John Vastola
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**Bistable switch $N$th order feedback (independent binding) notes**

List of species:

- $g_x^{ij}$: gene $X$ with $i$ protein $X$ bound and $j$ protein $Y$ bound ($i, j \in \{0, 1, ..., N_x\}$)
- $g_y^{ij}$: gene $Y$ with $i$ protein $X$ bound and $j$ protein $Y$ bound ($i, j \in \{0, 1, ..., N_y\}$)
- $m_x$: mRNA transcribed by gene $X$
- $m_y$: mRNA transcribed by gene $Y$
- $p_x$: protein produced by gene $X$
- $p_y$: protein produced by gene $Y$

List of reactions:

$$
\begin{aligned}
g_x^{ij} &\xrightarrow{k_{ij}^x} g_x^{ij} + m_x & \qquad g_y^{ij} &\xrightarrow{k_{ij}^y} g_y^{ij} + m_y \\
m_x &\xrightarrow{k_p^x} m_x + p_x & m_y &\xrightarrow{k_p^y} m_y + p_y \\
m_x &\xrightarrow{d_m^x} \varnothing & m_y &\xrightarrow{d_m^y} \varnothing \\
p_x &\xrightarrow{d_p^x} \varnothing & p_y &\xrightarrow{d_p^y} \varnothing \\
g_x^{ij} + p_x &\xrightarrow{f_i^{xx}} g_x^{i+1,j} & g_y^{ij} + p_y &\xrightarrow{f_j^{yy}} g_y^{i,j+1} \\
g_x^{ij} + p_x &\xleftarrow{r_i^{xx}} g_x^{i+1,j} & g_y^{ij} + p_y &\xleftarrow{r_j^{yy}} g_y^{i,j+1} \\
g_x^{ij} + p_y &\xrightarrow{f_j^{xy}} g_x^{i,j+1} & g_y^{ij} + p_x &\xrightarrow{f_i^{yx}} g_y^{i+1,j} \\
g_x^{ij} + p_y &\xleftarrow{r_j^{xy}} g_x^{i,j+1} & g_y^{ij} + p_x &\xleftarrow{r_i^{yx}} g_y^{i+1,j}
\end{aligned}
$$

Constraints:

$$
\begin{aligned}
\sum_{i=0,1,...,N_x}^{N_x} \sum_{j=0,1,...,N_y}^{N_y} g_x^{ij} &= G_x \\
\sum_{i=0,1,...,N_x}^{N_x} \sum_{j=0,1,...,N_y}^{N_y} g_y^{ij} &= G_y
\end{aligned}
$$

mRNA ODEs:

$$\dot{m}_x = \sum_{i,j} k^x_{ij} g^{ij}_x - d^x_m m_x$$
$$\dot{m}_y = \sum_{i,j} k^y_{ij} g^{ij}_y - d^y_m m_y$$

Protein SDEs:

$$\begin{aligned}
\dot{p}_x =& k^x_p m_x - d^x_p p_x + \sum_{i,j} \left[ r^{xx}_i g^{i+1,j}_x - f^{xx}_i g^{ij}_x p_x \right] + \left[ r^{yx}_i g^{i+1,j}_y - f^{yx}_i g^{ij}_y p_x \right] \\
&+ \sqrt{k^x_p m_x + d^x_p p_x + \sum_{i,j} \left[ r^{xx}_i g^{i+1,j}_x + f^{xx}_i g^{ij}_x p_x \right] + \left[ r^{yx}_i g^{i+1,j}_y + f^{yx}_i g^{ij}_y p_x \right]}\ \eta_x(t) \\
\dot{p}_y =& k^y_p m_y - d^y_p p_y + \sum_{i,j} \left[ r^{yy}_j g^{i,j+1}_y - f^{yy}_j g^{ij}_y p_y \right] + \left[ r^{xy}_j g^{i,j+1}_x - f^{xy}_j g^{ij}_x p_y \right] \\
&+ \sqrt{k^y_p m_y + d^y_p p_y + \sum_{i,j} \left[ r^{yy}_j g^{i,j+1}_y + f^{yy}_j g^{ij}_y p_y \right] + \left[ r^{xy}_j g^{i,j+1}_x + f^{xy}_j g^{ij}_x p_y \right]}\ \eta_y(t)
\end{aligned}$$

mRNA at QSS forces:

$$m_x = \frac{\sum_{i,j} k^x_{ij} g^{ij}_x}{d^x_m}$$
$$m_y = \frac{\sum_{i,j} k^y_{ij} g^{ij}_y}{d^y_m}$$

