BIOLOGICAL OSCILLATORS – REPRESSILATOR

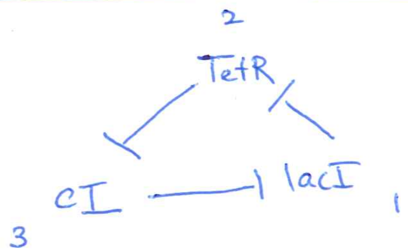
9/25/2018

Last Time: Ability to oscillate determined by system properties

Description of the System (Mass Balance/ODEs) $\xrightarrow{\text{Taylor Approx.}}$ Jacobian $\xrightarrow{\text{determinant}}$ eigenvalues (λ)

↓

oscillations possible if imaginary part $\neq 0$ & real part > 0



M = mRNA
P = protein

TetR Balance

$$\frac{dM}{dt} = \text{trxn} - \text{mRNA decay}$$

$$\frac{dP}{dt} = \text{trln} - \text{protein decay}$$

$$\Rightarrow \frac{dM_2}{dt} = k_2' + \frac{\beta_2 K_2^{n_2}}{K_2^{n_2} + P_1^{n_2}} - \underbrace{(\mu + k_{dm_2})}_{\eta} M_2$$

$$\frac{dP_2}{dt} = aM_2 - \underbrace{(\mu + k_{dp_2})}_{\nu} P_2$$

simplify:

$$\frac{dM_2}{dt} = k_2' + \frac{\beta_2}{1 + \left(\frac{P_1}{K_2}\right)^{n_2}} - \eta M_2$$

$$\frac{dP_2}{dt} = aM_2 - \nu P_2$$

Assume parameters for all 3 repressors the same

e.g. $n_1 = n_2 = n_3 = n$

(1) $$\frac{dM_2}{dt} = k' + \frac{\beta}{1 + \left(\frac{P_1}{K}\right)^n} - \eta M_2$$

(2) $$\frac{dP_2}{dt} = a M_2 - \nu P_2$$

Let's non-dimensionalize

$$\boxed{p_1 \equiv \frac{P_1}{K}} \quad \Rightarrow \quad \begin{aligned} P_1 &= p_1 K \\ dP_1 &= K dp_1 \end{aligned}$$

Sub into 1

$$\frac{dM_2}{dt} = k' + \frac{\beta}{1+p_1^n} - \eta M_2$$

$$\boxed{\frac{1}{\eta}\frac{dM_2}{dt}} = \frac{k'}{\eta} + \frac{\beta}{\eta}\left(\frac{1}{1+p_1^n}\right) - M_2 \qquad (1a)$$

$$\left.\begin{aligned} \tau &= \eta t \\ d\tau &= \eta\, dt \end{aligned}\right\} \text{ natural time scale}$$

Sub into 2 $\quad \eta \dfrac{K dp_2}{d\tau} = a M_2 - \nu K p_2$

$$\frac{dp_2}{d\tau} = \frac{a}{\eta K} M_2 - \underbrace{\frac{\nu}{\eta}}_{b} p_2$$

$b \equiv$ ratio of protein to mRNA decay

$$\frac{dp_2}{d\tau} = \boxed{\frac{a}{K\nu} b M_2} - b p_2$$

$a [\equiv]$ protein / mRNA $\cdot$ s

$K [\equiv]$ protein

$\nu [\equiv]$ s^{-1}

$$m_2 = \boxed{\frac{a}{K\nu}} M_2$$

translation efficiency

$$\Rightarrow \quad \frac{dp_2}{d\tau} = b m_2 - b p_2$$

$$\boxed{\frac{dp_2}{d\tau} = -b(p_2 - m_2)}$$

$$dM_2 = \frac{K\nu}{a} dm_2$$

sub into 1a

$$\Rightarrow \quad \frac{K\nu}{a}\frac{dm_2}{d\tau} = \frac{k'}{\eta} + \frac{\beta}{\eta}\left(\frac{1}{1+p_1^n}\right) - \frac{K\nu}{a} m_2$$

$$\Rightarrow \boxed{\begin{gathered} \frac{dm_2}{d\tau} = \alpha_0 + \frac{\alpha}{1+p_1^n} - m_2 \\ \text{where } \alpha_0 = \frac{k' a}{\eta K \nu} \qquad \alpha = \frac{\beta a}{\eta K \nu} \end{gathered}}$$

let $i = \begin{bmatrix} 1 = lacI \\ 2 = tetR \\ 3 = cI \end{bmatrix}$ $j = \begin{bmatrix} 1 = cI \\ 2 = lacI \\ 3 = tetR \end{bmatrix}$

$$\boxed{\begin{aligned} \frac{dm_i}{d\tau} &= \alpha_0 + \frac{\alpha}{1+p_j^n} - m_i \\ \frac{dp_i}{d\tau} &= -b(p_i - m_i) \end{aligned}}$$

