3000788 Intro to Comp Molec Biol

Lecture 16: Systems biology and dynamics

Fall 2025

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- Research Affairs
- Center of Excellence in Computational Molecular Biology (CMB)
- Center for Artificial Intelligence in Medicine (CU-AIM)

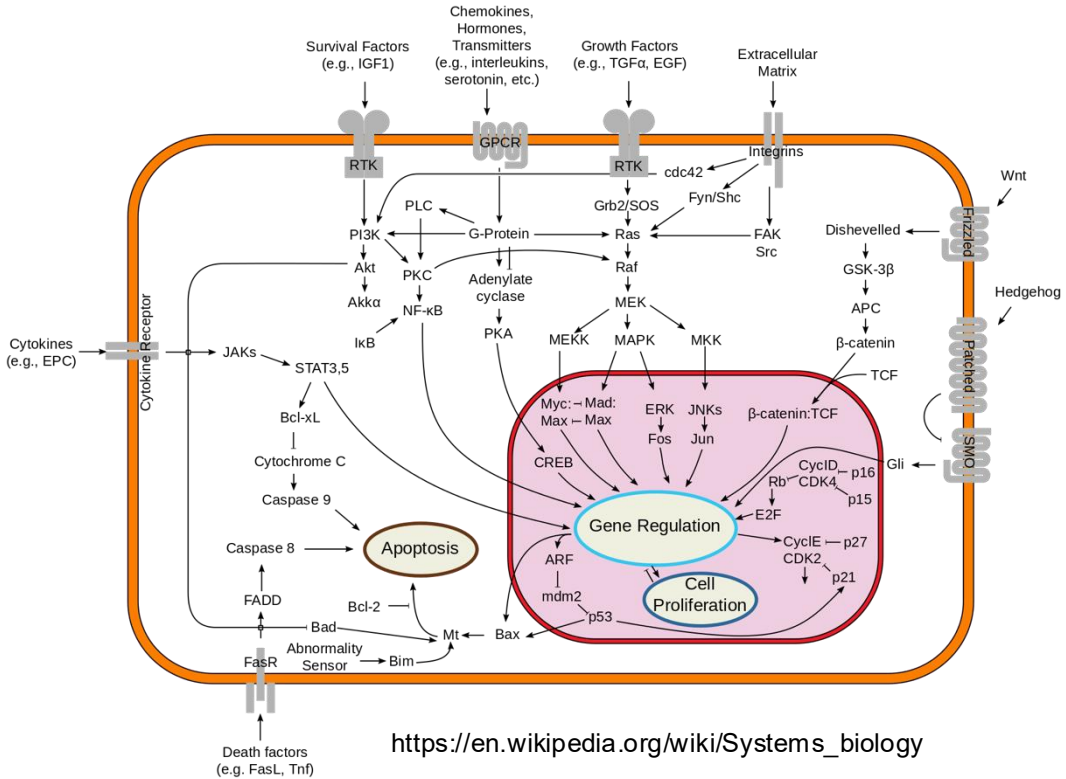
Today’s agenda

- Systems thinking

- Approaches in systems biology
  - Multi-omics integration
  - Biological network

- Temporal dynamics of gene and protein expression

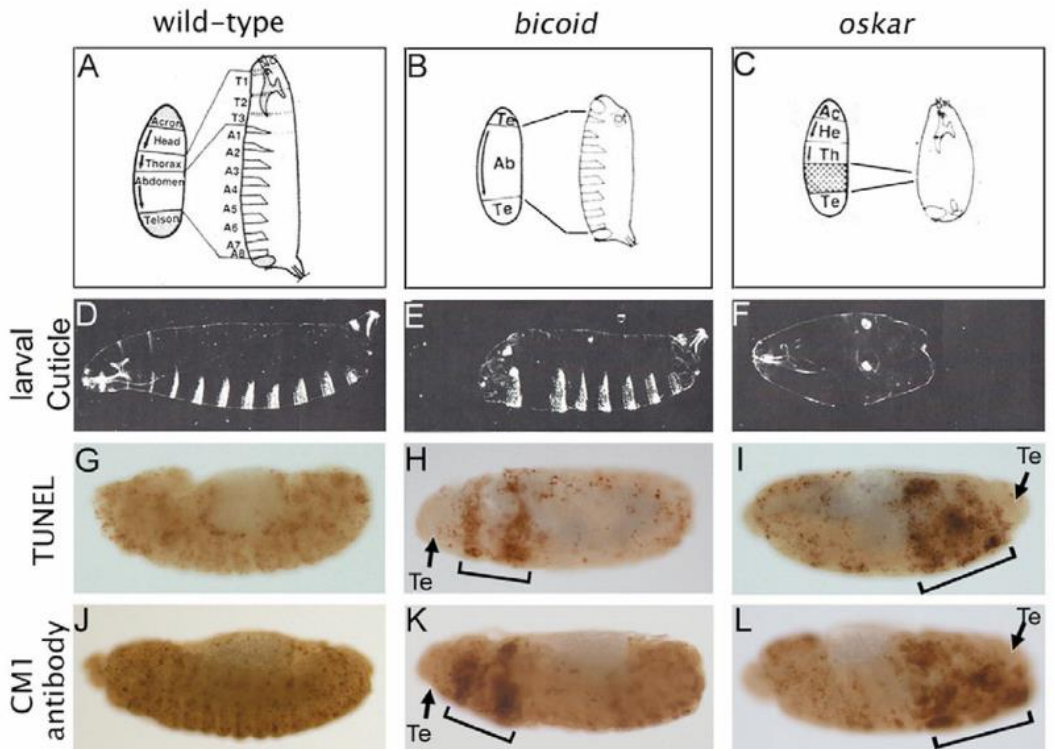
Systems thinking in biology



https://en.wikipedia.org/wiki/Systems_biology

- A (biological) system consists of components (genes) and rules (gene expression regulations) that control its characteristics (phenotypes)
- Systems biology = integration of multi-layered data and mechanistic model to fully understand a biological system

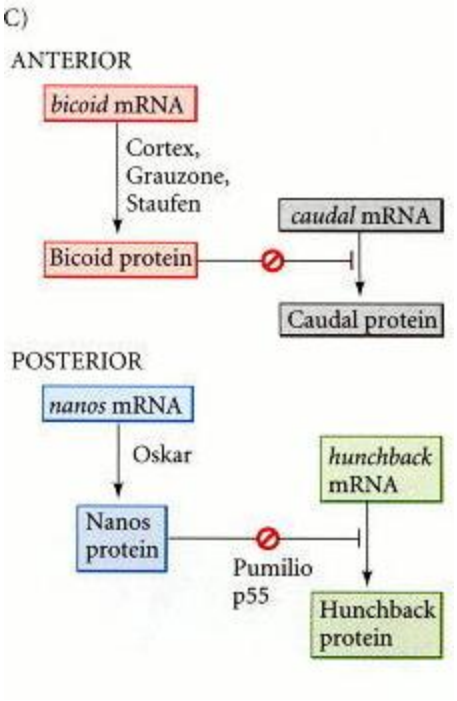
Systems thinking is needed to understand biology