Binding at QSS forces:

$$\begin{aligned}
r^{xx}_i g^{i+1,j}_x &= f^{xx}_i g^{ij}_x p_x \\
r^{yx}_i g^{i+1,j}_y &= f^{yx}_i g^{ij}_y p_x \\
r^{yy}_j g^{i,j+1}_y &= f^{yy}_j g^{ij}_y p_y \\
r^{xy}_j g^{i,j+1}_x &= f^{xy}_j g^{ij}_x p_y
\end{aligned}$$

In other words,

$$
\begin{aligned}
g_x^{i+1,j} &= \frac{f_i^{xx}}{r_i^{xx}} g_x^{ij} p_x \\
g_y^{i+1,j} &= \frac{f_i^{yx}}{r_i^{yx}} g_y^{ij} p_x \\
g_y^{i,j+1} &= \frac{f_j^{yy}}{r_j^{yy}} g_y^{ij} p_y \\
g_x^{i,j+1} &= \frac{f_j^{xy}}{r_j^{xy}} g_x^{ij} p_y
\end{aligned}
$$

Define

$$
\begin{aligned}
B_i^{xx} &:= \frac{f_i^{xx}}{r_i^{xx}} \\
B_i^{yx} &:= \frac{f_i^{yx}}{r_i^{yx}} \\
B_j^{yy} &:= \frac{f_j^{yy}}{r_j^{yy}} \\
B_j^{xy} &:= \frac{f_j^{xy}}{r_j^{xy}}
\end{aligned}
$$

for $i = 0, 1, ..., N_x - 1$ and $j = 0, 1, ..., N_y - 1$. Then we have

$$
\begin{aligned}
g_x^{i+1,j} &= B_i^{xx} g_x^{ij} p_x \\
g_y^{i+1,j} &= B_i^{yx} g_y^{ij} p_x \\
g_y^{i,j+1} &= B_j^{yy} g_y^{ij} p_y \\
g_x^{i,j+1} &= B_j^{xy} g_x^{ij} p_y
\end{aligned}
$$

Let's work out what $g_x^{ij}$ and $g_y^{ij}$ are in terms of $p_x$, $p_y$, and all of the kinetic parameters.

First, let's look at $g_x^{ij}$:

$$
\begin{aligned}
G_x = \sum_{i,j} g_x^{ij} &= \sum_j g_x^{0j} + g_x^{1j} + g_x^{2j} + \cdots + g_x^{N_x,j} \\
&= \sum_j g_x^{0j} + g_x^{0j} B_0^{xx} p_x + g_x^{1j} B_1^{xx} p_x + \cdots + g_x^{N_x-1,j} B_{N_x-1}^{xx} p_x \\
&= \sum_j g_x^{0j} + g_x^{0j} \left[B_0^{xx}\right] p_x + g_x^{0j} \left[B_0^{xx} B_1^{xx}\right] p_x^2 + \cdots + g_x^{0j} \left[B_0^{xx} B_1^{xx} \cdots B_{N_x-1}^{xx}\right] p_x^{N_x} \\
&= \left(1 + \left[B_0^{xx}\right] p_x + \left[B_0^{xx} B_1^{xx}\right] p_x^2 + \cdots + \left[B_0^{xx} B_1^{xx} \cdots B_{N_x-1}^{xx}\right] p_x^{N_x}\right) \sum_j g_x^{0j}
\end{aligned}
$$

Next, we can write

$$
\begin{aligned}
\sum_j g_x^{0j} &= g_x^{00} + g_x^{01} + g_x^{02} + \cdots + g_x^{0,N_y} \\
&= g_x^{00} + g_x^{00} B_0^{xy} p_y + g_x^{01} B_1^{xy} p_y + \cdots + g_x^{0,N_y-1} B_{N_y-1}^{xy} p_y \\
&= g_x^{00} + g_x^{00} \left[B_0^{xy}\right] p_y + g_x^{00} \left[B_0^{xy} B_1^{xy}\right] p_y^2 + \cdots + g_x^{00} \left[B_0^{xy} B_1^{xy} \cdots B_{N_y-1}^{xy}\right] p_y^{N_y} \\
&= g_x^{00} \left(1 + \left[B_0^{xy}\right] p_y + \left[B_0^{xy} B_1^{xy}\right] p_y^2 + \cdots + \left[B_0^{xy} B_1^{xy} \cdots B_{N_y-1}^{xy}\right] p_y^{N_y}\right)
\end{aligned}
$$

