Mapping Vector Field of Single Cells: the full derivation of the inclusive model of expression dynamics

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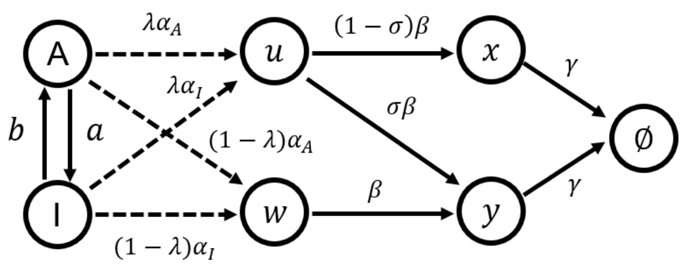
1 Model Setup

Denote the states of promoter as $s \in \{I, A\}$. Denote the number of unspliced, labeled (ul) mRNA as n_u, unspliced, unlabeled (uu) as n_w, spliced, labeled (sl) as n_x, and spliced, unlabeled (su) as n_y.



The master equations:

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}P(I, n_u, n_w, n_x, n_y) =& \lambda\alpha_I P(I, n_u - 1, n_w, n_x, n_y) - \lambda\alpha_I P(I, n_u, n_w, n_x, n_y) \\
&+ (1-\lambda)\alpha_I P(I, n_u, n_w - 1, n_x, n_y) - (1-\lambda)\alpha_I P(I, n_u, n_w, n_x, n_y) \\
&+ (1-\sigma)\beta(n_u + 1)P(I, n_u + 1, n_w, n_x - 1, n_y) + \sigma\beta(n_u + 1)P(I, n_u + 1, n_w, n_x, n_y - 1) \\
&- \beta n_u P(I, n_u, n_w, n_x, n_y) \\
&+ \beta(n_w + 1)P(I, n_u, n_w + 1, n_x, n_y - 1) - \beta n_w P(I, n_u, n_w, n_x, n_y) \\
&+ \gamma(n_x + 1)P(I, n_u, n_w, n_x + 1, n_y) - \gamma n_x P(I, n_u, n_w, n_x, n_y) \\
&+ \gamma(n_y + 1)P(I, n_u, n_w, n_x, n_y + 1) - \gamma n_y P(I, n_u, n_w, n_x, n_y) \\
&- bP(I, n_u, n_w, n_x, n_y) + aP(A, n_u, n_w, n_x, n_y) \qquad (1)
\end{aligned}
$$

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}P(A,n_u,n_w,n_x,n_y) =& \lambda\alpha_A P(A,n_u-1,n_w,n_x,n_y) - \lambda\alpha_A P(A,n_u,n_w,n_x,n_y)\\
&+ (1-\lambda)\alpha_A P(A,n_u,n_w-1,n_x,n_y) - (1-\lambda)\alpha_A P(A,n_u,n_w,n_x,n_y)\\
&+ (1-\sigma)\beta(n_u+1)P(A,n_u+1,n_w,n_x-1,n_y) + \sigma\beta(n_u+1)P(A,n_u+1,n_w,n_x,n_y-1)\\
&- \beta n_u P(A,n_u,n_w,n_x,n_y)\\
&+ \beta(n_w+1)P(A,n_u,n_w+1,n_x,n_y-1) - \beta n_w P(A,n_u,n_w,n_x,n_y)\\
&+ \gamma(n_x+1)P(A,n_u,n_w,n_x+1,n_y) - \gamma n_x P(A,n_u,n_w,n_x,n_y)\\
&+ \gamma(n_y+1)P(A,n_u,n_w,n_x,n_y+1) - \gamma n_y P(A,n_u,n_w,n_x,n_y)\\
&+ bP(I,n_u,n_w,n_x,n_y) - aP(A,n_u,n_w,n_x,n_y) \qquad (2)
\end{aligned}
$$

Since the dynamics of the promoter activation is unaffected by the dynamics of the downstream mRNAs, we could assume that the marginal probability distribution for the promoter state has reached the steady state:

$$
P(A) = \frac{b}{a+b},\ P(I) = \frac{a}{a+b}
$$

Then any moment can be computed as follows:

Suppose $\Big\langle f(n_a,n_b)\Big\rangle_s$ is the expectation of some function $f(n_a,n_b)$ based on the conditional probability $P(n_a,n_b|s)$, then,

$$
\begin{aligned}
\Big\langle f(n_a,n_b)\Big\rangle &= \sum_s \sum_{n_a,n_b} f(n_a,n_b)P(n_a,n_b,s)\\
&= \sum_s P(s) \sum_{n_a,n_b} f(n_a,n_b)P(n_a,n_b|s)\\
&= \sum_s P(s)\Big\langle f(n_a,n_b)\Big\rangle_s
\end{aligned}
$$

To utilize this technique, divide Eqn.1 by $P(I)$:

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}P(n_u,n_w,n_x,n_y|I) =& \lambda\alpha_I P(n_u-1,n_w,n_x,n_y|I) - \lambda\alpha_I P(I,n_u,n_w,n_x,n_y|I)\\
&+ (1-\lambda)\alpha_I P(n_u,n_w-1,n_x,n_y|I) - (1-\lambda)\alpha_I P(n_u,n_w,n_x,n_y|I)\\
&+ (1-\sigma)\beta(n_u+1)P(n_u+1,n_w,n_x-1,n_y|I) + \sigma\beta(n_u+1)P(n_u+1,n_w,n_x,n_y-1|I)\\
&- \beta n_u P(n_u,n_w,n_x,n_y|I)\\
&+ \beta(n_w+1)P(n_u,n_w+1,n_x,n_y-1|I) - \beta n_w P(n_u,n_w,n_x,n_y|I)\\
&+ \gamma(n_x+1)P(n_u,n_w,n_x+1,n_y|I) - \gamma n_x P(n_u,n_w,n_x,n_y|I)\\
&+ \gamma(n_y+1)P(n_u,n_w,n_x,n_y+1|I) - \gamma n_y P(n_u,n_w,n_x,n_y|I)\\
&- b\Big(P(n_u,n_w,n_x,n_y|I) - P(n_u,n_w,n_x,n_y|A)\Big) \qquad (3)
\end{aligned}
$$

