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Nth order feedback steady states (INCOMPLETE)

$$\begin{aligned}
\dot{p} =& \frac{k_p G}{d_m} \ \frac{k_0 + k_1 c_1 p + k_2 c_2 p^2 + \cdots + k_N c_N p^N}{1 + c_1 p + c_2 p^2 + \cdots + c_N p^N} - d_p p \\
=& \frac{k_p k_0 G}{d_m} \ \frac{1 + \frac{k_1}{k_0} c_1 p + \frac{k_2}{k_0} c_2 p^2 + \cdots + \frac{k_N}{k_0} c_N p^N}{1 + c_1 p + c_2 p^2 + \cdots + c_N p^N} - d_p p = 0 \\
\implies & \frac{k_p k_0 G}{d_p d_m} \ \left[\ 1 + \frac{k_1}{k_0} c_1 p + \frac{k_2}{k_0} c_2 p^2 + \cdots + \frac{k_N}{k_0} c_N p^N \ \right] = p \left[\ 1 + c_1 p + c_2 p^2 + \cdots + c_N p^N \ \right]
\end{aligned}$$

Define:

$$p_0 := \frac{k_p k_0 G}{d_p d_m}$$

$$K_i := \frac{k_i}{k_0} \ , \ i = 0, 1, 2, ..., N$$

We have

$$p_0 \ \left[\ 1 + K_1 c_1 p + K_2 c_2 p^2 + \cdots + K_N c_N p^N \ \right] = p \left[\ 1 + c_1 p + c_2 p^2 + \cdots + c_N p^N \ \right]$$

Rearranging:

$$c_N p^{N+1} + [c_{N-1} - p_0 K_N c_N] \, p^N + [c_{N-2} - p_0 K_{N-1} c_{N-1}] \, p^{N-1} + \cdots + [1 - p_0 K_1 c_1] \, p - p_0 = 0$$

1 General considerations

Define:

$$p_i := \frac{k_p k_i G}{d_p d_m} \ , \ i = 0, 1, 2, ..., N$$

Another way to write the polynomial equation

$$\frac{k_p G}{d_p d_m} \ \left[\ k_0 + k_1 c_1 p + k_2 c_2 p^2 + \cdots + k_N c_N p^N \ \right] = p \left[\ 1 + c_1 p + c_2 p^2 + \cdots + c_N p^N \ \right]$$

is

$$p_0 + p_1 c_1 p + p_2 c_2 p^2 + \cdots + p_N c_N p^N = p \left[\ 1 + c_1 p + c_2 p^2 + \cdots + c_N p^N \ \right]$$

or equivalently

$$c_N p^N (p - p_N) + c_{N-1} p^{N-1} (p - p_{N-1}) + \cdots + c_1 p (p - p_1) + (p - p_0) = 0$$

This form of the equation makes many intuitive observations clear. For example, if $p_0 = p_1 = \cdots = p_N$ (so that the transcription rate of each g^i is $k_0 = k_1 = \cdots = k_N$), the solution to the equation is just p_0; this can be understood by realizing that all the g^i together act like just one gene with transcription rate k_0.

Another easy conclusion: a solution to the equation of order N becomes a solution to the equation of order $N-1$ after one takes c_N to zero. In this way, the N_2 equation contains the solutions to the N_1 equation, for all $N_1 \leq N_2$.

If one takes all the c_i (except the jth one) to zero, then the solution is $p = p_j$; in other words, the system behaves like it has just one gene with transcription rate k_j, which agrees with our intuitive expectations (taking the rest of the c_i to zero means that the gene states g^i with $i \neq j$ are inaccessible).

Let $p_{max} := \max(p_0, p_1, ..., p_N)$ and $p_{min} := \min(p_0, p_1, ..., p_N)$. Note that

$$c_N p_{max}^N (p_{max} - p_N) + c_{N-1} p_{max}^{N-1} (p_{max} - p_{N-1}) + \cdots + c_1 p_{max} (p_{max} - p_1) + (p_{max} - p_0) \geq 0 \ ,$$

with possible equality only if $p = p_{max}$, since all $c_i \geq 0$ and $p_{max} - p_i \geq 0$ for all i. For $p > p_{max}$, the expression is strictly greater than zero. Hence, a true solution is less than or equal to p_{max}.

Also,

$$c_N p_{min}^N (p_{min} - p_N) + c_{N-1} p_{min}^{N-1} (p_{min} - p_{N-1}) + \cdots + c_1 p_{min} (p_{min} - p_1) + (p_{min} - p_0) \geq 0$$

with possible equality only if $p = p_{min}$, since all $c_i \geq 0$ and $p_{min} - p_i \leq 0$ for all i. For $p < p_{min}$, the expression is strictly *less* than zero. Hence, a true solution is greater than or equal to p_{min}.

In other words, $p \in [p_{min}, p_{max}]$. We might imagine the true solution as

$$p = \frac{k_p k_{eff} G}{d_p d_m} \ ,$$

where k_{eff} is an effective transcription rate (that is some kind of average over all the transcription rates $k_0, k_1, ..., k_N$). Our result makes sense given this mental picture.

