases}$$

$y_1 = ?$




Black-box model—abstraction of a system based on input-output description (top-down approach)

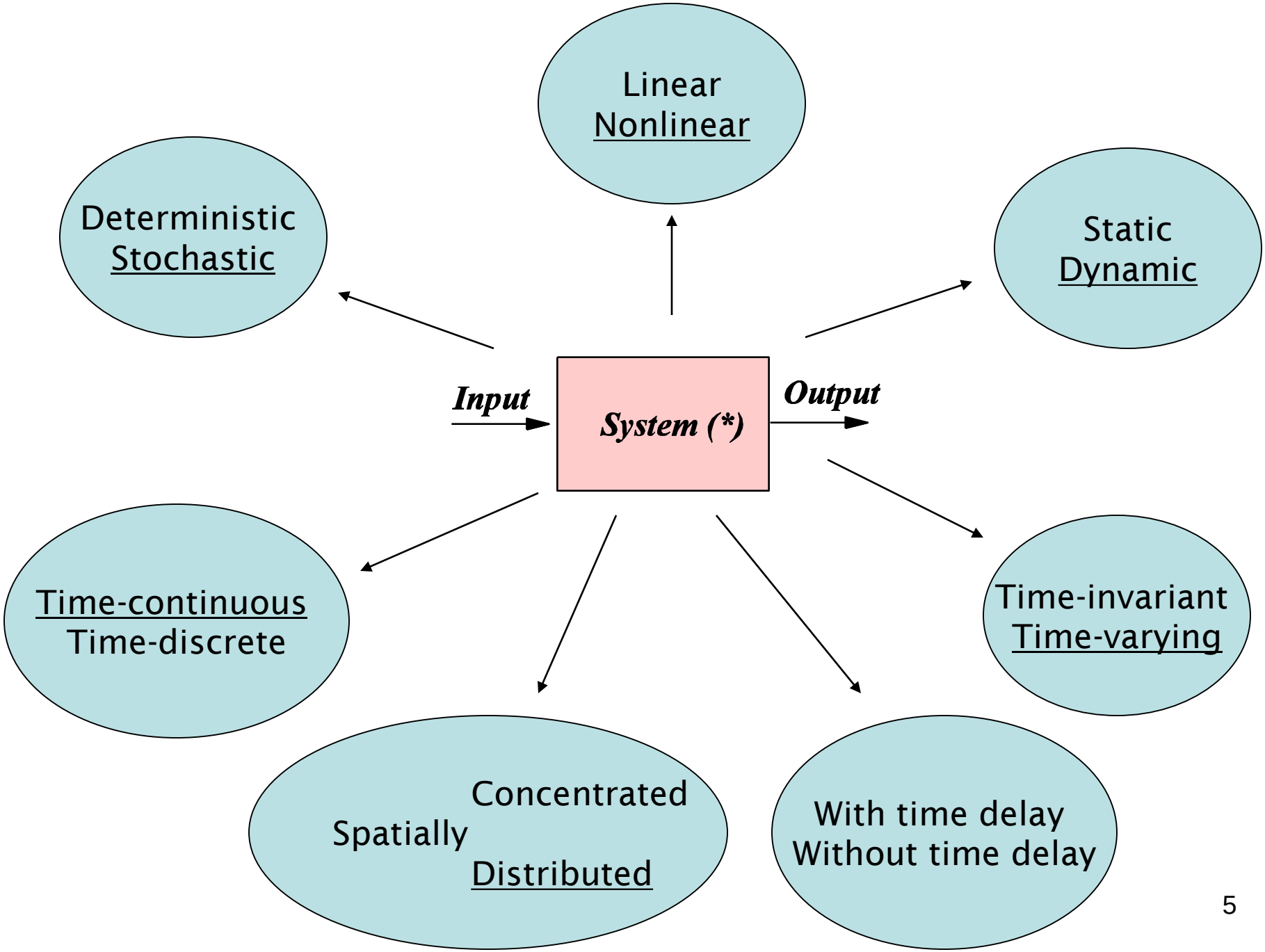
White-box model—known pieces are put together (bottom-up approach)

**Modeling**: Find mathematical equation(s) *(*)* that describe the system.

**Analysis**: What can be said about the behavior of the system? Are the outputs oscillatory, aperiodic? How quickly do they reach the steady state? What frequencies is the system tuned to, etc.?

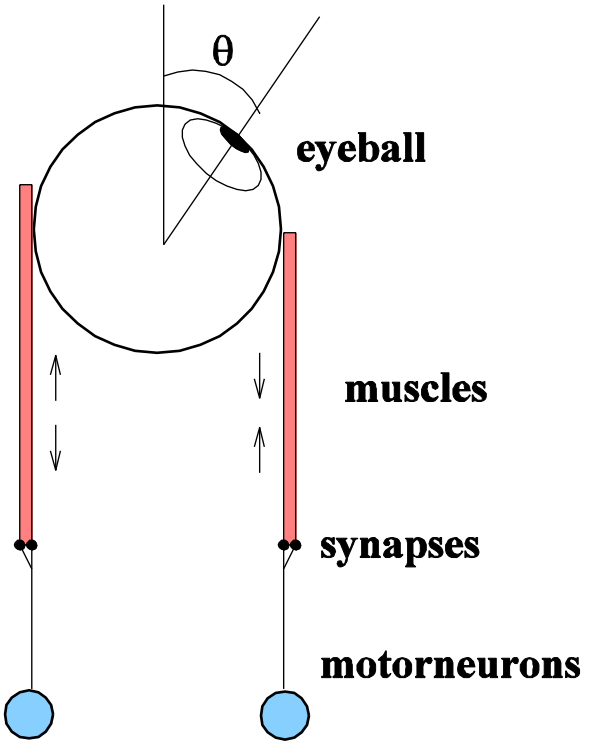
**Control**: Can we figure out how inputs affect outputs? Can we find a set of inputs so that outputs have a certain behavior?

**Sensitivity/Robustness analysis**: How are the changes in parameters affecting the behavior of the system?


Linear
Nonlinear
Deterministic
Stochastic
Static
Dynamic
Input
System (*)
Output
Time-continuous
Time-discrete
Time-invariant
Time-varying
Concentrated
Spatially
Distributed
With time delay
Without time delay

Example: *[Eye Movements]*

$$J\ddot{\theta}(t) + B\dot{\theta}(t) + K\theta(t) = \tau(t)$$

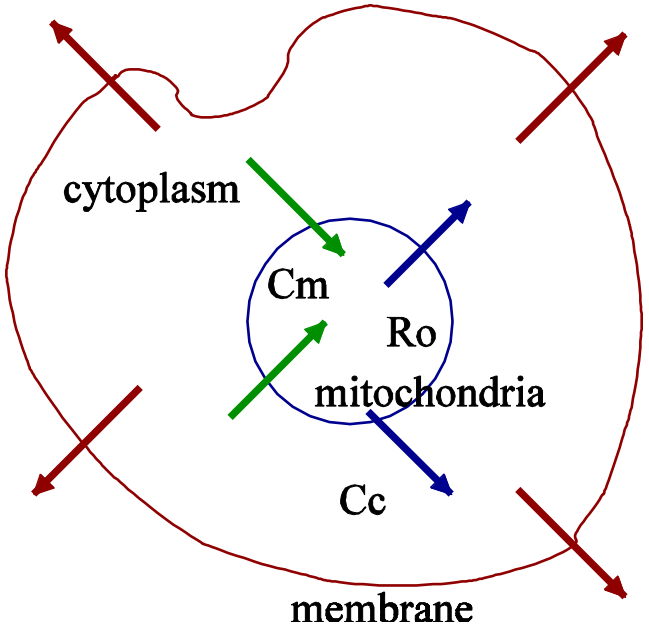



deterministic ◇ spatially concentrated ◇ dynamic ◇ time-invariant ◇ without delay ◇ linear ◇ time-continuous

