Realization theory for systems biology

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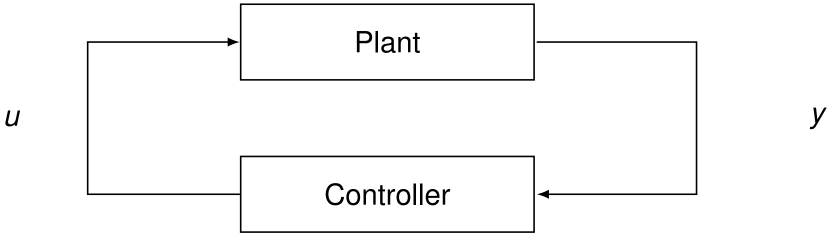
February 3, 2016

Outline

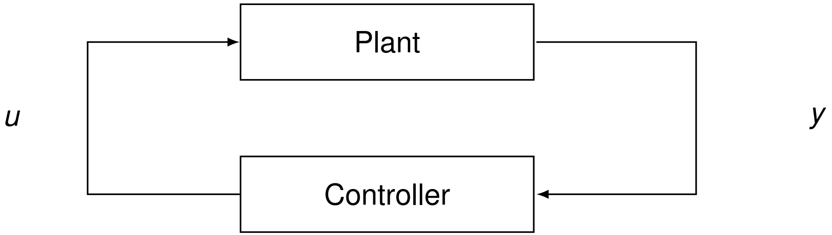
- Control theory and its role in biology.
- Realization problem: an abstract formulation.
- Realization theory of polynomial/rational/Nash systems.
- Realization theory of interconnection structure.

What is control theory about ?



- **Plant** – dynamical system (behavior changes with time)
- **Controller** – dynamical system

What is control theory about ?

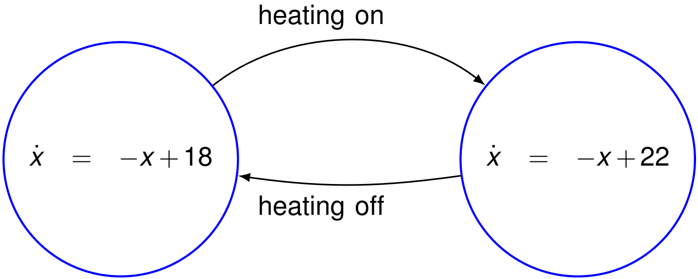


Task: find controller $u = \mathcal{C}(y)$ such that the y has the desired properties:

- $y \to 0$,
- $\int_0^\infty y^2(s)ds$ minimal, etc.

Example: thermostat

Plant



- Outputs: temperature x
- Control input: ‘heating on’ and ‘heating off’.

Control objective: maintain the temperature between $19.5 - 20.5^{\circ}\mathrm{C}$

Controller

$$\begin{array}{ll} \text{heating on} & \text{if } x < 19.5 \\ \text{heating off} & \text{if } x > 20.5 \end{array}$$

How do we solve control problems ?

Find a mathematical model (state-space representation)

$$\begin{aligned} \dot{x}(t) &= f(x(t), u(t)) \\ y(t) &= h(x(t), u(t)) \end{aligned}$$

of the input-output behavior of the plant

$$u \mapsto y.$$

Compute a controller

$$\begin{aligned} \dot{\xi}(t) &= M(\xi(t), y(t)) \\ u(t) &= C(\xi(t), y(t)) \end{aligned}$$

such that

$$y(.)$$

has the desired properties.

Mathematical tools for control

Tools for computing controllers:

- Stability theory of dynamical systems, Lyapunov's theory: the plant + controller

$$
\begin{aligned}
\dot{\xi}(t) &= M(\xi(t), y(t)) \\
u(t) &= C(\xi(t), y(t)) \\
\dot{x}(t) &= f(x(t), u(t)) \\
y(t) &= h(x(t))
\end{aligned}
$$

  should at least be (asymptotically) stable around a trajectory.

- Optimal control (calculus of variations): the control law $u(\cdot)$ should optimize a cost functional

$$\mathcal{J}(x, u)$$

- Controllers have to be computed: numerical methods, optimization.

Mathematical tools for control: cont

Making controllers requires models (differential/difference equations)

- How to estimate parameters of differential/difference equations from measured data (system identification: statistics, stochastic processes, optimization).
- How to simplify models without loosing too much of their observed behavior (model reduction).

