3000788 Intro to Comp Molec Biol

Lecture 30: Dynamics modeling for systems biology

November 29, 2022

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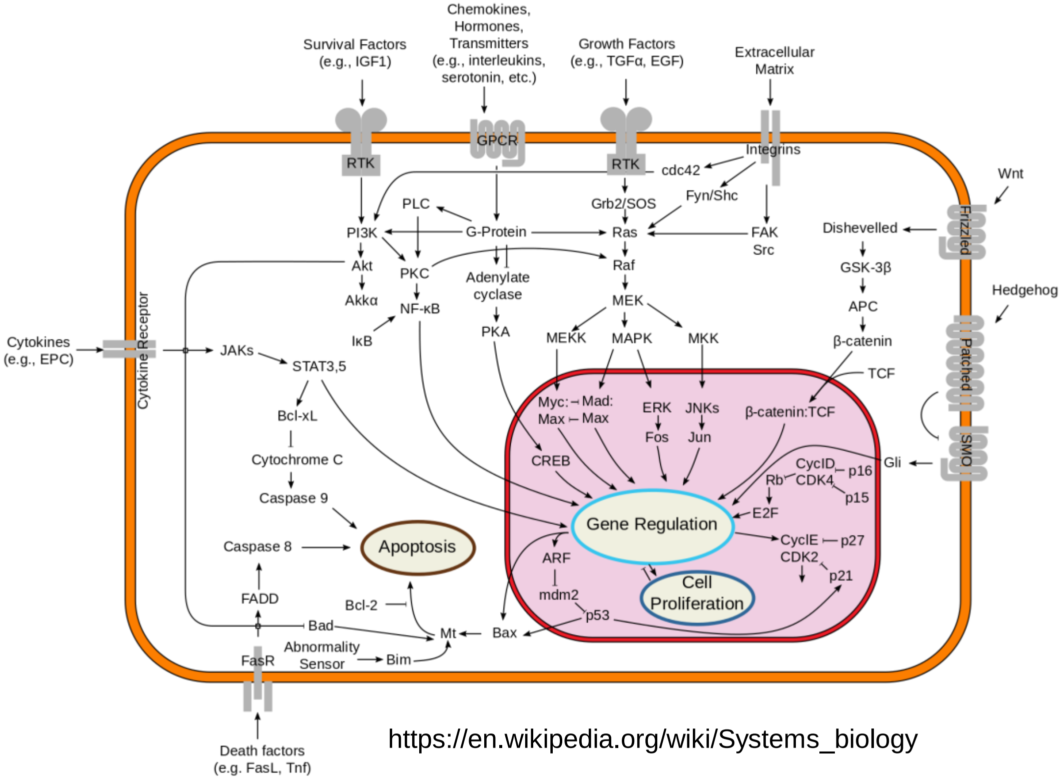
- Research Affairs
- Center of Excellence in Computational Molecular Biology (CMB)
- Center for Artificial Intelligence in Medicine (CU-AIM)

Systems biology

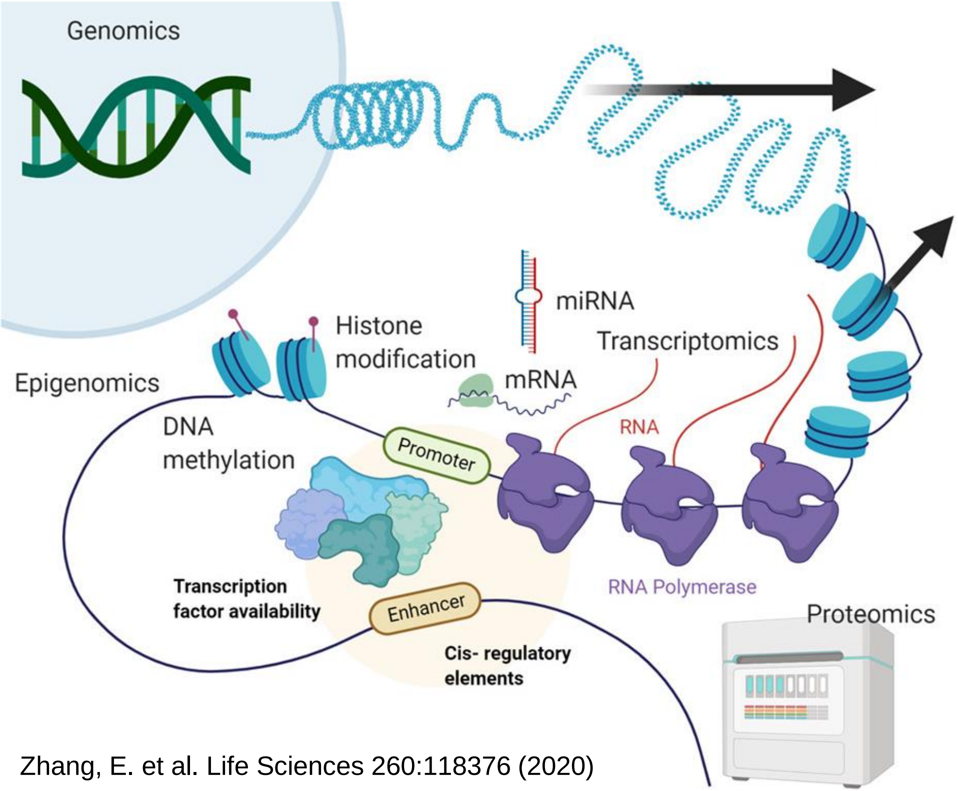


https://en.wikipedia.org/wiki/Systems_biology

- A (biological) system consists of components (genes) and rules (gene expression regulations) that control its characteristics (phenotypes)

