REPRESSILATOR: DERIVATION FROM FIRST PRINCIPLES

$$D = [DNA]$$

$$m = [mRNA]$$

$$p = [protein]$$

$$k_2 = translation\ rate$$

$$f(p) = transcription\ rate$$

GENE EXPRESSION:

Transcription: $D \xrightarrow{f(p)} D + m$

Translation: $m \xrightarrow{k_2} m + p$

Degradation of mRNA: $m \xrightarrow{d_1} \emptyset$

Degradation of protein: $p \xrightarrow{d_2} \emptyset$

ASSUMPTIONS:

1. Genes (DNA) are present in constant amounts and all have identical behavior.
2. Transcription and translation are operating under saturated conditions (polymerases, ribosomes, nucleotides and amino acids are present in large amounts).
3. Proteins and mRNA degrade by first order reactions.
4. Transcription rate is modelled by the Hill equation. This can be assumed because the level of production is determined by the concentration of protein (p). We are going to obtain protein that will be found in 3 states:
    - P: free protein.
    - Pn: repressor protein that could potentially bind to receptor.
    - Pn*D: protein that binds to receptor.

    The quantities of protein in each state in relation to the quantities of protein in the other states is represented by the following relation:

    P >>> Pn >>> Pn*D

    Since there is a very small amount that binds to a gene receptor, it is not worth modelling. We model that the proteins (repressors) will bind to regulatory regions of the gene and inhibit their expression, assuming that binding is faster than transcription and translation.
5. Hill equation assumptions:

- Ligand molecules bind to a receptor simultaneously.
- Hill coefficient (n) approximates the number of cooperative ligand binding sites on a receptor.

6. Translation rate is constant (k_2).

Ordinary Differential Equations (ODEs):

$$\frac{dm}{dt} = f(p) \cdot D - d_1 m$$

$$\frac{dp}{dt} = k_2 m - d_2 p$$

where $f(p) = \frac{\gamma}{1 + K_b p_{i-1}^n} + \gamma_0$ is the Hill function for repression considering leakiness.

$$\gamma = maximal\ repressor\ binding\ rate$$

$$\gamma_0 = leakiness\ of\ repressor$$

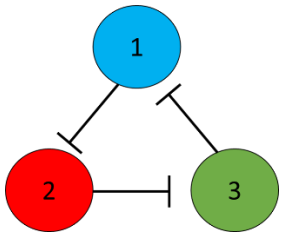
$$K_b = repression\ coefficient$$

Generalizing this system for the case of the repressilator formed by three repressor proteins results in the following ODEs:

$$\frac{dm_i}{dt} = f(p_{i-1}) \cdot D - d_1 m_i$$

$$\frac{dp_i}{dt} = k_2 m_i - d_2 p_i$$

where i = 1,2,3



To carry out dimension reduction and simplify the analysis of this system, we normalize the ODEs:

1) Normalization of $\frac{dm}{dt} = f(p) \cdot D - d_1 m$:
   - Write p_i in units of $K_b^{-1/n}$
   - Write m_i in units of $\frac{d_2}{(TK_b^{\frac{1}{n}})}$ where $T = transcription\ rate$
   - Write time in units of d_1^{-1}

Rewriting the equation following these statements results in:

$$\frac{dm_i}{dt} = -m_i + \frac{\alpha}{1 + p_{i-1}^n} + \alpha_0$$

where $\alpha = \frac{\gamma K_b^{1/n_T}}{d_1 d_2}$ and $\alpha = \frac{\gamma_0 K_b^{1/n_T}}{d_1 d_2}$

2) Normalization of $\frac{dp}{dt} = k_2 m - d_2 p$:

- Take λ as a free parameter and redefine ODE:

$$\frac{d(\frac{p}{\lambda})}{dt} = (\frac{k_2}{\lambda})m - d_2(\frac{p}{\lambda})$$

where the new variable is $\frac{p}{\lambda} = p'$

- We define:

$$\beta = d_2$$

$$d_2 = \frac{k_2}{\lambda}$$

$$\lambda = \frac{k_2}{d_2}$$

Rewriting the equation results in the ODE:

$$\frac{dp'}{dt} = \beta(m_i - p'_i)$$

The ODEs that now define the **repressilator** system are:

$$\boldsymbol{\frac{dm_i}{dt} = -m_i + \frac{\alpha}{1 + p_{i-1}^n} + \alpha_0}$$

$$\boldsymbol{\frac{dp}{dt} = \beta(m_i - p_i)}$$