  What is the relationship among various models which are observationally equivalent (realization theory) ?

Control theory and systems biology

- Feedback $\subseteq$ control theory $\subseteq$ cybernetics.
- Living organisms are control systems: plenty of feedback loops.
- Control theory tell us how to design feedback.
- Biologists want to understand why a particular feedback is there.

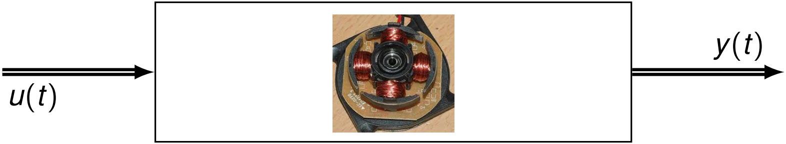
  Systems biology is about reverse engineering of feedback interconnection

Realization theory: reverse engineering of plant models

Realization theory: problem statement

We observe the input-output behavior (black-box)

of a physical process

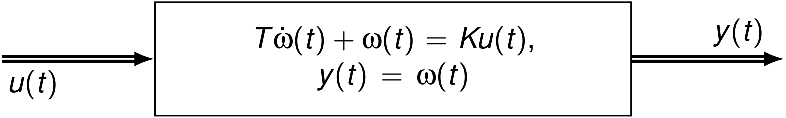


Realization theory: reverse engineering of plant models

Realization theory: problem statement

We observe the input-output behavior (black-box)

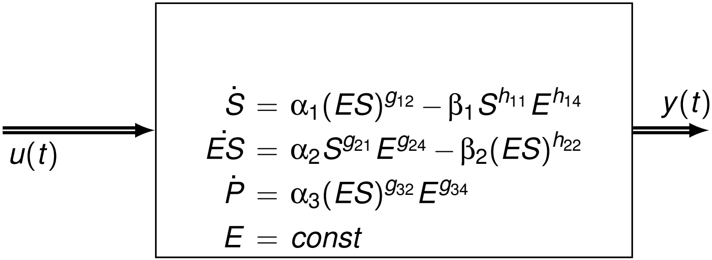
Which mathematical models (fixed structure)



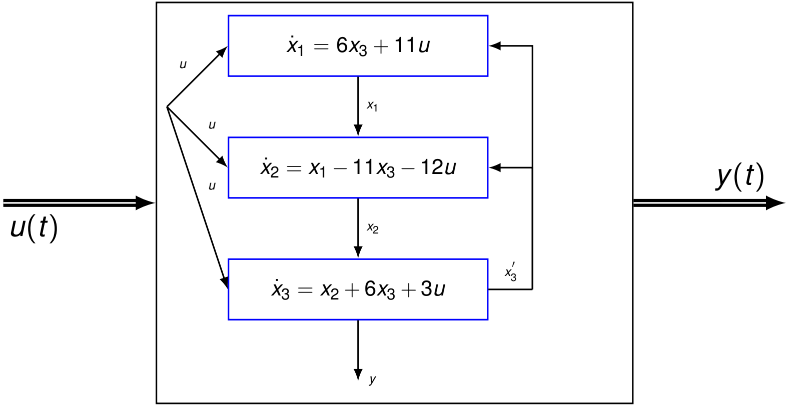
can describe the observed behavior of the black-box ?

Realization theory for biological systems

We can fix either the algebraic structure of the models.



or the interconnection structure



Polynomial/rational/Nash systems: biochemical reactions

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

mass-action kinetics: polynomial equations

$$\begin{aligned}
\dot{S} &= -k_1 E \cdot S + k_{-1} ES \\
\dot{ES} &= -\dot{E} = k_1 E \cdot S - (k_{-1} + k_2) ES \\
\dot{P} &= k_2 ES
\end{aligned}$$

Polynomial/rational/Nash systems: biochemical reactions

Michaelis-Menten kinetics: rational equations

$$\dot{S} = -k_1 \left(E_t - \frac{E_t S}{S + K_m} \right) S + k_{-1} \frac{E_t S}{S + K_m}$$
$$\dot{P} = \frac{v_{max} S}{S + K_m}$$

power-function models: Nash systems

$$\begin{aligned} \dot{S} &= \alpha_1 (ES)^{g_{12}} - \beta_1 S^{h_{11}} E^{h_{14}} \\ \dot{ES} &= \alpha_2 S^{g_{21}} E^{g_{24}} - \beta_2 (ES)^{h_{22}} \\ \dot{P} &= \alpha_3 (ES)^{g_{32}} E^{g_{34}} \\ E &= const \end{aligned}$$

