A Tutorial Overview of Control Theory for Non-Engineers

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ICM Satellite Meeting
Hyderabad, 16 August 2010

Outline

1. Basics of Control Systems
    - What is a Control System?
    - Examples of Control Systems
2. Modeling and Identification
    - Various Types of Control Systems Models
    - Considerations in Choosing a Model
3. Analysis
    - Feedback and Feedforward Control
    - Stability Analysis
4. Synthesis
    - Two Kinds of ‘Synthesis’

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What is a Control System?

A control system consists of

- Inputs, which are things that we can not only measure, but to which we can assign chosen values (constants or functions of time). Examples: Drug dosages and treatment regimens.
- Outputs, which are things that we can measure, but to which we cannot assign values. Examples: Concentrations of administered drug in urine, blood, etc.
- States, which are things that affect the outputs, but which cannot even measure because we cannot directly access them. Examples: Concentrations of drug in targeted organ.

A typical control problem consists of choosing the inputs so as to achieve one or more (possibly conflicting) objectives.

Abstract Depiction of a Control System

Inputs
(Assignable)

States
(Not Measurable)

Outputs
(Measurable)

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Examples of Control Systems

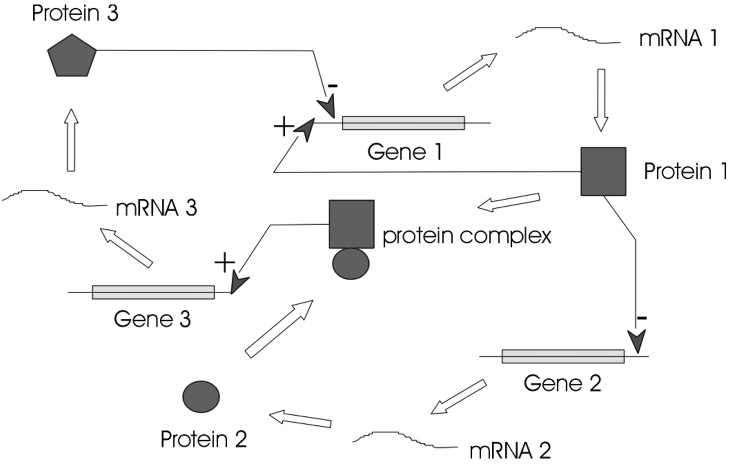
Traditional examples:

- Thermostats for controlling room (or furnace) temperature
- Pilot control systems for fighter planes (which are statically unstable)
- Automotive: anti-skidding, fuel efficiency, etc.

Biological examples:

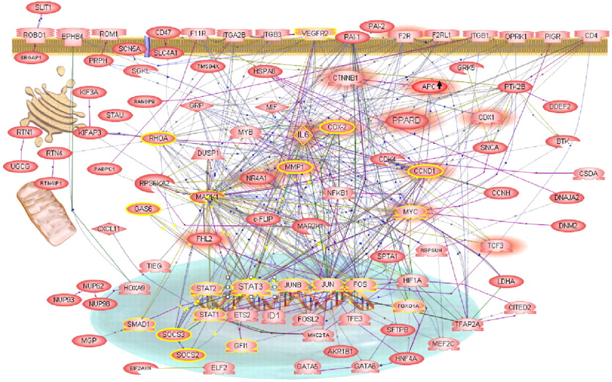
- Gene regulatory networks
- Insulin delivery and blood glucose regulation system (natural and artificial)
- Any orally administered drug passing through the body

A Typical Gene Regulatory Network



Source: Faigle/Schrader Group, University of Köln

An Angiogenic Regulatory Network



Source: "Transcriptional network governing the angiogenic switch in human pancreatic cancer" by A. Abdollahi et al., *PNAS*, July 31, 2007, Vol. 104, No. 31, pp. 12890-12895.

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Classes of Control Systems

We can classify control systems according to:

- Nature of time: Continuous-time versus discrete-time
- Nature of quantities: Continuous-state versus discrete-state
- Nature of behavior: Deterministic versus stochastic

All eight possible combinations have been (are being) studied.

Most books on control theory are too mathematically demanding for biologists. I recommend *Feedback Systems: An Introduction for Scientists and Engineers* by Karl-Johan Astrom and Richard M. Murray, Princeton University Press, 2008. (Freely downloadable!)

