Biocircuit 101

ODE models of biocircuits

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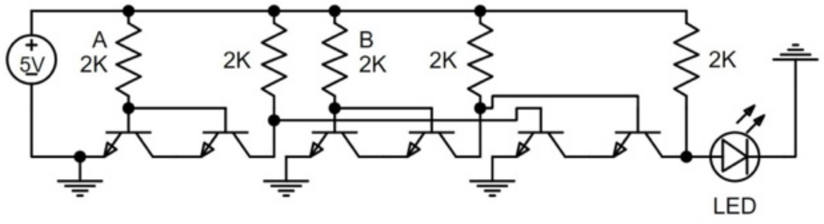
⭐ Resource: https://biocircuits.github.io/

Circuits do computation

Inputs → CIRCUITS → Outputs

E.g. **Electrical circuits** compute with electrons

Inputs
- ➢ Voltage source
- ➢ Electrical signals
- ➢ …

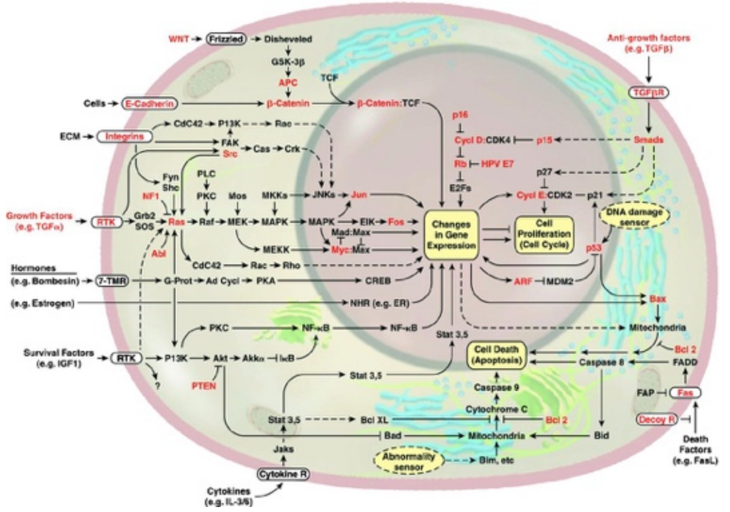


Outputs
- ➢ New electrical signals
- ➢ May be transduced into other energy forms (e.g. light, sound)

Biological circuits compute with biological components

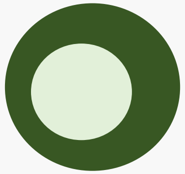
E.g. **Molecular circuits** compute with molecules