**L**inear **T**ime **I**nvariant = **LTI**

Example: *[Cellular Dynamics]* (LTI system)

$$V_m \dot{C}_m(t) = R_0(t) - K_{12}[C_m(t) - C_c(t)]$$
$$V_c \dot{C}_c(t) = K_{12}[C_m(t) - C_c(t)] - K_2 C_c(t)$$




demo: `cellular_dynamics.m`

Example: *[Population Dynamics]* (time-discrete LTI system)

$$N(t+1) = N(t) + \underbrace{\text{births}}_{BN(t)} - \underbrace{\text{deaths}}_{DN(t)} + \underbrace{\text{immigration}}_{IN(t)} - \underbrace{\text{emigration}}_{EN(t)}$$

$N(t)$ - population at year $t$

$B$ - birth rate (US: 1 person in 7 sec.)

$D$ - death rate (US: 1 person in 13 sec.)

$I$ - immigration rate

$E$ - emigration rate

$$N(t+1) = N(t) + \underbrace{(B - D + I - E)}_{\lambda} N(t) = (1+\lambda)N(t)$$

Solution: $\boxed{N(t_0 + T) = N(t_0)(1+\lambda)^T}$ - exponential growth

Does not quite fit the census data! Can we make better predictions?

| year | $\lambda$ (source: US Census Bureau) |
|---|---|
| 2008 | 0.93% |
| 1999 | 0.89% |
| 1991 | 1.08% |
| 1950 | 2.07% (baby boomers) |

Time-varying system: $B = B(t),\ D = D(t),\ I = I(t),\ E = E(t)$

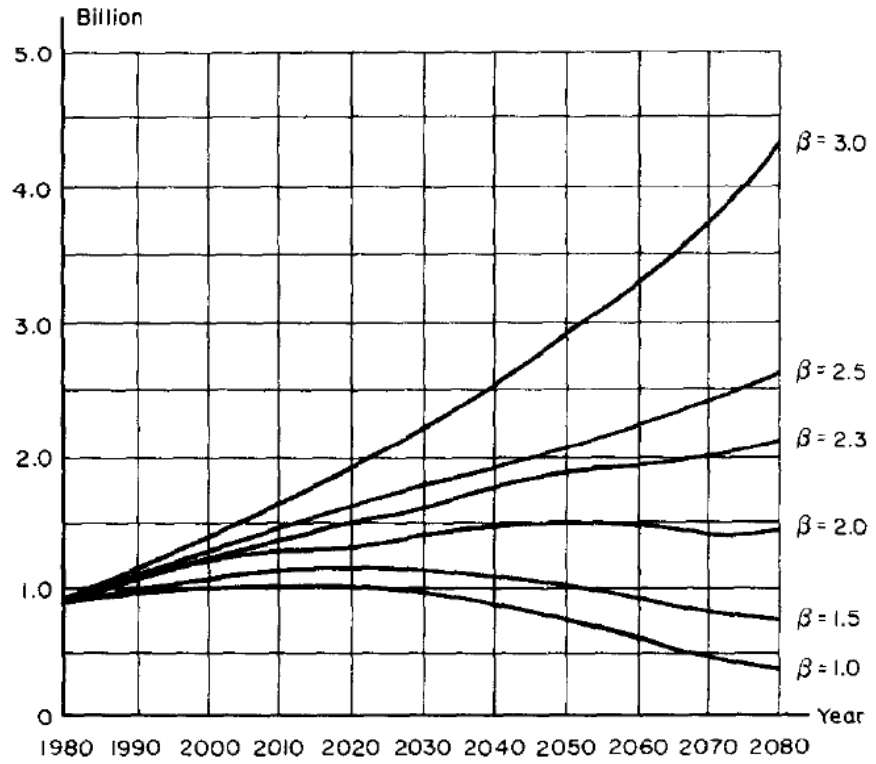
$$N(t+1) = [1 + \lambda(t)]N(t)$$

Tweaking the parameters $B(t), I(t)$, etc., we can control the growth of the population.

These manipulations are performed with the model, and predictions are made.

E.g. China's one-child policy from 1980 to 2015 originated from one such model.

Prediction of the Chinese population growth based on a mathematical model.




$\beta$ —the average number of childbearings per woman's lifetime

FIG. 1. Propects of population growth according to different fertility levels.

J. Song, *Theoretical Population Biology*, 1982

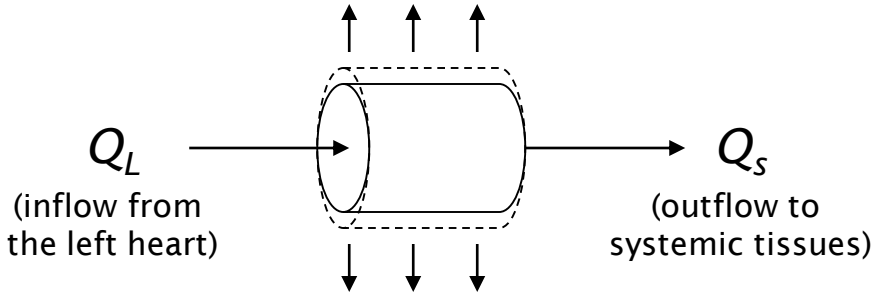
Example: *[Diffusion of Oxygen in a Living Tissue]*

$$\frac{\partial y(\xi,\eta,\zeta,\mathrm{t})}{\partial t} = D\left(\frac{\partial^2 y(\xi,\eta,\zeta,t)}{\partial \xi^2} + \frac{\partial^2 y(\xi,\eta,\zeta,t)}{\partial \eta^2} + \frac{\partial^2 y(\xi,\eta,\zeta,t)}{\partial \zeta^2}\right) - ky(\xi,\eta,\zeta,t)$$

(spatially distributed LTI system)