- Systems biology = integration of data and model to fully understand the system

Multi-omics approach

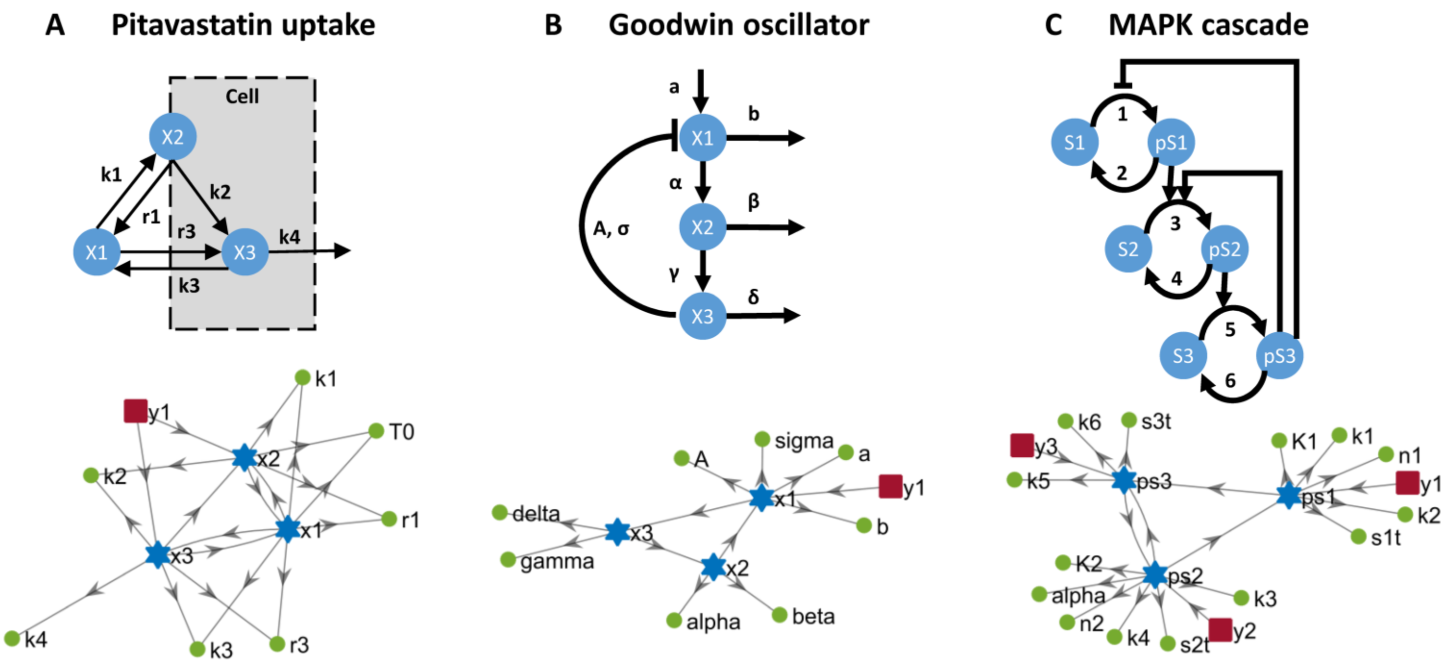


Zhang, E. et al. Life Sciences 260:118376 (2020)

- Genomics → gene state
- Epigenomics → chromatin state
- Transcriptomics → gene expression
- Proteomics → protein expression
- Other assays → protein function
- Provide mechanistic understanding

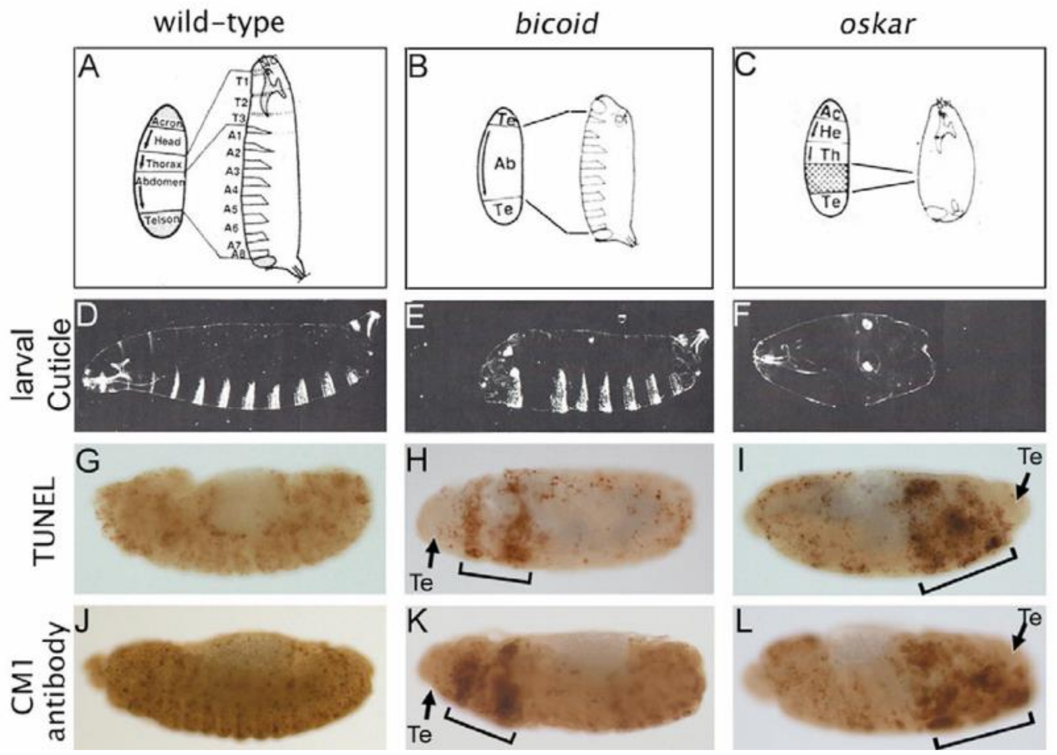
Modeling approach

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



- Represent molecular interaction as network of physical-chemical reactions

Why is systems biology interesting?

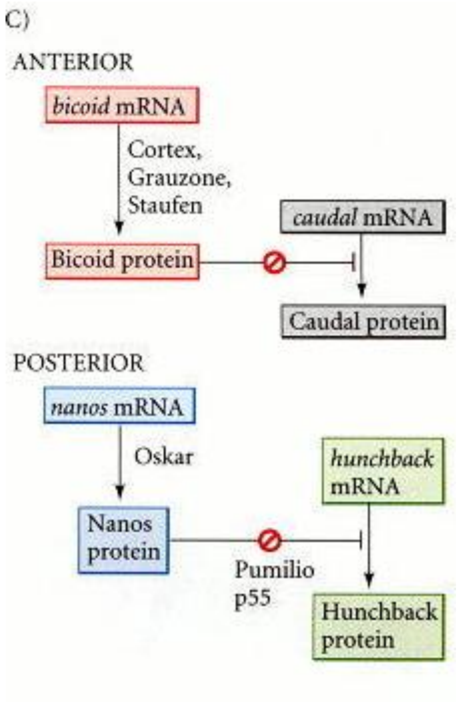


- How does gene and protein know where to activate in the body during development?