Same as in paper

For simplicity, neglect mRNA dynamics (much faster than protein)

$\hookrightarrow \frac{dm_i}{d\tau} = 0 \Rightarrow m_i = \alpha_0 + \frac{\alpha}{1+p_j^n}$

* Since parameters are all equal, steady state conc of p & m ~~than~~ same for all

$$f = \frac{dp_1}{d\tau} = -bp_1 + b\alpha_0 + \frac{b\alpha}{1+p_3^n}$$

$$g = \frac{dp_2}{d\tau} = -bp_2 + b\alpha_0 + \frac{b\alpha}{1+p_1^n}$$

$$h = \frac{dp_3}{d\tau} = -bp_3 + b\alpha_0 + \frac{b\alpha}{1+p_2^n}$$

$$\left.\frac{\partial f}{\partial p_3}\right|_{ss} = \frac{-b\alpha n p_{3_{ss}}^{n-1}}{(1+p_{3_{ss}}^n)^2}$$

$p_{3_{ss}} = p_{2_{ss}} = p_{1_{ss}} = p$

$$X = \frac{-\alpha n p^{n-1}}{(1+p^n)^2}$$

Jacobian $\Rightarrow$

$$\begin{array}{c} \\ f \\ g \\ h \end{array} \begin{array}{c} \begin{array}{ccc} p_1 & p_2 & p_3 \end{array} \\ \begin{bmatrix} -b & 0 & bX \\ bX & -b & 0 \\ 0 & bX & -b \end{bmatrix} \end{array}$$

Stability determined by eigenvalues given by

$$\det \begin{bmatrix} -b-\lambda & 0 & bX \\ bX & -b-\lambda & 0 \\ 0 & bX & -b-\lambda \end{bmatrix} = 0$$

$$(-b-\lambda)\left[(-b-\lambda)^2 - 0\right] - 0 + (bX)^3 = 0$$

$$\lambda_1 = X - b$$
$$\lambda_2 = -b - \tfrac{1}{2}X - i\tfrac{\sqrt{3}}{2}X$$
$$\lambda_3 = -b - \tfrac{1}{2}X + i\tfrac{\sqrt{3}}{2}X$$

oscillates if
$\lambda_I \neq 0$
$\lambda_{Re} > 0$

$\lambda_1 < 0$
$Re(\lambda_2)$ & $Re(\lambda_3)$ $\Rightarrow$ $-b - \tfrac{1}{2}X > 0$
$X < -2b$

system unstable & oscillations possible when

$$\boxed{\frac{\alpha n p^{n-1}}{(1+p^n)^2} > 2b}$$

where $p = \frac{\alpha}{1+p^n} + \alpha_0$

Assume protein & mRNA decay rates comparable

$\Rightarrow b = 1$

$$\frac{\alpha n p^{n-1}}{(1+p^n)^2} > 2$$

Assume no leaky expression $(\alpha_0 = 0)$

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

$$\frac{\alpha n p^{n-1}}{(1+p^n)^2} = \frac{(p+p^{n+1})\, n\, p^{n-1}}{(1+p^n)^2}$$

$$= \frac{n p^n \cancel{(1+p^n)}}{(1+p^n)^{\cancel{2}}}$$

$$= \frac{n p^n}{1+p^n}$$

$$\Rightarrow \quad \frac{np^n}{1+p^n} > 2$$

$\frac{p^n}{1+p^n}$ is bounded b/n 0 & 1

$\therefore \; n(1) > 2 \Rightarrow n > 2$

system must have cooperativity, with no leaky expression & comparable decay rates

What values of p will give this regime?

$$\frac{np^n}{1+p^n} > 2$$

$$\frac{p^n}{1+p^n} > \frac{2}{n}$$

$$p^n > \frac{2}{n} + \frac{2}{n}p^n$$

$$p^n > \frac{\frac{2}{n}}{1-\frac{2}{n}} = \frac{2}{n-2}$$

$$p > \sqrt[n]{\frac{2}{n-2}} \gg 1$$

[remember $n \sim 2$-4]

$\therefore$ instability (& possible limit cycles) for large p [high trxn/trln, strong promoter & efficient RBS]