# Gene Expression & Transcriptional Models

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# Gene expression modeled with differential equations

- Deal with rates of expression
- Parameters from biochemical properties
  - Production ✓
  - Degradation ✓

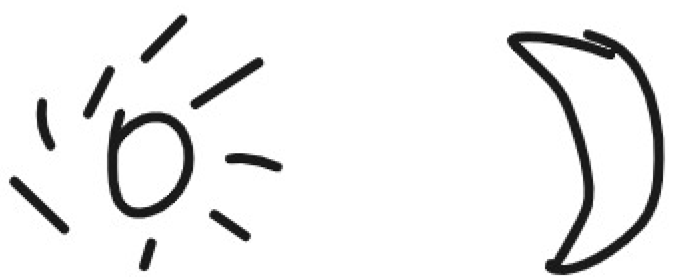
- Gene expression is dynamic
- Focus on changes over time
- Considers processes from DNA to protein

$$\frac{dA}{dt} = f(?)$$

change thru time

A, B, Temp

A ↑ → B ↓ ?



Gene A ↑ ↓

continuous var

discrete var

# Modeling protein production

- Consider concentration instead of number of molecules
- Differential equation (depends on time)
- Solve equation with integration

$$\frac{dP}{dt} = f(P)$$

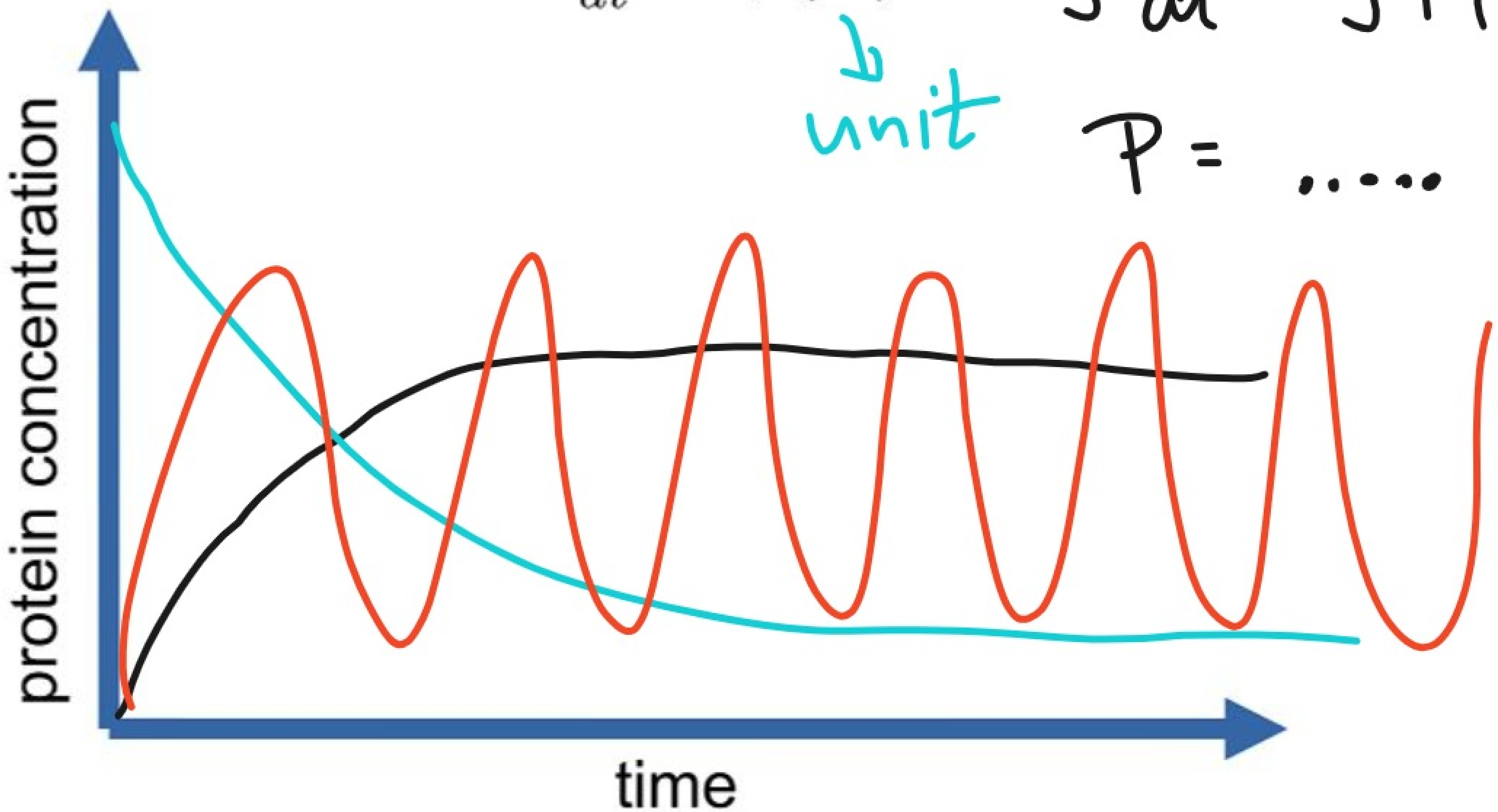
unit

$$\int \frac{dP}{dt} = \int f(P)$$

$$P = \ldots\ldots (t)$$

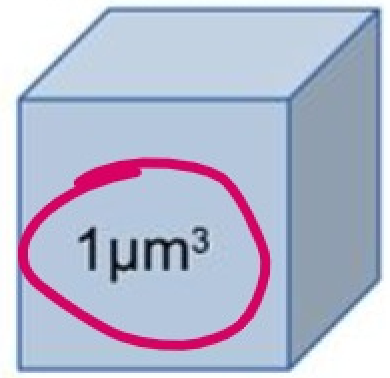
can be tough to solve analytically

use numerical methods!



# Common cellular concentrations

E. coli
cell volume




- Inferring protein concentration in cell
- 1 molecule/cell
- 1 M = 1 mol / L

$$\frac{1 molec}{cell} * \frac{1 mol}{6 * 10^{23} molec} * \frac{1 cell}{10^{-18} m^3}$$

$$= \frac{1}{6} * 10^{-8} M \approx 10^{-9} M = 1nM$$

- Volume
- Bacteria = 1μm³ > 1 nM
- Yeast = 10³ μm³ > 1 pM
- Mammalian = 10⁴ μm³ > 0.1 pM