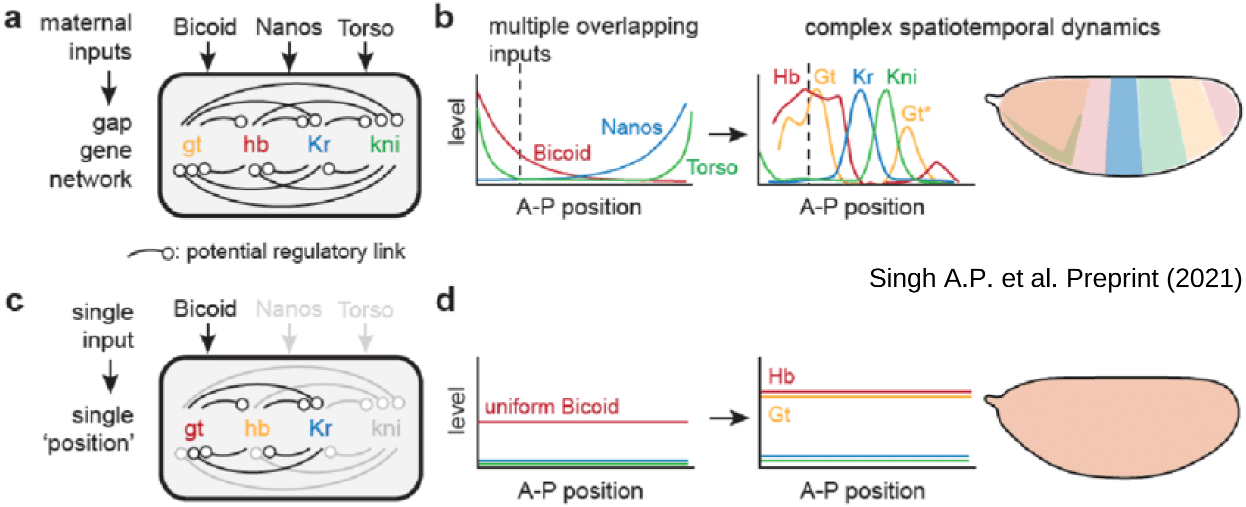
- Each cell starts in identical state!

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

Why is systems biology interesting?



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



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

- Gene regulatory dynamics lead to specific expression pattern over time

A simple enzymatic reaction

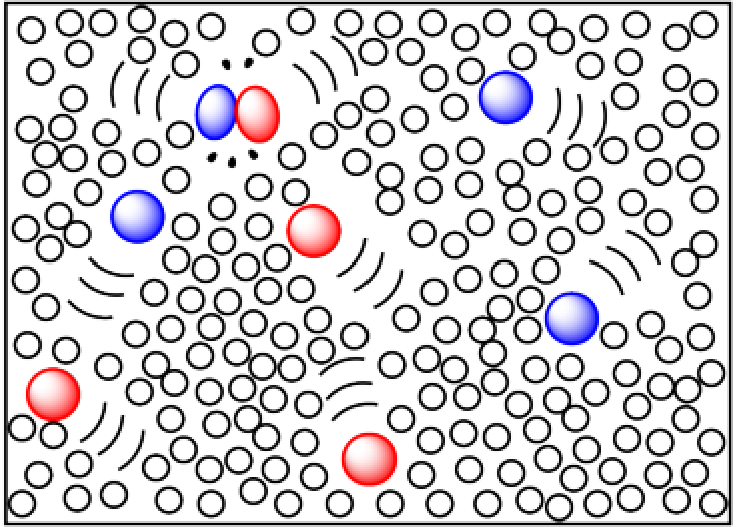
$$E + S \underset{\mathrm{k_{off}}}{\overset{\mathrm{k_{on}}}{\leftrightarrow}} ES \xrightarrow{\mathrm{k_{react}}} E + P$$

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

A key mental image

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

Rate of E + S → ES =
[E][S] x k



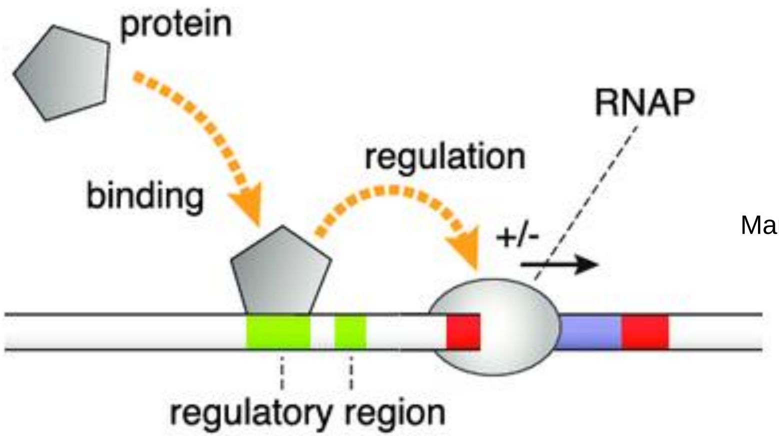
https://employees.csbsju.edu/cschaller/Reactivity/kinetics/rkphase.htm

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

Rate of binding is a constant for E and S

- Molecules must find each other in 3D to bind and interact
- Reaction takes time (and typically energy)

From enzymatic reaction to transcription



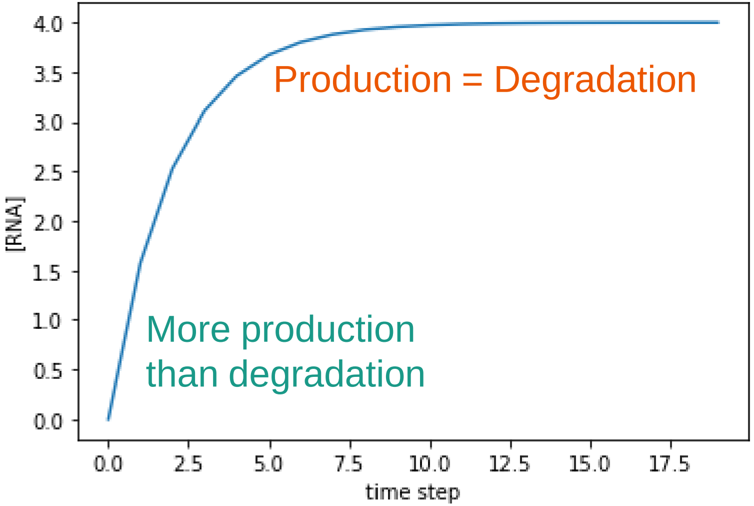
Marbach, D. et al. EvoBIO 2007

- $\mathrm{TF} + \mathrm{DNA}_{\mathrm{inactive}} \leftrightarrow \mathrm{TF\text{-}DNA}$
- $\mathrm{RNAP} + \mathrm{TF\text{-}DNA} \rightarrow \mathrm{RNAP} + \mathrm{TF\text{-}DNA} + \mathrm{RNA}$
- RNA → degraded RNA