Inputs
- ➢ + Molecules
- ➢ ↑ Temperature
- ➢ …

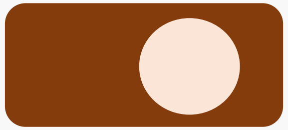


Hanahan and Weinberg 2000

Outputs (Reponse)
- ➢ Concentration vary
- ➢ Shape change
- ➢ …



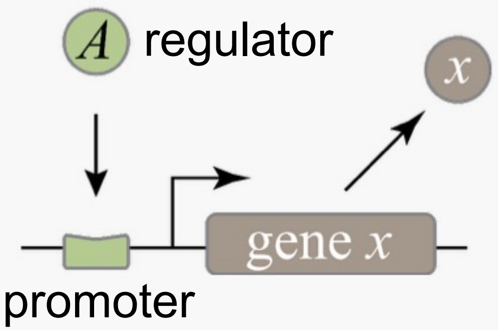
Cell A

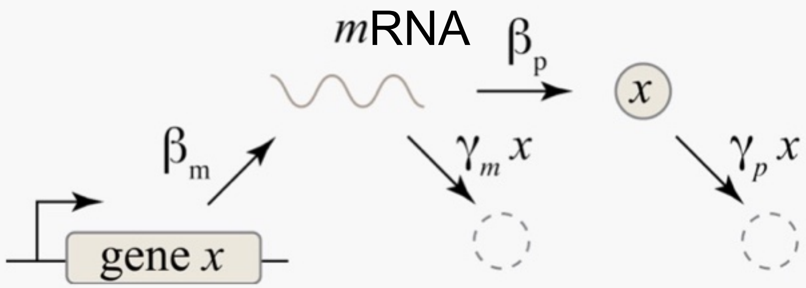


Cell B

Biological circuits are analogous to electrical circuits

Transcription Recap



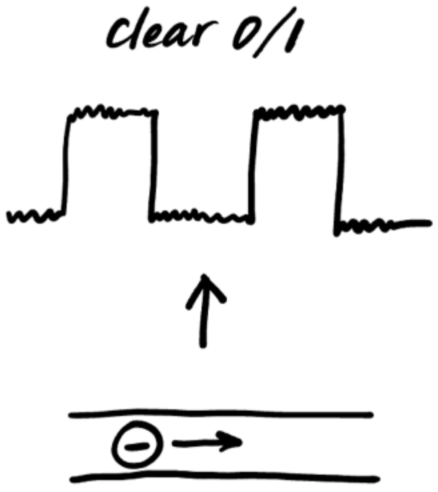


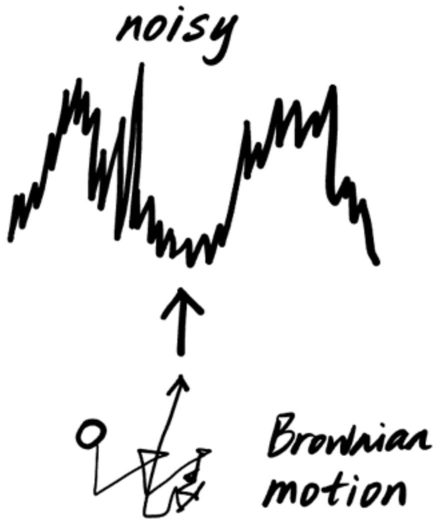
Electrical circuit	Molecular circuit
Voltage source	Energy (e.g. from ATP)
Switch	Regulator (e.g. TF, repressor)
Gate (e.g. AND)	Combination of regulators
Resistor	Binding affinity (Ribosome ↔ RBS, TF ↔ promoter) & degradation rate
Bulb	Reporter (e.g. GFP)

Biological circuits differ from electrical circuits in key ways!

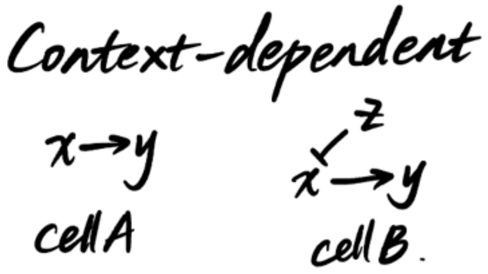
Electrical circuit | **Biological circuit**

Describe with **Boolean algebra** (mostly)





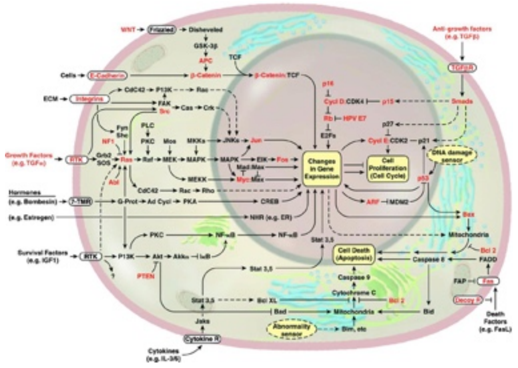
Describe with **stochastic differential equation** (SDE)



Isolate to analyze (simplification)

Deconstruct, model, and synthesize biocircuits

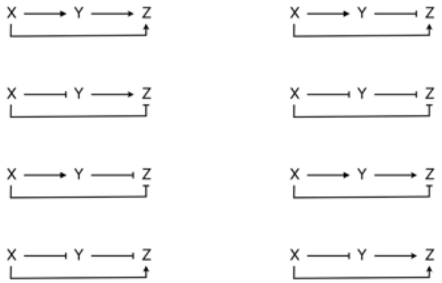
Real biocircuit network



[Hanahan and Weinberg 2000]

Reverse engineering

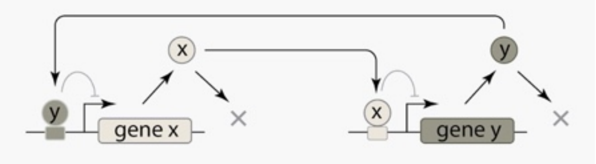
Deconstruct into motifs



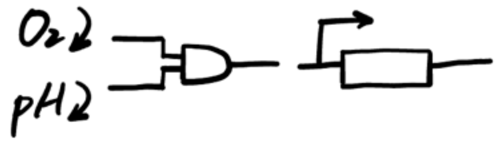
Forward engineering

Synthesize

e.g. build a **toggle switch**



e.g. **clinical application** build an AND gate that activates therapy only when both low O_2 and low pH are present



