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Bistable switch Nth order feedback (fully general) notes

In the previous version of these notes, I considered two genes whose proteins bind to each other and themselves—but I only considered the case where the binding of one kind of protein did not affect the binding of the other. In this version, I will proceed with full generality: it is assumed that the binding of protein X to gene Y might affect the likelihood that protein Y binds to gene Y.

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:

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

Constraints:

$$\sum_{i=0,1,\ldots,N_x}^{N_x} \sum_{j=0,1,\ldots,N_y}^{N_y} g_x^{ij} = G_x$$
$$\sum_{i=0,1,\ldots,N_x}^{N_x} \sum_{j=0,1,\ldots,N_y}^{N_y} g_y^{ij} = G_y$$

mRNA ODEs:

$$\dot{m}_x = \sum_{i,j} k_{ij}^x g_x^{ij} - d_m^x m_x$$
$$\dot{m}_y = \sum_{i,j} k_{ij}^y g_y^{ij} - d_m^y m_y$$

Protein SDEs:

$$\begin{aligned}
\dot{p}_x =& k_p^x m_x - d_p^x p_x + \sum_{i,j} \left[r_{ij}^{xx} g_x^{i+1,j} - f_{ij}^{xx} g_x^{ij} p_x \right] + \left[r_{ij}^{yx} g_y^{i+1,j} - f_{ij}^{yx} g_y^{ij} p_x \right] \\
&+ \sqrt{k_p^x m_x + d_p^x p_x + \sum_{i,j} \left[r_{ij}^{xx} g_x^{i+1,j} + f_{ij}^{xx} g_x^{ij} p_x \right] + \left[r_{ij}^{yx} g_y^{i+1,j} + f_{ij}^{yx} g_y^{ij} p_x \right]}\ \eta_x(t) \\
\dot{p}_y =& k_p^y m_y - d_p^y p_y + \sum_{i,j} \left[r_{ij}^{yy} g_y^{i,j+1} - f_{ij}^{yy} g_y^{ij} p_y \right] + \left[r_{ij}^{xy} g_x^{i,j+1} - f_{ij}^{xy} g_x^{ij} p_y \right] \\
&+ \sqrt{k_p^y m_y + d_p^y p_y + \sum_{i,j} \left[r_{ij}^{yy} g_y^{i,j+1} + f_{ij}^{yy} g_y^{ij} p_y \right] + \left[r_{ij}^{xy} g_x^{i,j+1} + f_{ij}^{xy} g_x^{ij} p_y \right]}\ \eta_y(t)
\end{aligned}$$

mRNA at QSS forces:

$$m_x = \frac{\sum_{i,j} k_{ij}^x g_x^{ij}}{d_m^x}$$
$$m_y = \frac{\sum_{i,j} k_{ij}^y g_y^{ij}}{d_m^y}$$

Binding at QSS forces:

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

In other words,

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

Define

$$\begin{aligned}
B_{ij}^{xx} &:= \frac{f_{ij}^{xx}}{r_{ij}^{xx}} \qquad && i < N_x \\
B_{ij}^{yx} &:= \frac{f_{ij}^{yx}}{r_{ij}^{yx}} \qquad && i < N_x \\
B_{ij}^{yy} &:= \frac{f_{ij}^{yy}}{r_{ij}^{yy}} \qquad && j < N_y \\
B_{ij}^{xy} &:= \frac{f_{ij}^{xy}}{r_{ij}^{xy}} \qquad && j < N_y
\end{aligned}$$

Then we have

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

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}:

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

where we will for convenience define

$$\begin{aligned}
c_{ij}^{xx} &:= \begin{cases} 1 & \text{if } i = 0 \\ B_{0j}^{xx} \cdots B_{i-1,j}^{xx} & \text{if } i = 1, 2, ..., N_x \end{cases} \\
c_{ij}^{xy} &:= \begin{cases} 1 & \text{if } j = 0 \\ B_{i0}^{xy} \cdots B_{i,j-1}^{xy} & \text{if } j = 1, 2, ..., N_y \end{cases} \\
c_{ij}^{yx} &:= \begin{cases} 1 & \text{if } i = 0 \\ B_{0j}^{yx} \cdots B_{i-1,j}^{yx} & \text{if } i = 1, 2, ..., N_x \end{cases} \\
c_{ij}^{yy} &:= \begin{cases} 1 & \text{if } j = 0 \\ B_{ij}^{yy} \cdots B_{i,j-1}^{yy} & \text{if } j = 1, 2, ..., N_y \end{cases}
\end{aligned}$$

Next, we can write

$$g_x^{0j} = B_{0,j-1}^{xy} g_x^{0,j-1} p_y = B_{0,j-2}^{xy} B_{0,j-1}^{xy} g_x^{0,j-2} p_y^2 = \cdots = c_{0j}^{xy} p_y^j g_x^{00}$$

so that

$$\begin{aligned}
G_x &= g_x^{00} \sum_j c_{0j}^{xy} p_y^j \sum_i c_{ij}^{xx} p_x^i \\
\implies \quad g_x^{00}(p_x, p_y) &= \frac{G_x}{\sum_{i,j} c_{ij}^{xx} c_{0j}^{xy} p_x^i p_y^j}
\end{aligned}$$

Similarly, we can find that

$$g_y^{00}(p_x, p_y) = \frac{G_y}{\sum_{i,j} c_{ij}^{yy} c_{i0}^{yx} p_x^i p_y^j}$$

We also have:

$$\begin{aligned} g_x^{ij}(p_x, p_y) &= \frac{G_x c_{ij}^{xx} c_{0j}^{xy} p_x^i p_y^j}{\sum_{i',j'} c_{i'j'}^{xx} c_{0j'}^{xy} p_x^{i'} p_y^{j'}} \\ g_y^{ij}(p_x, p_y) =& \frac{G_y c_{ij}^{yy} c_{i0}^{yx} p_x^i p_y^j}{\sum_{i',j'} c_{i'j'}^{yy} c_{i'0}^{yx} p_x^{i'} p_y^{j'}} \end{aligned}$$

Substituting m_x and m_y into the protein SDEs yields

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

Knowing we have QSS binding first gives:

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

Finally, we have

$$
\begin{aligned}
\dot{p}_x =& \frac{k_p^x G_x}{d_m^x} \frac{\sum_{i,j} k_{ij}^x c_{ij}^{xx} c_{0j}^{xy} p_x^i p_y^j}{\sum_{i',j'} c_{i'j'}^{xx} c_{0j'}^{xy} p_x^{i'} p_y^{j'}} - d_p^x p_x \\
& + \sqrt{k_p^x \frac{\sum_{i,j} k_{ij}^x g_x^{ij}}{d_m^x} + d_p^x p_x + \sum_{i,j} 2 f_{ij}^{xx} g_x^{ij} p_x + 2 f_{ij}^{yx} g_y^{ij} p_x}\ \eta_x(t) \\
\dot{p}_y =& \frac{k_p^y G_y}{d_m^y} \frac{\sum_{i,j} k_{ij}^y c_{ij}^{yy} c_{i0}^{yx} p_x^i p_y^j}{\sum_{i',j'} c_{i'j'}^{yy} c_{i'0}^{yx} p_x^{i'} p_y^{j'}} - d_p^y p_y \\
& + \sqrt{k_p^y \frac{\sum_{i,j} k_{ij}^y g_y^{ij}}{d_m^y} + d_p^y p_y + \sum_{i,j} 2 f_{ij}^{yy} g_y^{ij} p_y + 2 f_{ij}^{xy} g_x^{ij} p_y}\ \eta_y(t)
\end{aligned}
$$

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.