A simple gene expression model

$$DNA \xrightarrow{k_{transcription}} DNA + RNA$$

$$RNA \xrightarrow[k_{degradation}]{} \emptyset$$

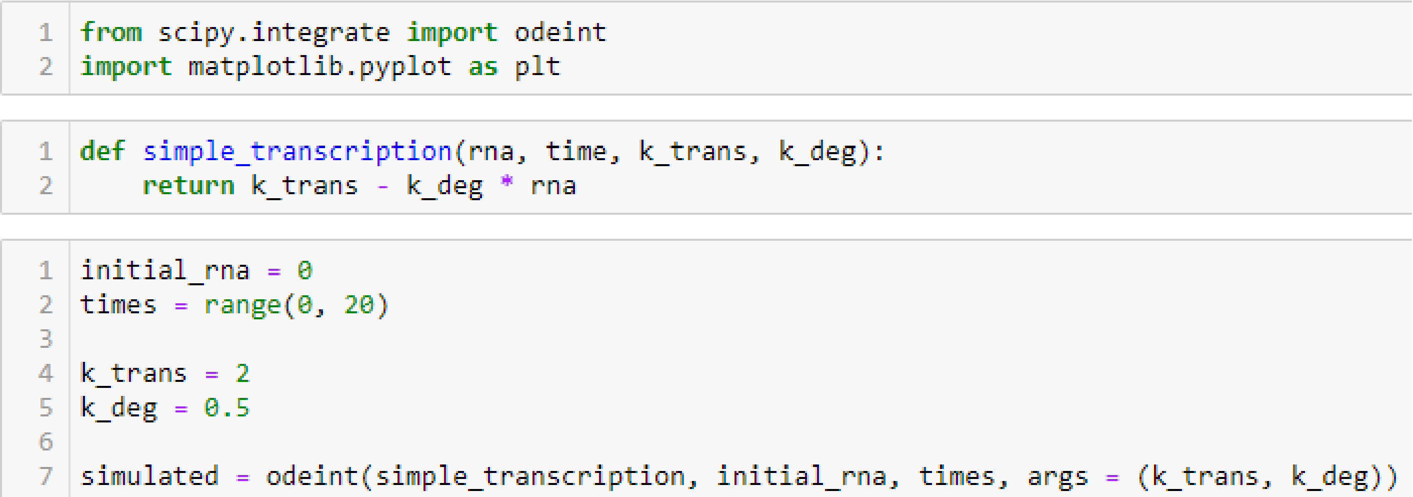


- $\frac{d[RNA]}{dt} = k_{transcription} - k_{degradation}[RNA]$
- What would the graph of [RNA] looks like?

How to simulate differential equation?

- $x_{t+1} = x_t + (x_{t+1} - x_t)$
- $x_{t+1} - x_t$ can be viewed as Δx at time t, or approximately $x'(t)$
- Differential equation defines $x'(t)$
- If we start with an initial condition x_0, we can determine x_1, x_2, ... by calculating $x'(0)$, $x'(1)$, ... and adding them

scipy.integrate.odeint



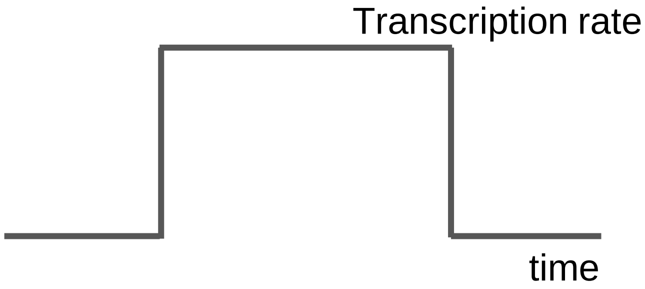
```python
from scipy.integrate import odeint
import matplotlib.pyplot as plt
```

```python
def simple_transcription(rna, time, k_trans, k_deg):
    return k_trans - k_deg * rna
```

```python
initial_rna = 0
times = range(0, 20)

k_trans = 2
k_deg = 0.5

simulated = odeint(simple_transcription, initial_rna, times, args = (k_trans, k_deg))
```

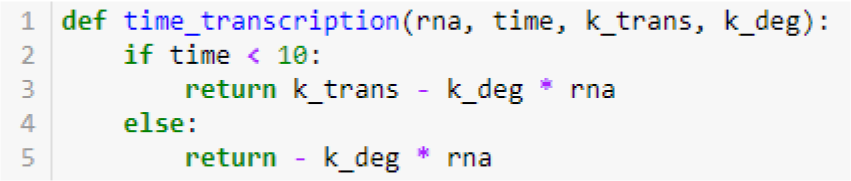
- odeint() takes a function that return derivative(s), initial condition, and time steps