2 $N = 1$ steady state

Our polynomial is

$$c_1 p^2 + [1 - p_0 K_1 c_1]\, p - p_0 = 0$$

The solutions are

$$p_\pm = \frac{K_1 c_1 p_0 - 1 \pm \sqrt{(K_1 c_1 p_0 - 1)^2 + 4 c_1 p_0}}{2c_1}$$

The negative sign solution is clearly spurious (since we need $p > 0$), so we have

$$\boxed{p = \frac{K_1 c_1 p_0 - 1 + \sqrt{(K_1 c_1 p_0 - 1)^2 + 4 c_1 p_0}}{2c_1}}$$

Consider two biologically interesting limits: (i) $c_1 \to \infty$ and (ii) $c_1 \to 0$. Since $c_1 = b_{01}/b_{10}$, the first limit corresponds to overwhelmingly strong binding (so that g^1 contributes almost all transcription activity), while the second limit corresponds to overwhelmingly weak binding (so that g^0 contributes almost all transcription activity).

Taking $c_1 \to \infty$, we have

$$\begin{aligned} p &\approx \frac{K_1 c_1 p_0 - 1 + \sqrt{(K_1 c_1 p_0)^2 + 4 c_1 p_0}}{2c_1} \\ &\approx \frac{K_1 c_1 p_0 - 1 + \sqrt{(K_1 c_1 p_0)^2}}{2c_1} \\ &\approx \frac{K_1 c_1 p_0 + \sqrt{(K_1 c_1 p_0)^2}}{2c_1} \\ &= K_1 p_0 \\ &= \frac{k_p k_1 G}{d_p d_m} \end{aligned}$$

which is exactly what we would expect.

Taking $c_1 \to 0$, we have

$$\begin{aligned} p &\approx \frac{K_1 c_1 p_0 - 1 + \sqrt{-2K_1 c_1 p_0 + 1 + 4 c_1 p_0}}{2c_1} \\ &\approx \frac{K_1 c_1 p_0 - 1 + 1 + \frac{1}{2}\left[-2K_1 c_1 p_0 + 4 c_1 p_0\right]}{2c_1} \\ &= p_0 = \frac{k_p k_0 G}{d_p d_m} \end{aligned}$$

which is again exactly what we would expect.

One more interesting limit: $K_1 = 1$. This corresponds to when g^0 and g^1 have identical transcription rates, so that it is as if there is just one gene site with transcription rate $k_0 = k_1$. We have

$$\begin{aligned} p &= \frac{c_1 p_0 - 1 + \sqrt{(c_1 p_0 - 1)^2 + 4 c_1 p_0}}{2c_1} \\ &= \frac{c_1 p_0 - 1 + \sqrt{(c_1 p_0 + 1)^2}}{2c_1} \\ &= \frac{c_1 p_0 - 1 + c_1 p_0 + 1}{2c_1} \\ &= p_0 \end{aligned}$$

as expected.

3 $N = 2$ steady state

INCOMPLETE: NOT SURE HOW TO WRITE DOWN THIS SOLUTION IN A COMPACT, READABLE WAY

Our polynomial is

$$c_2 p^3 + [c_1 - p_0 K_2 c_2]\, p^2 + [1 - p_0 K_1 c_1]\, p - p_0 = 0$$

There are three solutions, two of which are complex (in general). The real solution is

$$\frac{\sqrt[3]{2}\left(3c_2(1-c_1p_1)-(c_1-c_2p_2)^2\right)}{3c_2\sqrt[3]{-2c_1^3-9c_1^2c_2p_1+6c_1^2c_2p_2+\sqrt{\left(-2c_1^3-9c_1^2c_2p_1+6c_1^2c_2p_2+9c_1c_2^2p_1p_2-6c_1c_2^2p_2^2+9c_1c_2+2c_2^3p_2^3+27c_2^2p_0-9c_2^2p_2\right)^2+4(3c_2(1-c_1p_1)-(c_1-c_2p_2)^2)^3}+9c_1c_2^2p_1p_2-6c_1c_2^2p_2^2+9c_1c_2+2c_2^3p_2^3+27c_2^2p_0-9c_2^2p_2}}$$

$$A+B+C+D+E+F+G+H+I+J+K+L+M+N+O+P+Q+R+S+T+U+V+W+X+Y+Z \tag{1}$$

$$\frac{2\sqrt[3]{2}\left(c_1^2+c_1c_2(3p_1-2p_2)+c_2\left(c_2p_2^2-3\right)\right)}{\sqrt[3]{-2c_1^3+\sqrt{\left(-2c_1^3+c_1^2c_2(6p_2-9p_1)+3c_1c_2(c_2p_2(3p_1-2p_2)+3)+c_2^2\left(2c_2p_2^3+27p_0-9p_2\right)\right)^2-4(3c_2(c_1p_1-1)+(c_1-c_2p_2)^2)^3}+3c_2^2(p_2(3c_1p_1-2c_1p_2-3)+9p_0)+3c_1c_2(-3c_1p_1+2c_1p_2+3)+2c_2^3p_2^3}}$$