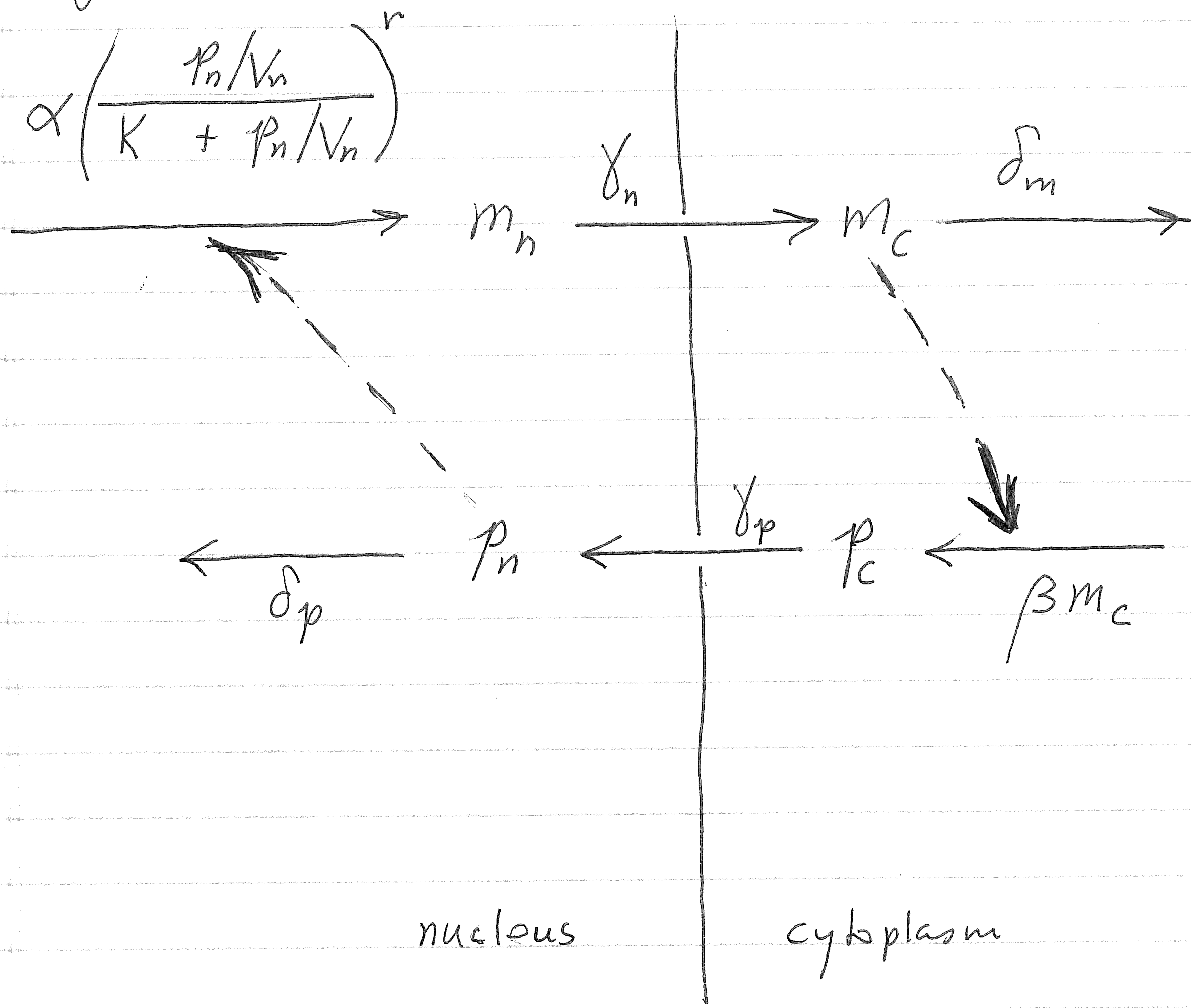
A genetic switch based on <u>positive</u> feedback



$$\frac{dm_n}{dt} = \alpha\left(\frac{p_n}{k+p_n}\right)^r - \gamma_m m_n \qquad (k = KV_n)$$