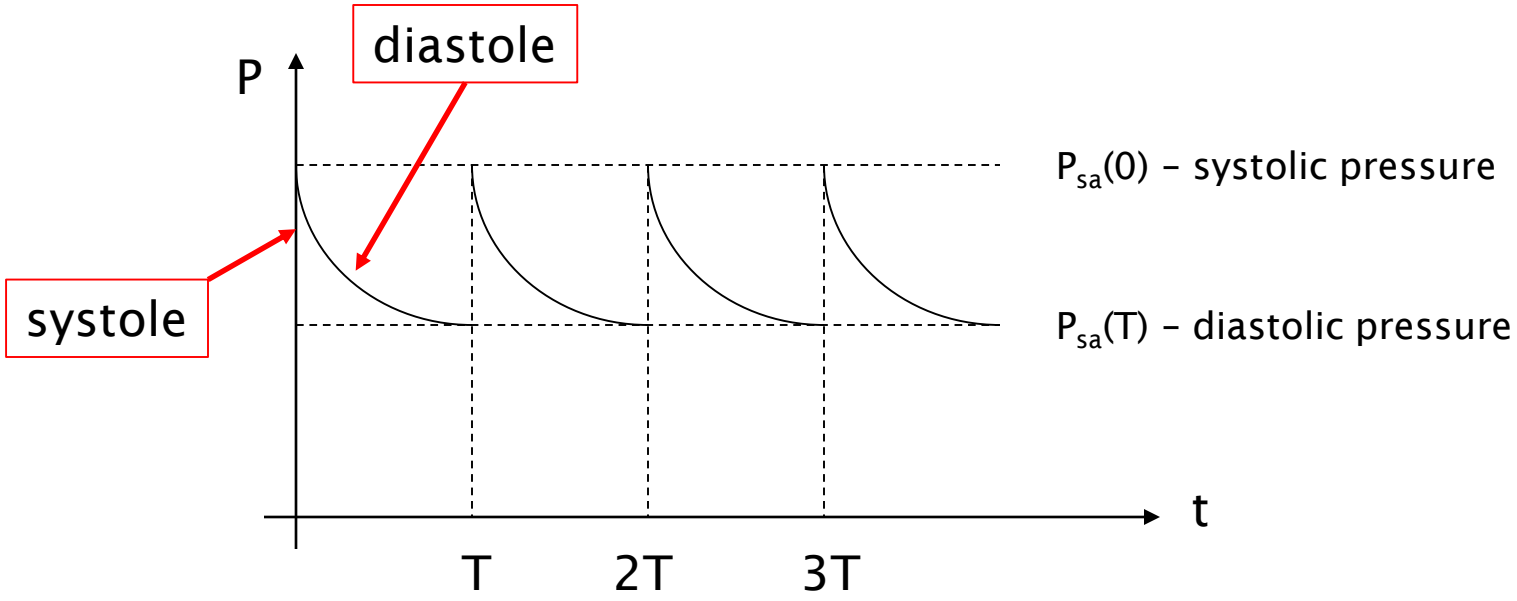
- $y(\xi,\eta,\zeta,t) \in \mathbb{R}$ is the oxygen concentration at a point $(\xi,\eta,\zeta)$ and time $t$
- $D$ is the diffusion constant
- $k$ is the oxygen uptake constant

## Example: *[Blood Pressure Dynamics]*




$$\dot{P}_{sa}(t) = -\frac{P_{sa}(t)}{R_s\, C_{sa}} \qquad \text{diastole } (Q_L = 0)$$

$$\triangle P_{sa} = P_{sa}(0) - P_{sa}(T) \qquad \text{systole}$$

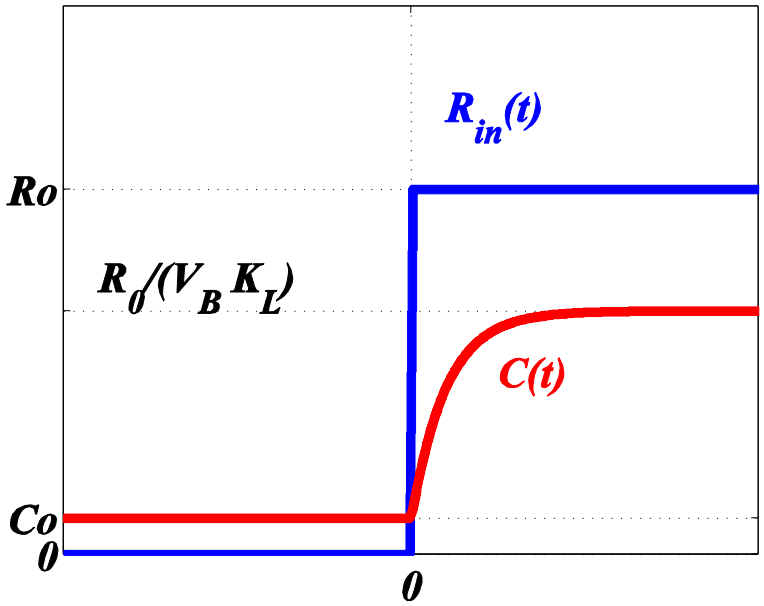


Example: *[Drug Delivery Dynamics]*

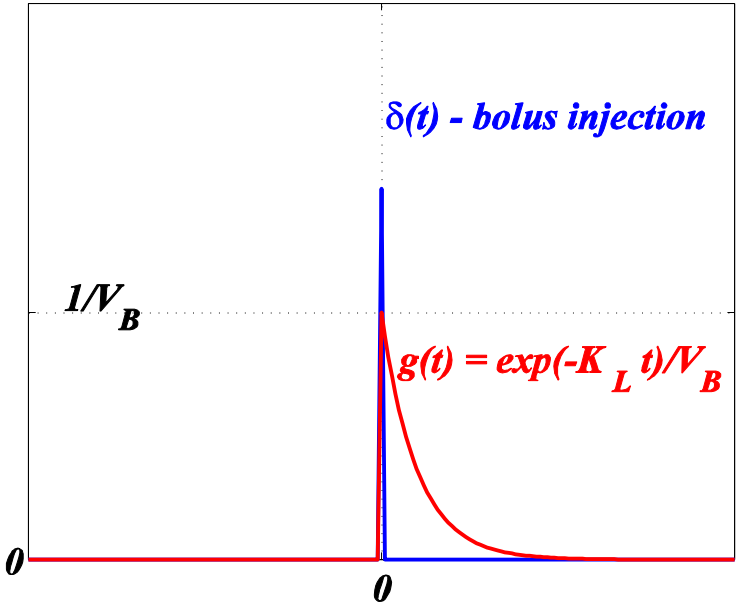
$$\dot{C}(t) = \underbrace{-K_L C(t)}_{\text{liver}} + \underbrace{\frac{1}{V_B} R_{in}(t)}_{\text{I.V. delivery}}$$

$C$ - drug concentration in blood [kg/m$^3$]
$K_L$ - liver constant [1/s]
$V_B$ - blood volume [m$^3$]
$R_{in}$ - rate of injection [kg/s]

I.V. drip




bolus injection

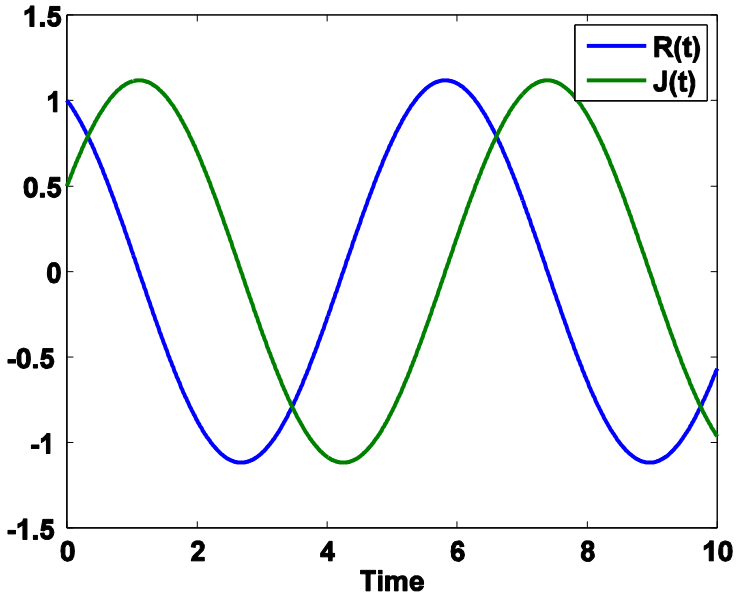


Example: *[Dynamics of Emotions]* (S. Strogatz, *Mathematics Magazine*, 1988)

