REPRESSILATOR: DERIVATION FROM FIRST PRINCIPLES

(1)

- Transcription: $D \xrightarrow{f(x)} D + m$
- Translation: $m \xrightarrow{k_2} m + P$

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

- Degradation:

$$m \xrightarrow{d_1} \phi$$
$$P \xrightarrow{d_2} \phi$$

Theory

(in practise:

- mRNA is targeted by cell machinery (halflife ≃ 5mins)
- proteins are stable but targeted by other pathways too. (e.g. enzymatic pathway)

D = [DNA]
m = [mRNA]
P = [protein]
k_2 = [translation rate]
$f(x)$ = [transcription rate]
↳ = k_1 (cte) if constitutive expression
↳ in practise: not a constant: Hill function
d_1 : mRNA degradation rate
d_2 : protein " "

(2) - ODEs:

$$\begin{cases} \frac{dm}{dt} = f(x) \cdot D - d_1 m \\ \frac{dP}{dt} = k_2 m - d_2 P \end{cases}$$

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

  - Take λ (free parameter of my choosing):

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

  - Say: $\begin{cases} \beta = d_2 \\ d_2 = \frac{k_2}{\lambda} \\ \lambda = \frac{k_2}{d_2} \end{cases} \Rightarrow \frac{dP^*}{dt} = \beta(m - P^*)$

  - We simply take P^* as our protein concentration, and will therefore use: $\boxed{\frac{dP}{dt} = \beta(m - P)}$ to model protein concentrati

→

- Normalisation of $\frac{dm}{dt} = f(p) \cdot D - d_1 m$ $\qquad f(p) = \frac{1}{1+p^n}$

$$\frac{dm}{dt} = \frac{D}{1+\left(\frac{p}{\lambda}\right)^n} - d_1 m$$

- 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: $m^* = m/\lambda$

$dt^* = d_1 dt$

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

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

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

⇓

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 = cte,

(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:

$P \gg P_n \gg P_n \cdot D$

- P: million
- P_n: few thousand (protein (repressor) that could potentially bind to DNA)
- $P_n \cdot D$: 0.9 (what actually binds to DNA) → Not worth modelling!

(5) Deg. rate equal for all proteins (d_2): $d_2 = d_r + d_{deg}$

- d_r: dilution rate → depends on chasis, experimental conditions ... (take from literature)
- d_{deg}: depends on proteins. These prots. are stable, therefore $d_{deg} \simeq 0$.

(6) Deg. rate d_1 is equal for all mRNAs. (d_1: much faster than d_2)