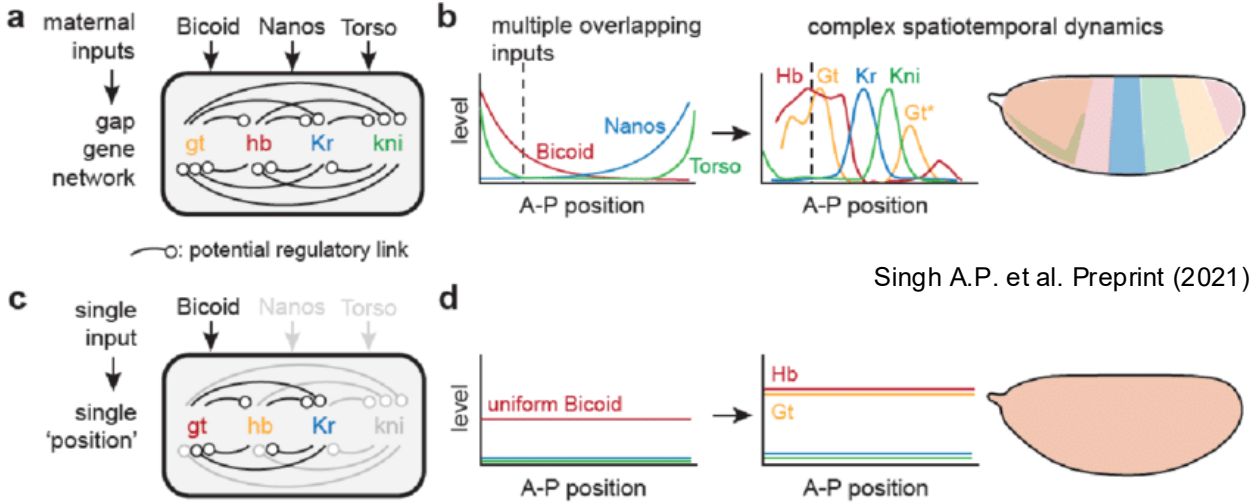


- How does gene and protein know when and where to express during development?
- Each cell starts in identical state
- Within-cell signals: epigenetics
- Cell-cell communication

Werz, C. Development 132:5343-52 (2006)

Anterior-posterior polarity in *drosophila* egg cells





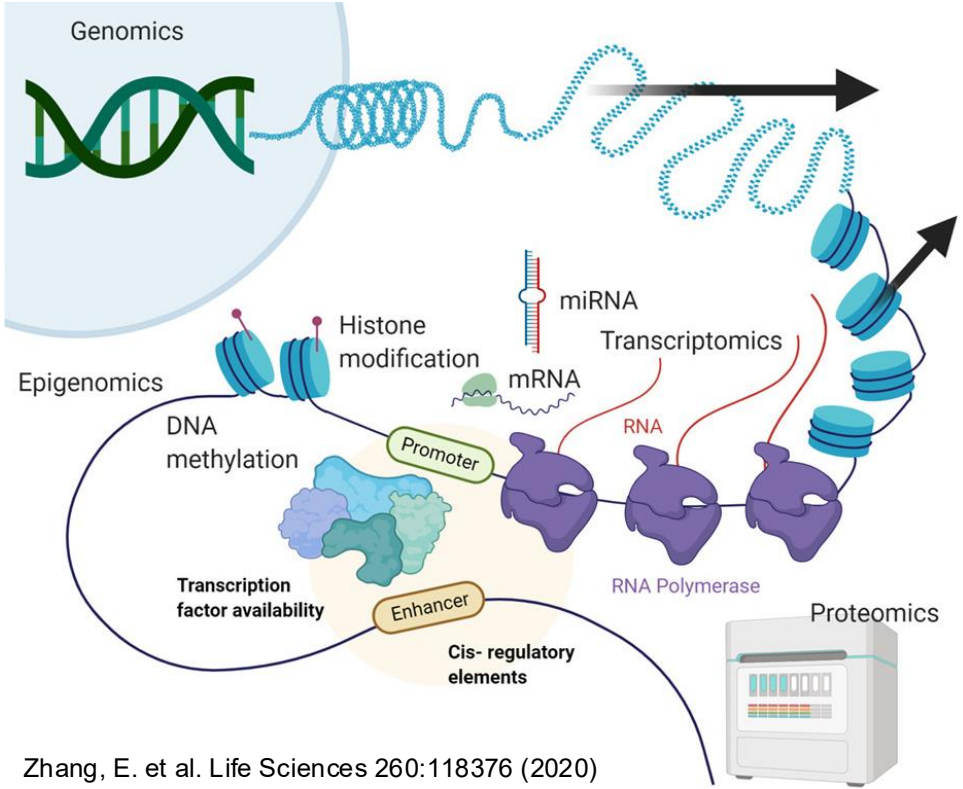
Singh A.P. et al. Preprint (2021)

- Localization of mRNA guided by cytoskeleton and communication with follicle cells

https://www.ncbi.nlm.nih.gov/books/NBK10039/

Approaches in systems biology

Multi-omics integration (Lecture 17)

