Ctrl & Comp in Bio Sys - Westlake Univ., Fall 2025

Lecture 05: Feedback, Feedforward, and Noise in Biosystems

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1 Introduction: The Biomachine Perspective

1.1 Motivation and Principles

Biomachine is a perspective we can take on understanding biological systems. We treat them like machines.

Biological systems perform various functions just like engineered systems and machines. So principles on how to design machines with these functions can be used to understand why biological systems are designed the way they are.

However, biological systems *implement* the same principles using different physical components. So there are comparisons and contrasts. Even new theories and principles from biology can flow back to engineering.

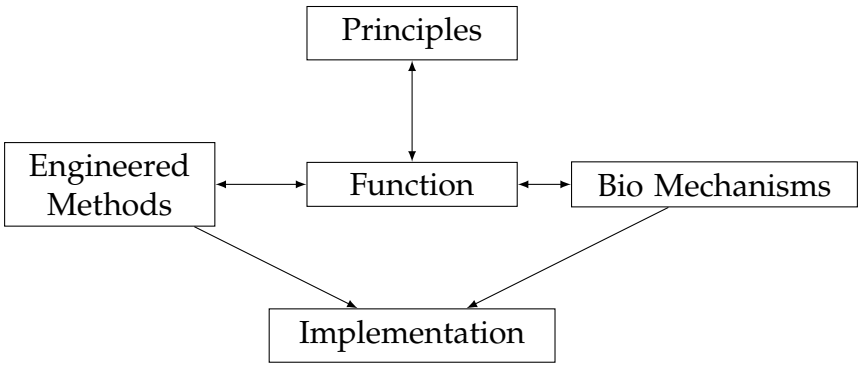


Figure 1 The relationship between principles, functions, and implementations in biological and engineered systems

1.2 Adaptation: The Function We Started With

Adaptation is a hallmark for biological systems and autonomous machines we build.

In control theory, we model a system as:

$$\dot{x} = f(x, w) \tag{1}$$

$$y = h(x, w) \tag{2}$$

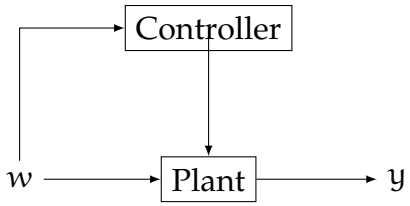
where w is a disturbance input and y is the output.

Perfect adaptation means: $y \to y_0$ as $t \to \infty$ for all constant w.

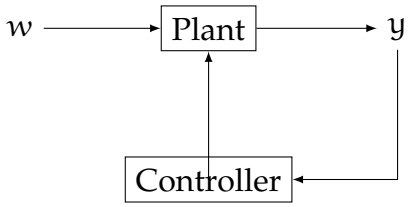
1.3 Controller Design Problem

There are two main control architectures:

1. **Feedforward Control:**



2. **Feedback Control:**



From a simple example we saw:

1. **Feedforward** requires perfect matching of parameters. Can't do adaptation.
2. **Feedback** uses the power of time, observes the past, acts accordingly.

2 PID Control and Integral Feedback

2.1 PID Controller

e also saw, naturally, a **PID controller** emerge, which can achieve perfect adaptation:

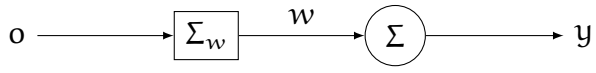
$$u = k_P y + k_I \int y \, dt + k_D \dot{y} \tag{3}$$

Question: Which part of PID is responsible for adaptation?

Answer: The **Integral** part.

2.2 Internal Model Principle

The **Internal Model Principle** states: Adapt to all w from $\Sigma_w \Leftrightarrow$ Internal model of Σ_w.



Perfect adaptation $\Leftrightarrow$ **Integral Feedback** (+ stable steady state).

2.3 Integral Feedback is Sufficient

Integral feedback is sufficient:

$$u = k_I \int y \, dt \quad \Rightarrow \quad \dot{u} = k_I y \tag{4}$$

At steady state: $y = 0$.

But requires **stability**!