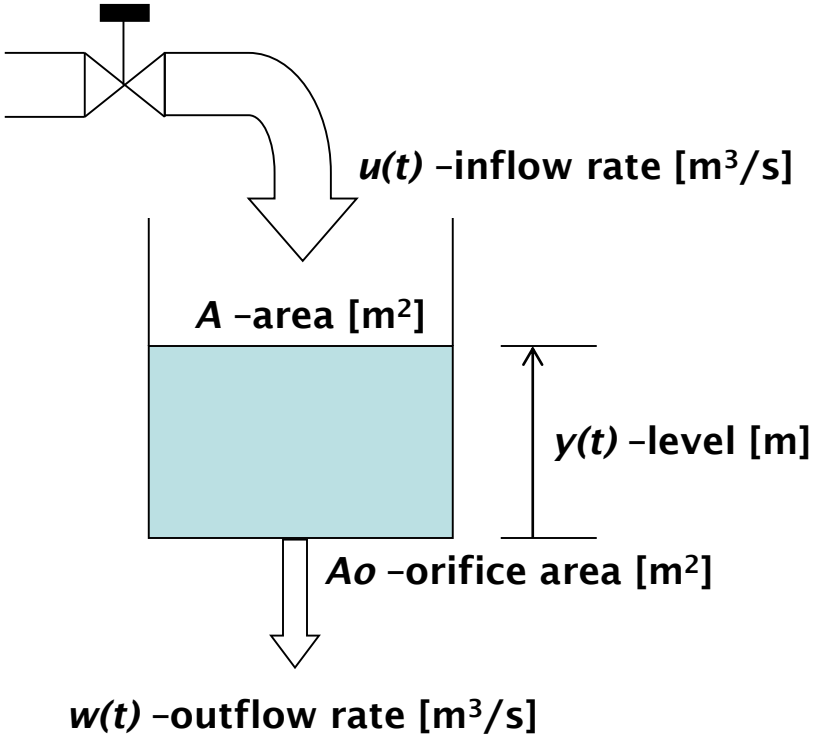
$$\dot{R}(t) = -aJ(t)$$
$$\dot{J}(t) = bR(t)$$

$R(t)$ – Romeo's love $(R > 0)$/hate $(R < 0)$ for Juliet
$J(t)$ – Juliet's love $(J > 0)$/hate $(J < 0)$ for Romeo
$a, b > 0$

Juliet's love echoes Romeo's. Romeo is a fickle lover. Their ill-fated romance consists of a never-ending cycle of love and hate.



# Canonical 1st Order LTI System




$$\frac{dV(t)}{dt} = \text{inflow rate} - \text{outflow rate}$$

$$A\dot{y}(t) = u(t) - \underbrace{w(t)}_{\mu Ao\sqrt{2gy(t)}}$$

$$A\dot{y}(t) + \mu Ao\sqrt{2gy(t)} = u(t)$$

(E. Torricelli 1643)

After linearization and change of variables: $\tau\,\dot{z}(t) + z(t) = kv(t)$

Transfer function (leaky integrator):

$$T(s) = \frac{k}{\tau s + 1}$$

DC gain

Time constant

# Canonical 2nd Order LTI System

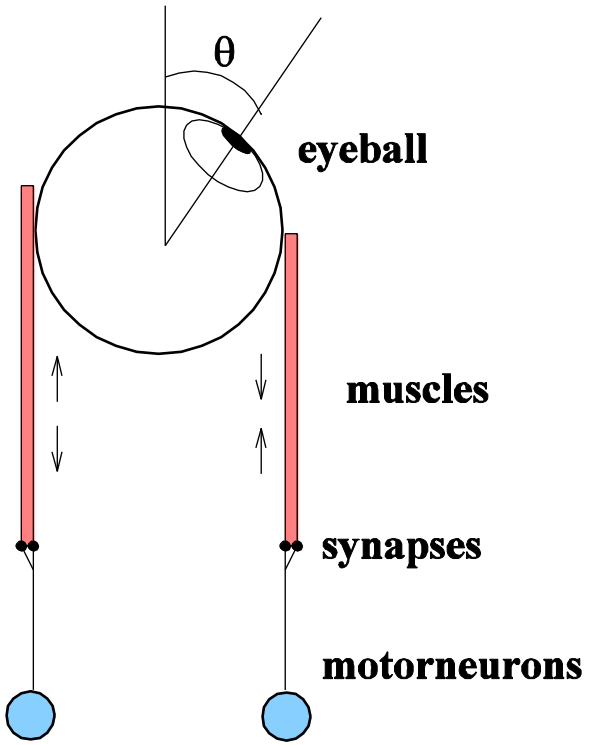
$$J\ddot{\theta}(t) + B\dot{\theta}(t) + K\theta(t) = \tau(t)$$

$$\omega_n := \sqrt{\frac{K}{J}}$$

$$if\ B^2 - 4KJ < 0, \qquad \zeta := \frac{B}{2\sqrt{KJ}}$$

$$T := \frac{2J}{B}$$

$$\ddot{\theta}(t) + 2\zeta\omega_n\dot{\theta}(t) + \omega_n^2\theta(t) = k\omega_n^2\tau(t)$$




Transfer function: $$T(s) = \frac{k\omega_n^2}{s^2 + 2\zeta\omega_n s + k\omega_n^2}$$

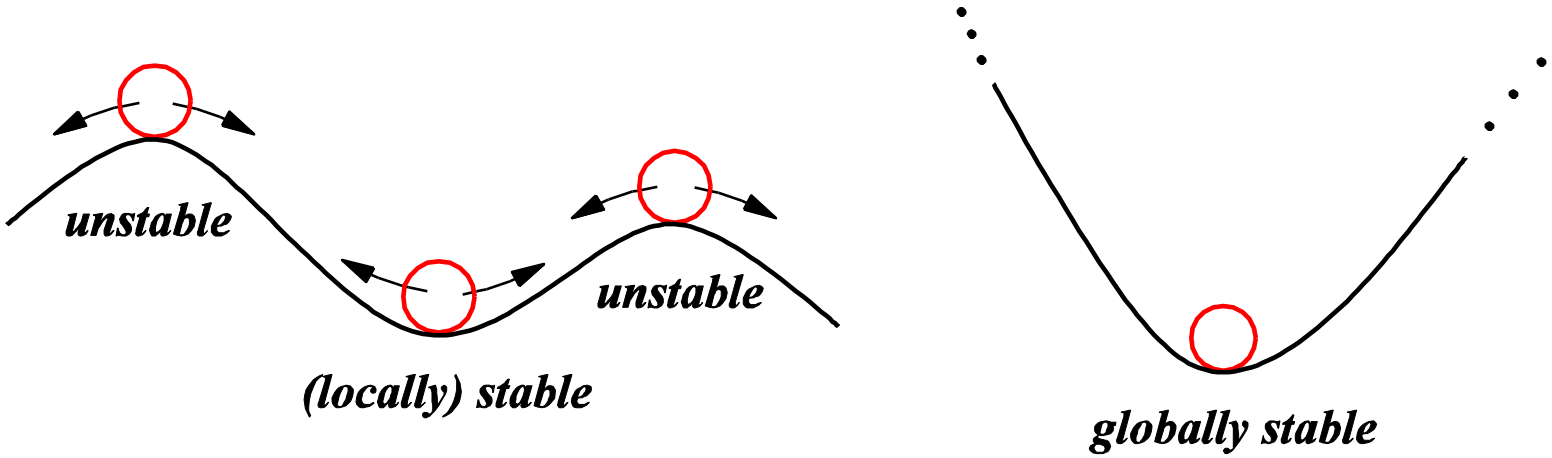
**Damping factor** **Natural frequency**