Features of tumor microenvironment

Model

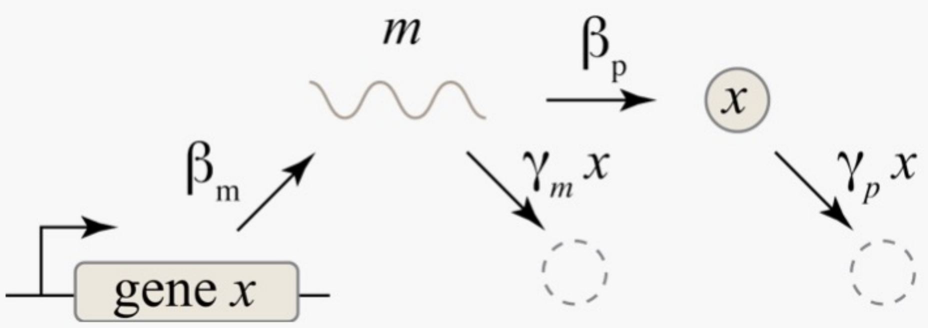
- Discovery: Model to test natural logic
- Design: Model before synthesis to **predict dynamics & tune parameters**
- Even build life bottom-up!

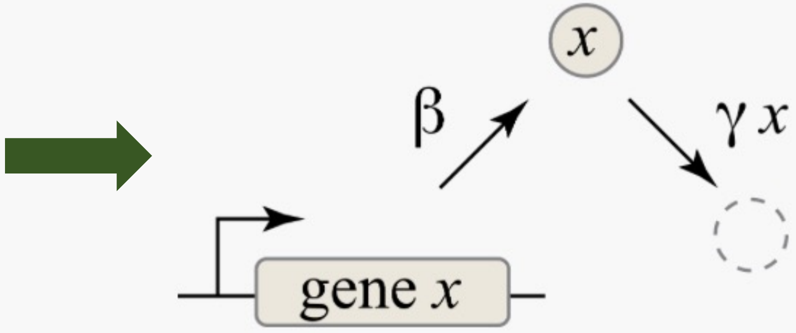
1. Use ODE to describe biocircuits

Simplification

mean(bulk noise)=0

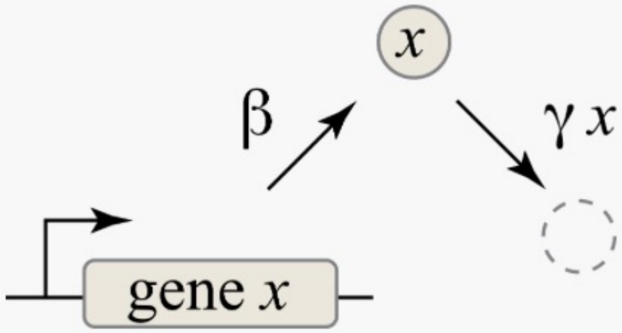
- Ignore the stochasticity (SDE → ODE, valid at high copy number)
- Skip intermediate mRNA





1. Use ODE to describe biocircuits

Refer to the jupyter notebook for details



① Describe

$$\frac{dx}{dt} = \text{production} - (\text{degradation} + \text{dilution}) = \beta - \gamma x$$