Time-dependent activation

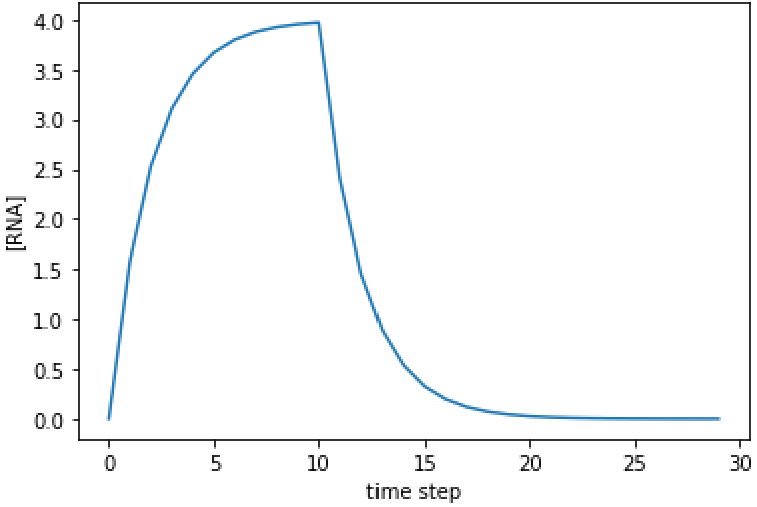


- First half of the dynamics is the same as before

- Second half is when RNA degrades until the [RNA] falls back to the basal level

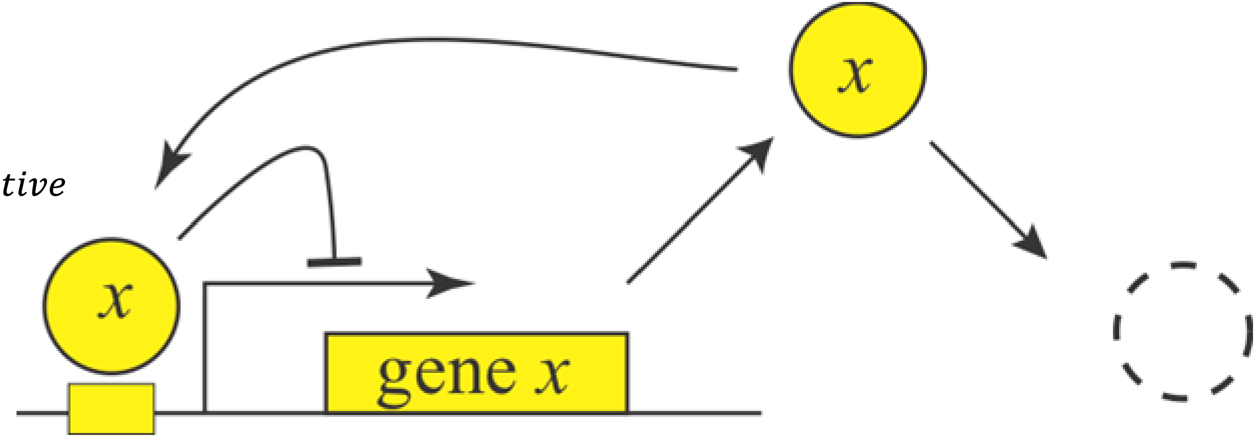


```python
def time_transcription(rna, time, k_trans, k_deg):
    if time < 10:
        return k_trans - k_deg * rna
    else:
        return - k_deg * rna
```



Negative auto-regulation

$$nX + DNA \underset{k_{unbind}}{\overset{k_{bind}}{\leftrightarrow}} DNA_{inactive}$$

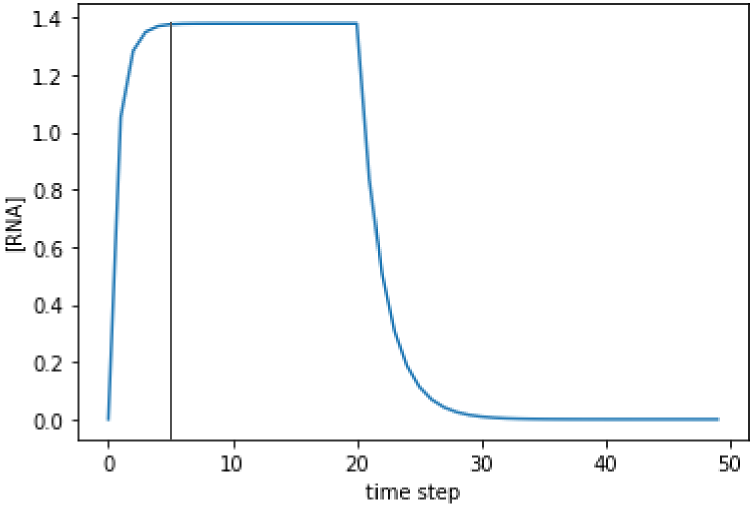


http://be150.caltech.edu/2019/handouts/03_small_circuits.html

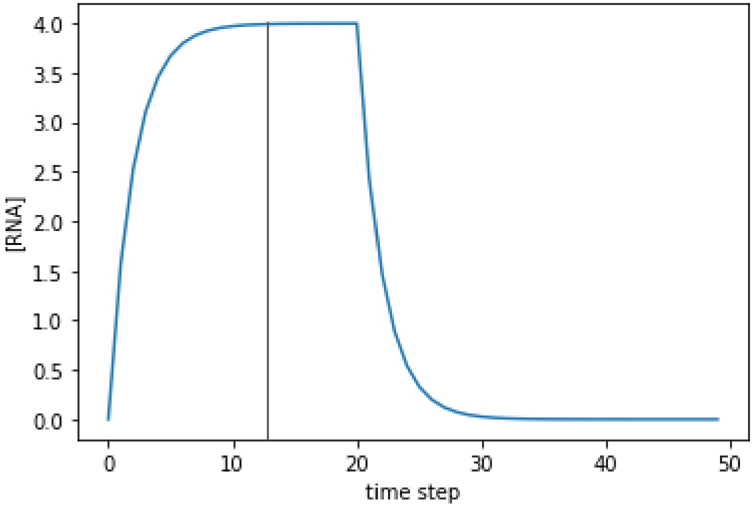
- $\frac{dDNA_{inactive}}{dt} = k_{bind}[X]^n[DNA] - k_{unbind}[DNA_{inactive}]$
- At equilibrium, fraction of unbound DNA $= \frac{[DNA]}{[DNA]+[DNA_{inactive}]} = \frac{k_{bind}[X]^n}{k_{unbind}+k_{bind}[X]^n}$
- Also known as Hill function

