Realization theory for systems biology

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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 $u = C(y)$ such that the $y$ has the desired properties:

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

Plant

\[
\dot{x} = -x + 18 \quad \text{heating on}
\]
\[
\dot{x} = -x + 22 \quad \text{heating off}
\]

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

**Control objective:** maintain the temperature between 19.5 – 20.5°C

**Controller**

- heating on if \( x < 19.5 \)
- heating off if \( x > 20.5 \)
How do we solve control problems?

Find a mathematical model (state-space representation)

\[
\begin{align*}
\dot{x}(t) &= f(x(t), u(t)) \\
y(t) &= h(x(t), u(t))
\end{align*}
\]

of the input-output behavior of the plant

\[ u \mapsto y. \]

Compute a controller

\[
\begin{align*}
\dot{\xi}(t) &= M(\xi(t), y(t)) \\
u(t) &= C(\xi(t), y(t))
\end{align*}
\]

such that

\[ y(\cdot) \]

has the desired properties.
Mathematical tools for control

Tools for computing controllers:

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

\[
\begin{align*}
\dot{\xi}(t) &= M(\xi(t), y(t)) \\
u(t) &= C(\xi(t), y(t)) \\
\dot{x}(t) &= f(x(t), u(t)) \\
y(t) &= h(x(t))
\end{align*}
\]

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

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

\[
J(x, u)
\]

- 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 ⊆ control theory ⊆ 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)

\[ y(t) \]
\[ u(t) \]

of a physical process

\[ y(t) \]
\[ u(t) \]
Realization theory: reverse engineering of plant models

Realization theory: problem statement
We observe the input-output behavior (black-box)

\[ y(t) = \omega(t) \]

Which mathematical models (fixed structure)

\[ T\dot{\omega}(t) + \omega(t) = Ku(t), \]
\[ y(t) = \omega(t) \]

can describe the observed behavior of the black-box?
Realization theory for biological systems

We can fix either the algebraic structure of the models.

\[
\begin{align*}
\dot{S} &= \alpha_1 (ES)^{g_{12}} - \beta_1 S^{h_{11}} E^{h_{14}} \\
\dot{ES} &= \alpha_2 S^{g_{21}} E^{g_{24}} - \beta_2 (ES)^{h_{22}} \\
\dot{P} &= \alpha_3 (ES)^{g_{32}} E^{g_{34}} \\
E &= \text{const}
\end{align*}
\]
or the interconnection structure

\[
\begin{align*}
\dot{x}_1 &= 6x_3 + 11u \\
\dot{x}_2 &= x_1 - 11x_3 - 12u \\
\dot{x}_3 &= x_2 + 6x_3 + 3u
\end{align*}
\]
Polynomial/rational/Nash systems: biochemical reactions

\[ E + S \xrightleftharpoons[k_1]{k_{-1}} ES \xrightarrow{k_2} E + P \]

mass-action kinetics: polynomial equations

\[
\begin{align*}
\dot{S} &= -k_1 E \cdot S + k_{-1} ES \\
\dot{ES} &= -\dot{E} = k_1 E \cdot S - (k_{-1} + k_2)ES \\
\dot{P} &= k_2 ES
\end{align*}
\]
Polynomial/rational/Nash systems: biochemical reactions

Michaelis-Menten kinetics: rational equations

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

Power-function models: Nash systems

\[
\dot{S} = \alpha_1 (ES)^{g_{12}} - \beta_1 S^{h_{11}} E^{h_{14}}
\]
\[
\dot{E}S = \alpha_2 S^{g_{21}} E^{g_{24}} - \beta_2 (ES)^{h_{22}}
\]
\[
\dot{P} = \alpha_3 (ES)^{g_{32}} E^{g_{34}}
\]
\[
E = \text{const}
\]
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 $\dot{x}(t) = f(x(t), u(t))$ ($\forall \alpha \in U : f_{\alpha,i} = f_i(x(\cdot), \alpha)$)
- output function $y(t) = h(x(t))$
- initial state $x(0) = x_0 \in X$
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 \( Q(X) \)

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

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

Nash manifold

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

Nash functions \( N(X) \)

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

\[ \Sigma = (X, f, h, x_0) - \text{polynomial / rational system} \]

- \( X \) - 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

\[
\begin{align*}
X &= \mathbb{R}^2, \quad h(x_1, x_2, x_3) = x_2 \\
\dot{x}_1 &= -ax_1 u + bx_3 \\
\dot{x}_2 &= cx_3 \\
\dot{x}_3 &= ax_1 u - (b + c)x_3 \\
x_0 &= (1, 1, 1)
\end{align*}
\]

Realization theory of polynomial/rational systems: [Sontag 1970’s, Bartuszewicz 1980’s, Nemcova & Van Schuppen 2000’s]:
Slides of Jana Nemcova
Nash systems

\[ \Sigma = (X, f, h, x_0) - \text{Nash system} \]

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

\[ X = \mathbb{R}^3, \quad h(x_1, x_2, x_3) = x_3 \]
\[ \begin{align*}
\dot{x}_1 &= 1.75817 \cdot 10^{-2.37} - 1.4489 \cdot x_1^2 \cdot x_2^{-1.05} \\
\dot{x}_2 &= 5^{0.5125} \cdot 6.04276 \cdot 10^{-2} \cdot x_1^{0.75} \cdot x_2^{-0.45625} - 1.93417 \cdot 10^{-4} \cdot x_2^{4.65} \cdot x_3^{-4.29} \\
\dot{x}_3 &= 1.93417 \cdot x_2^{4.65} \cdot x_3^{-4.29} - 3.4657 \cdot 10^{-2} \cdot x_3^{0.3} \\
x_0 &= (1, 1, 1)
\end{align*} \]
Admissible controls