$$\frac{dm_c}{dt} = \gamma_m m_n - \delta_m m_c$$

$$\frac{dp_c}{dt} = \beta m_c - \gamma_p p_c$$

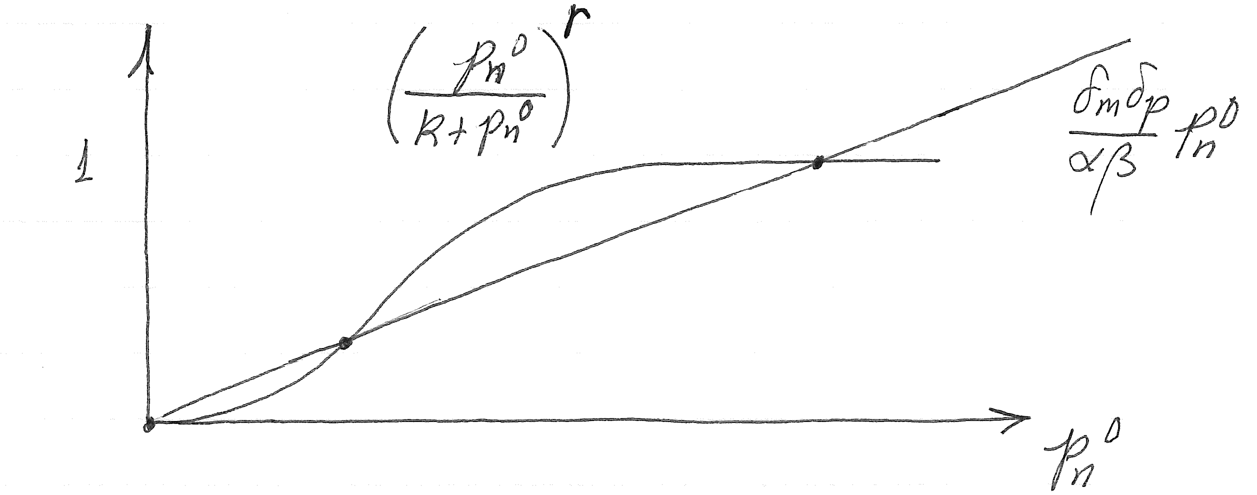
$$\frac{dp_n}{dt} = \gamma_p p_c - \delta_p p_n$$

Steady state:

$$\alpha\left(\frac{p_n^0}{k+p_n^0}\right)^r \cancel{\gamma_n m_n^0}\, \beta \cancel{m_c^0}\, \cancel{\gamma_p p_c^0}$$

$$= \cancel{\gamma_n m_n^0}\, \delta_m \cancel{m_c^0}\, \cancel{\gamma_p p_c^0}\, \delta_p p_n^0$$

$$\left(\frac{p_n^0}{k+p_n^0}\right)^r = \frac{\delta_m \delta_p}{\alpha\beta}\, p_n^0$$



Interesting case is $r \geq 2$, and $\frac{\delta_m \delta_p}{\alpha\beta}$

sufficiently small that there are three solutions

For example, if $r=2$

$$\left(\frac{p_n^0}{k+p_n^0}\right)^2 = \frac{p_n^0}{a}$$

Where

$$a = \frac{\alpha\beta}{\delta_m \delta_p}$$

$$a\,(p_n^0)^2 = p_n^0\,(k+p_n^0)^2$$

Therefore $p_n^0 = 0$ is one steady state, and the other two satisfy

$$a\,p_n^0 = (k+p_n^0)^2 = k^2 + 2k\,p_n^0 + (p_n^0)^2$$

$$(p_n^0)^2 + (2k-a)\,p_n^0 + k^2 = 0$$

$$p_n^0 = \frac{(a-2k) \pm \sqrt{(a-2k)^2 - 4k^2}}{2}$$

$$p_n^0 = \frac{(a-2k) \pm \sqrt{a^2-4ak}}{2}$$

$$= \frac{(a-2k) \pm \sqrt{a(a-4k)}}{2}$$

Thus, the requirement for 3 distinct, real, positive solutions in the special case $r=2$ is

$$a > 4k = 4KV_n$$

That is

$$\frac{\alpha\beta}{\delta_m \delta_m} > 4k = 4KV_n$$

Now we linearize the equations to study the stability of the steady states. Let

$$\mu = \alpha \left[\frac{d}{dp_n} \left(\left(\frac{p_n}{k+p_n} \right)^n \right) \right]_{p_n = p_n^0}$$