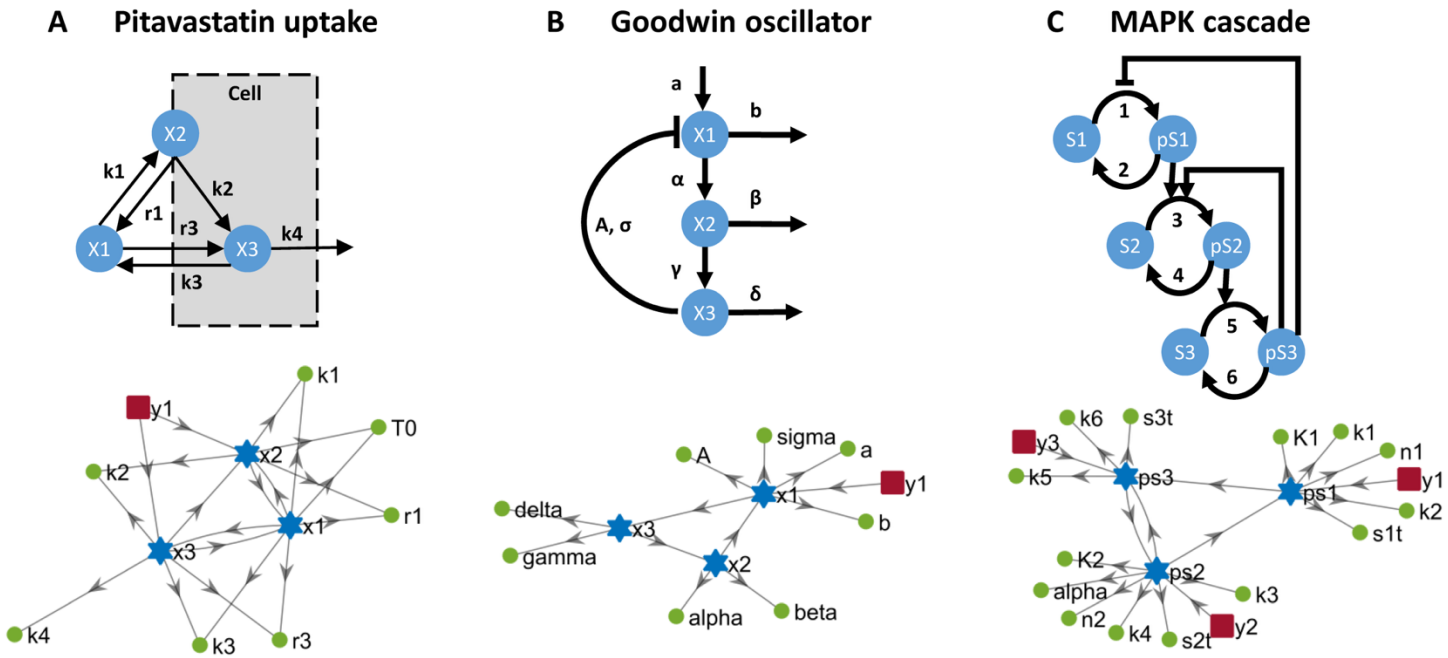


Zhang, E. et al. Life Sciences 260:118376 (2020)

- **Genomics** → gene state
- **Epigenomics** → chromatin state
- **Transcriptomics** → gene expression
- **Proteomics** → protein expression
- **Metabolomics** → flux analysis
- **Phenomics** → macro-level state

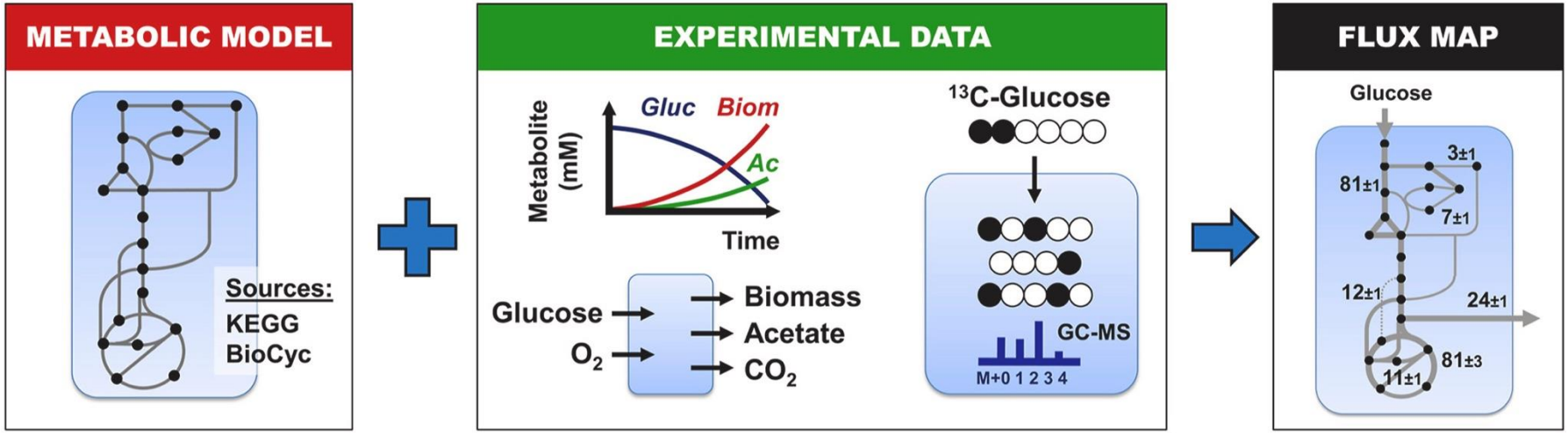
Regulatory network modeling (Lecture 18)

Villaverde, A.F. PLoS Comp Biol 12:e1005153 (2016)



- Describe how genes / proteins affect each other's expression and function

Metabolic flux analysis



Antoniewicz, M.R. Metabolic Engineering 63:2-12 (2021)

- Describe chemical reactions across metabolites (and proteins)
- Propagate changes in one metabolite across the whole system

Differential equation

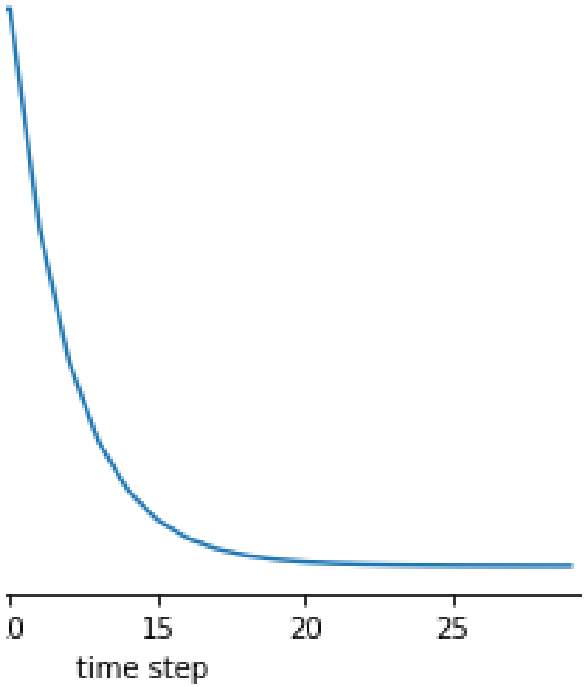
Differential equation

- Protein X is produced at a rate of 6 molecules per minute
  - $X_{t+1} - X_t = 6$
  - $\frac{X_{t+1}-X_t}{(t+1)-t} = \frac{dX}{dt} = 6$ Linear increase
  - $X_t = 6t + X_0$

- Protein X degrades at a rate of 1 in 10 per minute
  - $X_{t+1} = 0.9X_t$
  - $\frac{X_{t+1}-X_t}{(t+1)-t} = \frac{dX}{dt} = -0.1X_t$ Exponential decay
  - $X_t = 0.9^t X_0$

- Differential equation describes the rate of change of a system

Exponential decay described by differential equation



- $\frac{dX}{dt} = -k_{\text{degradation}}[X]$
- Fast decay in the beginning because there are a lot of molecules
- Slower decay towards the end because there are few molecules
- **General solution:** $\frac{de^{-kt}}{dt} = -ke^{-kt}$

Extrapolating a differential equation

- Protein X is produced at a rate of 1 molecules per minute and degrades at a rate of 1 in 2 per minute
  - $\frac{dX}{dt} = 1 - 0.5X_t$
  - $X_{t+1} = 1 + 0.5X_t$

Time	0	1	2	3	4	…	10	20
X	4	3	2.5	2.25	2.125	…	2.001953	**2.000002**

Time	0	1	2	3	4	…	10	20
X	10	6	4	3	2.5	…	2.007813	**2.000008**

Extrapolating a differential equation

- Protein X is produced at a rate of 1 molecules per minute and degrades at a rate of 1 in 2 per minute
  - $\frac{dX}{dt} = 1 - 0.5X_t$
  - $X_{t+1} = 1 + 0.5X_t$