Hence, we have

$$
\begin{aligned}
G_x =& g_x^{00} \left(1 + \left[B_0^{xx}\right] p_x + \left[B_0^{xx} B_1^{xx}\right] p_x^2 + \cdots + \left[B_0^{xx} B_1^{xx} \cdots B_{N_x-1}^{xx}\right] p_x^{N_x}\right) \\
&\times \left(1 + \left[B_0^{xy}\right] p_y + \left[B_0^{xy} B_1^{xy}\right] p_y^2 + \cdots + \left[B_0^{xy} B_1^{xy} \cdots B_{N_y-1}^{xy}\right] p_y^{N_y}\right) \\
\implies \quad g_x^{00}(p_x, p_y) =& \frac{G_x}{\left(1 + \cdots + \left[B_0^{xx} B_1^{xx} \cdots B_{N_x-1}^{xx}\right] p_x^{N_x}\right) \left(1 + \cdots + \left[B_0^{xy} B_1^{xy} \cdots B_{N_y-1}^{xy}\right] p_y^{N_y}\right)}
\end{aligned}
$$

Similarly,

$$
g_y^{00}(p_x, p_y) = \frac{G_y}{\left(1 + \cdots + \left[B_0^{yy} B_1^{yy} \cdots B_{N_y-1}^{yy}\right] p_y^{N_y}\right) \left(1 + \cdots + \left[B_0^{yx} B_1^{yx} \cdots B_{N_x-1}^{yx}\right] p_x^{N_x}\right)}
$$

For convenience, define

$$c_i^{xx} := \begin{cases} 1 & \text{if } i = 0 \\ B_0^{xx} \cdots B_{i-1}^{xx} & \text{if } i = 1, 2, ..., N_x \end{cases}$$
$$c_j^{xy} := \begin{cases} 1 & \text{if } j = 0 \\ B_0^{xy} \cdots B_{j-1}^{xy} & \text{if } j = 1, 2, ..., N_y \end{cases}$$
$$c_i^{yx} := \begin{cases} 1 & \text{if } i = 0 \\ B_0^{yx} \cdots B_{i-1}^{yx} & \text{if } i = 1, 2, ..., N_x \end{cases}$$
$$c_j^{yy} := \begin{cases} 1 & \text{if } j = 0 \\ B_0^{yy} \cdots B_{j-1}^{yy} & \text{if } j = 1, 2, ..., N_y \end{cases}$$

Then $g_x^{00}$ and $g_y^{00}$ are

$$\begin{aligned} g_x^{00}(p_x, p_y) =& \frac{G_x}{\sum_i \sum_j c_i^{xx} c_j^{xy} p_x^i p_y^j} \\ g_y^{00}(p_x, p_y) =& \frac{G_y}{\sum_i \sum_j c_i^{yx} c_j^{yy} p_x^i p_y^j} \end{aligned}$$

We also have:

$$\begin{aligned} g_x^{ij}(p_x, p_y) =& \frac{G_x c_i^{xx} c_j^{xy} p_x^i p_y^j}{\sum_{i'} \sum_{j'} c_{i'}^{xx} c_{j'}^{xy} p_x^{i'} p_y^{j'}} \\ g_y^{ij}(p_x, p_y) =& \frac{G_y c_i^{yx} c_j^{yy} p_x^i p_y^j}{\sum_{i'} \sum_{j'} c_{i'}^{yx} c_{j'}^{yy} p_x^{i'} p_y^{j'}} \end{aligned}$$

Substituting $m_x$ and $m_y$ into the protein SDEs yields

$$\begin{aligned} \dot{p}_x =& k_p^x \frac{\sum_{i,j} k_{ij}^x g_x^{ij}}{d_m^x} - d_p^x p_x + \sum_{i,j} \left[ r_i^{xx} g_x^{i+1,j} - f_i^{xx} g_x^{ij} p_x \right] + \left[ r_i^{yx} g_y^{i+1,j} - f_i^{yx} g_y^{ij} p_x \right] \\ &+ \sqrt{k_p^x \frac{\sum_{i,j} k_{ij}^x g_x^{ij}}{d_m^x} + d_p^x p_x + \sum_{i,j} \left[ r_i^{xx} g_x^{i+1,j} + f_i^{xx} g_x^{ij} p_x \right] + \left[ r_i^{yx} g_y^{i+1,j} + f_i^{yx} g_y^{ij} p_x \right]} \; \eta_x(t) \\ \dot{p}_y =& k_p^y \frac{\sum_{i,j} k_{ij}^y g_y^{ij}}{d_m^y} - d_p^y p_y + \sum_{i,j} \left[ r_j^{yy} g_y^{i,j+1} - f_j^{yy} g_y^{ij} p_y \right] + \left[ r_j^{xy} g_x^{i,j+1} - f_j^{xy} g_x^{ij} p_y \right] \\ &+ \sqrt{k_p^y \frac{\sum_{i,j} k_{ij}^y g_y^{ij}}{d_m^y} + d_p^y p_y + \sum_{i,j} \left[ r_j^{yy} g_y^{i,j+1} + f_j^{yy} g_y^{ij} p_y \right] + \left[ r_j^{xy} g_x^{i,j+1} + f_j^{xy} g_x^{ij} p_y \right]} \; \eta_y(t) \end{aligned}$$