2.4 Power of Integral Feedback

This is powerful: Adaptation *regardless of the plant*! (as long as the system can reach steady state)

Pretty much independent of everything!

(Look back at the simple example with only integral feedback.) Oscillation prevents perfect adaptation.

3 Implementation of Adaptation in Engineered Systems

3.1 Goal

Recall our goal: Use machine control principles to understand biology.

Control theory tells us that Perfect adaptation $\Leftrightarrow$ integral feedback.

But how to *implement* integral feedback? i.e., physically make it happen.

3.2 Electrical Circuits

Electrical circuits: variables are voltages V, currents I.

1. **Resistors:** $V = RI$, $I = \frac{V}{R}$
   This is **proportional control**.
2. **Inductor:**
$$V(t) = L\frac{dI(t)}{dt} \tag{5}$$
$$I(t) = I(0) + \int_0^t V(\tau)d\tau \tag{6}$$
   Integral or Derivative.
3. **Capacitor:**
$$V(t) = V(0) + \int_0^t I(\tau)d\tau \tag{7}$$
$$I(t) = C\frac{dV(t)}{dt} \tag{8}$$
   Integral or Derivative.

So, **PID control is very natural in electrical circuits!**

4 Implementation in Biological Reaction Networks (BRNs)

4.1 Constraints in Biology

But what about in biological reaction networks (BRNs)?

- Variables are **concentrations**, all **positive**. (Rule [P])
  (in contrast to V, I or position, velocity)
- Dynamics are, by default, **constrained polynomials**. (Rule [CP])

$$\frac{dx}{dt} = \Gamma^n x^\alpha \tag{9}$$

4.2 Control Types in BRNs

4.2.1 Proportional Control

Proportional: e.g., $u = k_P y = k_P(x_r - x)$

Often easy... $\dot{x} = \mu - px$, where $\mu = k_P x_r$, $p = k_P$.

Another example: $y = \frac{x}{x_r}$ (more natural!)

In fact, any static regulation $u(y)$ works as proportional feedback (upon linearization).

4.2.2 Derivative Control

Derivative: can often be done, but not often used.

Since biomolecular processes are **noisy**, and derivative control amplifies noise...

(not used much in highly noisy scenarios...)

4.2.3 Integral Control - The Challenge

Integral — important for perfect adaptation (if and only if).

But **not naturally achieved!** because of rule [CP].

$$z = \int y\, dt = \int (x_r - x)\, dt \tag{10}$$

$$\Rightarrow \quad \dot{z} = x_r - x \tag{11}$$

z **can't be a species** due to rule [CP]!

4.3 Strategies to Achieve Integral Control in Biology

To achieve integral control in biology needs further sophistication!

4.3.1 Strategy 1: Virtual Variable (Antithetic Integral Controller)

This is called **antithetic integral controller**. (Cell Systems 2016, Nature 2019, Mustafa Khammash group)

$$\dot{z}_1 = \mu - C \tag{12}$$

$$\dot{z}_2 = x - C \tag{13}$$

where $z_1, z_2 \xrightarrow{C} \varphi$ (annihilation reaction).

Let $z = z_1 - z_2$, then $\dot{z} = \mu - x$.

(Recall: this is like the dual rail strategy in last lecture to circumvent rule [P].)

But the problem is that rule [PU] makes it hard to directly use z in other variable's dynamics.

e.g., $\dot{x} = kz - \gamma x = kz_1 - kz_2 - \gamma x$

This requires kz_1 and kz_2 to have perfectly matching parameters, violating rule [PU]!

So, the best we can do is $\dot{x} = kz_1 - \gamma x$ for example.

This doesn't hurt Perfect Adaptation, since the integral variable still exists.

4.3.2 Strategy 2: Constrain to Certain Regimes

e.g.,

$$\dot{z} = \mu - C, \quad x + z \xrightarrow{k} x_f \tag{14}$$

In regime $C \ll x$, we have $\dot{z} \approx \mu - x$.

$$\begin{array}{c} C \to x_f \\ \downarrow \\ x_f + z \end{array}$$

5 Incoherent Feedforward Loops (IFFL)

5.1 Nonlinear Structure Revealed by IFFL Motifs

Previously, we adopted a machine perspective on biological systems.