Time	0	1	2	3	4	…	10	20
X	0	1	1.5	1.75	1.875	…	1.998047	**1.999998**

- X = 2 is the equilibrium of this system!
  - If $X_t = 2$, then $X_{t+1} = 1 + 0.5X_t = 2$ and so on

Impact of time resolution

- Protein X is produced at a rate of 2 molecules per 2 minutes and degrades at a rate of 3 in 4 per 2 minutes
  - $\frac{dX}{dt} = 2 - 0.75X_t$
  - $X_{t+1} = 2 + 0.25X_t$

Higher resolution (smaller time step) is better but need more computation

Original result

Time	0	1	2	3	4	…	10	20
X	4	3	2.5	2.25	2.125	…	2.001953	**2.000002**

Time	0	2	4	6	8	10	…	20
X	4	3	2.75	2.6875	2.671875	2.66769	…	**2.666667**

New result

A simple model for gene expression

Recalling enzymatic reaction

$$E + S \underset{k_{off}}{\overset{k_{on}}{\leftrightarrow}} ES \xrightarrow{k_{react}} E + P$$

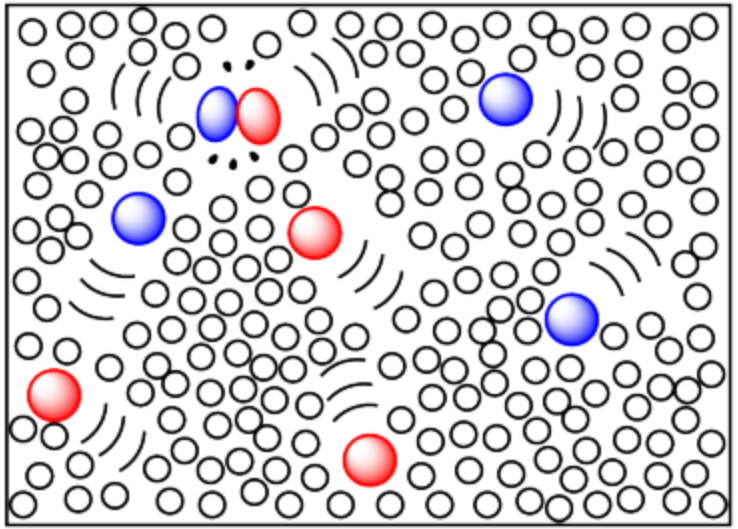
- $\frac{d[S]}{dt}$ = Rate of change in S = $-k_{on}[E][S] + k_{off}[ES]$
- $\frac{d[E]}{dt}$ = Rate of change in E = $-k_{on}[E][S] + k_{off}[ES] + k_{react}[ES]$
- $\frac{d[P]}{dt}$ = Rate of change in P = $k_{react}[ES]$

- Why do rates of change take these form?

A key mental image: molecules exist in 3D space

Rate of E + S → ES
Rate of E meeting S x
Rate of binding

Rate of E + S → ES =
[E][S] x k



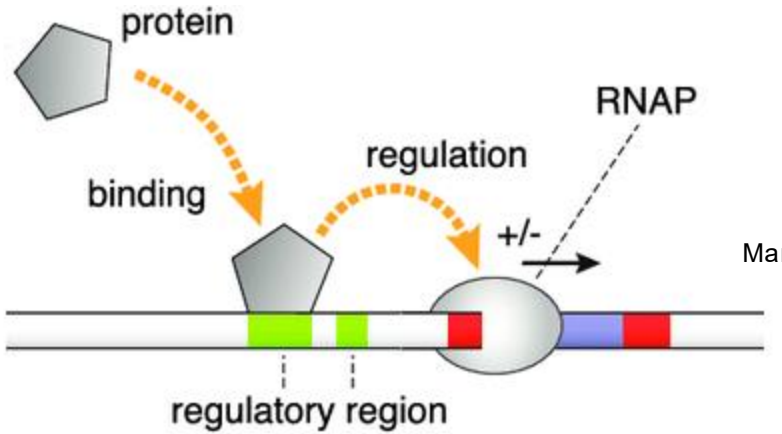
https://employees.csbsju.edu/cschaller/Reactivity/kinetics/rkphase.htm

Rate of E meeting S scales linearly with [E] and [S]

Rate of binding is a constant for E and S

- Reaction is a 2-step process: **Collision** & **Binding**
- P(collision) scales linearly with density, concentration, number of molecules

A reaction model for transcription



Marbach, D. et al. EvoBIO 2007

- **Transcription factor binding**: TF + DNA ↔ TF-DNA
- **Recruitment of polymerase**: RNAP + TF-DNA ↔ RNAP-TF-DNA
- **Transcription**: RNAP-TF-DNA → TF-DNA + RNAP + RNA

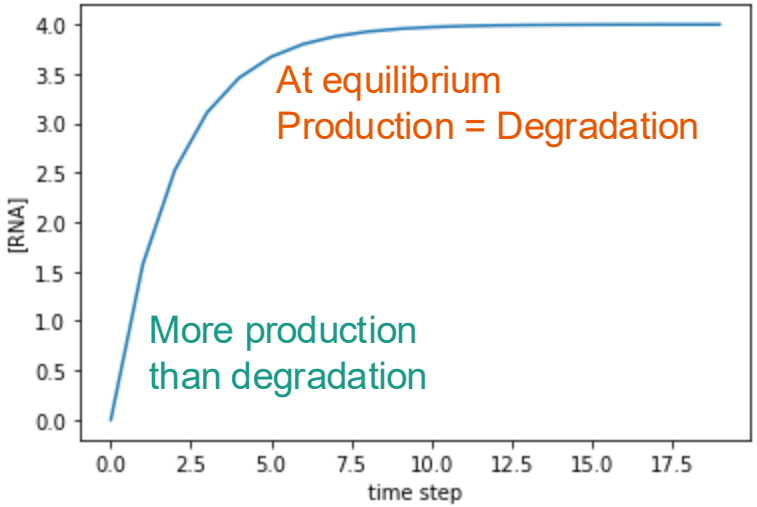
A simplified model for gene expression

$k_{transcription}$

$$DNA \rightarrow DNA + RNA$$

$$RNA \rightarrow \emptyset$$

$k_{degradation}$



- $\frac{d[RNA]}{dt}$ = rate of change of RNA = $k_{transcription} - k_{degradation}[RNA]$
- What would the graph of [RNA] look like?