Faster equilibrium & response time

With negative auto-regulation

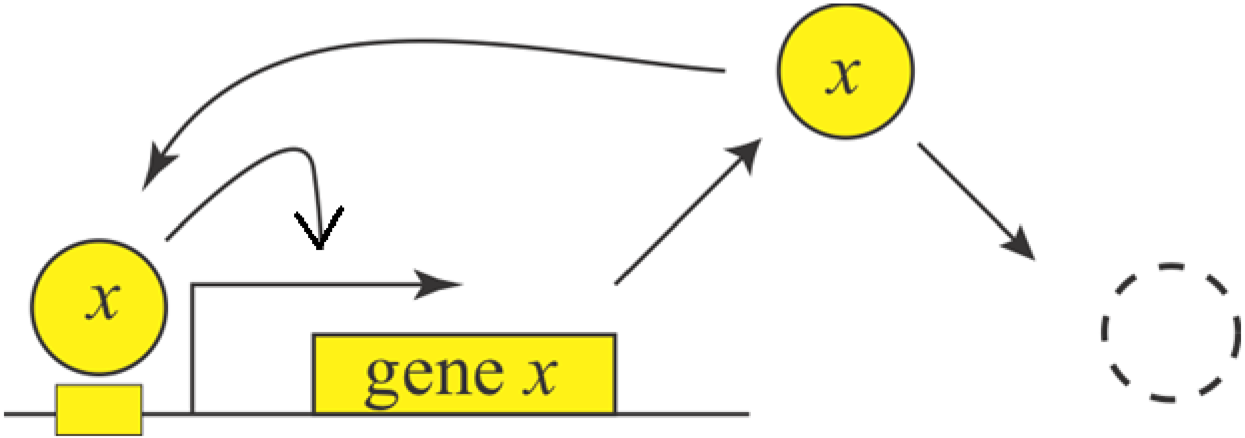


Without negative auto-regulation



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

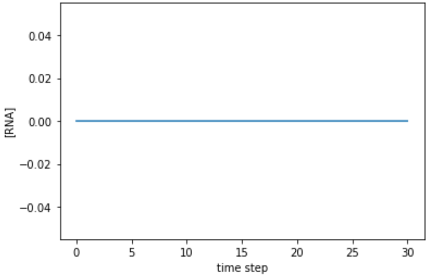
Positive auto-regulation



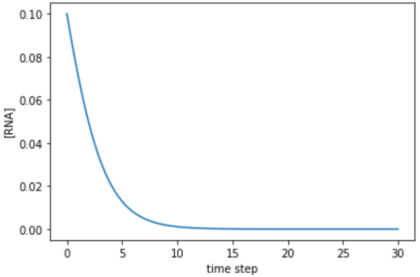
- $\frac{d[X]}{dt} = \frac{k_{transcription}(k[X])^n}{1+(k[X])^n} - k_{degradation}[X]$
- Can you guess what would happen to the system when n = 2?

Bistability

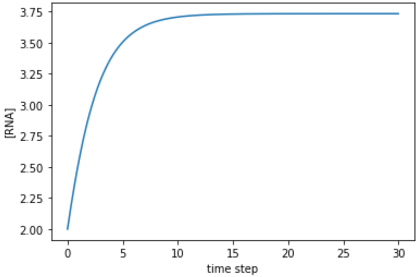
Initial [X] = 0



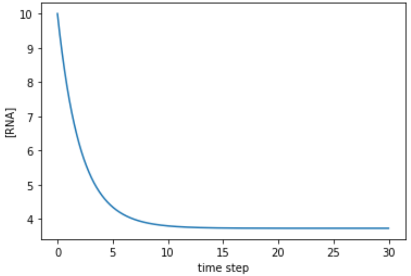
Initial [X] = 0.1



Initial [X] = 2

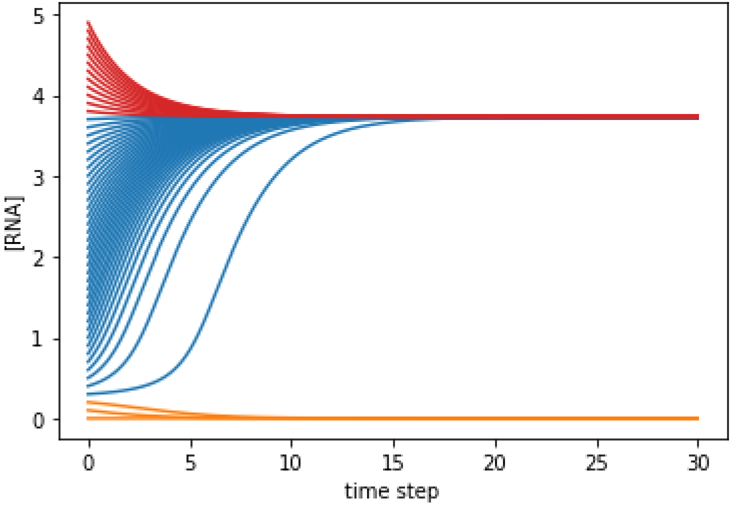


Initial [X] = 10



- At equilibrium, $\frac{k_{transcription}(k[X])^2}{1+(k[X])^2} = k_{degradation}[X]$
- There are two solutions, one of which is $[X] = 0$
- Depending on the current $[X]$, the system can converge to either equilibrium

Bistability

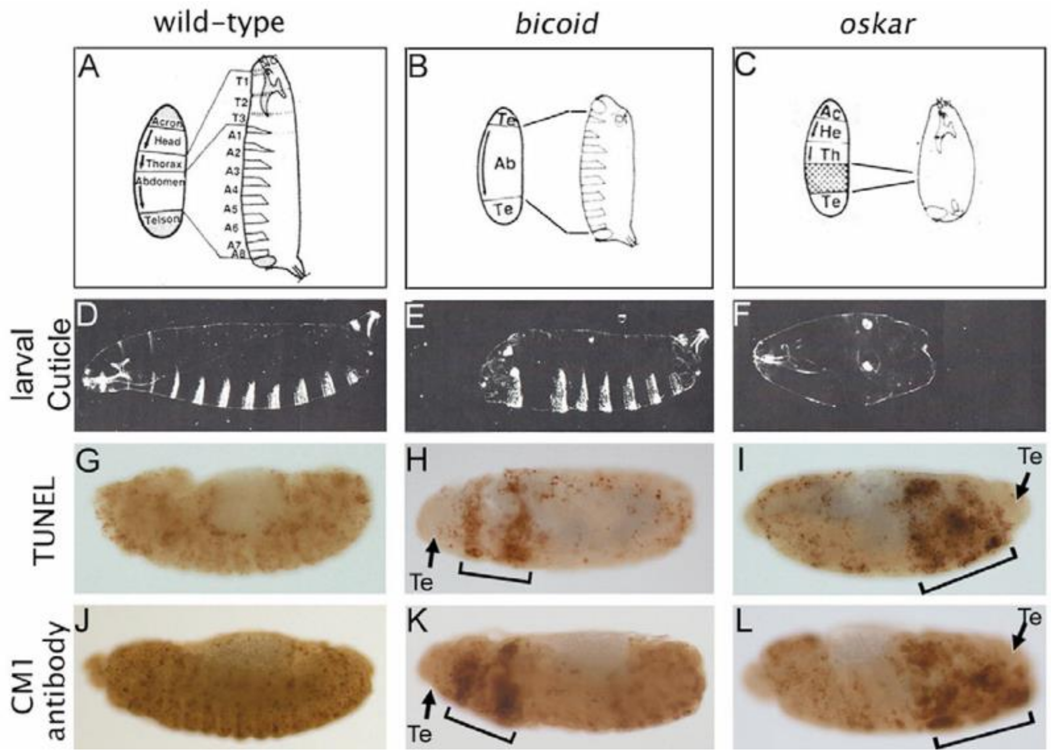


- For **low** [X], the degradation term wins over the transcription and [X] decays down to zero

- For **intermediate** [X], the transcription term wins over degradation and [X] increases until reaching the other equilibrium

- For **high** [X], the degradation term wins over the transcription and [X] decays down to the nearest equilibrium