Systems

input space $U \subseteq \mathbb{R}^k$

output space $\mathbb{R}^r$

$\Sigma = (X, f, h, x_0)$

- state-space $X = \mathbb{R}^n$
- dynamics $\dot{x}(t) = f(x(t), u(t))$ $\quad (\forall \alpha \in U : f_{\alpha,i} = f_i(x(\cdot), \alpha))$
- output function $y(t) = h(x(t))$
- initial state $x(0) = x_0 \in X$

Framework

Irreducible variety

$$X = X(\{f_1, \ldots, f_s\} \subseteq \mathbb{R}[X_1, \ldots, X_n]) = \{a \in \mathbb{R}^n \mid \forall 1 \leq i \leq s : f_i(a) = 0\}$$

Polynomial functions $A(X)$ and rational functions $Q(X)$

$$A(X) = \{p : X \to \mathbb{R} \mid \exists f \in \mathbb{R}[X_1, \ldots, X_n]\ \forall a \in X : p(a) = f(a)\}$$

$$Q(X) = \{p/q \mid p, q \in A, q \neq 0\}$$

Nash manifold

$$X = \bigcap_{i=1}^{d} \bigcup_{j=1}^{m_i} \{a \in \mathbb{R}^n \mid p_{ij}(a)\, \varepsilon_{ij}\, 0\} \qquad p_{ij} \in \mathbb{R}[X_1, \ldots, X_n], \varepsilon_{ij} \in \{<, =\}$$

Nash functions $N(X)$

analytic $f : X \to \mathbb{R}$ s.t. $\{(x, y) \in \mathbb{R}^{n+1} \mid f(x) = y\}$ is semi-algebraic

Polynomial and rational systems

$\Sigma = (X, f, h, x_0)$ - polynomial / rational system

- X - irreducible variety
- $\dot{x}(t) = f(x(t), u(t)) \quad \forall \alpha \in U : f_{\alpha,i} = f_i(x(\cdot), \alpha) \in A(X)$ / $Q(X)$
- $h : X \to \mathbb{R}^r$ - output map with $h_i \in A(X)$ / $Q(X)$
- $x_0 \in X$ - initial state

$$X = \mathbb{R}^2, \; h(x_1, x_2, x_3) = x_2$$
$$\dot{x}_1 = -ax_1 u + bx_3$$
$$\dot{x}_2 = cx_3$$
$$\dot{x}_3 = ax_1 u - (b+c)x_3$$
$$x_0 = (1, 1, 1)$$

$$X = \mathbb{R}^2, \; h(x_1, x_2) = x_2$$
$$\dot{x}_1 = -ax_1 + \frac{cx_1 + bx_1^2}{x_1 + d}$$
$$\dot{x}_2 = \frac{ex_1}{x_1 + d}$$
$$x_0 = (1, 1)$$

Realization theory of polynomial/rational systems: [Sontag 1970's, Bartuszewicz 1980's, Nemcova & Van Schuppen 2000's]:w

Nash systems

$\Sigma = (X, f, h, x_0)$ - Nash system

- X - semi-alg. connected Nash manifold
- $\dot{x}(t) = f(x(t), u(t)) \qquad \forall \alpha \in U : f_{\alpha,i} = f_i(x(\cdot), \alpha) \in N(X)$
- $h : X \to \mathbb{R}^r$ - output map with $h_i \in N(X)$
- $x_0 \in X$ - initial state

$$X = \mathbb{R}^3_+, \ h(x_1, x_2, x_3) = x_3$$
$$\dot{x}_1 = 1.75817.10^{-2.37} - 1.4489\, x_1^2 x_2^{-1.05}$$
$$\dot{x}_2 = 5^{0.5125} 6.04276.10^{-2}\, x_1^{0.75} x_2^{-0.45625} - 1.93417.10^{-4}\, x_2^{4.65} x_3^{-4.29}$$
$$\dot{x}_3 = 1.93417\, x_2^{4.65} x_3^{-4.29} - 3.4657.10^{-2}\, x_3^{0.3}$$
$$x_0 = (1, 1, 1)$$