$\frac{dP}{dt}$ — nM, μM ; s, min, hr, days

P = protein  t = time

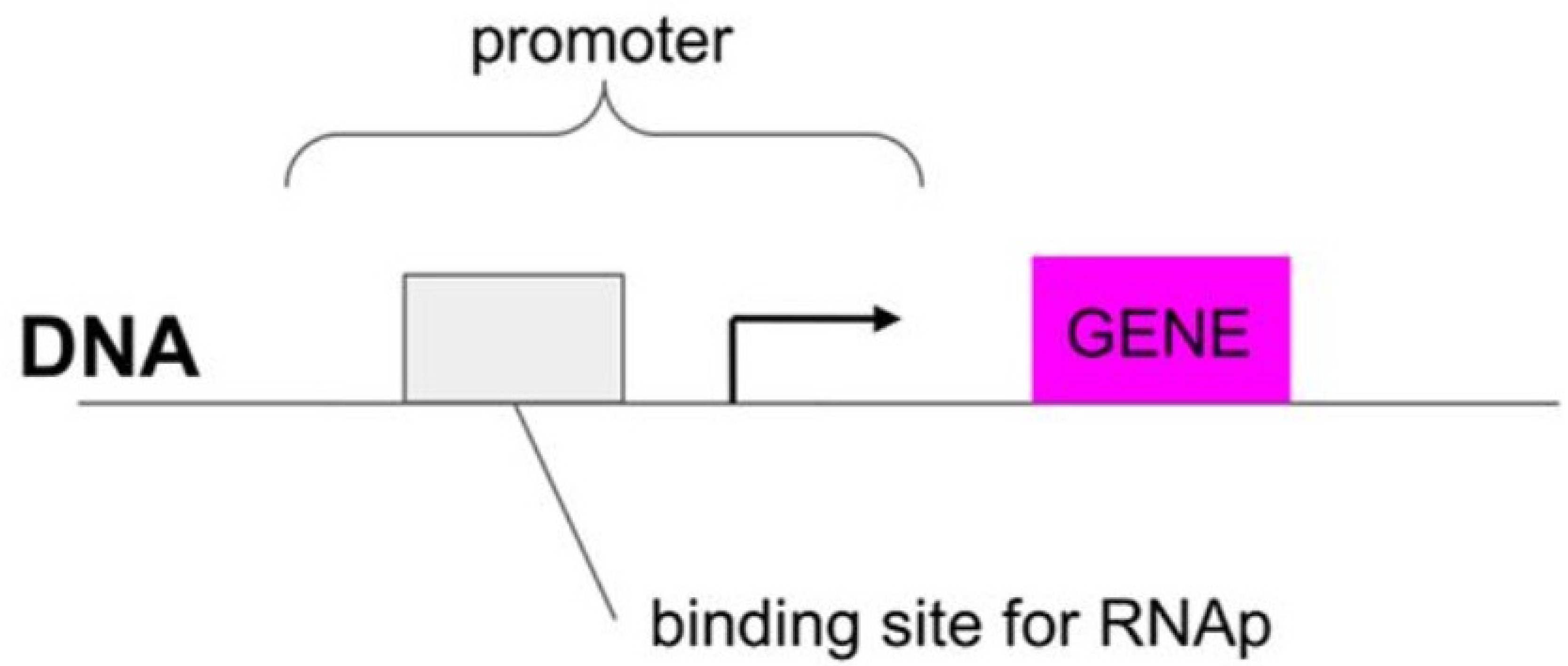
# Cellular properties

| Property | E. coli (bacteria) | S. cerevisae (yeast) | Fibroblast (human) |
|---|---|---|---|
| cell volume | 1 $\mu m^3$ | 1,000 $\mu m^3$ | 10,000 $\mu m^3$ |
| proteins/cell | $4*10^5$ | $4*10^9$ | $4*10^{10}$ |
| genome size | $4.6 * 10^6$ bp<br>4,500 genes | $1.3*10^7$ bp<br>6,600 genes | $3*10^9$ bp<br>30,000 genes |
| gene size | 1000 bp | 1000 bp | $10^4 - 10^6$ bp |
| concentration of One protein/cell | 1 nM | 1 pM | 0.1 pM |