Extrapolating the differential equation

$$x(t+1) = x(t) + (x(t+1) - x(t)) = x(t) + \frac{x(t+1) - x(t)}{(t+1) - t} \approx x(t) + x'(t)$$

- Differential equation defines $x'(t)$
  - $x'(t) = \frac{dx}{dt} = k_{transcription} - k_{degradation}x$
- Given an initial condition $x(0) = x_0$,
  - $x(1) = x(0) + x'(0) = x_0 + k_t - k_d x_0$
  - $x(2) = x(1) + x'(1) = x(1) + k_t - k_d x(1)$
    $= (x_0 + k_t - k_d\, x_0) + k_t - k_d(x_0 + k_t - k_d\, x_0)$
  - …

A toy example

- $\frac{d[RNA]}{dt} = 4 - 0.2\,[RNA]$

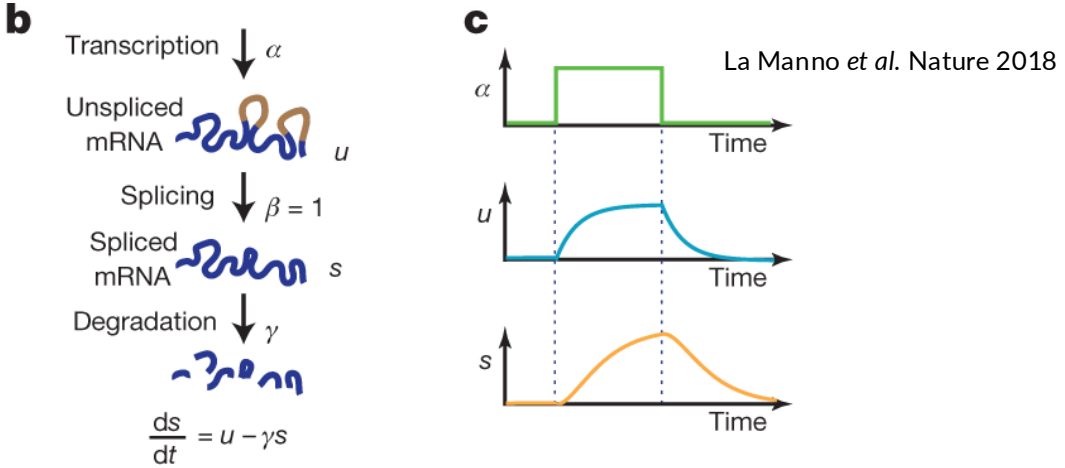
- Given an initial condition $x(0) = 100$:
  - $x(1) = 100 + 4 - 20 = 84$
  - $x(2) = 84 + 4 - 17 = 71$
  - $x(3) = 71 + 4 - 14 = 61$
  - $x(4) = 61 + 4 - 12 = 53$
  - $x(5) = 53 + 4 - 10 = 47$
  - Approaching the equilibrium [RNA] = 20

Another toy example

- $\frac{d[RNA]}{dt} = 4 - 0.2\,[RNA]$

- Given an initial condition $x(0) = 0$:
  - $x(1) = 0 + 4 - 0 = 4$
  - $x(2) = 4 + 4 - 1 = 7$
  - $x(3) = 7 + 4 - 1 = 10$
  - $x(4) = 10 + 4 - 2 = 12$
  - $x(5) = 12 + 4 - 2 = 14$
  - Approaching the equilibrium [RNA] = 20

RNA velocity is a two-stage model

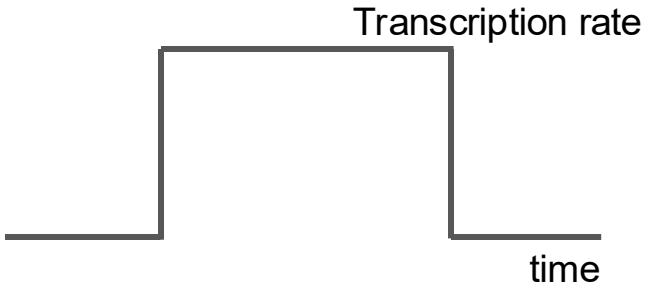


La Manno *et al.* Nature 2018

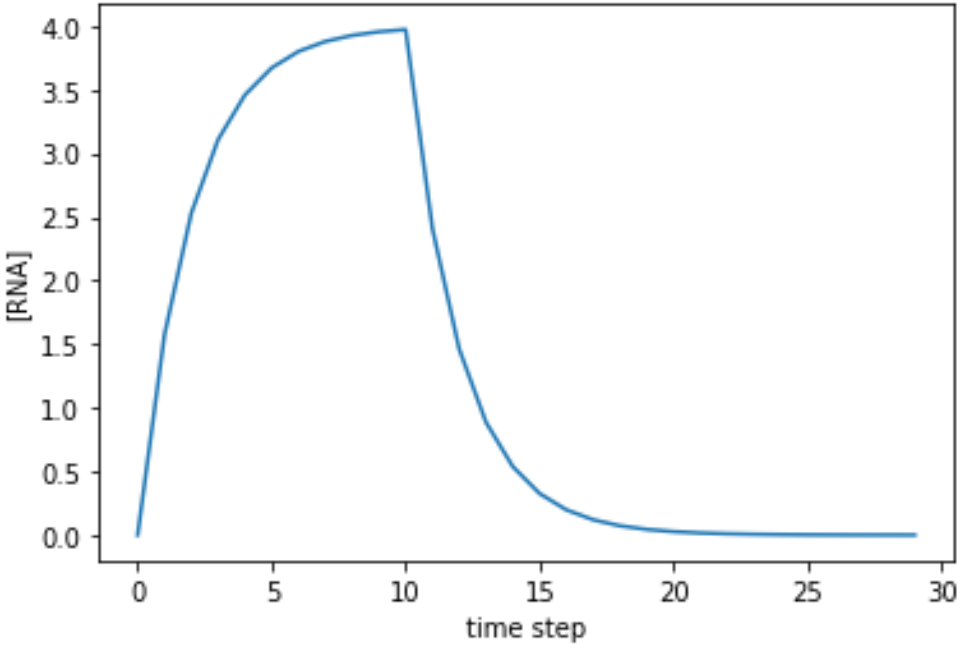
- **Two-step process**: From DNA to unspliced RNA to spliced RNA
- $\frac{d[U]}{dt} = \alpha - \beta[U], \frac{d[S]}{dt} = \beta[U] - \gamma[S] \rightarrow \frac{d[U]+[S]}{dt} = \alpha - \gamma[S]$
- Not the same dynamics as one-step: $\frac{d[S]}{dt} = \alpha - \gamma[S]$