Tunable cell state based on equilibria

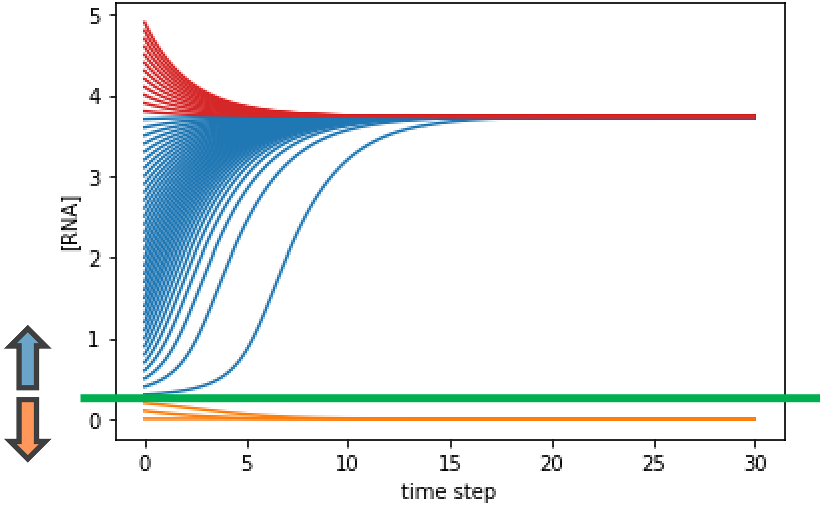


- With more genes and regulatory interactions, many more equilibria can exist

- Gradient of gene expression can establish position-specific cell states

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

Cell memory

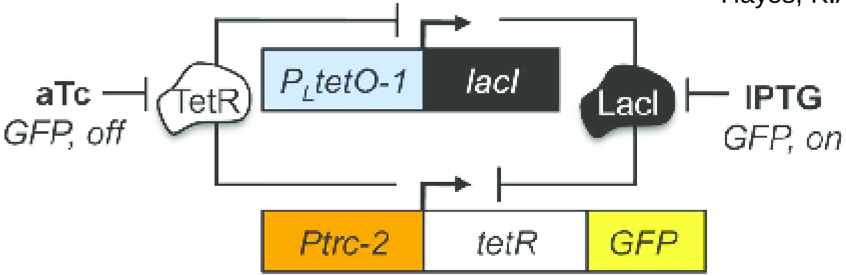


- Once a cell gets pass the green boundary, small changes in gene expression will not be able to bring it back to the other side

- The cell “remembers” its state

Memory from gene toggle switch

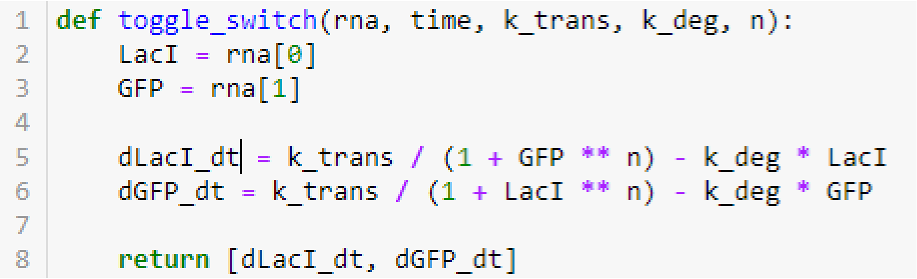
Hayes, K.A. et al. J of Cell Biology 187:589-96 (2009)



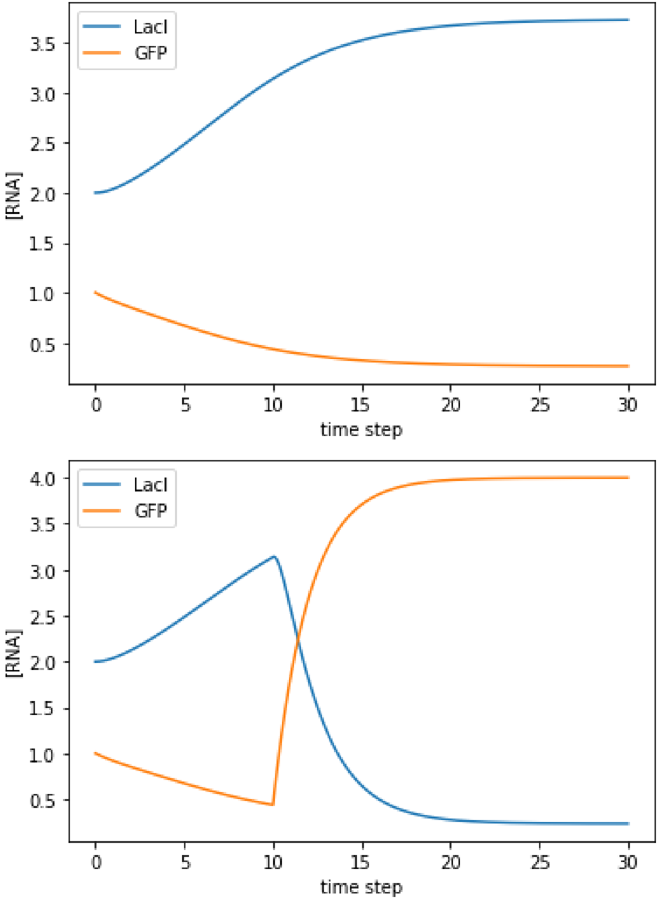
- Two genes repressing each other
- **Two equilibria**: High LacI or high GFP

- If GFP is ON, how can we turn it off? Adding aTc or IPTG?
- Once GFP is OFF, do we need to continue adding those molecules to keep it OFF?

Toogle switch simulation



```python
def toggle_switch(rna, time, k_trans, k_deg, n):
    LacI = rna[0]
    GFP = rna[1]

    dLacI_dt = k_trans / (1 + GFP ** n) - k_deg * LacI
    dGFP_dt = k_trans / (1 + LacI ** n) - k_deg * GFP

    return [dLacI_dt, dGFP_dt]
```



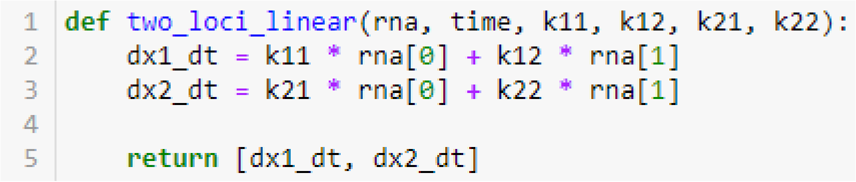
- odeint() can handle multiple equations
- Input rna is a list [LacI, GFP]