② Solve for the dynamics

Boundary condition

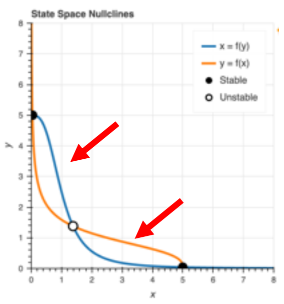
$$x(0) = 0$$

$$x(t) = \frac{\beta}{\gamma}(1 - e^{-\gamma t})$$

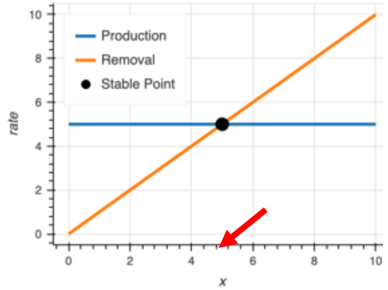
③ Nullcline Anslysis

Care about steady state, where cells spend most time

Nullcline: locus where dX/dt=0



The curves
dX/dt=0
dY/dt=0



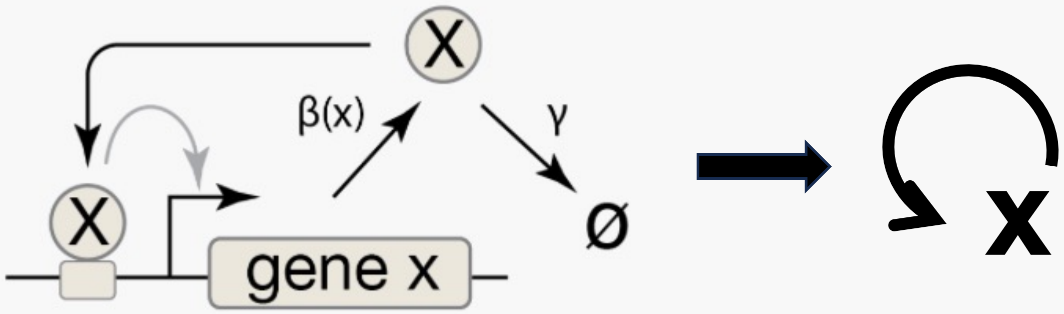
The point
dX/dt=0

In this simple case

$$\frac{dx}{dt} = \beta - \gamma x = 0$$

$$\Rightarrow x_{\text{ss}} = \beta/\gamma$$

2. Describe biocircuits with feedback



① Describe

$$\frac{dx}{dt} = \text{production} - (\text{degradation} + \text{dilution})$$

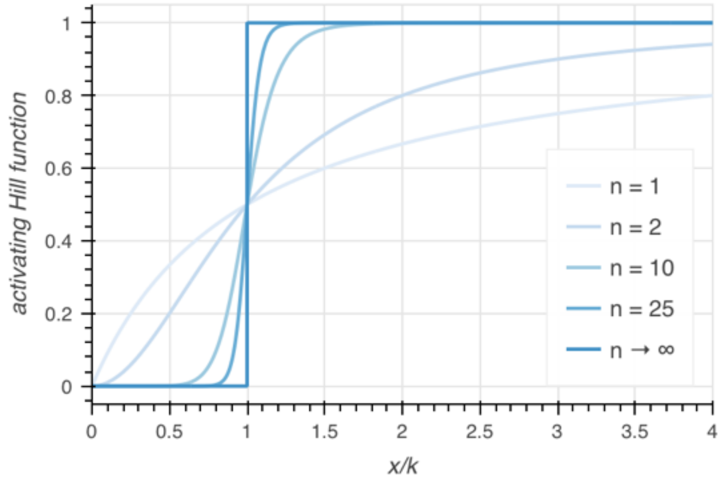
$$\frac{\mathrm{d}x}{\mathrm{d}t} = \beta \boxed{\frac{(x/k)^n}{1+(x/k)^n}} - \gamma x$$

Activating Hill function

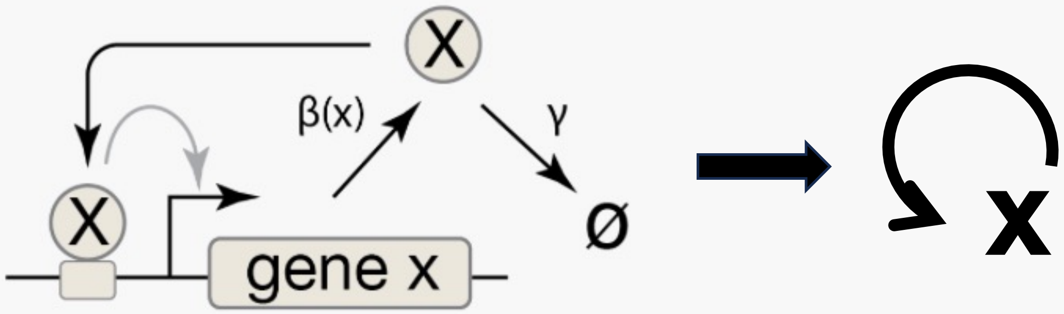
Hill function

Empirical, not derived mechanistically

- **Phenomenologically** describes ultrasensitive responses
- Used to describe the coorperativity of Hemoglobin binding O_2