Admissible controls

Inputs: piecewise-constant

$$u : \langle 0, T_u \rangle \to \Omega$$
$$\langle 0, T_u \rangle = \{s \in \mathbb{T} : 0 \leq s \leq t\}$$

$$\mathbb{T} = [0, +\infty) : \langle 0, T_u \rangle = [0, T_u]$$

Constant inputs:

$$[\omega, t] : \langle 0, t \rangle \ni s \mapsto \omega \in \Omega$$

Concatenation of inputs: $u : \langle 0, T_u \rangle \to \Omega$, $v : \langle 0, T_v \rangle \to \Omega$

$$u \sqcup v : \langle 0, T_u + T_v \rangle \ni t \mapsto \begin{cases} u(t) & t \in t \leq T_u \\ v(t - T_u) & t > T_u \end{cases}$$

Admissible controls: continued

Set of admissible control inputs $\mathcal{U}_{pc}$
– a set of piecewise-constant controls such that

- constant inputs belong $\mathcal{U}_{pc}$

$$\forall \omega \in \Omega\ \exists t \in \mathbb{T} : \ [\omega, t] \in \mathcal{U}_{pc}$$

- $\mathcal{U}_{pc}$ is closed under restricting inputs to an interval

$$\forall u \in \mathcal{U}_{pc}\ \forall t \in \langle 0, T_u \rangle : \ u|_{\langle 0,t \rangle} \in \mathcal{U}_{pc}$$

- Inputs from $\mathcal{U}_{pc}$ can be extended on a small time interval with any constant.

$$\forall u \in \mathcal{U}_{pc}\ \forall \omega \in \Omega\ \exists \varepsilon > 0 : \ \text{and } u \sqcup [\omega, \varepsilon] \in \mathcal{U}_{pc}$$

Problem formulation

Response maps

$p : \mathcal{U}_{pc} \to \mathbb{R}^r$ is a response map if $(p_j \in \mathcal{A}(\mathcal{U}_{pc} \to \mathbb{R}))$

$$p_j(u) = p_j((\alpha_1, t_1)\cdots(\alpha_k, t_k)) = p_{j_{\alpha_1,\ldots,\alpha_k}}(t_1, \ldots, t_k)$$
$$= \sum_{j_1,\ldots,j_k=0}^{\infty} a_{j_1,\ldots,j_k} \Pi_{i=1}^{k} t_i^{j_i} \qquad \forall u \in \mathcal{U}_{pc}$$

Realization problem - existence

Given a response map $p : \mathcal{U}_{pc} \to \mathbb{R}^r$

Find a system $\Sigma = (X, f, h, x_0)$ such that

$$p(u) = h(x_\Sigma(T_u; x_0, u)) \text{ for all } u \in \mathcal{U}_{pc} \subseteq \mathcal{U}_{pc}(\Sigma)$$

Rational systems: some definitions

Σ is reachable if the set of reachable states $x(t)$ is Zariski dense.

The observation algebra $Q(\Sigma)$ is the smallest algebra which contains h and which is closed under the Lie-derivative L_{f_α}, $\alpha \in \mathbb{R}^m$.
Σ is observable, if $Q(\Sigma)$ equals the ring of rational functions.

For simplicity: output dimension 1.

D_α – derivation on the space of input-output maps

$$D_\alpha \varphi(u)(s) = \frac{d}{dt} \varphi(u \sqcup (\alpha, t))(t+s)|_{t=0^+}$$

$A(p)$ – be the smallest algebra which contains p and which is closed under derivation D_α.

$Q(p)$ – the quotient field of $A(p)$.

Realization theory of rational systems [Nemcova, Van Schuppen]

Σ rational system

- If Σ is observable and reachable, then it is minimal. The converse is true under further conditions.
- Σ is minimal if and only if $\mathrm{trdeg}\, Q(\Sigma) = \dim A(p)$.
- If two rational systems are both realizations of p, they are both reachable and observable, then they are birationally isomorphic.
- Any rational system can be converted to a reachable and observable one, while preserving the input-output behavior.
- p has a realization by a rational system if and only if $Q(p)$ is finitely generated.