Since adaptation is a hallmark behavior in biology, we reasoned that an *adaptation machine* must achieve adaptation following similar design principles as engineered adaptation machines.

According to the internal model principle in control theory,

$$\text{perfect adaptation} \iff \text{integral feedback.} \tag{15}$$

Due to physical constraints on biomolecular reactions, it then seemed that biochemical reaction networks (BRNs) should achieve perfect adaptation by implementing integral feedback, perhaps via more sophisticated strategies. However, this is not an accurate picture of what is happening in reality.

5.2 Empirical Evidence for Feedforward Network Prevalence

In 2002, Shen-Orr *et al.*, *Nature Genetics*, examined all three-node network topologies formed by transcription factors and operons in *E. coli*. The study catalogued 115 transcription factors and 424 operons and analyzed the resulting interaction topologies.

They found that certain *network motifs*—subgraphs that occur far more frequently than in randomized networks—tend to be *feedforward*. This is surprising from the engineered-systems viewpoint: in engineered control systems, perfect adaptation cannot be achieved with purely feedforward architectures because it requires perfect matching of the parameters of two processes.

Thus the questions arise:

- How come biology is different?
- What happened to the design rule "perfect adaptation $\Leftrightarrow$ integral feedback"?

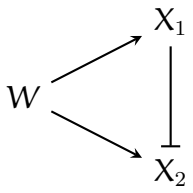


Figure 2 Incoherent feedforward loop (IFFL) motif: a three-node feedforward network where the upstream node W regulates both X_1 and X_2, and X_1 also regulates X_2.

Figure 2 shows a schematic three-node IFFL motif, representative of the structures over-represented in transcriptional networks.

5.3 The "Sniffer" as a Canonical IFFL Example

A concrete example of an incoherent feedforward loop is the so-called *"Sniffer"* circuit. The underlying reactions are:

$$W \xrightarrow{k_1} W + X_1, \tag{16}$$

$$W \xrightarrow{k_2} W + X_2, \tag{17}$$

$$X_1 + X_2 \xrightarrow{\delta} X_2, \tag{18}$$

$$X_2 \xrightarrow{\gamma} \varnothing. \tag{19}$$

The corresponding dynamics for the concentrations x_1 and x_2 of X_1 and X_2 are

$$\frac{dx_1}{dt} = k_1 W - \delta x_1 x_2, \tag{20}$$

$$\frac{dx_2}{dt} = k_2 W - \gamma x_2. \tag{21}$$

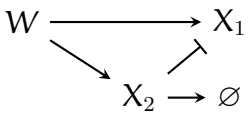


Figure 3 The "Sniffer" IFFL reaction network. The input W produces both X_1 and X_2; X_1 promotes the degradation of X_2, and X_2 is additionally degraded to a sink.

At steady state, from (21) we have

$$x_2^* = \frac{k_2}{\gamma} W. \tag{22}$$

Substituting into (20) and setting $\frac{dx_1}{dt} = 0$,

$$x_1^* = \frac{k_1 W}{\delta x_2^*} = \frac{k_1 W}{\delta \frac{k_2}{\gamma} W} = \frac{k_1 \gamma}{k_2 \delta}. \tag{23}$$

Thus,

$$x_1^* \text{ is invariant with respect to } W, \tag{24}$$

which is precisely *perfect adaptation*. Crucially, this invariance is independent of the exact parameter values in the sense of fine-tuned equality between gains; no perfect matching of parameters is required.

5.4 Reaction Orders as the Source of Nonlinearity

The key to understanding this behavior lies in the *exponents* appearing in the rate laws, that is, the *reaction orders*. For a generic reaction rate of the form

$$v = k x^{\alpha}, \tag{25}$$

the exponent α is the mass–action order in simple reactions, but can be more complicated when there are additional mechanisms or time-scale separation.

This structure—nonlinear dependence on concentration via reaction orders—is a feature that biological systems can exploit. It is typically not present, or is not fully utilized, in engineered systems, which are often modeled and analyzed after linearization.