Various Types of Control Systems Models

For the most part (though not always), *models* of control systems fall into one of two types: State-space, and input-output.

State-space models usually arise from ‘first-principles modeling’ or ‘bottom-up modeling’. In the continuous-time, continuous-state case, the models usually take the form

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}), \mathbf{y} = \mathbf{h}(\mathbf{x}, \mathbf{u}),$$

where $\mathbf{u}, \mathbf{y}, \mathbf{x}$ denote respectively the input variables, the output variables, and the state variables.

If $\mathbf{f}, \mathbf{h}$ are linear functions of their arguments, then the system itself is said to be linear.

Role of Physiological Parameters

If we wish, we can separately identify a set of *physiological parameters* $\mathbf{p}$ and display the state equations in the form

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}, \mathbf{p}), \mathbf{y} = \mathbf{h}(\mathbf{x}, \mathbf{u}, \mathbf{p}).$$

Example: Michelis-Menten kinetics (compartmental) model of drug concentrations in various organs.

$$\dot{c}_i(t) = \frac{V_{\max} \delta_i(t)}{K_i + \delta_i(t)},$$

where

$$\delta_i(t) = -\sum_{j=1}^{n} \lambda_{ij} c_j(t) + u_i(t), \ \forall i.$$

Here K_i, λ_{ij} are physiological parameters.

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Identification of Parameters

Once a model of the form

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}, \mathbf{p}), \mathbf{y} = \mathbf{h}(\mathbf{x}, \mathbf{u}, \mathbf{p})$$

is formulated, the next step is to *identify* the parameters.

Useful rule of thumb: If there are n parameters in the vector $\mathbf{p}$, at least n^2 data points are needed for a statistically significant estimate of $\mathbf{p}$.

If data size is too small, we get into a problem known as 'memorization' – the model perfectly reproduces observed data but 'generalizes' very poorly.

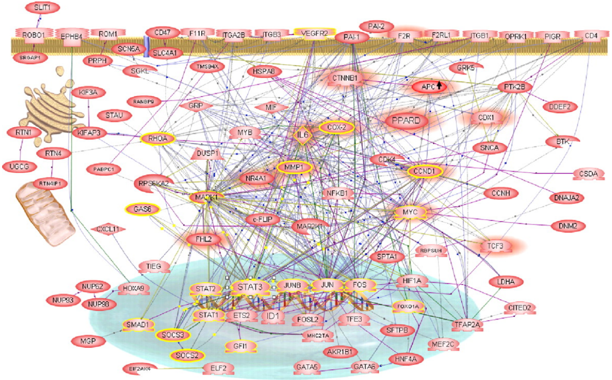
Input-Output (Black-Box) Models

In this kind of modeling, we perform experiments by applying various input signals $\mathbf{u}(\cdot)$ and measure the resulting output signals $\mathbf{y}(\cdot)$. Then we fit some models to the observations.

Advantages of I/O-models: Model size is chosen in accordance with available data; so 'memorizing' data is avoided.

Advantages of first-principles models: Every number in the model has a 'physical interpretation'. But usually the models are *far too complex*.

An Overly Complex Model of a Control System



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Pitfalls in Overly Complex Models

When the model is overly complex, *all attempts to fit the model to data will only result in garbage!*

System simplification *must be practiced* before trying to fit parameters (models) to data.

Need of the hour: A model simplification methodology that keeps in tact the subsystem of interest while simplifying everything else. Well-established with linear input-output models and state-space models. Not so well-established for nonlinear models.

In most problems involving drug delivery, simple input-output models are more than adequate.

Example: Work of Prof. Frank Doyle on insulin control systems.

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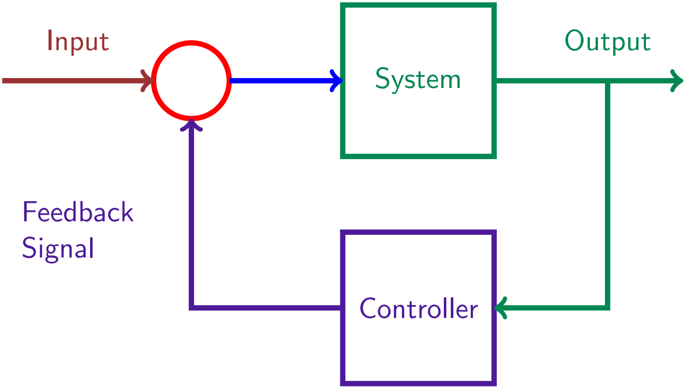
What is Feedback?