Nondimensionalization simplify the description



① Describe

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \beta\,\frac{(x/k)^n}{1+(x/k)^n} - \gamma x$$

nondimensionalization

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \beta\,\frac{x^n}{1+x^n} - x$$

Nondimensionalization

- Reduce parameter number
- Make parameters comparable
- Reveal the real controling parameter

$t = [T]$, $\gamma = [\frac{1}{T}]$ $\quad t \leftarrow \gamma t$

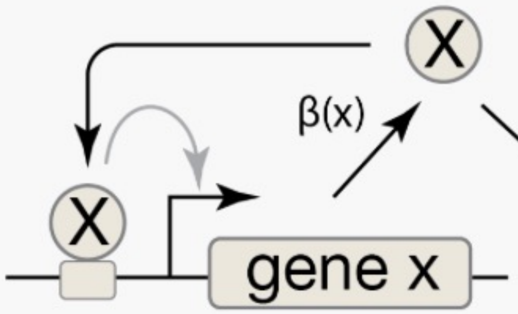
$x = [\frac{N}{L^3}] = k$ $\quad x \leftarrow x/k$

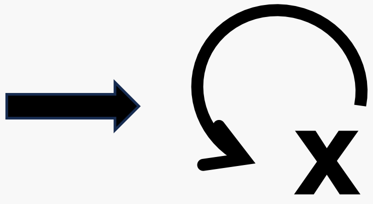
$\beta = [\frac{N}{L^3 \cdot T}]$ $\quad \beta \leftarrow \beta/\gamma \cdot k$

$$\underbrace{\frac{1/k}{\gamma}\frac{dx}{dt}}_{dx/dt} = \underbrace{\frac{1/k}{\gamma}\beta}_{\beta}\,\frac{\overset{x}{(x/k)}^n}{1+\underset{x}{(x/k)}^n} - \underbrace{\frac{1/k}{\gamma}\gamma\cdot x}_{x}$$

Positive autoregulation allows bistability

Refer to the jupyter notebook for details





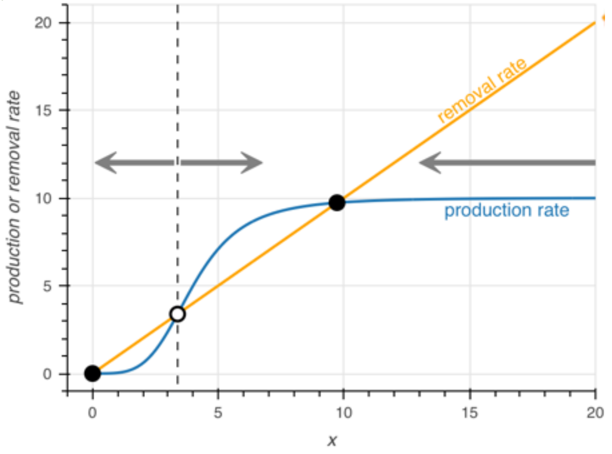
① **Describe**

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \beta \frac{x^n}{1 + x^n} - x$$

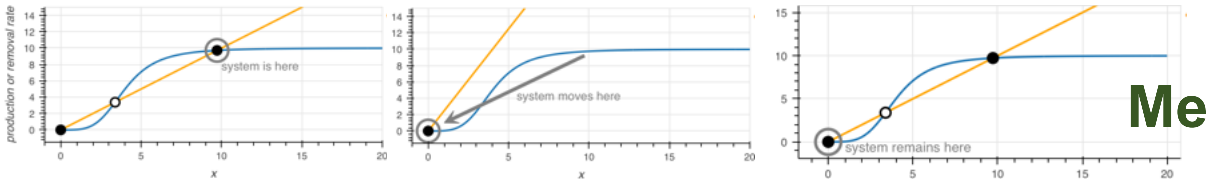
② **Solve for the dynamics**

The introduction of nonlinear hill function generally requires **numerical methods**