5.5 Identifying the Implicit Integral Variable

Given the perfect adaptation property of the Sniffer circuit, it is natural to ask: *Where is the integral variable?*

Define the composite variable

$$z = k_2 x_1 - k_1 x_2. \tag{26}$$

Differentiating and substituting from (20)–(21) gives

$$\dot{z} = k_2\dot{x}_1 - k_1\dot{x}_2 \tag{27}$$
$$= k_2(k_1 W - \delta x_1 x_2) - k_1(k_2 W - \gamma x_2) \tag{28}$$
$$= -k_2\delta x_1 x_2 + \gamma k_1 x_2 \tag{29}$$
$$= x_2\big(\gamma k_1 - \delta k_2 x_1\big). \tag{30}$$

The dynamics of z integrate the mismatch between the term $\delta k_2 x_1$ and the constant γk_1, revealing how an effective integral feedback is hidden in the nonlinear reaction structure of the IFFL. This provides a mechanism for perfect adaptation in a purely feedforward network, reconciling biological observation with control-theoretic principles.

5.6 Comparison: Feedforward vs. Feedback

Although both Integral Feedback and IFFL can achieve adaptation, their mechanisms and philosophies differ significantly:

1. **"Cheating" vs. Robustness:** Integral Feedback is robust to *unknown* disturbances. It monitors the error and corrects it regardless of the source. In contrast, IFFL can be viewed as a form of "cheating." The system "knows" the specific noise/input (because it measures w directly) and calculates a precise cancellation via the parallel path. This requires the parameters (e.g., the ratio of production/degradation rates) to be finely tuned. If the nature of the disturbance changes, IFFL might fail, whereas Integral Feedback would still adapt.
2. **Specific vs. General Components:** In electrical engineering, Integral Feedback is often implemented using general-purpose components (like Op-Amps) designed to handle all types of noise. Biological systems, however, tend to evolve unique, specific feedback or feedforward loops for specific parts. There is no "universal integrator" protein; instead, each pathway has its own specific regulatory wiring tailored to its specific biological context.
3. **Mathematical Relationship:** In linear systems, at steady state, IFFL and IFB both require $\mathbf{d} - \mathbf{cA^{-1}b} = \mathbf{0}$, but with different structure. IFFL can have $\mathbf{d} > \mathbf{0}$ and $\mathbf{cA^{-1}b} > \mathbf{0}$, but IFB requires both $\mathbf{d} = \mathbf{0}$ and $\mathbf{cA^{-1}b} = \mathbf{0}$.

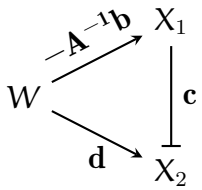


Figure 4 Three Nodes Again: a three-node feedforward network where the upstream node W regulates both X_1 and X_2, and X_1 also regulates X_2.

6 Noise in Biosystems

6.1 Introduction: The Biomachine Perspective

The biomachine perspective on biology we took was a systems engineering perspective.

It underlies the field of **systems and synthetic biology** that started in 2000.

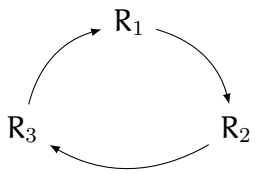
With the completion of the human genome project, we had a glance at "all components in a cell", so we could start to reason about it as a system, and engineer it like a machine (like an electrical circuit).

$\Rightarrow$ The phrase: **biocircuit**.

6.2 The Repressilator

Repressilator. Elowitz 2000 Science. Was one of first work pioneering this perspective. (reading in HW 1).

Three genes' expression oscillates in E.coli:



Prediction: Smooth oscillations (single cell trajectory).

Reality: Not much of an oscillation.

Limitations of theory for design at the time... (ours based on regimes doesn't make Hill-type limiting assumptions).

But another big observation: **Noise!** between cells and within one cell.

GFP under the microscope.

6.3 Origin of Noise: Stochasticity

But where does noise come from, and when does it matter?

- E.coli cells from the same clone, so not genetic difference.
- $\Rightarrow$ Origin of noise is in **stochasticity of cellular processes**. Namely, chemical reactions.

Reaction events happen by molecules $E + S \xrightarrow{k}$ products encountering each other.

