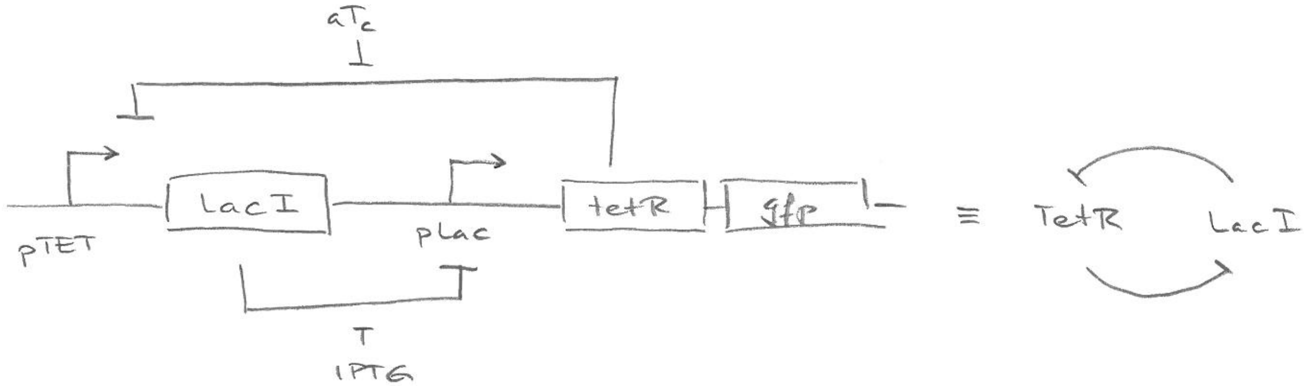
4. SYNTHETIC TRANSCRIPTIONAL CIRCUITS

4.1 A BISTABLE SWITCH

(T.S. GARDNER ET AL. NATURE <u>403</u>, p.339 (2000))



LacI, TetR: REPRESSORS

plac, pTet : PROMOTERS

IPTG, aTc : INDUCERS

lacI binds plac and IPTG (~ allolactose) binds LacI and inhibits
TetR pTet aTc

binding to the promoter.

Q: what state is this system in? (Discuss promoter strength, inducers)

MODEL FOR THE BISTABLE SWITCH:

$i, j = 1, 2$ (tet, lac) $i \neq j$

$$\dot{m}_i = \frac{\alpha_{mj}}{1 + R_j^{n_j}/K_j} + \alpha_{0j} - \gamma_{m_i} m_i$$

$$\dot{P}_i = \alpha_i m_i - \gamma_{P_i} P_i$$

ASSUMPTIONS

(i) NO LEAK : $\alpha_{io} = 0$

(ii) FAST mRNA DYNAMICS (mRNA IN STEADY STATE) : $\dot{m} = 0$

$$m_i = \frac{\alpha_{mj} / \gamma_{mi}}{1 + R_j^{n_j} / K_j}$$

(iii) IDENTICAL PROMOTERS, DEGRADATION TIMES

$\alpha_{m1} = \alpha_{m2} = \alpha_m$, $\gamma_{m1} = \gamma_{m2} = \gamma_m$ (same for p) ; $n_1 = n_2$

$$\dot{P}_1 = \frac{\alpha}{1 + P_2^n / K} - \gamma_p P_1$$

$$\dot{P}_2 = \frac{\alpha}{1 + P_1^n / K} - \gamma_p P_2$$

EQUILIBRIUM (INTUITION) : $\dot{P}_1 = 0$, $\dot{P}_2 = 0$

Q: Are these equilibria stable or unstable?

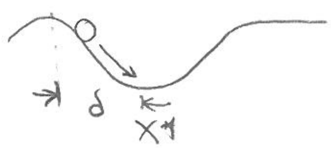
FOR BISTABILITY WE NEED 2 STABLE EQUILIBRIUM POINTS.

4.2 MATHEMATICAL EXCURSION: EQUILIBRIA AND STABILITY

$\dot{x} = f(x,t) \qquad x = (x_1, x_2 \ldots)$

Equilibrium point x^* : $f(x^*, t) = 0 = \dot{x}$

<u>Def:</u> x^* is locally asymptotically stable if $\exists\, \delta > 0$ such that if $\| x(0) - x^* \| < \delta \Rightarrow \lim\limits_{t \to 0} x(t) = x^*$.



δ arbitrary: globally asymptotically stable

EXAMPLE:

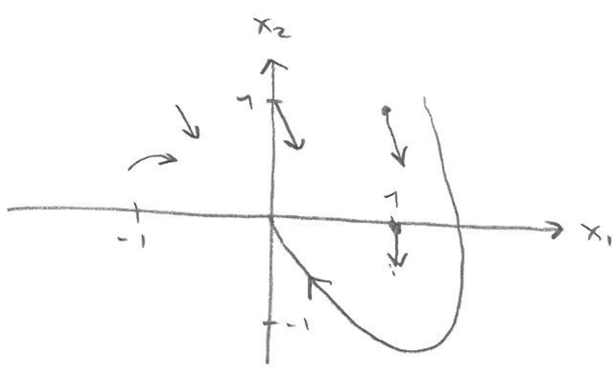
$\dot{x}_1 = x_2$

$\dot{x}_2 = -x_1 - 2x_2$

$\dot{x} = f(x) \quad f(x) = \begin{pmatrix} x_2 \\ -x_1 - 2x_2 \end{pmatrix}$

$x^* = (0,0)$

Use a <u>phase portrait</u> to build intuition about stability



$\begin{pmatrix} 1 \\ 1 \end{pmatrix} : f(\vec{x}) = \begin{pmatrix} 1 \\ -3 \end{pmatrix}$

$\begin{pmatrix} 1 \\ 0 \end{pmatrix} : f(x) = \begin{pmatrix} 0 \\ -2 \end{pmatrix}$

STEP 1: CHOOSE POINT (x_1, x_2)

STEP 2: DRAW VECTOR IN DIRECTION OF f