Knowing we have QSS binding first gives:

$$\begin{aligned}
\dot{p}_x =& k_p^x \frac{\sum_{i,j} k_{ij}^x g_x^{ij}}{d_m^x} - d_p^x p_x \\
&+ \sqrt{k_p^x \frac{\sum_{i,j} k_{ij}^x g_x^{ij}}{d_m^x} + d_p^x p_x + \sum_{i,j} 2 f_i^{xx} g_x^{ij} p_x + 2 f_i^{yx} g_y^{ij} p_x}\ \eta_x(t) \\
\dot{p}_y =& k_p^y \frac{\sum_{i,j} k_{ij}^y g_y^{ij}}{d_m^y} - d_p^y p_y \\
&+ \sqrt{k_p^y \frac{\sum_{i,j} k_{ij}^y g_y^{ij}}{d_m^y} + d_p^y p_y + \sum_{i,j} 2 f_j^{yy} g_y^{ij} p_y + 2 f_j^{xy} g_x^{ij} p_y}\ \eta_y(t)
\end{aligned}$$

Simplifying a little bit more, we have

$$\begin{aligned}
\dot{p}_x =& k_p^x \frac{\sum_{i,j} k_{ij}^x g_x^{ij}}{d_m^x} - d_p^x p_x \\
&+ \sqrt{d_p^x p_x + k_p^x \frac{\sum_j k_{N_x,j}^x g_x^{N_x,j}}{d_m^x} + \sum_{i<N_x,j} g_x^{ij} \left( \frac{k_p^x k_{ij}^x}{d_m^x} + 2 f_i^{xx} p_x \right) + 2 f_i^{yx} g_y^{ij} p_x}\ \eta_x(t) \\
\dot{p}_y =& k_p^y \frac{\sum_{i,j} k_{ij}^y g_y^{ij}}{d_m^y} - d_p^y p_y \\
&+ \sqrt{d_p^y p_y + k_p^y \frac{\sum_i k_{i,N_y}^y g_y^{i,N_y}}{d_m^y} + \sum_{i,j<N_y} g_y^{ij} \left( \frac{k_p^y k_{ij}^y}{d_m^y} + 2 f_j^{yy} p_y \right) + 2 f_j^{xy} g_x^{ij} p_y}\ \eta_y(t)
\end{aligned}$$

Finally, we have

$$\begin{aligned}
\dot{p}_x =& \frac{k_p^x G_x}{d_m^x} \frac{\sum_{i,j} k_{ij}^x c_i^{xx} c_j^{xy} p_x^i p_y^j}{\sum_{i'} \sum_{j'} c_{i'}^{xx} c_{j'}^{xy} p_x^{i'} p_y^{j'}} - d_p^x p_x \\
&+ \sqrt{d_p^x p_x + \sum_j \frac{k_p^x}{d_m^x} k_{N_x,j}^x g_x^{N_x,j} + \sum_{i<N_x,j} g_x^{ij} \left( \frac{k_p^x k_{ij}^x}{d_m^x} + 2 f_i^{xx} p_x \right) + 2 f_i^{yx} g_y^{ij} p_x}\ \eta_x(t) \\
\dot{p}_y =& \frac{k_p^y G_y}{d_m^y} \frac{\sum_{i,j} k_{ij}^y c_i^{yx} c_j^{yy} p_x^i p_y^j}{\sum_{i'} \sum_{j'} c_{i'}^{yx} c_{j'}^{yy} p_x^{i'} p_y^{j'}} - d_p^y p_y \\
&+ \sqrt{d_p^y p_y + \sum_i \frac{k_p^y}{d_m^y} k_{i,N_y}^y g_y^{i,N_y} + \sum_{i,j<N_y} g_y^{ij} \left( \frac{k_p^y k_{ij}^y}{d_m^y} + 2 f_j^{yy} p_y \right) + 2 f_j^{xy} g_x^{ij} p_y}\ \eta_y(t)
\end{aligned}$$

where I have not everywhere substituted in our expressions for $g_x^{ij}$ and $g_y^{ij}$ since the equations wouldn't fit within the page.