What's the distribution for the # of reaction events in a time interval Δt?

- Reactions happen when E and S hits

- Reaction rate is constant $a = kES$, unless E, S changes
- The events are independent of each other; they only depend on E and S's conc. and k

$\Rightarrow$ **Poisson distribution** with parameter $\lambda = a\Delta t$ (average # events in this interval).

Chemical reaction rate: $a = kES$.

6.4 Poisson Distribution

$X \sim \text{Poisson}(\lambda)$:

$$P\{X = k\} = \frac{\lambda^k}{k!} e^{-\lambda} \tag{31}$$

$$\mathbb{E}(X) = \text{Var}(X) = \lambda \tag{32}$$

$$\Rightarrow CV = \frac{\text{Var}(X)}{\mathbb{E}(X)} = \frac{\sqrt{\lambda}}{\lambda} = \frac{1}{\sqrt{\lambda}} \tag{33}$$

Coefficient of Variation (CV):

- $\lambda = 1$: $CV = 1$
- $\lambda = 100$: $CV = \frac{1}{10}$
- $\lambda = 10000$: $CV = \frac{1}{100}$

6.5 When Does Process Noise Matter?

Process noise becomes important when # events is small!

6.5.1 Translation to Molecule Numbers

events $\rightarrow$ production events in balance with dilution by growth (i.e., no active degradation).

Then, if N_X = number of molecule X in cell:

- $\Rightarrow N_X$ produced every generation
- If one molecule X produced every event $\Rightarrow N_X$ events

Typical molecule numbers:

- $N_X \sim 10^2$ to 10^3 for proteins in E.coli: $CV \sim 0.1$
- $N_X \sim 10^5$ to 10^6 for metabolites in E.coli: $CV \sim 10^{-3}$

So, noise typically doesn't matter, even in E.coli.

- (Eukaryotes? Even less so...)