Models for transcriptional regulation

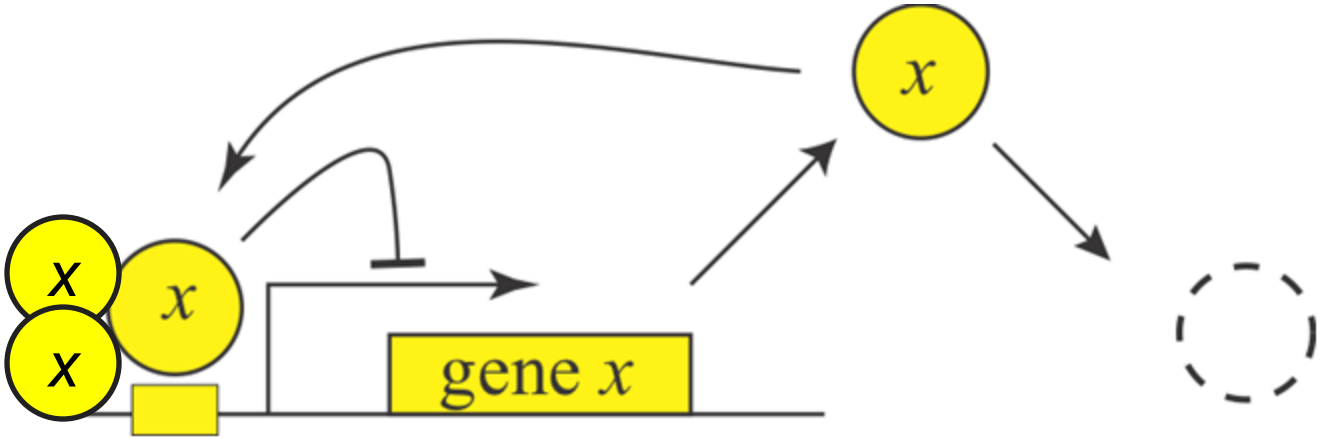
Time-dependent activation



- Constant transcription for a period of time
- Followed by RNA degradation
- Similar to RNA velocity plot



Negative auto-regulation



http://be150.caltech.edu/2019/handouts/03_small_circuits.html

- X assembles and binds to DNA to deactivate transcription
- $\frac{d[X]}{dt} = k_{transcription}[DNA_{unbound}] - k_{degradation}[X]$
- $[DNA_{unbound}]$ depends on [X] through binding

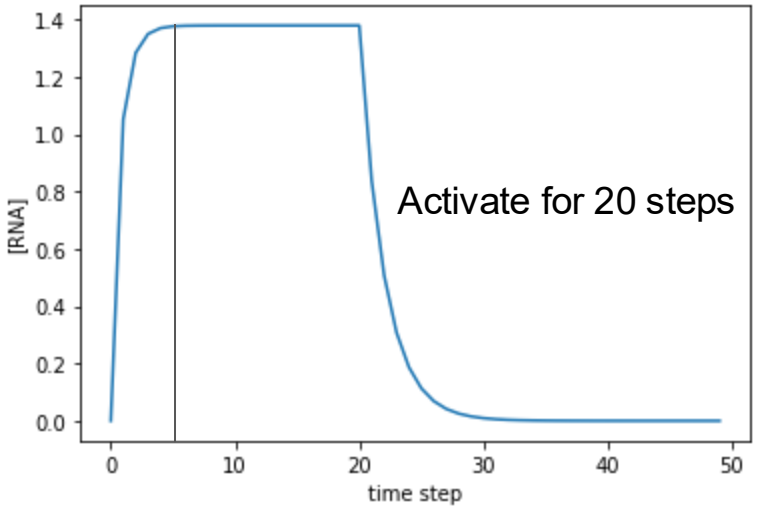
Negative auto-regulation

$$nX + DNA_{unbound} \underset{k_{unbind}}{\overset{k_{bind}}{\leftrightarrow}} DNA_{bound}$$

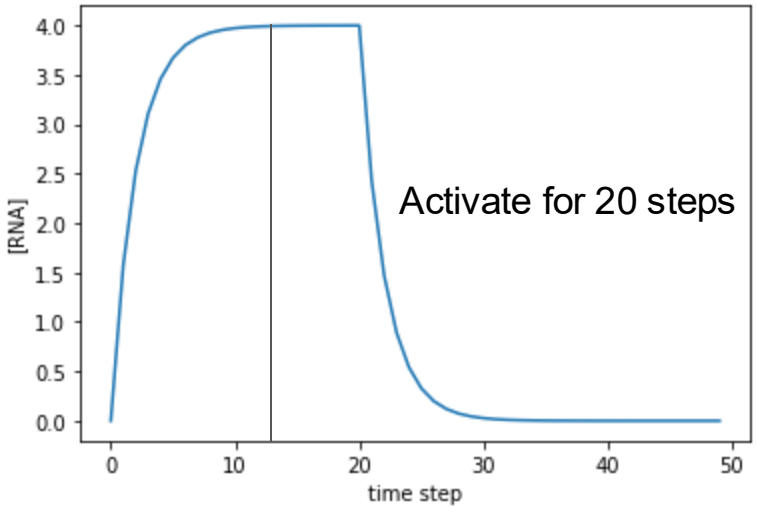
- n molecules of X assemble as a complex
- $\frac{dDNA_{bound}}{dt} = k_{bind}[X]^n[DNA_{unbound}] - k_{unbind}[DNA_{bound}]$
- At equilibrium, fraction of unbound DNA $= \frac{k_{bind}[X]^n}{k_{unbind}+k_{bind}[X]^n}$
  - Also known as Hill function