The last line is because:

$$
a\frac{P(A,\boldsymbol{n})}{P(I)} = aP(\boldsymbol{n}|A)\frac{P(A)}{P(I)} = bP(\boldsymbol{n}|A)
$$

The master equation for $s = A$ can be treated in a similar way. More generally, let c_s be a variable depending on the promoter state s, such that $c_A = a$ and $c_I = -b$. Then:

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}P(n_u, n_w, n_x, n_y|s) =& \lambda\alpha_s P(n_u - 1, n_w, n_x, n_y|s) - \lambda\alpha_s P(I, n_u, n_w, n_x, n_y|s) \\
&+ (1-\lambda)\alpha_s P(n_u, n_w - 1, n_x, n_y|s) - (1-\lambda)\alpha_s P(n_u, n_w, n_x, n_y|s) \\
&+ (1-\sigma)\beta(n_u+1)P(n_u+1, n_w, n_x - 1, n_y|s) + \sigma\beta(n_u+1)P(n_u+1, n_w, n_x, n_y - 1|s) \\
&- \beta n_u P(n_u, n_w, n_x, n_y|s) \\
&+ \beta(n_w+1)P(n_u, n_w+1, n_x, n_y-1|s) - \beta n_w P(n_u, n_w, n_x, n_y|s) \\
&+ \gamma(n_x+1)P(n_u, n_w, n_x+1, n_y|s) - \gamma n_x P(n_u, n_w, n_x, n_y|s) \\
&+ \gamma(n_y+1)P(n_u, n_w, n_x, n_y+1|s) - \gamma n_y P(n_u, n_w, n_x, n_y|s) \\
&+ c_s\Big(P(n_u, n_w, n_x, n_y|I) - P(n_u, n_w, n_x, n_y|A)\Big) \qquad (4)
\end{aligned}$$

2 Moment Equations

For simplicity, define the following notations:

$$\begin{aligned}
\Delta X &= X_I - X_A \\
\overline{X} &= \frac{a}{a+b}X_I + \frac{b}{a+b}X_A
\end{aligned}$$

Apply the moment generating function technique to the master equations:

$$\begin{aligned}
\frac{\partial F_s}{\partial t} =& \lambda\alpha_s(z_u - z_w)F_s + \alpha_s(z_w - 1)F_s \\
&+ \beta(z_x - z_u)\frac{\partial F_s}{\partial z_u} + \sigma\beta(z_y - z_x)\frac{\partial F_s}{\partial z_u} \\
&+ \beta(z_y - z_w)\frac{\partial F_s}{\partial z_w} + \gamma(1 - z_x)\frac{\partial F_s}{\partial z_x} + \gamma(1 - z_y)\frac{\partial F_s}{\partial z_y} \\
&+ c_s\Delta F
\end{aligned}$$

First order derivatives:

$$\begin{aligned}
\frac{\partial}{\partial t}\frac{\partial F_s}{\partial z_u} =& \lambda\alpha_s\Big(F_s + (z_u - z_w)\frac{\partial F_s}{\partial z_u}\Big) + \alpha_s(z_w - 1)\frac{\partial F_s}{\partial z_u} \\
&+ \beta\Big(-\frac{\partial F_s}{\partial z_u} + (z_x - z_u)\frac{\partial^2 F_s}{\partial z_u^2}\Big) + \sigma\beta(z_y - z_x)\frac{\partial^2 F_s}{\partial z_u^2} \\
&+ \beta(z_y - z_w)\frac{\partial^2 F_s}{\partial z_w \partial z_u} + \gamma(1 - z_x)\frac{\partial^2 F_s}{\partial z_x \partial z_u} + \gamma(1 - z_y)\frac{\partial^2 F_s}{\partial z_y \partial z_u} \\
&+ c_s\frac{\partial \Delta F}{\partial z_u}
\end{aligned}$$

$$\begin{aligned}\frac{\partial}{\partial t}\frac{\partial F_s}{\partial z_x} =& \lambda\alpha_s(z_u - z_w)\frac{\partial F_s}{\partial z_x} + \alpha_s(z_w - 1)\frac{\partial F_s}{\partial z_x}\\ &+ \beta\Big(\frac{\partial F_s}{\partial z_u} + (z_x - z_u)\frac{\partial^2 F_s}{\partial z_u \partial z_x}\Big) + \sigma\beta\Big(-\frac{\partial F_s}{\partial z_u} + (z_y - z_x)\frac{\partial^2 F_s}{\partial z_u \partial z_x}\Big)\\ &+ \beta(z_y - z_w)\frac{\partial^2 F_s}{\partial z_w \partial z_x} + \gamma\Big(-\frac{\partial F_s}{\partial z_x} + (1 - z_x)\frac{\partial^2 F_s}{\partial z_x^2}\Big) + \gamma(1 - z_y)\frac{\partial^2 F_s}{\partial z_x \partial z_y}\\ &+ c_s\frac{\partial \Delta F}{\partial z_x}\end{aligned}$$

$$\begin{aligned}\frac{\partial}{\partial t}\frac{\partial F_s}{\partial z_w} =& \lambda\alpha_s\Big(-F_s + (z_u - z_w)\frac{\partial F_s}{\partial z_w}\Big) + \alpha_s\Big(F_s + (z_w - 1)\frac{\partial F_s}{\partial z_w}\Big)\\ &+ \beta(z_x - z_u)\frac{\partial^2 F_s}{\partial z_u \partial z_w} + \sigma\beta(z_y - z_x)\frac{\partial^2 F_s}{\partial z_u \partial z_w}\\ &+ \beta\Big(-\frac{\partial F_s}{\partial z_w} + (z_y - z_w)\frac{\partial^2 F_s}{\partial z_w^2}\Big) + \gamma(1 - z_x)\frac{\partial^2 F_s}{\partial z_x \partial z_w} + \gamma(1 - z_y)\frac{\partial^2 F_s}{\partial z_y \partial z_w}\\ &+ c_s\frac{\partial \Delta F}{\partial z_w}\end{aligned}$$