Application of realization theory: identifiability

Parametrized system $\Sigma(P) = \{\Sigma(\theta) = (X^{\theta}, f^{\theta}, h^{\theta}, x_0^{\theta}) \mid \theta \in P\}$

- $P \subseteq \mathbb{R}^s$ an irreducible variety - parameter set
- the same input spaces $U \subseteq \mathbb{R}^m$ and output spaces $\mathbb{R}^r$

A parametrization $\mathcal{P} : P \to \Sigma(P)$ is

- globally identifiable if each θ can be determined uniquely from the input-output map of $\Sigma(\theta)$.
- structurally identifiable if each θ outside an algebraic set (of measure zero) can be determined uniquely from the input-output map of $\Sigma(\theta)$

Identifiability ensures that the parameter estimation problem is well posed.!

Application of realization theory: identifiability

Theorem

$\Sigma(P)$ - structured rational system:

- *structurally canonical ($\Sigma(\theta)$ reachable and observable for almost all θ)*
- *structurally distinguishes parameters ($\Sigma(\theta)$ is injective except on a set of measure zero)*

Then the following are equivalent

- $\mathcal{P} : \theta \to \Sigma(\theta)$ *is structurally identifiable*
- *For almost all θ_1, θ_2 the only isomorphism between $\Sigma(\theta_1)$ and $\Sigma(\theta_2)$ is the identity.*

.... can be extended to global identifiability.

Existence of Nash realizations

Theorem (Nemcova,Petreczky,Van Schuppen)

p has a Nash realization $\Rightarrow$ $\mathrm{trdeg}\, A_{obs}(p) < +\infty$

$\mathrm{trdeg}\, A_{obs}(p) < +\infty$ $\Rightarrow$ p has a Nash realization - open problem

Local realizations

Theorem (Nemcova, Petreczky)

$\mathrm{trdeg}\, A_{obs}(p) < +\infty, \ \ |U| < +\infty \quad \Rightarrow$
$\exists\, u \in \mathcal{U}_{pc} :$ p_u has a local Nash realization

local Nash realization $\Sigma = (X, f, h, x_0)$:

$$p(u) = h(x_\Sigma(T_u; x_0, u)) \qquad \forall\, u \in \mathcal{U}_{pc} \cap \mathcal{U}_{pc}(\Sigma) \text{ small enough}$$

shifted response map p_u:

$$p_u(v) = p(u \sqcup v) \qquad \forall\, v \in \mathcal{U}_{pc} \text{ s.t. } u \sqcup v \in \mathcal{U}_{pc}$$

Proof relies on implicit function theorem for Nash functions.

Semialgebraic reachability

$\Sigma = (X, f, h, x_0)$ Nash system

Σ semialgebraically reachable, if Σ semi-algebraically reachable if any Nash functions which vanishes on the reachable set equals zero, i.e.

$$\forall g \in N(X) : (g = 0 \text{ on } \mathcal{R}(x_0) \Rightarrow g = 0)$$

$$\mathcal{R}(x_0) = \{x_\Sigma(T_u; x_0, u) | u \in \mathcal{U}_{pc}(\Sigma)\}$$

Reachability reduction Every Nash system can be converted to a semi-algebraically reachable one, while remaining a local realization of the same input-output map.

The procedure relies on implicit function theorem for Nash functions.

Semialgebraic observability

$\Sigma = (X, f, h, x_0)$ Nash system
$A_{obs}(\Sigma)$ algebra generated by

$$h_i, \quad L_{\omega_1} \cdots L_{\omega_k} h_i \quad \forall i = 1, \dots, r, \omega_1, \dots, \omega_k \in \Omega, k \in \mathbb{N}.$$

$L_\omega g$ – Lie derivative
Σ semialgebraically observable $\Leftrightarrow$ $\mathrm{trdeg}\, A_{obs}(\Sigma) = \mathrm{trdeg}\, N(X)$

Observability reduction Every Nash system can be converted to a semi-algebraically observable one, while remaining a local realization of the same input-output map.

The procedure relies on implicit function theorem for Nash functions.