# Equilibrium, Stability

$$\underbrace{\dot{x}_e}_{0} = Ax_e + B\underbrace{u}_{0}$$

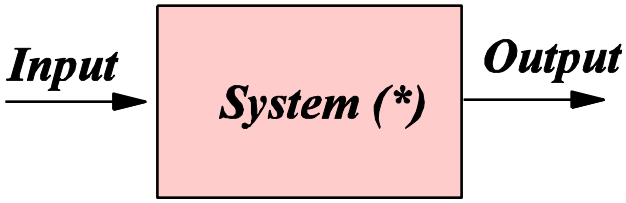
$$Ax_e = 0$$

$$x_e = 0$$

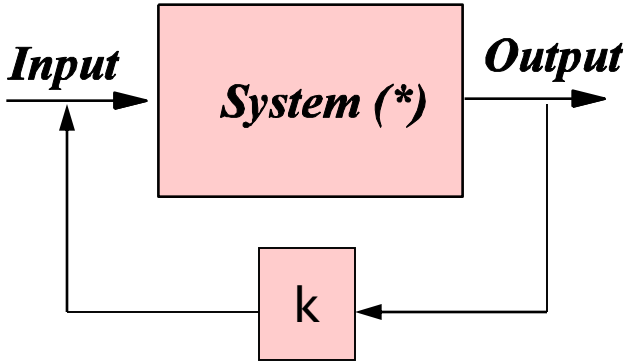



(A. Lyapunov 1892)

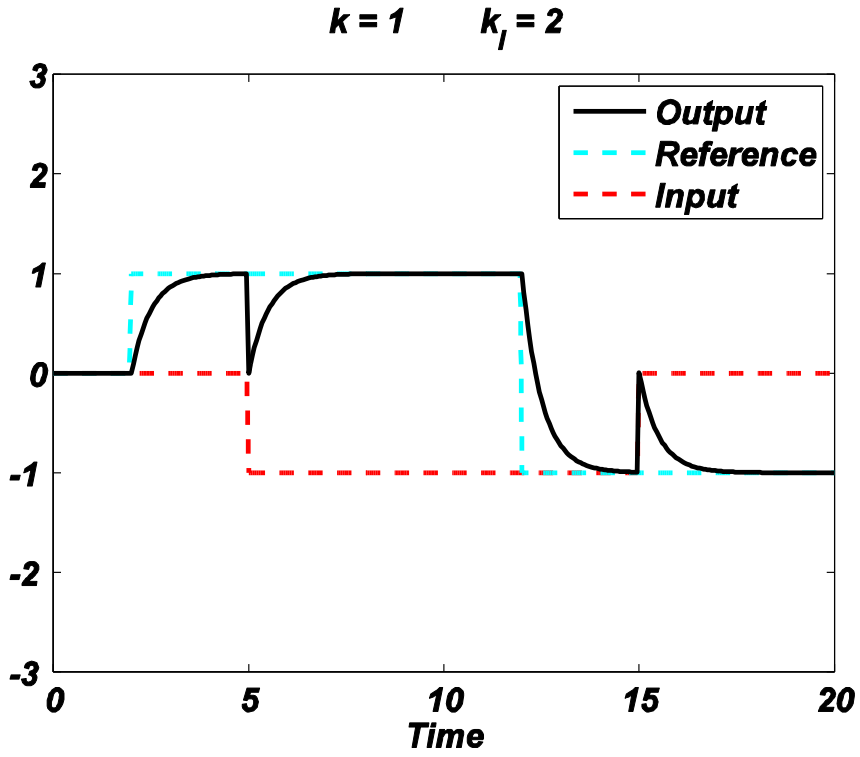
# Feedback and Control




(unstable system)




(stable system)



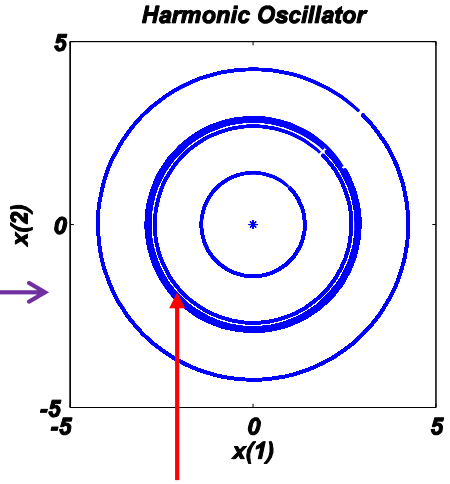

asymptotic
i) reference tracking
ii) disturbance rejection

# Nonlinear Systems

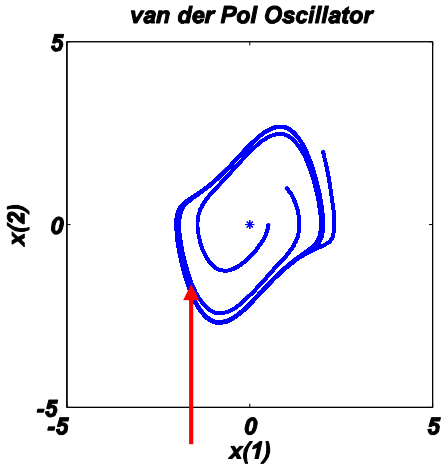
- Compared to linear systems, nonlinear systems are poorly understood.
- Nonlinear systems are by far more interesting than linear systems.
- Virtually all systems in nature are nonlinear.

Some Distinct Properties:

1) Frequency Mixing
2) Intermodulation Distortion
3) Resonant Jump Phenomenon
4) Limit Cycle Phenomenon
5) Finite Escape Time
6) Strange Attractors/Chaos




closed but not isolated




closed and isolated

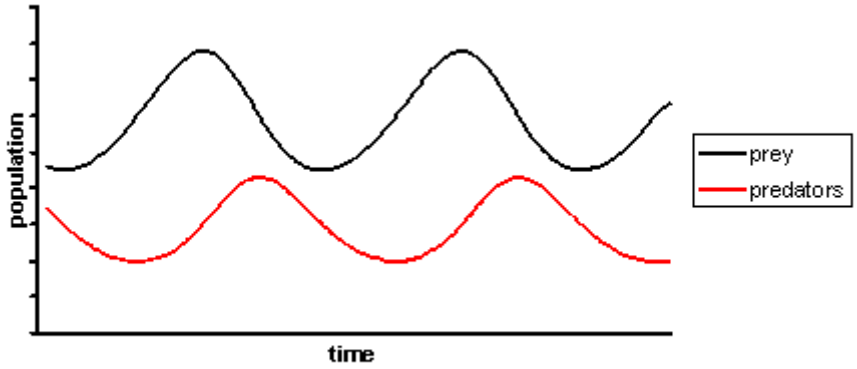
$$\dot{y}(t) = y^2(t)$$

$$y(t) = \frac{y(t_0)}{1 - (t - t_0)y(t_0)}$$

Example: *[Predator-prey equations]* (Lotka-Volterra)

$$\dot{x}(t) = \alpha x(t) - \beta x(t)y(t)$$
$$\dot{y}(t) = \delta x(t)y(t) - \gamma y(t)$$

(time invariant, nonlinear system)
$x$ - the size of prey population at time $t$;
$y$ - the size of predator population at time $t$;
$\alpha, \beta, \gamma, \delta$ - parameters representing the interaction of the two species.