$$\begin{aligned}\frac{\partial}{\partial t}\frac{\partial F_s}{\partial z_y} =& \lambda\alpha_s(z_u - z_w)\frac{\partial F_s}{\partial z_y} + \alpha_s(z_w - 1)\frac{\partial F_s}{\partial z_y}\\ &+ \beta(z_x - z_u)\frac{\partial^2 F_s}{\partial z_u \partial z_y} + \sigma\beta\Big(\frac{\partial F_s}{\partial z_u} + (z_y - z_x)\frac{\partial^2 F_s}{\partial z_y \partial z_u}\Big)\\ &+ \beta\Big(\frac{\partial F_s}{\partial z_w} + (z_y - z_w)\frac{\partial^2 F_s}{\partial z_w \partial z_y}\Big) + \gamma(1 - z_x)\frac{\partial^2 F_s}{\partial z_x \partial z_y} + \gamma\Big(-\frac{\partial F_s}{\partial z_y} + (1 - z_y)\frac{\partial^2 F_s}{\partial z_y^2}\Big)\\ &+ c_s\frac{\partial \Delta F}{\partial z_y}\end{aligned}$$

Second order derivatives:

$$\begin{aligned}\frac{\partial}{\partial t}\frac{\partial^2 F_s}{\partial z_u^2} =& \lambda\alpha_s\Big(2\frac{\partial F_s}{\partial z_u} + (z_u - z_w)\frac{\partial^2 F_s}{\partial z_u^2}\Big) + \alpha_s(z_w - 1)\frac{\partial^2 F_s}{\partial z_u^2}\\ &+ \beta\Big(-2\frac{\partial^2 F_s}{\partial z_u^2} + (z_x - z_u)\frac{\partial^3 F_s}{\partial z_u^3}\Big) + \sigma\beta(z_y - z_x)\frac{\partial^3 F_s}{\partial z_u^3}\\ &+ \beta(z_y - z_w)\frac{\partial^3 F_s}{\partial z_w \partial z_u^2} + \gamma(1 - z_x)\frac{\partial^3 F_s}{\partial z_x \partial z_u^2} + \gamma(1 - z_y)\frac{\partial^3 F_s}{\partial z_y \partial z_u^2}\\ &+ c_s\frac{\partial^2 \Delta F}{\partial z_u^2}\end{aligned}$$