Faster time to equilibrium, at lower expression level

With negative auto-regulation

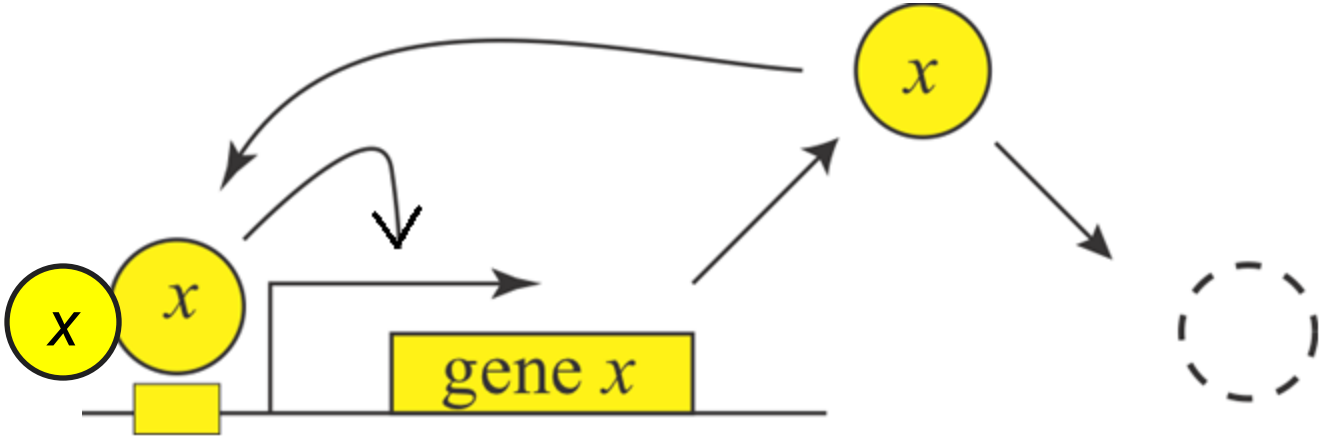


Without negative auto-regulation



- $\frac{d[X]}{dt} = \frac{k_{transcription}}{1+(k[X])^n} - k_{degradation}[X]$

Positive auto-regulation

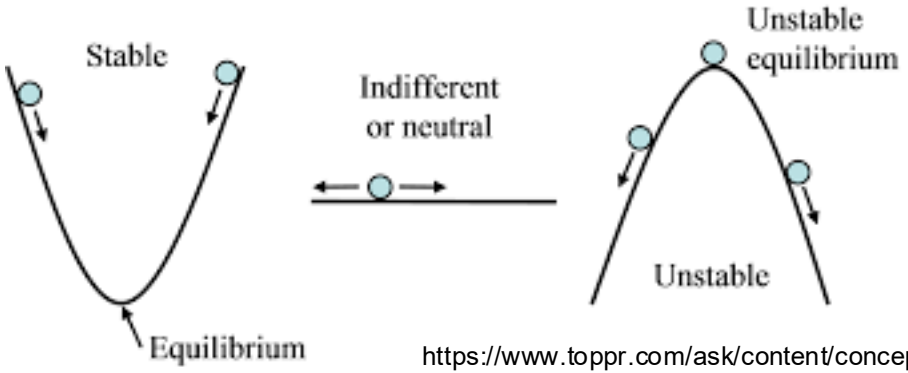


- X assembles and binds to DNA to further activate transcription
- $\frac{d[X]}{dt} = \frac{k_{transcription}(k[X])^2}{1+(k[X])^2} - k_{degradation}[X]$
  - Would the expression level rise indefinitely?

Equilibrium of positive auto-regulation

- $\frac{d[X]}{dt} = \frac{k_{transcription}(k[X])^2}{1+(k[X])^2} - k_{degradation}[X]$
- There are three equilibria (three solutions to $\frac{d[X]}{dt} = 0$)
  - $0 = k_t(k[X])^2 - k_d[X] - k_d[X](k[X])^2$ is a polynomial with degree 3
- Let's solve: $0 = [X](k_t k^2[X] - k_d - k_d k^2[X]^2)$
  - **Trivial root**: [X] = 0
  - **Quadratic roots**: [X] = $\frac{k_t k^2 \pm \sqrt{k_t^2 k^4 - 4k_d^2 k^2}}{2k_d k^2}$

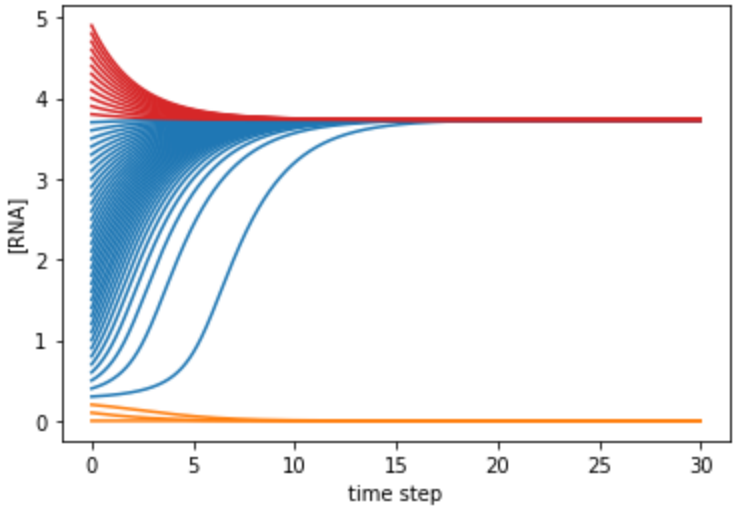
Stability of an equilibrium



https://www.toppr.com/ask/content/concept/equilibrium-and-its-types-208616/

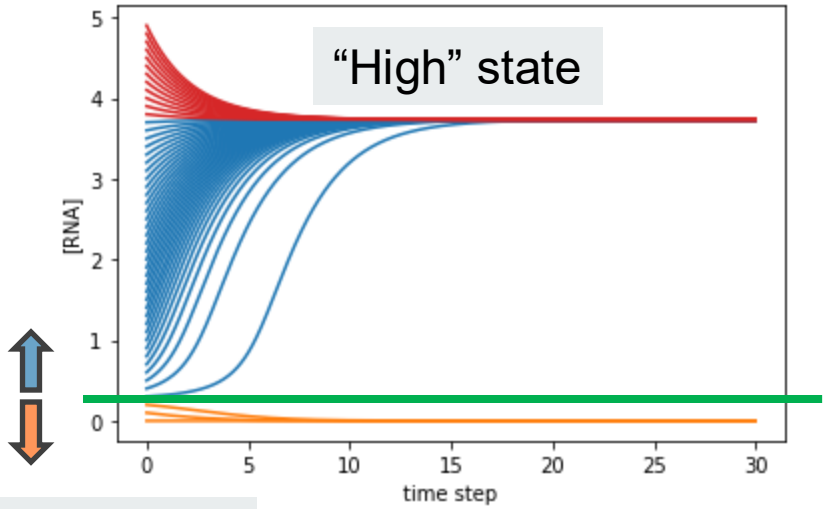
- Among three equilibria for positive autoregulation, one is unstable and the other two are stable
- Depending on the initial $[X]$, this system will converge to one of the two stable equilibria

Bistability of positive autoregulation



- For **low** [X], degradation dominates, and [X] goes down to zero
- For **intermediate** [X], transcription dominates, and [X] increases until reaching the stable equilibrium
- For **high** [X], the degradation dominates, and [X] goes down to the stable equilibrium

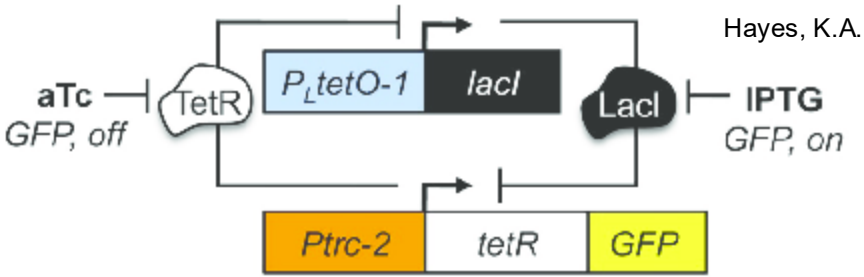
Bistability as controllable cell memory



- Cells in low- or high-expression states will remain in their states
  - Robust to expression fluctuation
- In the gene is activate in a “low-expression” cell and the expression rises above the **threshold**, the cell will be locked in “high” state
- Cells memorize their states