Example: *[Enzyme Kinetics]* (Michaelis-Menten)

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

*E* - enzyme, *S* - substrate, *ES* - enzyme-substrate complex, *P* - product

$k_1, k_2, k_{-1}$ - the reaction rate constants

$[S], [ES], [P]$ - concentrations

$$\begin{aligned}
\frac{d[S]}{dt} &= -k_1[E][S] + k_{-1}[ES] \\
\frac{d[ES]}{dt} &= k_1[E][S] - k_{-1}[ES] - k_2[ES] \\
\frac{d[P]}{dt} &= k_2[ES]
\end{aligned}$$

Can predict (and manipulate) the rate of product formation.

Example: *[Disease Outbreak]* (foot and mouth disease, UK 2001, Ferguson et al., *Science*, 2001)

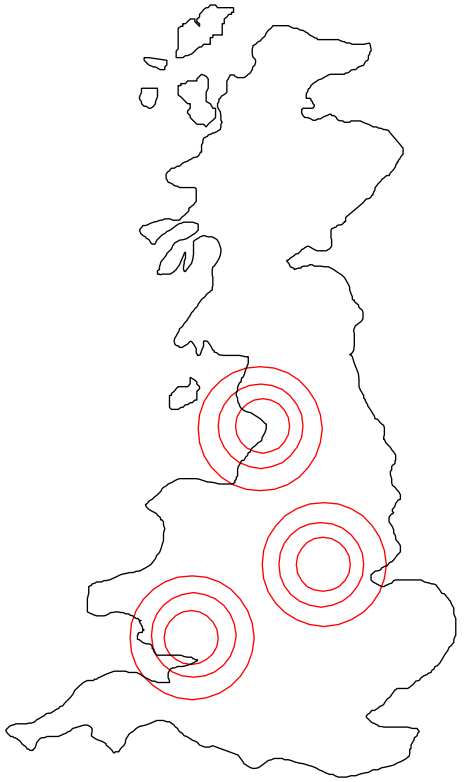
$$\mathcal{F}\left(\frac{\partial y(\xi,\eta,t)}{\partial t}, \frac{\partial y(\xi,\eta,t)}{\partial \xi}, \frac{\partial y(\xi,\eta,t)}{\partial \eta}, \theta(\xi,\eta,t), \ldots\right) = u(\xi,\eta,t)$$

(spatially distributed, nonlinear system)

$y(\xi,\eta,t)$ - degree of infection at place $(\xi,\eta)$ and time t.

$u(\xi,\eta,t)$ - control variable (slaughter, vaccinate, etc.)

What is the best control strategy?



Example: *[Model of Barnacle Giant Muscle Fiber]* (Morris & Lecar, *Biophys.J.*, 1981)

$$
\begin{aligned}
C\,\dot{V}(t) &= I(t) - g_{Ca} m_\infty(V)(V - V_{Ca}) - g_K w(t)(V - V_K) \\
&- g_L(V - V_L) \\
\tau_m(V)\,\dot{m}(t) &= \phi_m(m_\infty(V) - m(t)) \\
\tau_w(V)\,\dot{w}(t) &= \phi_w(w_\infty(V) - w(t))
\end{aligned}
$$

where

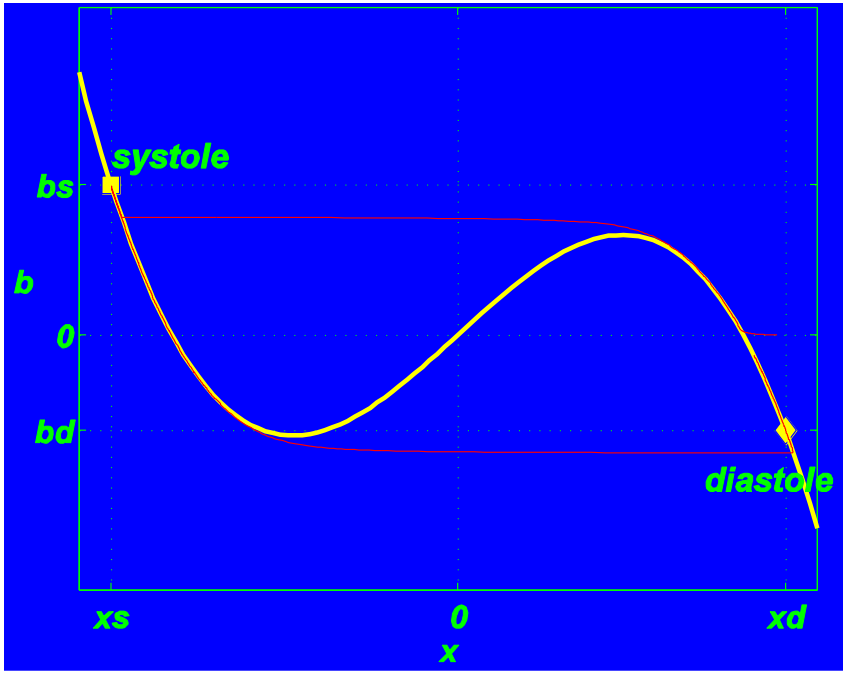
$$
\begin{aligned}
m_\infty(V) &= 0.5\left(1 + \tanh\left(\frac{V - V_1}{V_2}\right)\right) \\
\tau_m(V) &= \frac{1}{\cosh((V - V_1)/2V_2)} \\
w_\infty(V) &= 0.5\left(1 + \tanh\left(\frac{V - V_3}{V_4}\right)\right) \\
\tau_w(V) &= \frac{1}{\cosh((V - V_3)/2V_4)}
\end{aligned}
$$

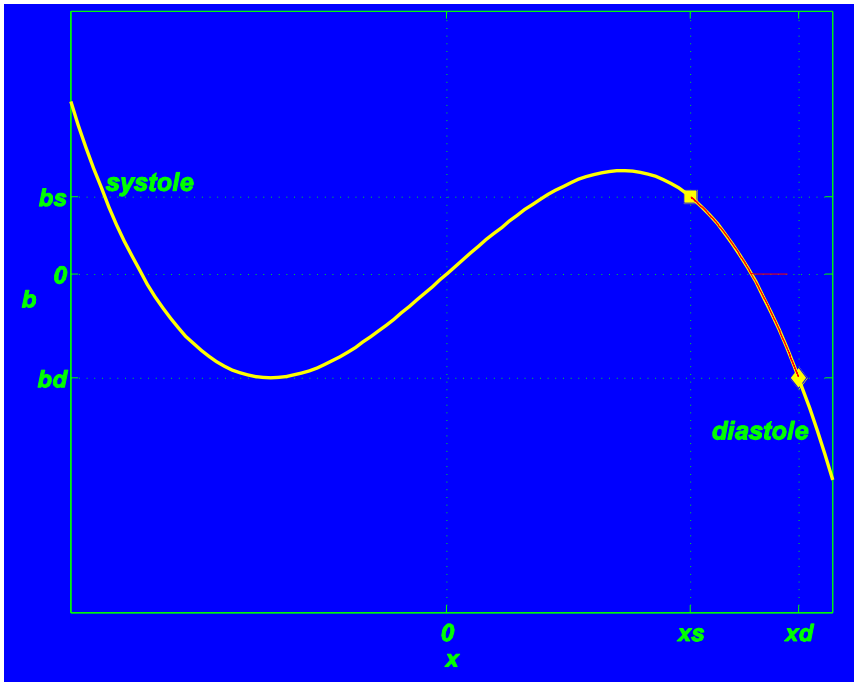
Example: *[Heart Dynamics]* (Zeeman, 1972)

$$\begin{aligned} \varepsilon \dot{x}(t) &= -\left[x^3(t) - Tx(t) + b(t)\right] \\ \dot{b}(t) &= [x(t) - x_d] + (x_d - x_s)\, u(x(t), b(t)) \end{aligned}$$

where

$$u(x,b) = \begin{cases} 1, & \begin{cases} (i) & b_d \le b \le b_s \quad \text{and} \quad x^3 - Tx + b > 0 \\ (ii) & b > b_s \quad \forall x \end{cases} \\ 0, & \text{otherwise} \end{cases}$$