- **Bottom Panel**: add IPTG to neutralize LacI at time = 10

Two-gene linear system

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

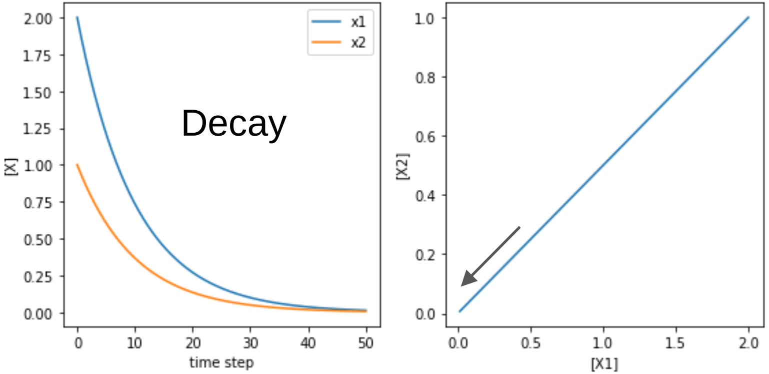
$$\frac{d[X2]}{dt} = k_{2,1}[X1] + k_{2,2}[X2]$$

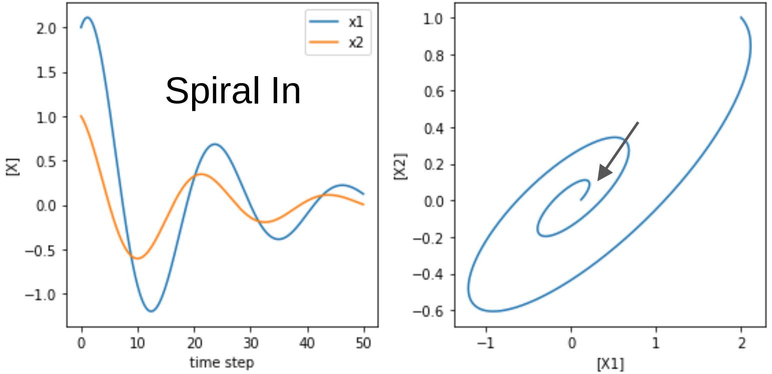


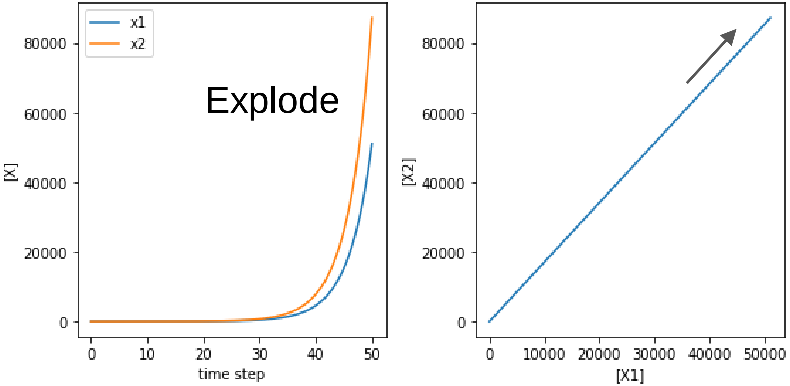
```python
def two_loci_linear(rna, time, k11, k12, k21, k22):
    dx1_dt = k11 * rna[0] + k12 * rna[1]
    dx2_dt = k21 * rna[0] + k22 * rna[1]

    return [dx1_dt, dx2_dt]
```

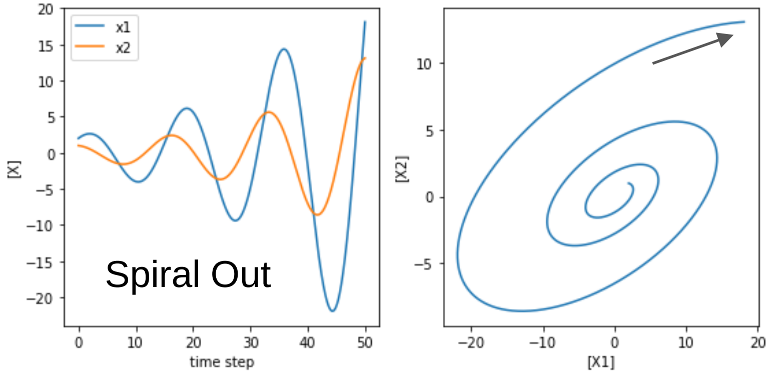
- Depending on the values of $k_{i,j}$, diverse dynamics can be obtained
  - Actually, depending on Trace and Determinant of the matrix $\{k_{i,j}\}$

Some possible dynamics

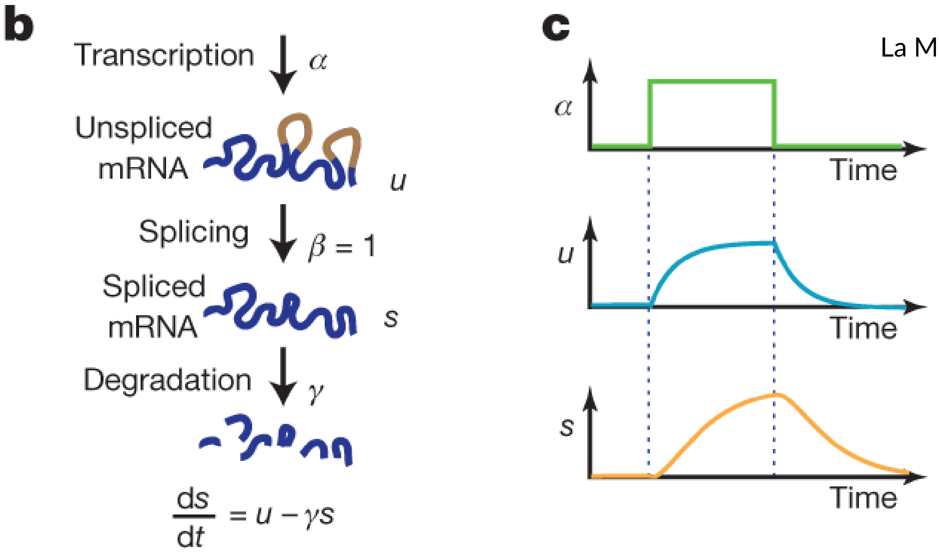








RNA velocity model



La Manno *et al.* Nature 2018

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

Summary

- Systems biology = gain mechanistic understanding of a biological systems
  - Combine multi-omics data
  - Model the dynamics

- Different stable cell states arise from multiple gene expression equilibria

- Diverse dynamics can originate from a simple two-gene system

- **Next**: Gene expression simulation with Python

Any question?

- See you on December 1st at 1pm for our last session