| transcribe gene | 1 min<br>80 bp/sec | 1 min | 30 min |
| translate protein | 2 min<br>40 aa/sec | 2 min | 30 min |

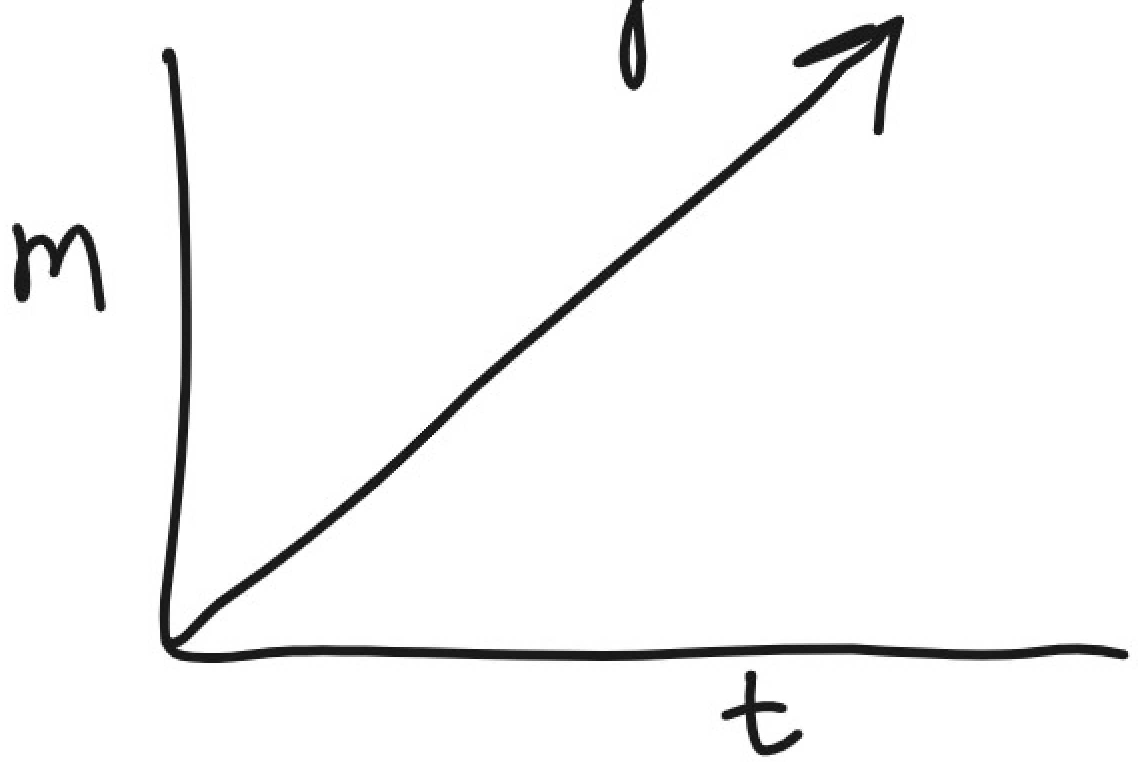
Milo, R., Phillips, R., Orme, N. (2008). *Cell Biology by the Numbers*. Garland Science. https://doi.org/10.1142/9781848162013_0010

# mRNA expression

Promoter
- region of DNA before gene
- binds with protein
- starts RNA synthesis




How does exp. change over time?




$$\frac{dm}{dt} = \alpha \longrightarrow \text{constitutive expression}$$

m = mRNA concentration

alpha = transcription rate

0.0001 - 1 nM/s

degradation missing!