$$
\begin{aligned}
\frac{\partial}{\partial t}\frac{\partial^2 F_s}{\partial z_x^2} =& \lambda\alpha_s(z_u - z_w)\frac{\partial^2 F_s}{\partial z_x^2} + \alpha_s(z_w - 1)\frac{\partial^2 F_s}{\partial z_x^2} \\
&+ \beta\Big(2\frac{\partial^2 F_s}{\partial z_x \partial z_u} + (z_x - z_u)\frac{\partial^3 F_s}{\partial z_x^2 \partial z_u}\Big) + \sigma\beta\Big(-\frac{\partial^2 F_s}{\partial z_x \partial z_u} + (z_y - z_x)\frac{\partial^3 F_s}{\partial z_x^2 \partial z_u}\Big) \\
&+ \beta(z_y - z_w)\frac{\partial^3 F_s}{\partial z_w \partial z_x^2} + \gamma\Big(-\frac{\partial^2 F_s}{\partial z_x^2} + (1 - z_x)\frac{\partial^3 F_s}{\partial z_x^3}\Big) + \gamma(1 - z_y)\frac{\partial^3 F_s}{\partial z_y \partial z_x^2} \\
&+ c_s\frac{\partial^2 \Delta F_I}{\partial z_x^2}
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial}{\partial t}\frac{\partial^2 F_s}{\partial z_w^2} =& \lambda\alpha_s\Big(-2\frac{\partial F_s}{\partial z_w} + (z_u - z_w)\frac{\partial^2 F_s}{\partial z_w^2}\Big) + \alpha_s\Big(2\frac{\partial F_s}{\partial z_w} + (z_w - 1)\frac{\partial^2 F_s}{\partial z_w^2}\Big) \\
&+ \beta(z_x - z_u)\frac{\partial^3 F_s}{\partial z_u \partial z_w^2} + \sigma\beta(z_y - z_x)\frac{\partial^3 F_s}{\partial z_u \partial z_w^2} \\
&+ \beta\Big(-2\frac{\partial^2 F_s}{\partial z_w^2} + (z_y - z_w)\frac{\partial^3 F_s}{\partial z_w^3}\Big) + \gamma(1 - z_x)\frac{\partial^3 F_s}{\partial z_x \partial z_w^2} + \gamma(1 - z_y)\frac{\partial^3 F_s}{\partial z_y \partial z_w^2} \\
&+ c_s\frac{\partial^2 \Delta F}{\partial z_w^2}
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial}{\partial t}\frac{\partial^2 F_s}{\partial z_y^2} =& \lambda\alpha_s(z_u - z_w)\frac{\partial^2 F_s}{\partial z_y^2} + \alpha_s(z_w - 1)\frac{\partial^2 F_s}{\partial z_y^2} \\
&+ \beta(z_x - z_u)\frac{\partial^3 F_s}{\partial z_u \partial z_y^2} + \sigma\beta\Big(2\frac{\partial^2 F_s}{\partial z_y \partial z_u} + (z_y - z_x)\frac{\partial^3 F_s}{\partial z_y^2 \partial z_u}\Big) \\
&+ \beta\Big(2\frac{\partial^2 F_s}{\partial z_w \partial z_y} + (z_y - z_w)\frac{\partial^3 F_s}{\partial z_w \partial z_y^2}\Big) + \gamma(1 - z_x)\frac{\partial^3 F_s}{\partial z_x \partial z_y^2} \\
&+ \gamma\Big(-2\frac{\partial^2 F_s}{\partial z_y^2} + (1 - z_y)\frac{\partial^3 F_s}{\partial z_y^3}\Big) + c_s\frac{\partial^2 \Delta F_I}{\partial z_x^2}
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial}{\partial t}\frac{\partial^2 F_s}{\partial z_u \partial z_w} =& \lambda\alpha_s\Big(\frac{\partial F_s}{\partial z_w} - \frac{\partial F_s}{\partial z_u} + (z_u - z_w)\frac{\partial^2 F_s}{\partial z_u \partial z_w}\Big) + \alpha_s\Big(\frac{\partial F_s}{\partial z_u} + (z_w - 1)\frac{\partial^2 F_s}{\partial z_w \partial z_u}\Big) \\
&+ \beta\Big(-\frac{\partial^2 F_s}{\partial z_u \partial z_w} + (z_x - z_u)\frac{\partial^3 F_s}{\partial z_w \partial z_u^2}\Big) \\
&+ \sigma\beta(z_y - z_x)\frac{\partial^3 F_s}{\partial z_w \partial z_u^2} + \beta\Big(-\frac{\partial^2 F_s}{\partial z_w \partial z_u} + (z_y - z_w)\frac{\partial^3 F_s}{\partial z_w^2 \partial z_u}\Big) \\
&+ \gamma(1 - z_x)\frac{\partial^3 F_s}{\partial z_x \partial z_u \partial z_w} + \gamma(1 - z_y)\frac{\partial^3 F_s}{\partial z_y \partial z_u \partial z_w} \\
&+ c_s\frac{\partial^2 \Delta F}{\partial z_w \partial z_u}
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial}{\partial t}\frac{\partial^2 F_s}{\partial z_x \partial z_u} =& \lambda\alpha_s\Big(\frac{\partial F_s}{\partial z_x} + (z_u - z_w)\frac{\partial^2 F_s}{\partial z_x \partial z_u}\Big) + \alpha_s(z_w - 1)\frac{\partial^2 F_s}{\partial z_x \partial z_u} \\
&+ \beta\Big(\frac{\partial^2 F_s}{\partial z_u^2} - \frac{\partial^2 F_s}{\partial z_x \partial z_u} + (z_x - z_u)\frac{\partial^3 F_s}{\partial z_x \partial z_u^2}\Big) \\
&+ \sigma\beta\Big(- \frac{\partial^2 F_s}{\partial z_u^2} + (z_y - z_x)\frac{\partial^3 F_s}{\partial z_x \partial z_u^2}\Big) + \beta(z_y - z_w)\frac{\partial^3 F_s}{\partial z_w \partial z_u \partial z_x} \\
&+ \gamma\Big(- \frac{\partial^2 F_s}{\partial z_x \partial z_u} + (1 - z_x)\frac{\partial^3 F_s}{\partial z_x^2 \partial z_u}\Big) + \gamma(1 - z_y)\frac{\partial^3 F_s}{\partial z_y \partial z_u \partial z_x} \\
&+ c_s\frac{\partial^2 \Delta F}{\partial z_x \partial z_u}
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial}{\partial t}\frac{\partial^2 F_s}{\partial z_y \partial z_u} =& \lambda\alpha_s\Big(\frac{\partial F_s}{\partial z_y} + (z_u - z_w)\frac{\partial^2 F_s}{\partial z_y \partial z_u}\Big) + \alpha_s(z_w - 1)\frac{\partial^2 F_s}{\partial z_y \partial z_u} \\
&+ \beta\Big(- \frac{\partial^2 F_s}{\partial z_u \partial z_y} + (z_x - z_u)\frac{\partial^3 F_s}{\partial z_u^2 \partial z_y}\Big) \\
&+ \sigma\beta\Big(\frac{\partial^2 F_s}{\partial z_u^2} + (z_y - z_x)\frac{\partial^3 F_s}{\partial z_y \partial z_u^2}\Big) + \beta\Big(\frac{\partial^2 F_s}{\partial z_w \partial z_u} + (z_y - z_w)\frac{\partial^3 F_s}{\partial z_w \partial z_u \partial z_y}\Big) \\
&+ \gamma(1 - z_x)\frac{\partial^3 F_s}{\partial z_u \partial z_x \partial z_y} + \gamma\Big(- \frac{\partial^2 F_s}{\partial z_y \partial z_u} + (1 - z_y)\frac{\partial^3 F_s}{\partial z_y^2 \partial z_u}\Big) \\
&+ c_s\frac{\partial^2 \Delta F}{\partial z_u \partial z_y}
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial}{\partial t}\frac{\partial^2 F_s}{\partial z_y \partial z_w} =& \lambda\alpha_s\Big(- \frac{\partial F_s}{\partial z_y} + (z_u - z_w)\frac{\partial^2 F_s}{\partial z_y \partial z_w}\Big) + \alpha_s\Big(\frac{\partial F_s}{\partial z_y} + (z_w - 1)\frac{\partial^2 F_s}{\partial z_y \partial z_w}\Big) \\
&+ \beta(z_x - z_u)\frac{\partial^3 F_s}{\partial z_u \partial z_w \partial z_y} \\
&+ \sigma\beta\Big(\frac{\partial^2 F_s}{\partial z_u \partial z_w} + (z_y - z_x)\frac{\partial^3 F_s}{\partial z_y \partial z_u \partial z_w}\Big) + \beta\Big(- \frac{\partial^2 F_s}{\partial z_w \partial z_y} + \frac{\partial^2 F_s}{\partial z_w^2} + (z_y - z_w)\frac{\partial^3 F_s}{\partial z_w^2 \partial z_y}\Big) \\
&+ \gamma(1 - z_x)\frac{\partial^3 F_s}{\partial z_u \partial z_w \partial z_y} + \gamma\Big(- \frac{\partial^2 F_s}{\partial z_y \partial z_w} + (1 - z_y)\frac{\partial^3 F_s}{\partial z_y^2 \partial z_w}\Big) \\
&+ c_s\frac{\partial^2 \Delta F}{\partial z_w \partial z_y}
\end{aligned}
$$