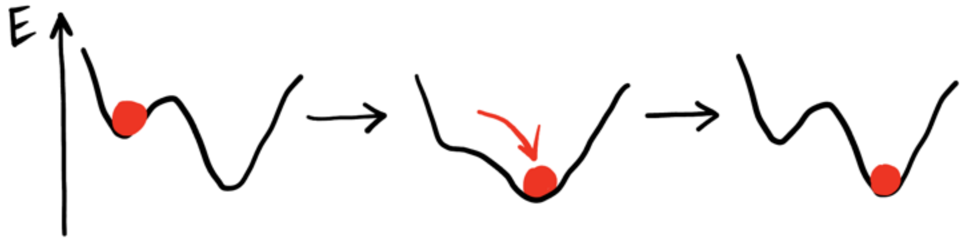
③ **Nullcline Anslysis**



Tune the parameters and interpret the results 🤔 …



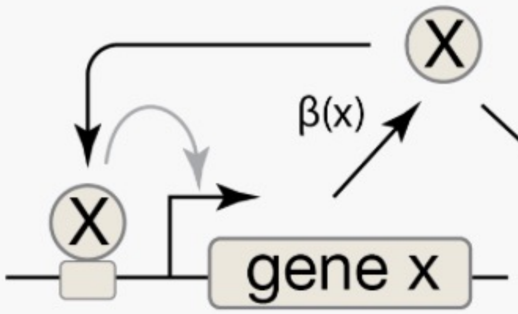
Memory!

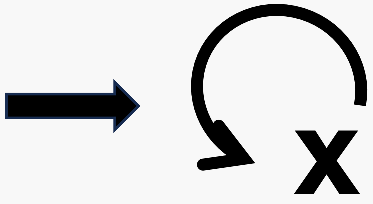


🤔 **How to reverse?**

Positive autoregulation allows bistability

Refer to the jupyter notebook for details





① **Describe** $$\frac{\mathrm{d}x}{\mathrm{d}t} = \beta\frac{x^n}{1+x^n} - x$$

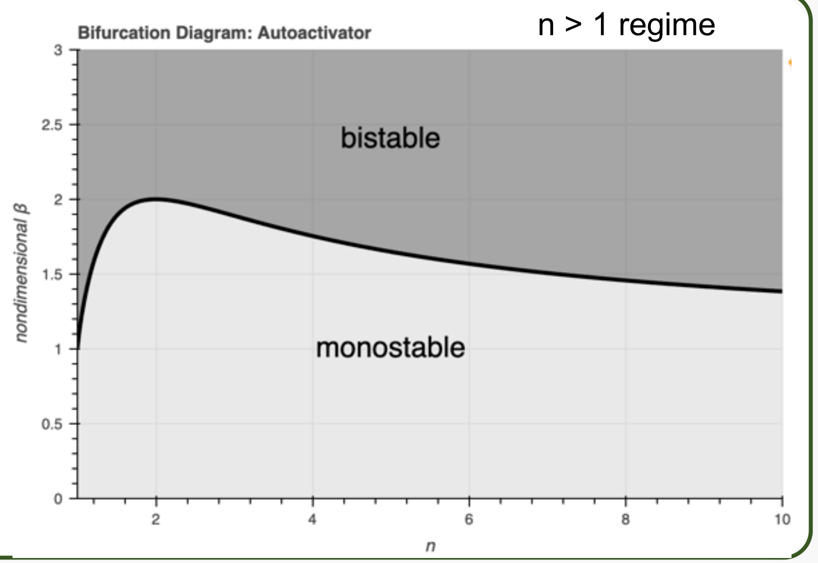
② **Solve for the dynamics**

③ **Nullcline Anslysis**

Can have bistability

④ **Bifurcation Anslysis**

Answers when will the biocircuit have certain behavior (e.g. bistability)



To find the boundary

$$f(x) = \beta\frac{x^n}{1+x^n} - x = 0$$

$$g(x) = x^n - \beta x^{n-1} + 1 = 0$$

steady state = # roots

For have some x s.t. g(x) < 0

$$\beta > n(n-1)^{(1-n)/n}$$

3. Build and analyze the toggle switch

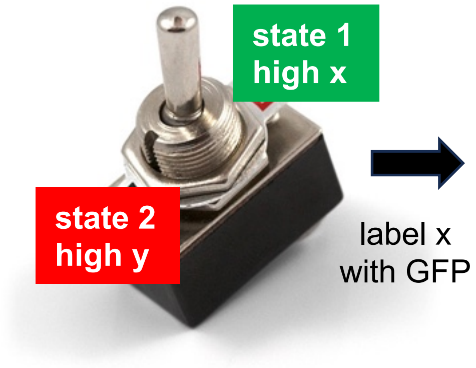
Refer to the jupyter notebook for details