# Mass-action kinetics

$$\frac{dP}{dt} = ?$$

$$A + B \xrightarrow{K} C + D$$

$$\begin{cases} \boxed{\dfrac{dC}{dt} = KAB} \\ \boxed{\dfrac{dD}{dt} = KAB} \\ \boxed{\dfrac{dA}{dt} = -KAB} \\ \boxed{\dfrac{dB}{dt} = -KAB} \end{cases}$$

$$K \rightarrow [nM^{-1} s^{-1}]$$

$$\alpha \rightarrow nM/s$$

$$K \rightarrow 1/(nM \cdot s)$$

$$nM^{-1} s^{-1}$$

$$\frac{dC}{dt} = KAB$$

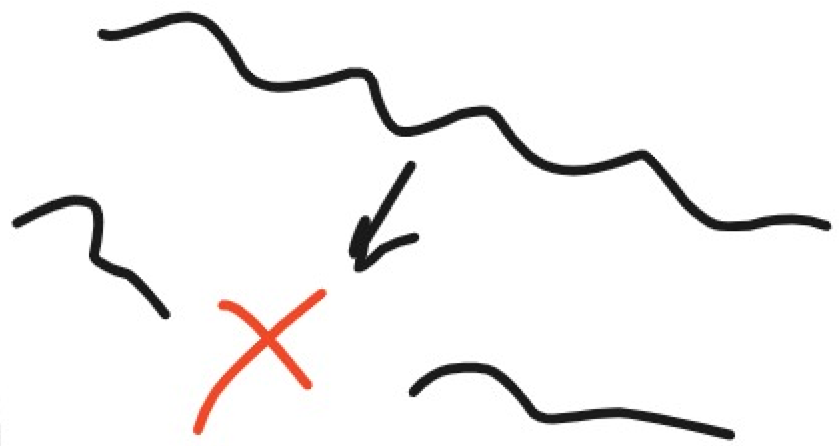
$$\begin{array}{ccc} K & A & B \\ \left[\dfrac{1}{s \cdot \cancel{nM}}\right] & [\cancel{nM}] & [nM] \end{array}$$

$$\frac{nM}{s} = \frac{nM}{s}$$

# mRNA degradation

conc. → for equation

- Concentration → *m = (number of molecules) / (number of cells)*
- Two forms for decrease in mRNA concentration
  - Degradation
  - Cell division



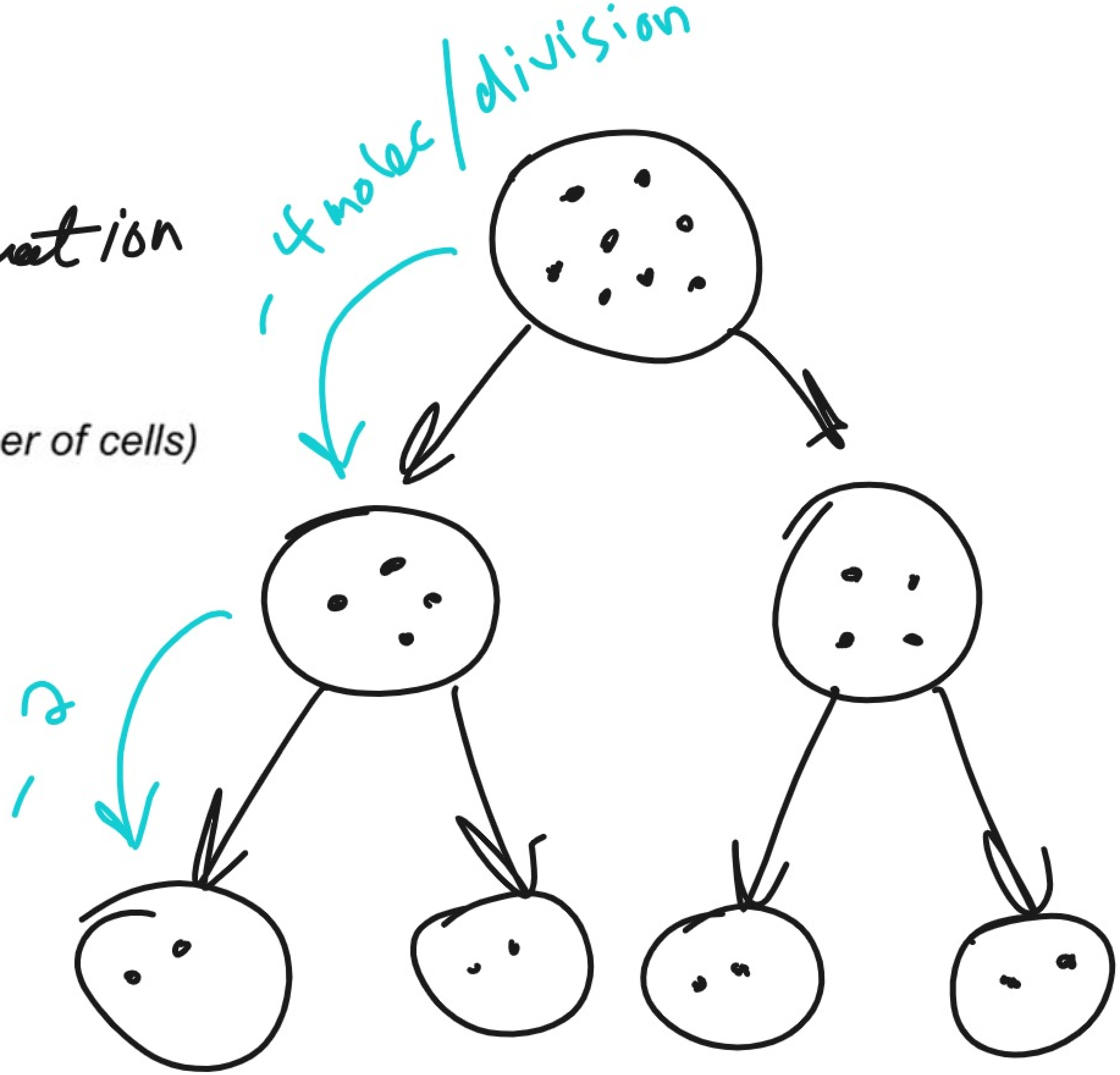
- Exponential cell growth
- Exponential decay of protein concentration