Evaluating the above equations at $z_u, z_w, z_x, z_y = 1$, we get the first moments:

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u\rangle_s =& \lambda\alpha_s - \beta\langle n_u\rangle_s + c_s\Delta\langle n_u\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_x\rangle_s =& \beta(1-\sigma)\langle n_u\rangle_s - \gamma\langle n_x\rangle_s + c_s\Delta\langle n_x\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_w\rangle_s =& (1-\lambda)\alpha_s - \beta\langle n_w\rangle_s + c_s\Delta\langle n_w\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_y\rangle_s =& \sigma\beta\langle n_u\rangle_s + \beta\langle n_w\rangle_s - \gamma\langle n_y\rangle_s + c_s\Delta\langle n_y\rangle
\end{aligned}
$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_u\rangle_s = \sum_s p_s\Big(\lambda\alpha_s - \beta\langle n_u\rangle_s + c_s\Delta\langle n_u\rangle\Big)$$
$$\Rightarrow \frac{\mathrm{d}}{\mathrm{d}t}\langle n_u\rangle = \lambda\alpha_I\frac{a}{a+b} + \lambda\alpha_A\frac{b}{a+b} - \beta\langle n_u\rangle$$
$$\Rightarrow \boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u\rangle = \lambda\bar{\alpha} - \beta\langle n_u\rangle}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_x\rangle_s = \sum_s p_s\Big(\beta(1-\sigma)\langle n_u\rangle_s - \gamma\langle n_x\rangle_s + c_s\Delta\langle n_x\rangle\Big)$$
$$\Rightarrow \boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_x\rangle = \beta(1-\sigma)\langle n_u\rangle - \gamma\langle n_x\rangle}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_w\rangle_s = \sum_s p_s\Big((1-\lambda)\alpha_s - \beta\langle n_w\rangle_s + c_s\Delta\langle n_w\rangle\Big)$$
$$\Rightarrow \boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_w\rangle = (1-\lambda)\bar{\alpha} - \beta\langle n_w\rangle}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_y\rangle_s = \sum_s p_s\Big(\sigma\beta\langle n_u\rangle_s + \beta\langle n_w\rangle_s - \gamma\langle n_y\rangle_s + c_s\Delta\langle n_y\rangle\Big)$$
$$\Rightarrow \boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_y\rangle = \sigma\beta\langle n_u\rangle + \beta\langle n_w\rangle - \gamma\langle n_y\rangle}$$

And the second moments:

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u(n_u-1)\rangle_s &= 2\lambda\alpha_s\langle n_u\rangle_s - 2\beta\langle n_u(n_u-1)\rangle_s + c_s\Delta\langle n_u(n_u-1)\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_x(n_x-1)\rangle_s &= 2\beta(1-\sigma)\langle n_u n_x\rangle_s - 2\gamma\langle n_x(n_x-1)\rangle_s + c_s\Delta\langle n_x(n_x-1)\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_w(n_w-1)\rangle_s &= 2(1-\lambda)\alpha_s\langle n_w\rangle_s - 2\beta\langle n_w(n_w-1)\rangle_s + c_s\Delta\langle n_w(n_w-1)\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_y(n_y-1)\rangle_s &= 2\sigma\beta\langle n_u n_y\rangle_s + 2\beta\langle n_w n_y\rangle_s - 2\gamma\langle n_y(n_y-1)\rangle_s + c_s\Delta\langle n_y(n_y-1)\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u n_w\rangle_s &= \lambda\alpha_s\langle n_w\rangle_s + (1-\lambda)\alpha_s\langle n_u\rangle_s - 2\beta\langle n_w n_u\rangle_s + c_s\Delta\langle n_u n_w\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u n_x\rangle_s &= \lambda\alpha_s\langle n_x\rangle_s + \beta(1-\sigma)\langle n_u(n_u-1)\rangle_s - (\beta+\gamma)\langle n_u n_x\rangle_s + c_s\Delta\langle n_u n_x\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u n_y\rangle_s &= \lambda\alpha_s\langle n_y\rangle_s + \sigma\beta\langle n_u(n_u-1)\rangle_s + \beta\langle n_u n_w\rangle_s - (\beta+\gamma)\langle n_u n_y\rangle_s + c_s\Delta\langle n_u n_y\rangle \\
\frac{\mathrm{d}}{\mathrm{d}t}\langle n_w n_y\rangle_s &= (1-\lambda)\alpha_s\langle n_y\rangle_s + \sigma\beta\langle n_u n_w\rangle_s + \beta\langle n_w(n_w-1)\rangle_s - (\beta+\gamma)\langle n_w n_y\rangle_s + c_s\Delta\langle n_w n_y\rangle
\end{aligned}$$

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_u(n_u-1)\rangle_s = \sum_s p_s\Big(2\lambda\alpha_s\langle n_u\rangle_s - 2\beta\langle n_u(n_u-1)\rangle_s + c_s\Delta\langle n_u(n_u-1)\rangle\Big)\\
\Rightarrow\ &\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u(n_u-1)\rangle = 2\lambda\alpha_I\frac{a}{a+b}\langle n_u\rangle_I + 2\lambda\alpha_A\frac{b}{a+b}\langle n_u\rangle_A - 2\beta\langle n_u(n_u-1)\rangle\\
\Rightarrow\ &\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u(n_u-1)\rangle = 2\lambda\overline{\alpha\langle n_u\rangle} - 2\beta\langle n_u(n_u-1)\rangle}
\end{aligned}$$