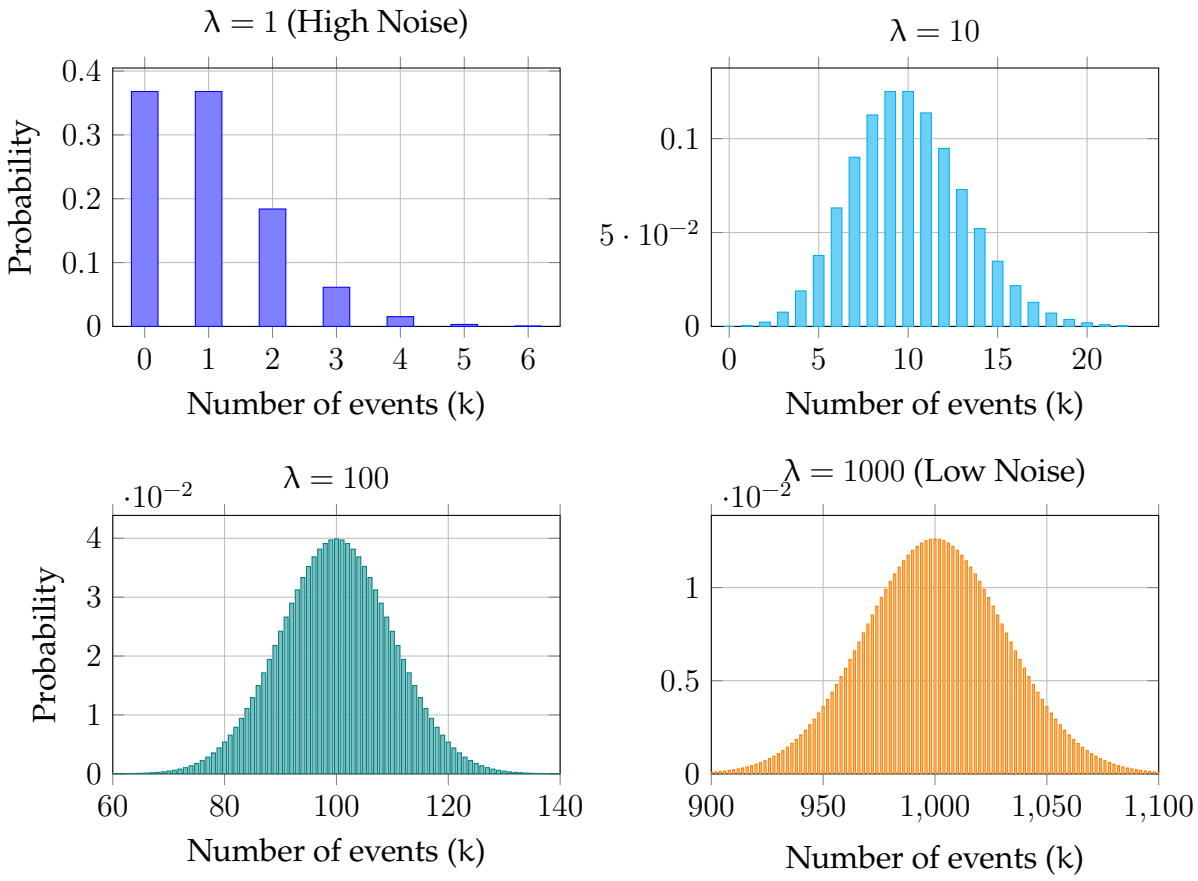


Figure 5 Poisson distributions for $\lambda = 1, 10, 100, 1000$. Note that as λ increases, the relative width (CV) decreases, representing lower noise relative to the mean.

- (Active degradation? More events, less noise.)

6.5.2 What's Missing? Burstiness in Gene Expression

We do see a lot of heterogeneity in single cells under the microscope!

What's missing? Burstiness in gene expression.

Several proteins produced per event, amplified by the **TX-TL process** (Transcription-Translation).

If 100 proteins per event:

$$N_{\text{event}} \sim \frac{N_X}{100} \sim 1 \text{ to } 10 \text{ for proteins in E.coli}$$

So, noise starts to matter.

6.5.3 "Critical Threshold" Concept

Typical burstiness ~ # proteins in cells.

- Low expression $\rightarrow$ noise dominates
- High expression $\rightarrow$ noise doesn't matter

Could be a strategy for bacteria:

- e.g., bet hedging... utilizing noise...
- Yet noise's role/importance is tunable.

6.5.4 Despite Burstiness: Noise Doesn't Play a Big Role in Most Biological Processes!

For noise to be important, need following factors (typically):

- Small cell size (e.g., not Eukaryotes)
- Low flux (not much degradation)
- Low concentration (e.g., genome)
- Large molecule size (e.g., not metabolites)
- Burstiness (e.g., not metabolic reactions)

6.5.5 CAUTION! Important Distinction

Comment: Noise $\neq$ Stochasticity (in processes) vs. Unknown (mechanisms)

Intrinsic randomness of underlying mechanisms vs. lack of information.

We are talking about noise from **process stochasticity** here, not "a wide spread in data" that also includes unknown mechanisms.

Example: A deterministic process can look "noisy" in data just because we don't know the mechanism.

- Like whether you bring umbrella to school: if you don't observe the weather.

Noise in data is a completely different topic because it's more about **inference of the unknown mechanisms**, not about stochasticity.

6.6 Chemical Master Equation (CME)

To formally describe this stochasticity, we use the CME.

Stochasticity in chemical reactions.

Now we have some confidence on the role noise plays in biological systems. We would like a way to formally describe and analyze them.

6.6.1 Setup: A Simple Reaction System (Elementary)

Consider: $\emptyset \xrightarrow{\mu} X \xrightarrow{k} \emptyset$

We could write this in **net-change form**:

$$X \xrightarrow{\nu_1} X + 1 \quad \nu_1 = \mu \tag{34}$$

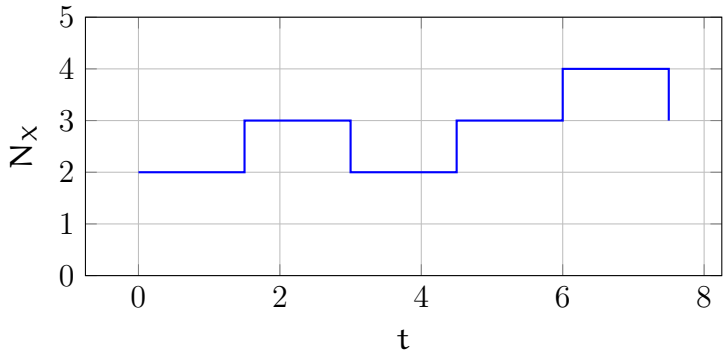
$$X \xrightarrow{\nu_2} X - 1 \quad \nu_2 = kX \tag{35}$$