$$N = N_0 e^{\delta t}$$

$$\boxed{m = m_0 e^{-\delta t}} \longleftrightarrow \boxed{\frac{dm}{dt} = -\delta m}$$

analytical ✓

degradation rate

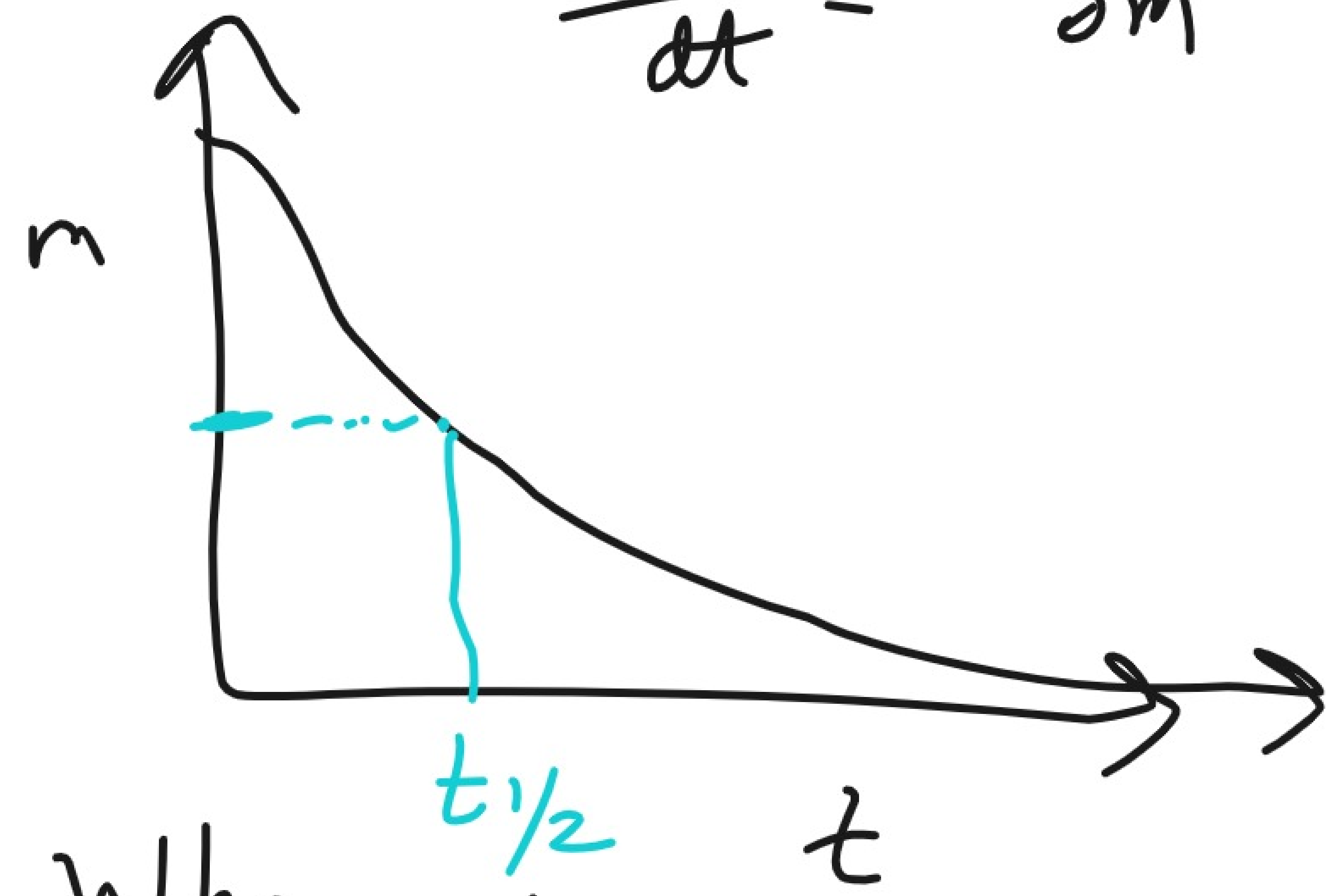



$\delta \rightarrow [s^{-1}]$

$\delta m \rightarrow [\frac{1}{s}][nM] = [\frac{nM}{s}]$

$$\ln\left(\tfrac{1}{2}\right) = \ln\left(2^{-1}\right) = (-1)\ln(2)$$

$$\frac{\delta m}{dt} = -\delta m$$




When does it get to 0?