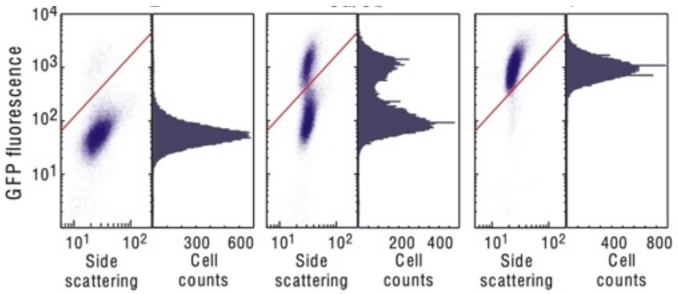
Letter | Published: 20 January 2000

Construction of a genetic toggle switch in *Escherichia coli*

Timothy S. Gardner, Charles R. Cantor & James J. Collins

For now, ignore the molecular details





A simplified version

1. **Write ODEs (dimensionless)**
2. **Numerically Solve**
3. **Nullcline Analysis**
4. **Bifurcation Analysis**

3. Build and analyze the toggle switch

Refer to the jupyter notebook for details

① Describe the circuit with ODEs and do nondimensionalization

$$\frac{dx}{dt} = \frac{\beta_x}{1 + y^n} - x$$

$$\gamma^{-1}\frac{dy}{dt} = \frac{\beta_y}{1 + x^n} - y$$

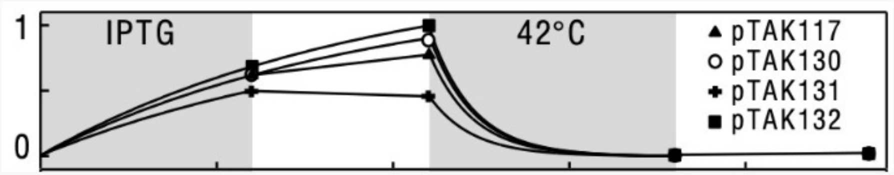
Simplification

- same lifetime for protein x and y → $\gamma = 1$
- symmetric parameters n for gene x and y
- Investigate the dynamic of x, fix β_y

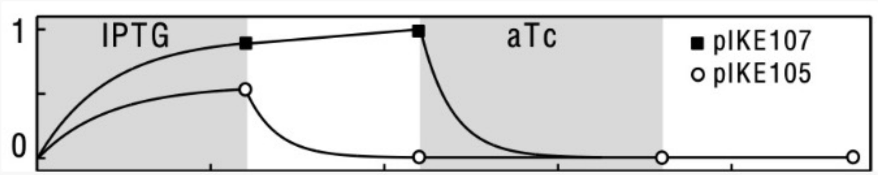
② Solve the ODEs and read the dynamics

③ Do nullcline analysis to gain intuition about the steady states

④ Do bifurcation analysis to determine when the circuit exhibits bistability, identify the parameter range that reproduces the experimental observations, and simulate them



low inhibition | high inhibition | High degradation landscape change



low inhibition | high inhibition | High degradation landscape change

Extended task

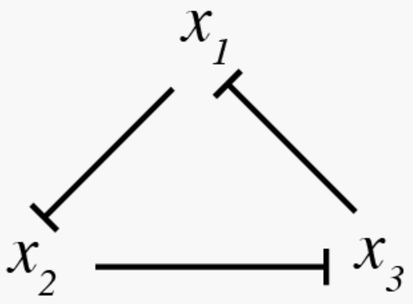
4. Build the repressilator with one more molecules

Letter | Published: 20 January 2000

A synthetic oscillatory network of transcriptional regulators

Michael B. Elowitz & Stanislas Leibler

Nature **403**, 335–338 (2000) | Cite this article



5. Open challenge

- Design a new biological circuit that can realize an interesting behavior you could think of.
- Starting with a concrete biological or clinical problem, design a useful and elegant biological circuit.
- ... Feel free to propose your own!