Example: *[Genetic Toggle Switch (E. Coli)]* (Gardner et al. *Nature*, 2000)

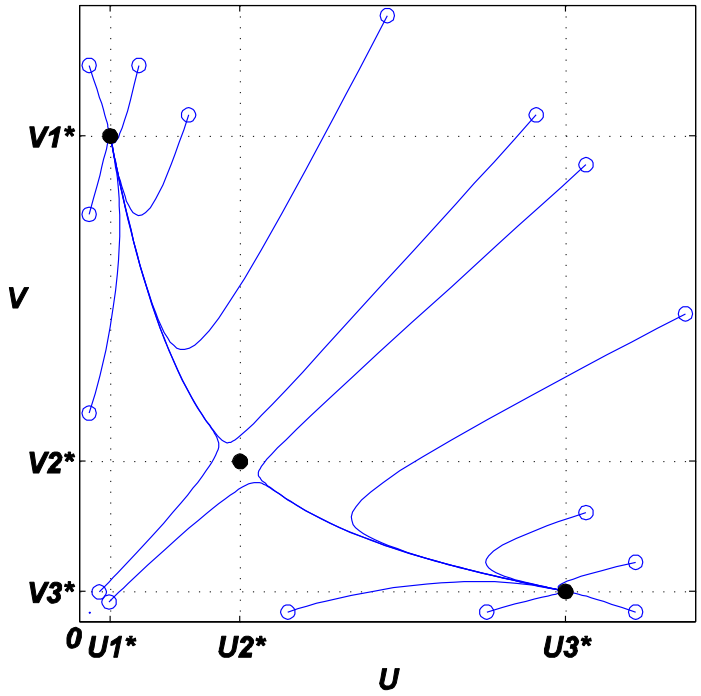
$$\dot{u}(t) = -u(t) + \frac{\alpha_u}{1 + v(t)^\beta}$$

$$\dot{v}(t) = -v(t) + \frac{\alpha_v}{1 + u(t)^\gamma}$$

$u(t)$ – concentration of repressor #1,

$v(t)$ – concentration of repressor #2

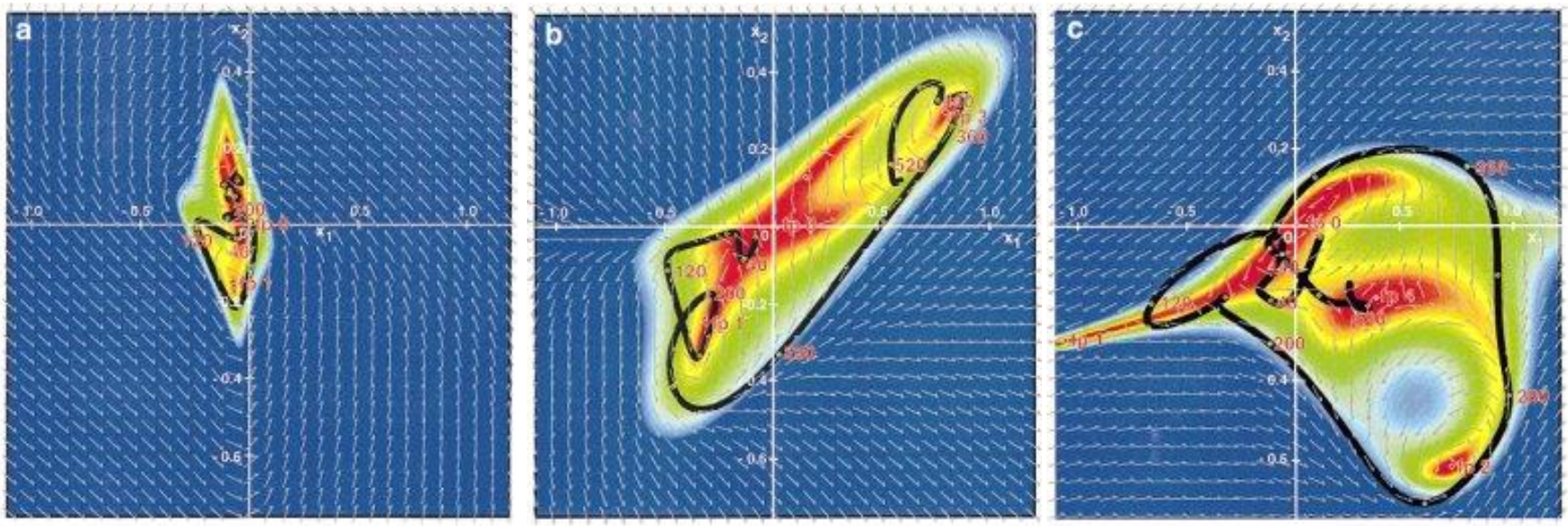
Each repressor inhibits the synthesis of the mRNA for the other.
By analyzing these equations, new bacteria can be engineered that have specific properties (e.g. we can design a gene network that is bi-stable)