When does it get to $\frac{1}{2} m_0$?

$$m = m_0 e^{-\delta t}$$

$$\frac{1}{2}\cancel{m_0} = \cancel{m_0} e^{-\delta t}$$

$$\frac{1}{2} = e^{-\delta t}$$

## mRNA degradation

$$\frac{dm}{dt} = -\delta m \longrightarrow \delta_{dilution} = \frac{ln(2)}{\tau_{divide}}$$

- Other sources of mRNA loss

$$\delta_m = \delta_{dilution} + \delta_{degradation}$$

$$\downarrow$$

$$\delta_{degradation} \approx 0.01 s^{-1}$$

$$\tau_{1/2} \approx 1\text{min}$$

$$\ln\left(\tfrac{1}{2}\right) = \ln\left(e^{-\delta t}\right)$$

$$\frac{\ln\left(\frac{1}{2}\right)}{t} = -\delta \Rightarrow \frac{\ln(2)}{t} = \delta \Rightarrow t = \frac{\ln 2}{\delta}$$

$$\frac{dm}{dt} = 10 - 2m$$

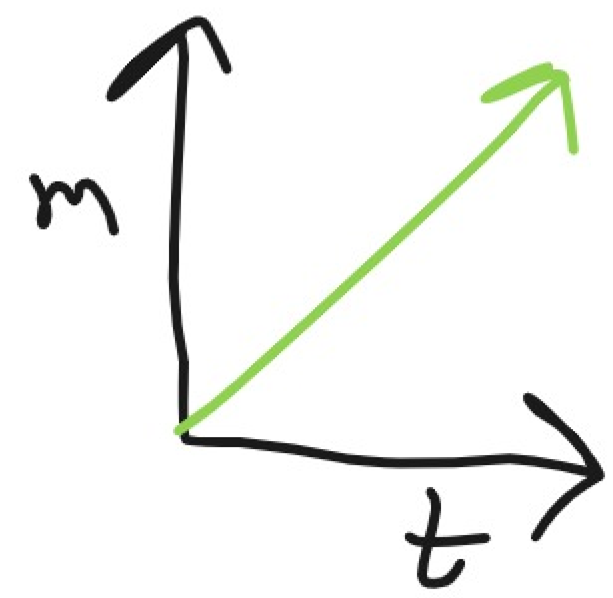
$$m^* = 5$$

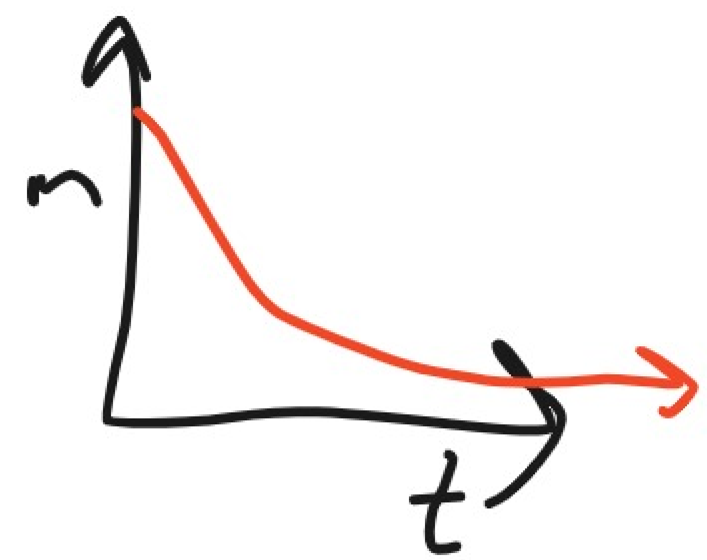
# Combining mRNA expression and degradation