Inputs: piecewise-constant

\[ u : \langle 0, T_u \rangle \rightarrow \Omega \]
\[ \langle 0, T_u \rangle = \{ s \in T : 0 \leq s \leq t \} \]

\[ T = [0, +\infty) : \langle 0, T_u \rangle = [0, T_u] \]

Constant inputs:

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

Concatenation of inputs: \( u : \langle 0, T_u \rangle \rightarrow \Omega \), \( v : \langle 0, T_v \rangle \rightarrow \Omega \)

\[ u \sqcup v : \langle 0, T_u + T_v \rangle \ni t \mapsto \begin{cases} u(t) & t \in t \leq T_u \\ v(t - T_u) & t > T_u \end{cases} \]
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 (\( p_j \in \mathcal{A}(\mathcal{U}_pc \to \mathbb{R}) \))

\[
p_j(u) = p_j((\alpha_1, t_1) \cdots (\alpha_k, t_k)) = p_{\alpha_1,\ldots,\alpha_k}(t_1, \ldots, t_k)
\]

\[
= \sum_{j_1,\ldots,j_k=0}^{\infty} a_{j_1,\ldots,j_k} \prod_{i=1}^{k} t_i^{j_i} \quad \forall u \in \mathcal{U}_pc
\]

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 \( L_{f\alpha}, \alpha \in \mathbb{R}^m \).

Σ is observable, if \( Q(\Sigma) \) equals the ring of rational functions.

For simplicity: output dimension 1.

\( D_\alpha \) – 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 \( D_\alpha \).

\( Q(p) \) – 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 trdeg Q(Σ) = 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 \( \mathcal{P} : P \rightarrow \Sigma(P) \) is

- **globally identifiable** if each \( \theta \) can be determined uniquely from the input-output map of \( \Sigma(\theta) \).
- **structurally identifiable** if each \( \theta \) 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 \( \theta \))
- structurally distinguishes parameters (\( \Sigma(\theta) \) is injective except on a set of measure zero)

Then the following are equivalent

- \( \mathcal{P} : \theta \rightarrow \Sigma(\theta) \) is structurally identifiable
- For almost all \( \theta_1, \theta_2 \) 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 $\Rightarrow \text{trdeg } A_{obs}(p) < +\infty$

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

Theorem (Nemcova, Petreczky)

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

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

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

shifted response map \( p_u \):

\[ p_u(v) = p(u \sqcup v) \quad \forall v \in \mathcal{U}_{pc} \text{ s.t. } u \sqcup v \in \mathcal{U}_{pc} \]

Proof relies on implicit function theorem for Nash functions.
Semialgebraic reachability

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

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

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

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

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.

Slides of Jana Nemcova
Semialgebraic observability

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

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

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

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 \( p \) ⇔ \( \dim \Sigma \leq \dim \Sigma' \) for all local realizations \( \Sigma' \) of \( p \)

Main results

- \( \Sigma \) local Nash realization of \( p_u \)
  \[ \Sigma \text{ minimal} \iff \dim \Sigma = \text{trdeg} A_{obs}(p) \iff \Sigma \text{ reachable + observable} \]

- \( \Sigma_1, \Sigma_2 \) reachable + observable local Nash realization of \( p \)
  \[ \exists u, V_1 \subseteq X_{\Sigma_1}, V_2 \subseteq X_{\Sigma_2} : \Sigma_1^{V_1}, \Sigma_2^{V_2} \text{ isomorphic local realizations of } p_u \]
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)

\[ y(t) \]  
\[ u(t) \]

**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

\[ u \rightarrow x_1 \rightarrow x_2 \]

\[ x_3 \rightarrow y \]

\[ \implies \text{we are looking for systems} \]

\[ \Sigma' \]

\[ \Sigma_1' \rightarrow x_1' \rightarrow \Sigma_2' \]

\[ u(t) \rightarrow \Sigma_3' \rightarrow y \]

\[ y(t) \]
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.

\[ \dot{x}_1 = 2x_1 + u \]
\[ \dot{x}_2 = 3x_2 + u \]
\[ \dot{x}_3 = 3x_3 + u \]
\[ y = \Sigma_{i=1}^{3} x_i \]
has the same input-output behavior from zero initial state as

\[
\begin{align*}
\dot{x}_1 &= 6x_3 + 11u \\
\dot{x}_2 &= x_1 - 11x_3 - 12u \\
\dot{x}_3 &= x_2 + 6x_3 + 3u
\end{align*}
\]

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 \( G = (V, E) \)

- \( V = \{x_1, \ldots, x_n, u, y\} \) vertices, \( x_1, \ldots, x_n, u, y \) symbols.

- \( E \) edges:

\[ e \in E \iff \begin{cases} e = (x_j, x_i) & A_{i,j} \neq 0 \\ e = (y, x_i) & C_i \neq 0 \\ e = (x_i, u) & B_i \neq 0 \end{cases} \]

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

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

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

- \( y \) – MRI signal
- \( x_1, \ldots, x_4 \) – neuronal activity
- \( u \) – cognitive input.
Example: model of fMRI signal

Linearization:

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

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

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

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.