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_x(n_x-1)\rangle_s = \sum_s p_s\Big(2\beta(1-\sigma)\langle n_u n_x\rangle_s - 2\gamma\langle n_x(n_x-1)\rangle_s + c_s\Delta\langle n_x(n_x-1)\rangle\Big)\\
\Rightarrow\ &\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_x(n_x-1)\rangle = 2\beta(1-\sigma)\langle n_u n_x\rangle - 2\gamma\langle n_x(n_x-1)\rangle}
\end{aligned}$$

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_w(n_w-1)\rangle_s = \sum_s p_s\Big(2(1-\lambda)\alpha_s\langle n_w\rangle_s - 2\beta\langle n_w(n_w-1)\rangle_s + c_s\Delta\langle n_w(n_w-1)\rangle\Big)\\
\Rightarrow\ &\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_w(n_w-1)\rangle = 2(1-\lambda)\overline{\alpha\langle n_w\rangle} - 2\beta\langle n_w(n_w-1)\rangle}
\end{aligned}$$

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_y(n_y-1)\rangle_s = \sum_s p_s\Big(2\sigma\beta\langle n_u n_y\rangle_s + 2\beta\langle n_w n_y\rangle_s - 2\gamma\langle n_y(n_y-1)\rangle_s + c_s\Delta\langle n_y(n_y-1)\rangle\Big)\\
\Rightarrow\ &\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_y(n_y-1)\rangle = 2\sigma\beta\langle n_u n_y\rangle + 2\beta\langle n_w n_y\rangle - 2\gamma\langle n_y(n_y-1)\rangle}
\end{aligned}$$

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_u n_w\rangle_s = \sum_s p_s\Big(\lambda\alpha_s\langle n_w\rangle_s + (1-\lambda)\alpha_s\langle n_u\rangle_s - 2\beta\langle n_u n_w\rangle_s + c_s\Delta\langle n_u n_w\rangle\Big)\\
\Rightarrow\ &\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u n_w\rangle = \lambda\overline{\alpha\langle n_w\rangle} + (1-\lambda)\overline{\alpha\langle n_u\rangle} - 2\beta\langle n_u n_w\rangle}
\end{aligned}$$

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_u n_x\rangle_s = \sum_s p_s\Big(\lambda\alpha_s\langle n_x\rangle_s + \beta(1-\sigma)\langle n_u(n_u-1)\rangle_s - (\beta+\gamma)\langle n_u n_x\rangle_s + c_s\Delta\langle n_u n_x\rangle\Big)\\
\Rightarrow\ &\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u n_x\rangle = \lambda\overline{\alpha\langle n_x\rangle} + \beta(1-\sigma)\langle n_u(n_u-1)\rangle - (\beta+\gamma)\langle n_u n_x\rangle}
\end{aligned}$$

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_u n_y\rangle_s = \sum_s p_s\Big(\lambda\alpha_s\langle n_y\rangle_s + \sigma\beta\langle n_u(n_u-1)\rangle_s + \beta\langle n_u n_w\rangle_s - (\beta+\gamma)\langle n_u n_y\rangle_s + c_s\Delta\langle n_u n_y\rangle\Big)\\
\Rightarrow\ &\boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_u n_y\rangle = \lambda\overline{\alpha\langle n_y\rangle} + \sigma\beta\langle n_u(n_u-1)\rangle + \beta\langle n_u n_w\rangle - (\beta+\gamma)\langle n_u n_y\rangle}
\end{aligned}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{s\in\{I,A\}} p_s\langle n_w n_y\rangle_s = \sum_s p_s\Big((1-\lambda)\alpha_s\langle n_y\rangle_s + \sigma\beta\langle n_u n_w\rangle_s + \beta\langle n_w(n_w-1)\rangle_s - (\beta+\gamma)\langle n_w n_y\rangle_s + c_s\Delta\langle n_w n_y\rangle\Big)$$

$$\Rightarrow \boxed{\frac{\mathrm{d}}{\mathrm{d}t}\langle n_w n_y\rangle = (1-\lambda)\overline{\alpha\langle n_y\rangle} + \sigma\beta\langle n_u n_w\rangle + \beta\langle n_w(n_w-1)\rangle - (\beta+\gamma)\langle n_w n_y\rangle}$$

3 Matrix Form

Let,

$$\begin{aligned}
\vec{u} &= \Big[\langle n_u\rangle_A, \langle n_u\rangle_I, \langle n_w\rangle_A, \langle n_w\rangle_I\Big]^{\mathsf{T}}, \\
\vec{x} &= \Big[\langle n_x\rangle_A, \langle n_x\rangle_I, \langle n_y\rangle_A, \langle n_y\rangle_I\Big]^{\mathsf{T}}, \\
\vec{v} &= \Big[\Big\langle(n_u-1)n_u\Big\rangle, \Big\langle(n_w-1)n_w\Big\rangle, \Big\langle(n_x-1)n_x\Big\rangle, \Big\langle(n_y-1)n_y\Big\rangle\Big]^{\mathsf{T}}, \\
\vec{c} &= \Big[\langle n_u n_w\rangle, \langle n_u n_x\rangle, \langle n_u n_y\rangle, \langle n_w n_y\rangle\Big]^{\mathsf{T}}
\end{aligned}$$

Then the moment equations can be written in the following matrix form:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix}\vec{u}\\ \vec{x}\\ \vec{v}\\ \vec{x}\end{bmatrix} = \begin{bmatrix}\boldsymbol{E}_1 & \boldsymbol{O} & \boldsymbol{O} & \boldsymbol{O}\\ \boldsymbol{F}_{21} & \boldsymbol{E}_2 & \boldsymbol{O} & \boldsymbol{O}\\ \boldsymbol{F}_{31} & \boldsymbol{O} & \boldsymbol{E}_3 & \boldsymbol{F}_{34}\\ \boldsymbol{F}_{41} & \boldsymbol{F}_{42} & \boldsymbol{F}_{43} & \boldsymbol{E}_4\end{bmatrix}\begin{bmatrix}\vec{u}\\ \vec{x}\\ \vec{v}\\ \vec{x}\end{bmatrix} + \begin{bmatrix}\vec{p}\\ \vec{0}\\ \vec{0}\\ \vec{0}\end{bmatrix}$$

$$\Rightarrow \frac{\mathrm{d}}{\mathrm{d}t}\vec{y} = \boldsymbol{K}\vec{y} + \vec{b}$$