bi-stable system

Example: *[Brain Dynamics]*

standard deviant novel

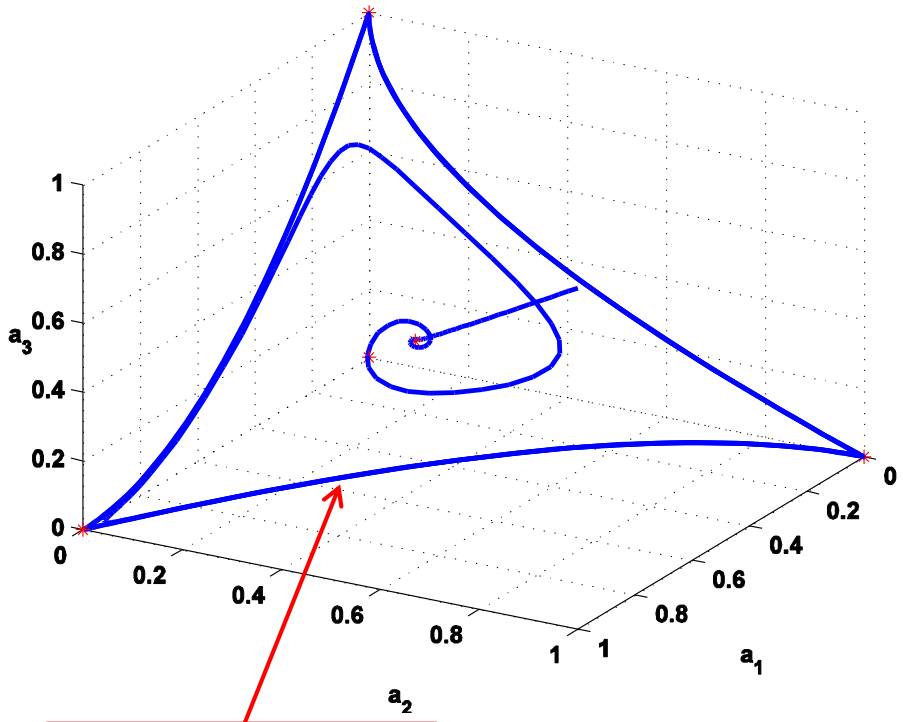


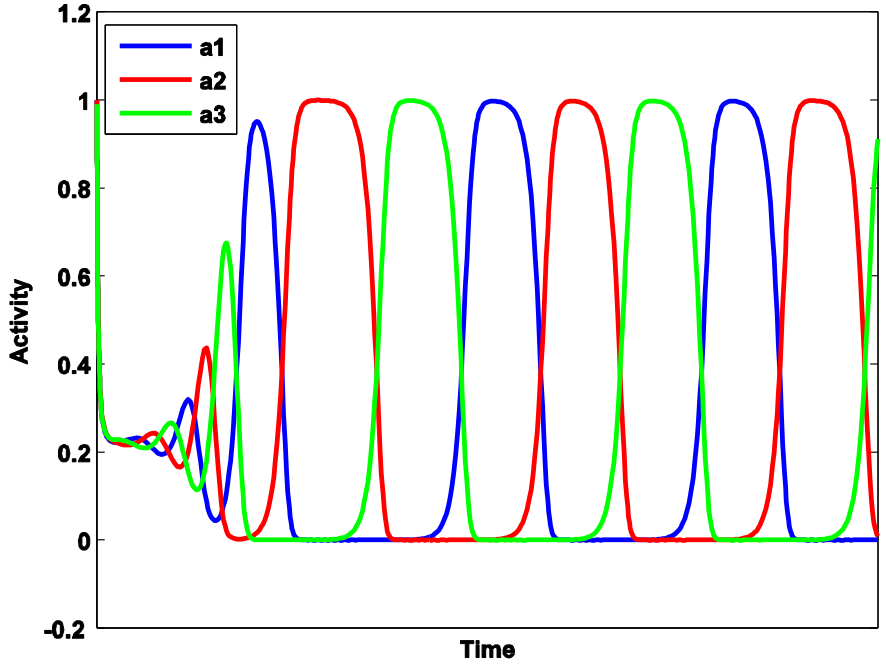

(courtesy of Prof. F. Kruggel)

## Example: *[Winnerless Competition Neural Dynamics]*

$$\begin{aligned}
\dot{a}_1(t) &= a_1(t)\left[1-(a_1(t)+\rho a_2(t)+\alpha a_3(t))\right] \\
\dot{a}_2(t) &= a_2(t)\left[1-(a_2(t)+\alpha a_1(t)+\rho a_3(t))\right] \\
\dot{a}_3(t) &= a_3(t)\left[1-(a_3(t)+\rho a_1(t)+\alpha a_2(t))\right]
\end{aligned}$$

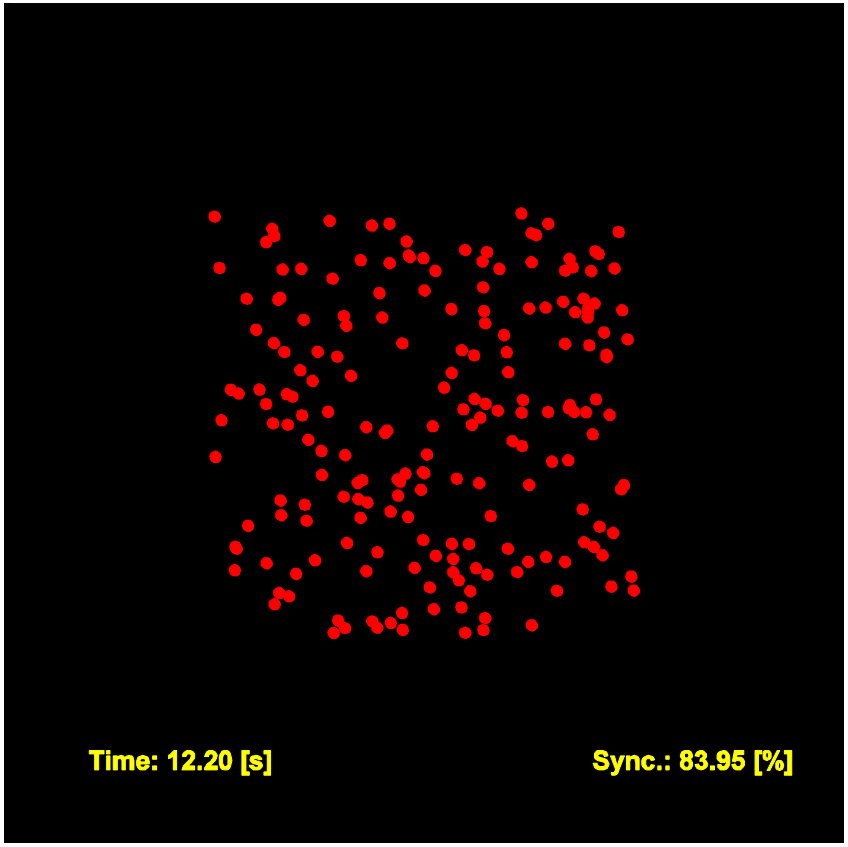
$\alpha, \rho$ - inhibitory coupling coefficients



## Example: *[Firefly Phase Dynamics]*

$$\dot{\theta}_i(t) = \omega_i + a\sum_{j\neq i}^{N_n} \sin\Big(\theta_j(t) - \theta_i(t)\Big), \quad \forall i = \{1,2,\cdots,N\}$$




demo:
`firefly_synch_neighbor.m`

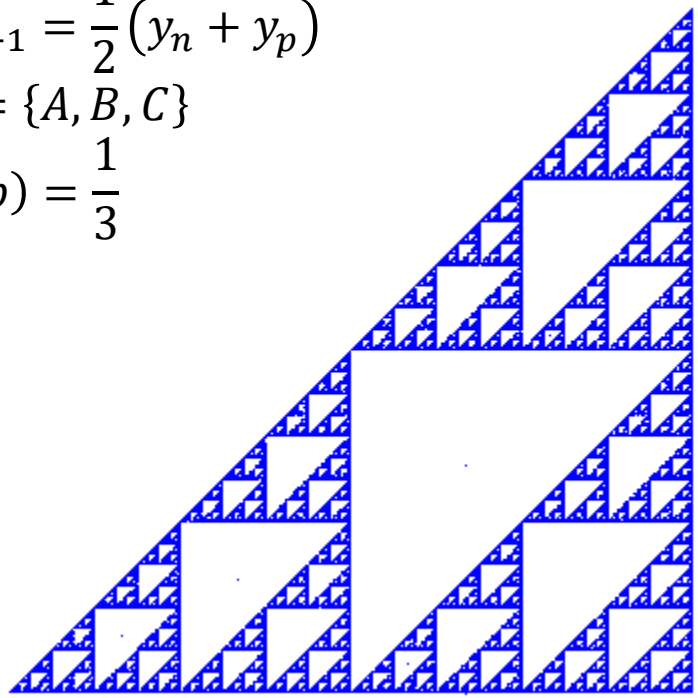
Example: *[Sierpinski triangle—stochastic chaos]*

$$x_{n+1} = \frac{1}{2}(x_n + x_p)$$

$$y_{n+1} = \frac{1}{2}(y_n + y_p)$$

$$p = \{A, B, C\}$$

$$P(p) = \frac{1}{3}$$




Barnsley's fern

demo: `fern_simulation.m`
`fern.m`

And many other examples:

- Modeling and controlling the depth of anesthesia.
- Modeling the lead uptake in children (lead exposure remains a problem)
- Modeling of arsenic transport and metabolism in animals, and trying to generalize models to humans.
- Modeling cancer spread and chemotherapy.
- Modeling chemical reaction (e.g. Belousov-Zhabotinsky), and designing new chemical experiments.
- etc.