Feedback refers to the process whereby the measured output is processed and then used to adjust the input to the control system.



Kinds of Feedback

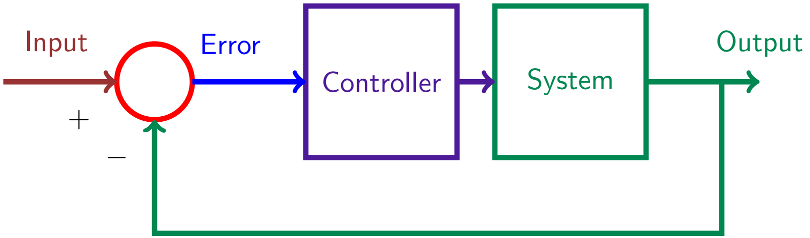
Feedback can be of two kinds: Positive and negative.

Negative feedback is by far the most common and used in problems of *stabilization and regulation*.

Positive feedback is used to cause *controlled instability*, which is required to maintain periodic processes, for example circadian rhythm.

Tracking Via Unit Negative Feedback

To ensure that the output signal ‘tracks’ the input signal, the following configuration is used.



The tracking error, processed by the controller, drives the system.

Type 1 Control Systems

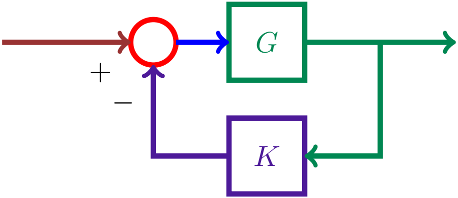
Unit feedback systems were used by James Watt in his governor in 1788!

Contemporary examples are: Thermostats used in air conditioners, and almost all instances of 'homeostasis' in biology.

In order to ensure that the tracking error goes to zero in response to a 'step' input, even if the system is imprecisely known, the controller must incorporate an integrator. This is known as a 'Type 1' control system.

Much of what is called 'homeostasis' in biology can be given this interpretation.

Feedback Reduces Sensitivity and Uncertainty



Suppose G, K are just constants. Overall (static) gain is

$$H = \frac{G}{1+GK} \approx \frac{1}{K} \text{ if } GK \gg 1.$$

$$S := \frac{d \log H}{d \log G} = \frac{dH/dG}{H/G} = \frac{1}{1+GK} \approx 0 \text{ if } GK \gg 1.$$

Closed-loop gain is *virtually insensitive to G!* (Black 1927)

Disturbances: Measured and Unmeasured

In addition to the control inputs, measured outputs, and non-measurable states, there can also be ‘disturbances’ in the system.

Disturbances can be of two kinds:

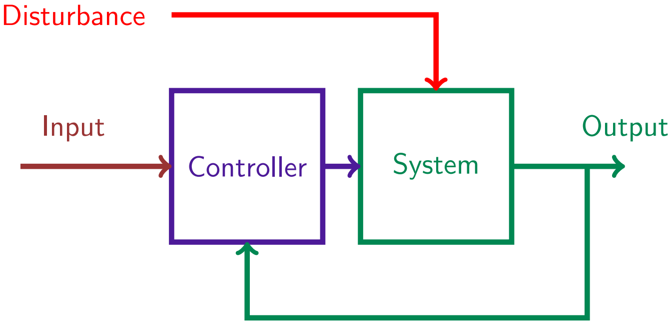
- Non-measurable, such as measurement errors (noise).
- Measurable (or at least, ‘estimable’), such as food intake for a diabetic.

For the former, ‘filtering’ is the only approach (not discussed here).

For the latter, ‘feedforward’ is a widely used approach.

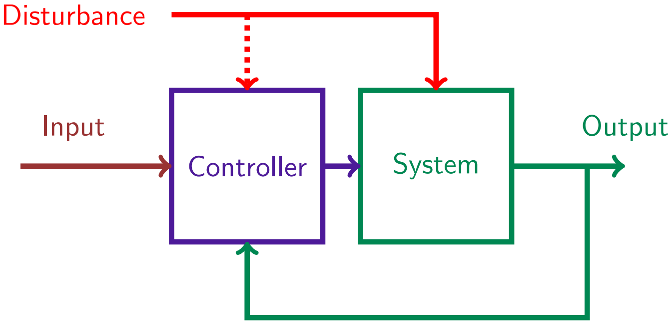
The next slides show a control system with disturbance, and with feedforward control.