Where $\boldsymbol{O}$ is a 4-by-4 zero matrix and $\vec{0}$ a 4-dimensional zero vector. $\vec{p}$ is the vector accounting for the production of mRNA by the promoter:

$$\vec{p} = \begin{bmatrix}\lambda\alpha_A\\ \lambda\alpha_I\\ (1-\lambda)\alpha_A\\ (1-\lambda)\alpha_I\end{bmatrix}$$

and the diagonal blocks:

$$\boldsymbol{E}_1 = \begin{bmatrix} -\beta - a & a & 0 & 0 \\ b & -\beta - b & 0 & 0 \\ 0 & 0 & -\beta - a & a \\ 0 & 0 & b & -\beta - b \end{bmatrix}$$

$$\boldsymbol{E}_2 = \begin{bmatrix} -\gamma - a & a & 0 & 0 \\ b & -\gamma - b & 0 & 0 \\ 0 & 0 & -\gamma - a & a \\ 0 & 0 & b & -\gamma - b \end{bmatrix}$$

$$\boldsymbol{E}_3 = \begin{bmatrix} -2\beta & 0 & 0 & 0 \\ 0 & -2\beta & 0 & 0 \\ 0 & 0 & -2\gamma & 0 \\ 0 & 0 & 0 & -2\gamma \end{bmatrix}$$

$$\boldsymbol{E}_4 = \begin{bmatrix} -2\beta & 0 & 0 & 0 \\ 0 & -\beta - \gamma & 0 & 0 \\ \beta & 0 & -\beta - \gamma & 0 \\ \sigma\beta & 0 & 0 & -\beta - \gamma \end{bmatrix}$$

The off-diagonal blocks are:

$$\boldsymbol{F}_{21} = \begin{bmatrix} (1-\sigma)\beta & 0 & 0 & 0 \\ 0 & (1-\sigma)\beta & 0 & 0 \\ \sigma\beta & 0 & \beta & 0 \\ 0 & \sigma\beta & 0 & \beta \end{bmatrix}$$

$$\boldsymbol{F}_{31} = \begin{bmatrix} \frac{2\lambda\alpha_A b}{a+b} & \frac{2\lambda\alpha_I a}{a+b} & 0 & 0 \\ 0 & 0 & \frac{2(1-\lambda)\alpha_A b}{a+b} & \frac{2(1-\lambda)\alpha_I a}{a+b} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\boldsymbol{F}_{34} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 2(1-\sigma)\beta & 0 & 0 \\ 0 & 0 & 2\sigma\beta & 2\beta \end{bmatrix}$$

$$\boldsymbol{F}_{41} = \begin{bmatrix} \frac{(1-\lambda)\alpha_A b}{a+b} & \frac{(1-\lambda)\alpha_I a}{a+b} & \frac{\lambda\alpha_A b}{a+b} & \frac{\lambda\alpha_I a}{a+b} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\boldsymbol{F}_{42} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ \frac{\lambda\alpha_A b}{a+b} & \frac{\lambda\alpha_I a}{a+b} & 0 & 0 \\ 0 & 0 & \frac{\lambda\alpha_A b}{a+b} & \frac{\lambda\alpha_I a}{a+b} \\ 0 & 0 & \frac{(1-\lambda)\alpha_A b}{a+b} & \frac{(1-\lambda)\alpha_I a}{a+b} \end{bmatrix}$$

$$\boldsymbol{F}_{43} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ (1-\sigma)\beta & 0 & 0 & 0 \\ \sigma\beta & 0 & 0 & 0 \\ 0 & \beta & 0 & 0 \end{bmatrix}$$

With this representation, we could first solve for the steady state:

$$\vec{y}_{ss} = -\boldsymbol{K}^{-1}\vec{b}$$

This comes with the requirement that $\boldsymbol{K}$ has to be invertible – and it should be; otherwise it means the system is at a bifurcation point. Now we could do the following transform:

$$\tilde{\boldsymbol{y}} = \vec{y} - \vec{y}_{ss}$$

so that the differential equations become homogeneous:

$$\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\vec{y} = \boldsymbol{K}\vec{y} + \vec{b} \\
\Rightarrow\ &\frac{\mathrm{d}}{\mathrm{d}t}\Big(\tilde{\boldsymbol{y}} + \vec{y}_{ss}\Big) = \boldsymbol{K}\Big(\tilde{\boldsymbol{y}} + \vec{y}_{ss}\Big) + \vec{b} \\
\Rightarrow\ &\frac{\mathrm{d}}{\mathrm{d}t}\tilde{\boldsymbol{y}} = \boldsymbol{K}\tilde{\boldsymbol{y}} - \boldsymbol{K}\boldsymbol{K}^{-1}\vec{b} + \vec{b} \\
\Rightarrow\ &\frac{\mathrm{d}}{\mathrm{d}t}\tilde{\boldsymbol{y}} = \boldsymbol{K}\tilde{\boldsymbol{y}}
\end{aligned}$$

Given initial condition $\tilde{\boldsymbol{y}}_0$ at $t = t_0$, the solution to the above equation is:

$$\begin{aligned}
&\tilde{\boldsymbol{y}} = e^{\boldsymbol{K}(t-t_0)}\tilde{\boldsymbol{y}}_0 \\
\Rightarrow\ &\tilde{\boldsymbol{y}} = \boldsymbol{U}e^{\boldsymbol{D}(t-t_0)}\boldsymbol{U}^{-1}\tilde{\boldsymbol{y}}_0
\end{aligned}$$