production

degradation

(constant) constitutive expression

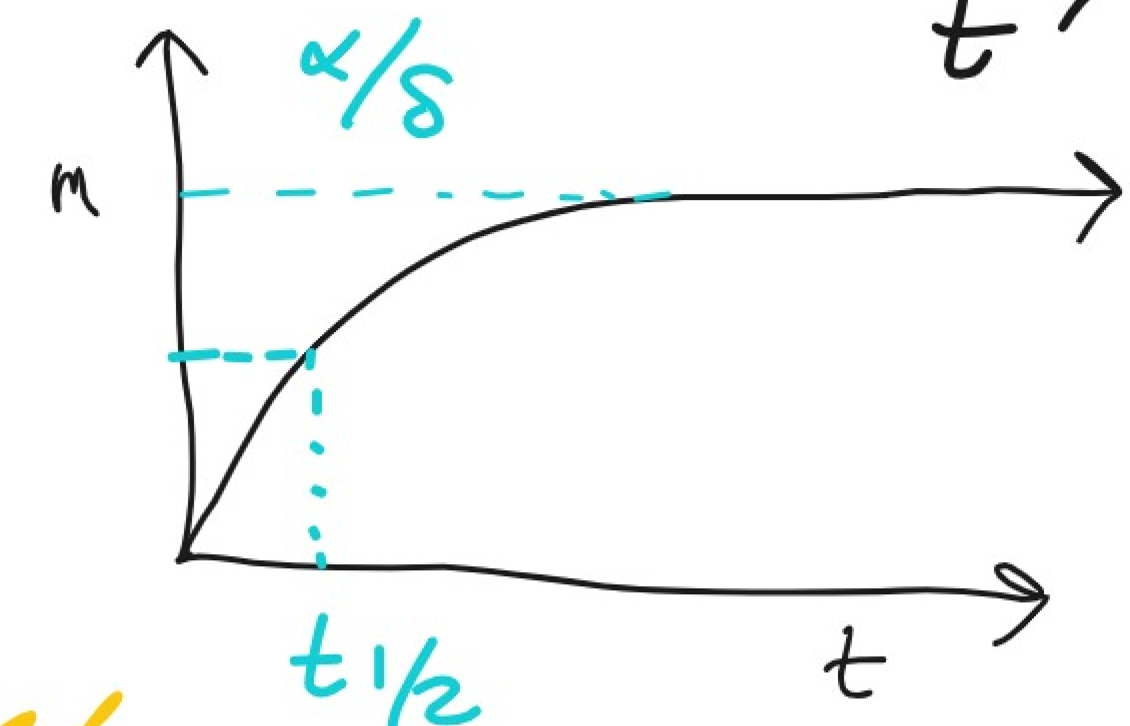



$$\frac{dm}{dt} = \alpha_m - \delta_m m$$

$$\boxed{m = \frac{\alpha_m}{\delta_m}(1 - e^{-\delta_m t})}$$

analytical

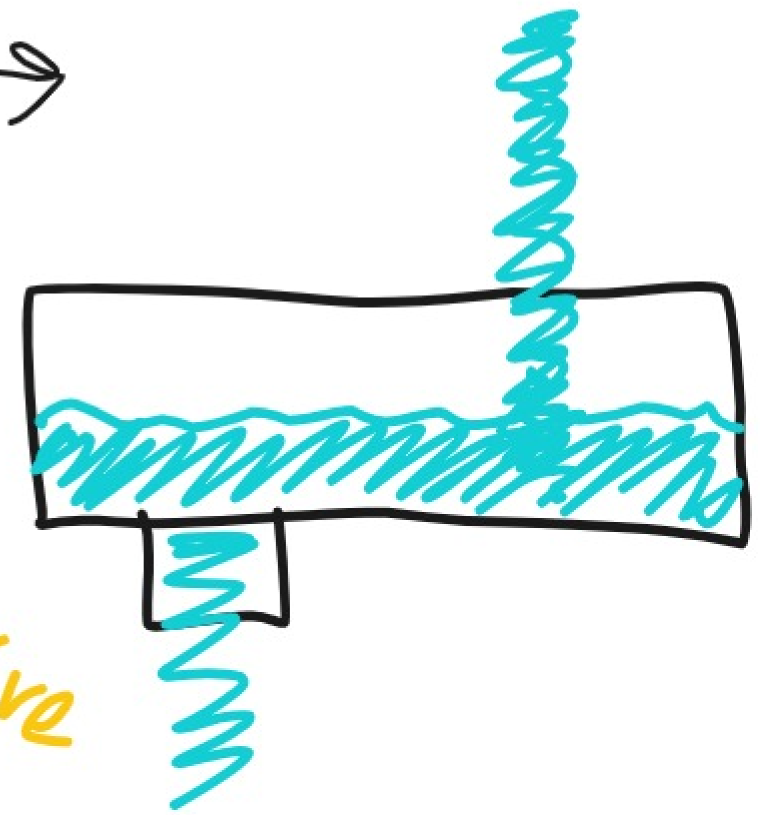



- mRNA concentration reaches...
  - steady state
  - equilibrium
  - fixed point

$$m^* = \frac{\alpha_m}{\delta_m}$$

$$\tau_{1/2} = \frac{ln2}{\delta_m}$$

steady state for constitutive



$$\frac{dm}{dt} = \alpha - \delta m = 0 \text{ at fixed point}$$

$\frac{dm}{dt} = \alpha - \delta m$ Change $\alpha$? Change $\delta$?