Control System with Disturbance



If disturbance cannot be measured, the controller has to incorporate 'filtering' to attenuate effect of disturbance.

Control System with Feedforward Control



If disturbance can be measured, it can be another input to the controller.

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Lyapunov Stability

For the usual parametrized model

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}, \mathbf{p}), \mathbf{y} = \mathbf{h}(\mathbf{x}, \mathbf{u}, \mathbf{p}),$$

suppose that (i) $\mathbf{u} = \mathbf{0}$, so that the system is 'unforced' (no input), and (ii) a state vector $\mathbf{x}_0$ has the property that $\mathbf{f}(\mathbf{x}_0, \mathbf{0}, \mathbf{p}) = \mathbf{0}$. Then $\mathbf{x}_0$ is called an **equilibrium**.

Lyapunov stability theory addresses the question of what happens if the initial state of the system $\mathbf{x}(0)$ is *close to* the equilibrium. Specifically, is it the case that $\mathbf{x}(t) \to \mathbf{x}_0$ as $t \to \infty$? If so the equilibrium $\mathbf{x}_0$ is said to be **asymptotically stable**.

The Lyapunov Function

The basic idea of Lyapunov stability theory is that of the energy function, usually denoted by V. If V achieves its (local) minimum at the equilibrium $\mathbf{x}_0$ and if $V(\mathbf{x}(t))$ is strictly decreasing along the solution trajectories, then $\mathbf{x}(t) \to \mathbf{x}_0$ as $t \to \infty$ and the equilibrium $\mathbf{x}_0$ is asymptotically stable.

The same methodology can also be used to analyze the stability of *periodic orbits* also.

Input-Output Stability

Given the system

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}, \mathbf{p}), \mathbf{y} = \mathbf{h}(\mathbf{x}, \mathbf{u}, \mathbf{p}),$$

we can also ask, what kind of state trajectory $\mathbf{x}(\cdot)$ or output trajectory $\mathbf{y}(\cdot)$ results from applying an input signal $\mathbf{u}(\cdot)$?

Such questions form the domain of input-output stability theory.

Though connections exist between Lyapunov and I/O stability, in general the latter requires more advanced mathematics. But its applicability is also broader. For instance, the presence of delays (omnipresent in biology) is easily handled in I/O framework, not so easily in Lyapunov framework.

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Conventional Controller Design

In conventional control theory, 'synthesis' usually refers to the process of designing a controller (as shown on the next slide) for a given system, so as to make the overall system behave as desired (or close to it).

The premise is that before coming to this stage, the system has already been 'optimized' (fine-tuned) as much as possible.

This kind of philosophy is quite pertinent in problems where there is an external control signal being applied, e.g. insulin delivery (or more generally drug delivery of any sort), pacemakers, etc.

Standard methods exist, ranging from very elementary (PID, MPC) to very advanced (H_∞ control).

‘Synthesis’ in the Context of Biological Systems

In biological contexts, often ‘synthesis’ is the mirror image of ‘analysis’ whereby one keeps tinkering with the system until it behaves as desired – *without any controller*.

Example: Synthetic biology, design (*not control*) of genetic regulatory networks.

In this case ‘synthesis’ becomes essentially iterative analysis.

Special Features of Biological Control Systems

- Control enters via ‘parameters’ and is often just a constant, not a function of time. (Example: HIV).
- Strong role of physical topology (e.g. compartmental models in PK/PD)
- Control and state variables restricted to be nonnegative-valued (e.g. drug can only be injected, not taken out; concentrations can only be nonnegative)
- Presence of significant measurement delays.

Existing control theory does not always take into account these special features.

Conclusions

Control theory can only provide the *methodology and broad concepts* needed to analyze and synthesize biological systems.

Specific procedures and results can only come from thinking deeply about the problems at hand.

In the 1960s (my Ph.D. days) we discovered that solutions to control theory problems aren't found in mathematics books – we had to invent our own theories!

Today the same is also true about computational (or systems of synthetic) biology too!

Thank You!