Two-gene systems

Cell memory from gene toggle switch

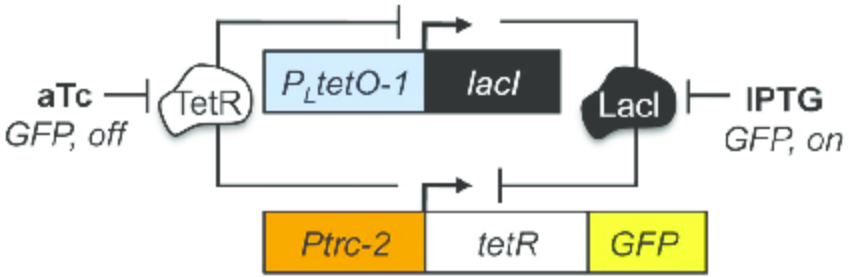


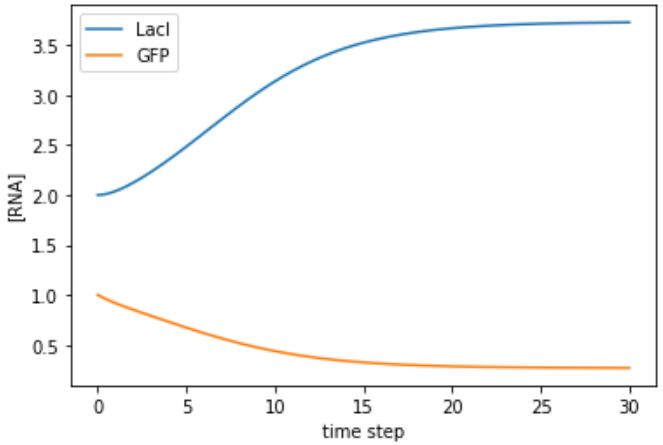
Hayes, K.A. et al. J of Cell Biology 187:589-96 (2009)

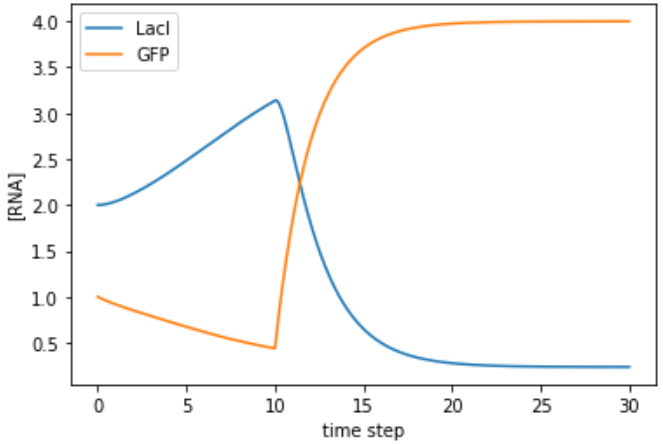
- A system of two genes repressing each other
  - **Two equilibria**: High **lacI** OR high **tetR**

- Once expression of **lacI** is established, it will constantly repress **tetR**
- Once expression of **tetR** is established, it will constantly repress **lacI**

Gene toggle switch simulation







- **Top panel**: High **lacI** represses **tetR-GFP**
- **Bottom panel**:
  - Add IPTG to neutralize **lacI** at t = 10
  - **tetR-GFP** rises

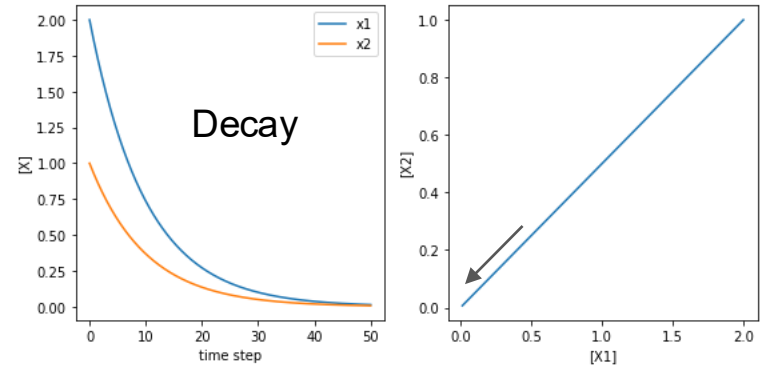
Linear two-gene system

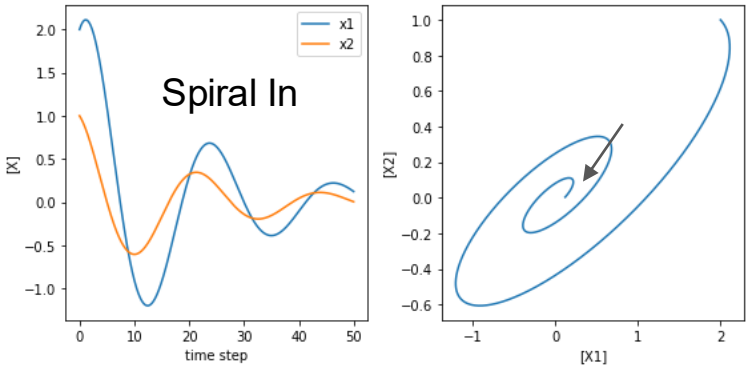
$$\frac{d[X1]}{dt} = k_{1,1}[X1] + k_{1,2}[X2]$$

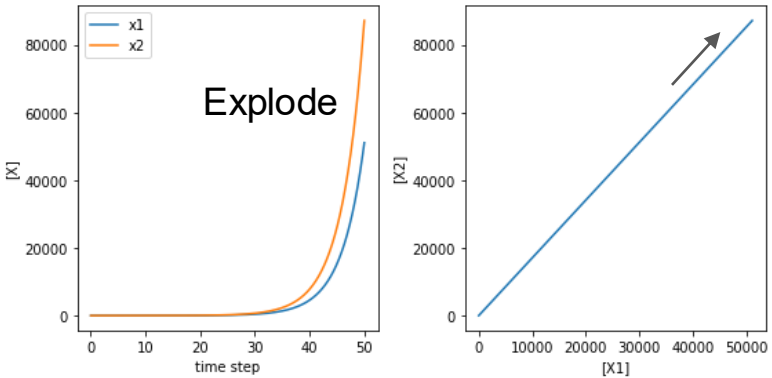
$$\frac{d[X2]}{dt} = k_{2,1}[X1] + k_{2,2}[X2]$$

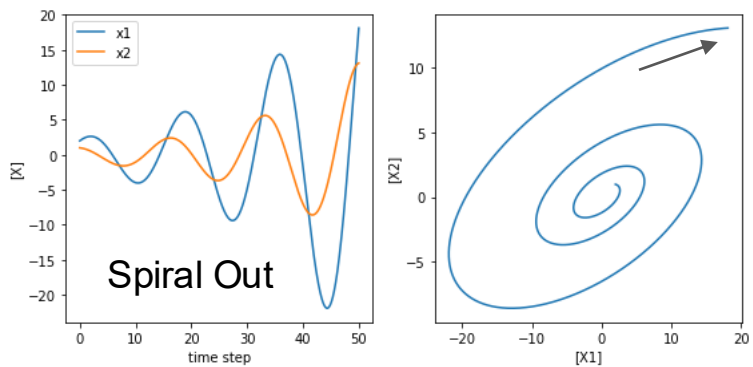
- Simple system with only linear effects
- Depending on the sign and magnitude of $k_{i,j}$ interesting dynamics can be derived
  - **Trace** and **Determinant** of the matrix $\{k_{i,j}\}$

Non-linear dynamics from a linear system









Summary

- Biological system consists of components that interact with each other to drive the changes of the system

- Changes over time can be described with differential equations

- Properties of a system extend beyond gene/protein expression levels
  - How many equilibria?
  - Stability / cell memory
  - Response time (time to equilibrium)

Any question?

- See you next time