## Analysis of the system for mRNA dynamics

- How does steady state change? → $m^* = \frac{\alpha}{\delta}$
- How does time to half steady state change? $t_{1/2} = \frac{\ln 2}{\delta}$

analytical

$\alpha \uparrow$ SS $\uparrow$

$\alpha \downarrow$ SS $\downarrow$

$\delta \uparrow$ SS $\downarrow$

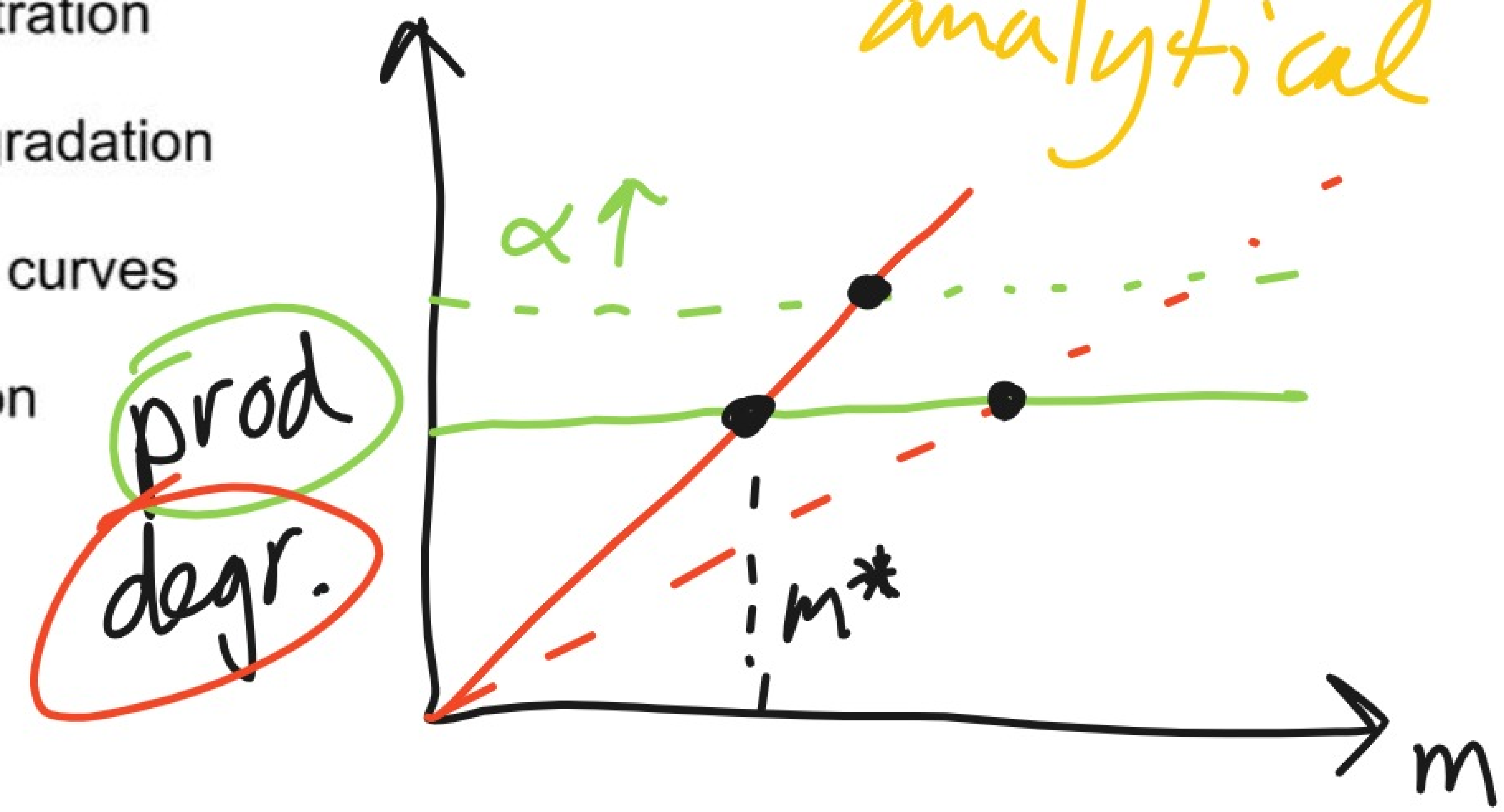
$\delta \downarrow$ SS $\uparrow$

$\delta \uparrow$ $t_{1/2} \downarrow$

$\delta \downarrow$ $t_{1/2} \uparrow$

Can visualize with **phase line**

- Phase line is 1-D system
- x-axis is mRNA concentration
- y-axis is production/degradation
- Find intersection of two curves
- production = degradation




$\frac{dm}{dt} = 0$

prod = degr

# Bifurcation of the system for mRNA dynamics

- Graph of changes in steady state
  - Vary parameters ($\alpha$, $\delta$)
  - x-axis is parameter
  - y-axis is steady state value