Then

$$\frac{d\tilde{m}_n}{dt} = \mu \tilde{p}_n - \gamma_m \tilde{m}_n$$

$$\frac{d\tilde{m}_c}{dt} = \gamma_m \tilde{m}_n - \delta_m \tilde{m}_c$$

$$\frac{d\tilde{p}_c}{dt} = \beta \tilde{m}_c - \gamma_p \tilde{p}_c$$

$$\frac{d\tilde{p}_n}{dt} = \gamma_p \tilde{p}_c - \delta_p \tilde{p}_n$$

That is

$$\frac{d\tilde{x}}{dt} = A\tilde{x}$$

where

$$\tilde{x} = \begin{pmatrix} \tilde{m}_n \\ \tilde{m}_c \\ \tilde{p}_c \\ \tilde{p}_n \end{pmatrix}$$

$$A = \begin{pmatrix} -\gamma_m & 0 & 0 & \mu \\ \gamma_m & -\delta_m & 0 & 0 \\ 0 & \beta & -\gamma_p & 0 \\ 0 & 0 & \gamma_p & -\delta_p \end{pmatrix}$$

The eigenvalues of A satisfy

$$0 = \det(\lambda I - A)$$

$$= \begin{vmatrix} \lambda+\gamma_m & 0 & 0 & -\mu \\ -\gamma_m & \lambda+\delta_m & 0 & 0 \\ 0 & -\beta & \lambda+\gamma_p & 0 \\ 0 & 0 & -\gamma_p & \lambda+\delta_p \end{vmatrix}$$

$$= (\lambda+\gamma_m)(\lambda+\delta_m)(\lambda+\gamma_p)(\lambda+\delta_p) - \mu\gamma_m\beta\gamma_p$$

Let G be defined by

$$\mu\beta = G\,\delta_m\delta_p$$

so that

$$G = \frac{\alpha\beta}{\delta_m\delta_p}\left[\frac{d}{dp_n}\left(\left(\frac{p_n}{k+p_n}\right)^r\right)\right]_{p_n=p_n^0}$$

Then the equation for the eigenvalues becomes

$$0 = (\lambda+\gamma_m)(\lambda+\delta_m)(\lambda+\gamma_p)(\lambda+\delta_p) - G\,\gamma_m\delta_m\gamma_p\delta_p$$
$$= P(\lambda)$$

Note that

$$P(0) = (1-G)\,\gamma_m\delta_m\gamma_p\delta_p$$

If $G > 1$, then $P(0) < 0$.

On the other hand, considering real λ, we see that

$$P(\lambda) \rightarrow +\infty \text{ as } \lambda \rightarrow +\infty$$

so $P(\lambda)$ has at least one real, positive root for $G > 1$, and the system is therefore unstable.

On the other hand, for $G < 1$ all <u>real</u> roots of $P(\lambda)$ must be negative, since $P(\lambda)$ has only positive coefficients.

Indeed, for $G < 1$ all roots of $P(\lambda)$ lie in the left-half plane. To prove this we note that for $G = 0$ the roots are specifically

$$-\gamma_m, -\delta_m, -\gamma_p, -\delta_p$$

all of which are in the left-half plane. Now by continuity if there is a root in the right-half plane for $G < 1$ there must exist some $G_* < G < 1$ for which there is a root of the form $i\omega$ where ω is real and non-zero (see above). This gives the equation

$$(i\omega + \gamma_m)(i\omega + \delta_m)(i\omega + \gamma_p)(i\omega + \delta_p)$$

$$= G_* \gamma_m \delta_m \gamma_p \delta_p$$

which cannot be satisfied for $\omega \neq 0$ since the four angles are each less than $\pi/2$ and cannot add up to 2π.

Note that G can be written as

$$G = \frac{\left[\frac{d}{dp_n}\left(\left(\frac{p_n}{k+p_n}\right)^r\right)\right]_{p_n=p_n^0}}{\left[\frac{d}{dp_n}\left(\frac{\delta_m\delta_p}{\alpha\beta}\,p_n\right)\right]_{p_n=p_n^0}}$$

which is the ratio of the slopes of the curves that determine p_n^0 in the graphical solution of the steady-state problem. Thus, for $r>1$ and with three intersections, we have