Minimality

Σ is minimal local realization of p $\Leftrightarrow$ $\dim \Sigma \leq \dim \Sigma'$ for all local realizations Σ' of p

Main results

- Σ local Nash realization of p_u

$$\Sigma \text{ minimal } \Leftrightarrow \dim \Sigma = \operatorname{trdeg} A_{obs}(p)$$
$$\Leftrightarrow \Sigma \text{ reachable + observable}$$

- Σ_1, Σ_2 reachable + observable local Nash realization of p

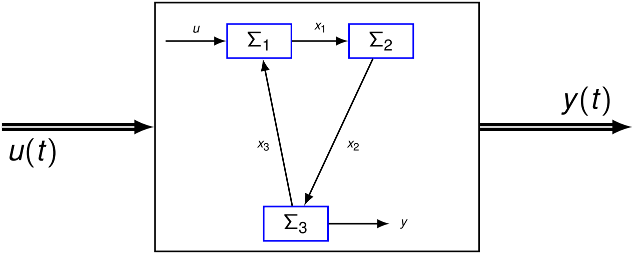
$\exists\, u, V_1 \subseteq X_{\Sigma_1}, V_2 \subseteq X_{\Sigma_2}: \; \Sigma_1^{V_1}, \Sigma_2^{V_2}$ isomorphic local realizations of p_u

Summary

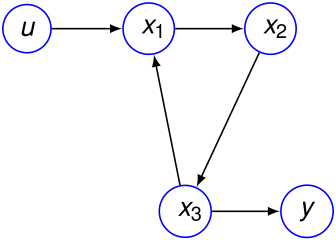
- Conditions for existence of a Nash system realizing the given input-output behavior
- Conditions for minimality, minimal systems are locally unique.
- We can convert any realization to a minimal one.

Problem formulation: interconnection structure

Interconnected system, $\Sigma_1, \Sigma_2, \Sigma_3$ subsystems



Its interconnection structure is the graph

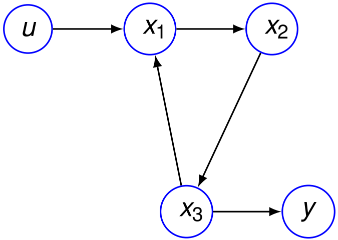


Realization with interconnection structure

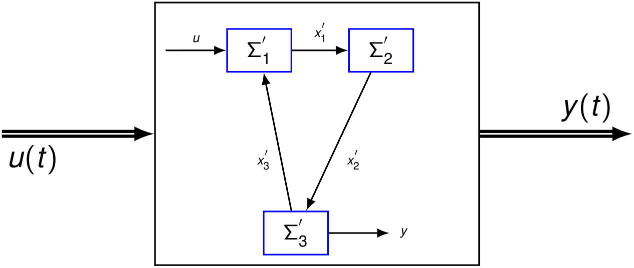
We observe the input-output behavior (black-box)

Problem: Given a graph find a complex system which reproduces the input-output behavior and has the same interconnection structure as this graph:

Example: interconnection structure



$\Longrightarrow$ we are looking for systems

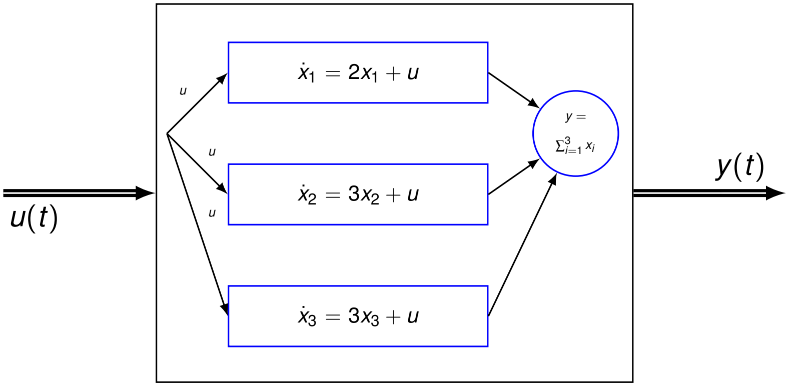


Realization of connectivity structure: motivation

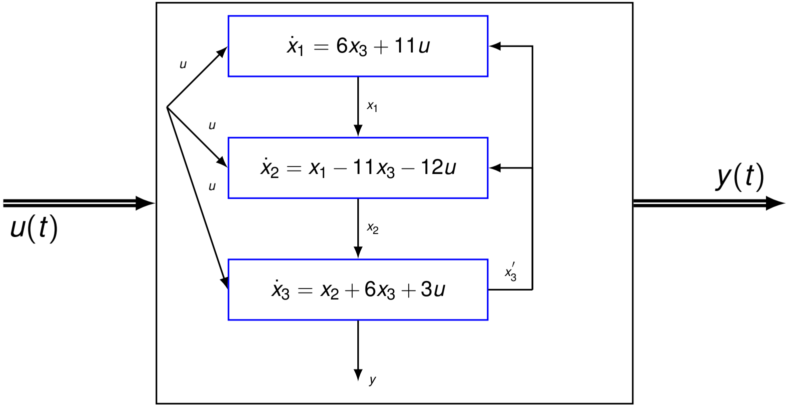
- Discovering the topology of gene regulatory networks.
- Drug design: if we know the topology, we know which link to cut.
- Discovering interaction between regions of brain using fMRI.

