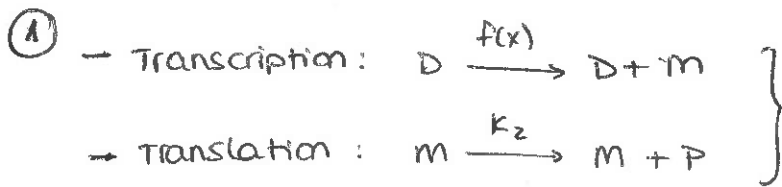


REPRESSILATOR: DERIVATION FROM FIRST PRINCIPLES



$D = [\text{DNA}]$

$m = [\text{mRNA}]$

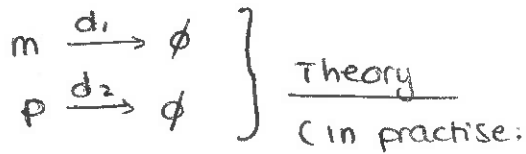
$p = [\text{protein}]$

$k_2 = [\text{translation rate}]$

$f(x) = [\text{transcription rate}]$

A. (1), (2), (3), (4), (5), (6)

- Degradation:



- mRNA is targeted by cell machinery (half-life ≈ 5 mins)

- proteins are stable but targeted by other pathways too. (e.g. enzymatic pathway)

$\rightarrow = k_1$ (cte) if constitutive expression
in practise: not a constant: Hill function

d_1 : mRNA degradation rate

d_2 : protein " "

② - ODEs:

$$\left\{ \begin{array}{l} \frac{dm}{dt} = f(x) \cdot D - d_1 m \\ \frac{dp}{dt} = k_2 m - d_2 p \end{array} \right.$$

- Normalisation of $\frac{dp}{dt}$:

• Take λ (free parameter of my choosing):

$$\frac{d(p/\lambda)}{dt} = \left(\frac{k_2}{\lambda}\right)m - d_2 \left(\frac{p}{\lambda}\right) \Rightarrow \text{our new variable: } (p/\lambda) = p^*$$

• Say: $\left\{ \begin{array}{l} \beta = d_2 \\ d_2 = \frac{k_2}{\lambda} \\ \lambda = \frac{k_2}{d_2} \end{array} \right. \Rightarrow \frac{dp^*}{dt} = \beta(m - p^*)$

• We simply take p^* as our protein concentration, and will therefore use:

$$\boxed{\frac{dp}{dt} = \beta(m - p)} \text{ to model protein concentration}$$

\rightarrow

- Normalisation of $\frac{dm}{dt} = f(p) \cdot D - d \cdot m$

$$f(p) = \frac{1}{1+p^n}$$

$$\frac{dm}{dt} = \frac{D}{1+\left(\frac{P}{\lambda}\right)^n} - d \cdot m$$

• To normalise it:

→ Time: in units of mRNA lifetime (equal for all genes)
 → mRNA and protein levels in units of Michaelis constants (in same units!)



Rescale mRNA concentrations by ratio of protein degradation and translation rate: $\lambda = \frac{k_2}{d_2}$

$$\Rightarrow \frac{d(m/\lambda)}{d_1 \cdot dt} = \frac{D/d_1}{1+(P/\lambda)^n} - (m/\lambda)$$

• Say: $m^* = m/\lambda$

$$dt^* = d_1 \cdot dt$$

$\alpha = D/d_1$: regulated transcription rate

α_0 = unregulated transcription rate (leakiness term in saturating repressor)

~~Page 7 of 7~~

$$\frac{dm^*}{dt^*} = \frac{\alpha}{1+(p^*)^n} - m^* + \alpha_0$$



To model mRNA concentration:

$$\frac{dm}{dt} = \frac{\alpha}{1+(p)^n} + \alpha_0 - m$$

Assumptions:

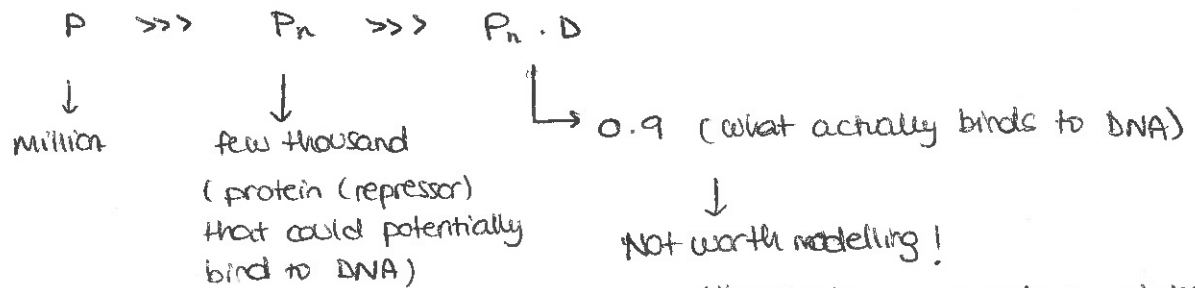
* General assumptions on notebook

- (1) Transcription rate = Hill function (can be applied because the parent gene is being regulated by transcription factors)
(2) Translation rate = c_{tr}
(3) Hill function assumptions:

- 3.1. Ligand molecules bind to a receptor simultaneously.
3.2. n : Hill coeff: approximation of the number of cooperative ligand binding sites on a receptor.

(4) Reason why we use Hill function:

- Level of production will be determined by P .
- We are going to obtain P :



- (5) Deg. rate equal for all proteins (d_2): $d_2 = \overset{\text{dilution rate}}{\text{dr}} + \text{ddeg}$ depends on proteins. These prote. are stable, therefore $\text{ddeg} \approx 0$.
- (6) Deg. rate d_1 is equal for all mRNAs. (d_1 : much faster than d_2) \rightarrow depends on chasis, experimental conditions ... (take from literature)