(Deterministic) rate equation:

$$\frac{dX}{dt} = \mu - kX$$

Stochastic case: N_X is discrete. $N_X = 0, 1, 2, \ldots$

It's a **random variable** that changes over time $\Rightarrow$ a **stochastic process**.



So its dynamics is described in terms of **probabilities**:

$$P_n(t) = \mathbb{P}\{N_X(t) = n\}$$

6.6.2 What's the Dynamics of $P_n(t)$? How Do Reactions Change It?

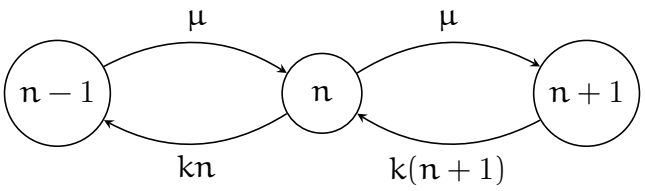
Consider the degradation reaction: $X \xrightarrow{\nu_2} X - 1$

This says: $\mathbb{P}\{\text{reaction happen in } [t, t+dt]\} = \nu_2(t)\,dt = kN_X(t)\,dt$

Deterministic: rate equation $\frac{dX}{dt} = \mu - kX$

Stochastic: N_X is discrete, $N_X = 0, 1, 2, \ldots$

6.6.3 State Transitions



6.6.4 Derivation for Degradation Only

So, just consider this one reaction. It's:

$$P_n(t+dt) = P_n(t) \cdot \mathbb{P}\{\text{no reaction in } [t, t+dt]\} \tag{36}$$
$$+ P_{n+1}(t) \cdot \mathbb{P}\{\text{reaction in } [t, t+dt]\} \tag{37}$$

(At $t \to 0$: either one reaction or no reaction.)

$$P_n(t+dt) = P_n(t)(1 - kn\,dt) + P_{n+1}(t) \cdot k(n+1)\,dt \tag{38}$$
$$= P_n(t) + k(n+1)P_{n+1}(t)\,dt - knP_n(t)\,dt \tag{39}$$

$$\Rightarrow \frac{P_n(t+dt) - P_n(t)}{dt} = k(n+1)P_{n+1}(t) - knP_n(t)$$

$$\Rightarrow \text{as } dt \to 0, \quad \frac{dP_n}{dt} = k(n+1)P_{n+1} - knP_n \quad (n = 0, 1, 2, \ldots)$$

6.6.5 Now Add Production: $\emptyset \xrightarrow{\mu} X$

$$\frac{dP_n(t)}{dt} = k(n+1)P_{n+1}(t) - knP_n(t) + \mu P_{n-1}(t) - \mu P_n(t)$$

Chemical Master Equation:

$$\boxed{\frac{dP_n}{dt} = \mu P_{n-1} - \mu P_n + k(n+1)P_{n+1} - knP_n}$$

for $n = 0, 1, 2, 3, \ldots$ (Assume $P_{-1} = 0$ always.)

6.6.6 Interpretation

This is the **Chemical Master Equation**, about distributions.

Viewed as a dynamical system, this is **infinite dimensional**.

But it has **strong structure**. So we can simulate/analyze accordingly.

7 Credit

Contributor	Sections
Kaijun Wang	• 1 Introduction: The Biomachine Perspective • 2 PID Control and Intergral Feedback • 3 Implementation of Adaptation in Engineered Systems
Xiaowen Zhang	• 4 Implementation in Biological Reaction Networks • 5 Incoherent Feedforward Loops(IFFL)
Shuo Wang	• 5.6 Comparison: Feedforward vs. Feedback • 6 Noise in Biosystems