Reverse engineering of interconnection structure

It would be tempting to find the interconnection structure of a complete black-box: problem is not well posed.



has the the same input-output behavior from zero initial state as



but the connectivity structures are totally different !

Connectivity structure for linear system

A linear system is a diff. equation

$$\dot{x} = Ax + Bu, \quad y = Cx, \quad x(0) = 0$$

$A \in \mathbb{R}^{n\times n}, C \in \mathbb{R}^{1\times n}, B \in \mathbb{R}^{n\times 1}$.

Connectivity structure is a directed graph $G = (V, E)$

- $V = \{\mathbf{x}_1, \ldots, \mathbf{x}_n, \mathbf{u}, \mathbf{y}\}$ vertices, $\mathbf{x}_1, \ldots, \mathbf{x}_n, \mathbf{u}, \mathbf{y}$ symbols.
- E edges:

$$e \in E \iff \begin{cases} e = (\mathbf{x}_j, \mathbf{x}_i) & A_{i,j} \neq 0 \\ e = (\mathbf{y}, \mathbf{x}_i) & C_i \neq 0 \\ e = (\mathbf{x}_i, \mathbf{u}) & B_i \neq 0 \end{cases}$$

Condensed graph GS: graph formed by strongly connected components of G

Connectivity structure for linear system

Suppose $H(s) = \frac{b(s)}{a(s)}$ and $\deg a(s) = n$

Theorem (Bras,Petreczky,Westra,Roebroeck,Peeters)

A condensed subgraph cannot have more components than the number of divisors of $a(s)$ *over reals.*

Extension to several outputs, further results exist.

Example: model of fMRI signal

$$\dot{\mathbf{x}} = \begin{bmatrix} 0.5u - 1.25x_1 - 2.5(x_2 - 1) \\ x_1 \\ x_2 - x_3^5 \\ 1.25x_2\left(1 - 0.2^{\frac{1}{x_2}}\right) - x_3^4 x_4 \end{bmatrix} \tag{1}$$

$$y = -0.04\frac{x_4}{x_3} - 0.112x_4 - 0.028x_3 + 0.18 \tag{2}$$

- y – MRI signal
- $x_1, \ldots, x_4$ – neuronal activity
- u – cognitive input.

Example: model of fMRI signal

Linearization:

$$\dot{\mathbf{z}} = \begin{bmatrix} -1.25 & -2.5 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 1 & -5 & 0 \\ 0 & 0.6 & -4 & -1 \end{bmatrix} \mathbf{z} + \begin{bmatrix} 0.5 \\ 0 \\ 0 \\ 0 \end{bmatrix} u \tag{3}$$

$$y = \begin{bmatrix} 0 & 0 & 0.012 & -0.152 \end{bmatrix} \mathbf{z} \tag{4}$$

$H(s) = \frac{0.082 - 0.0396s}{s^4 + 7.25s^3 + 15s^2 + 21.25s + 12.5}$

Divisors of the denominator: $s+1, s+2$ and $s^2+1.25s+2.5$

H cannot be realized by a system whose graph has more than 3 components.

H can be realized by a system whose graph has exactly 3 components.

Coordinated stochastic linear systems: discussion

- We characterized connectivity in terms of output processes.
- Old tool: Granger noncausality.

In neuroscience connectivity of brain regions is investigated, using:

- Recursive models relating future outputs to past ones, using Granger causality
- Difference equations in state-space form, using the graph of the system

The results above are the first step to reconcile these two approaches.

Conclusions

- Control theory could be useful for systems biology.
- Realization theory is important for biological modelling: sanity check.

Open problems:

- Is it relevant for biology ?
- We looked at the algebraic structure and the network topology: how to combine the two worlds ?
- For mathematicians: a lot of non-trivial (at least for control theorists) mathematics.