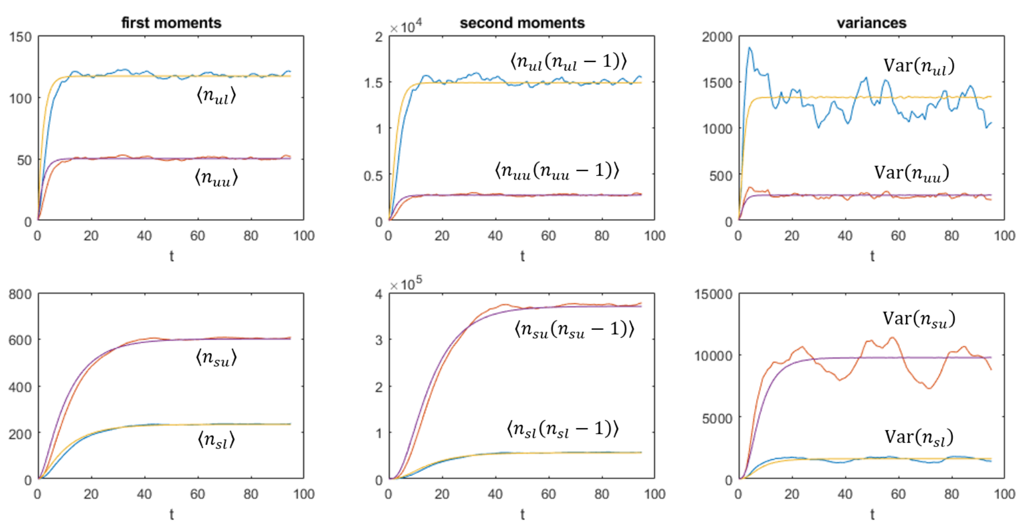
Transform back to $\vec{y}$:

$$\begin{aligned}
&\vec{y} - \vec{y}_{ss} = \boldsymbol{U}e^{\boldsymbol{D}(t-t_0)}\boldsymbol{U}^{-1}\Big(\vec{y}_0 - \vec{y}_{ss}\Big) \\
\Rightarrow\ &\vec{y} = \boldsymbol{U}e^{\boldsymbol{D}(t-t_0)}\boldsymbol{U}^{-1}\Big(\vec{y}_0 + \boldsymbol{K}^{-1}\vec{b}\Big) - \boldsymbol{K}^{-1}\vec{b}
\end{aligned}$$

4 Simulation

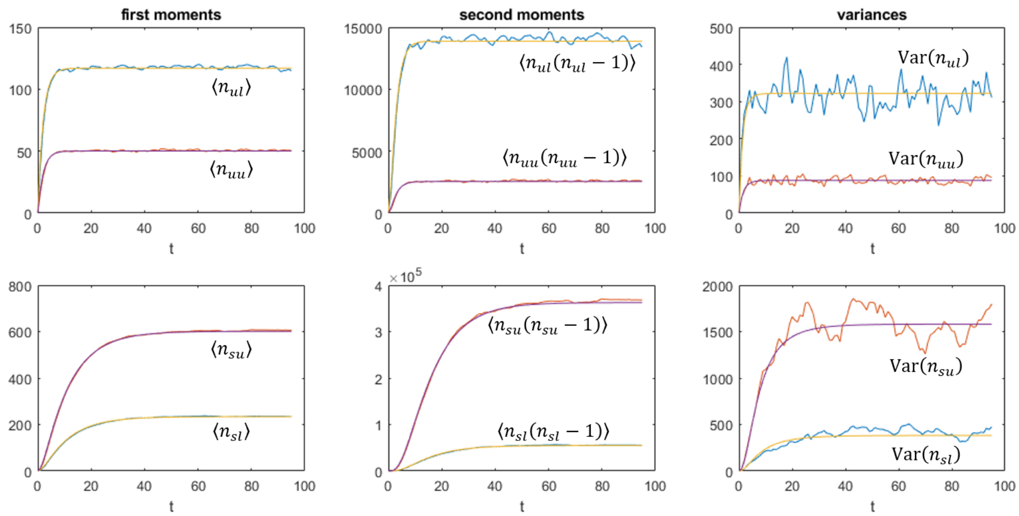
Under the slow promoter switching condition:

$$\begin{aligned}
&a = 0.1, b = 0.5, \\
&\lambda = 0.7, \alpha_A = 100, \alpha_I = 1, \\
&\sigma = 0.6, \beta = 0.5, \gamma = 0.1.
\end{aligned}$$



Under the fast promoter switching condition:

$$
\begin{aligned}
&a = 1, b = 5, \\
&\lambda = 0.7, \alpha_A = 100, \alpha_I = 1, \\
&\sigma = 0.6, \beta = 0.5, \gamma = 0.1.
\end{aligned}
$$



5 Appendix: Moment Generating Function

The moment generating function is defined as:

$$F(z_a, z_b, t) = \sum_{n_a} \sum_{n_b} z_a^{n_a} z_b^{n_b} P(n_a, n_b, t)$$

It has the following properties:

$$F(z_a, z_b)\Big|_{z_a=1, z_b=1} = 1 \tag{5}$$

$$\frac{\partial}{\partial z_a} F(z_a, z_b)\Big|_{z_a=1, z_b=1} = \langle n_a \rangle \tag{6}$$

$$\frac{\partial^2}{\partial z_a^2} F(z_a, z_b)\Big|_{z_a=1, z_b=1} = \langle n_a(n_a - 1) \rangle \tag{7}$$

$$\frac{\partial^2}{\partial z_a \partial z_b} F(z_a, z_b)\Big|_{z_a=1, z_b=1} = \langle n_a n_b \rangle \tag{8}$$

and,

$$\begin{aligned}
\sum_{n_a}\sum_{n_b} z_a^{n_a} z_b^{n_b} P_1(n_a-1,n_b) &= z_a \sum_{n_a}\sum_{n_b} z_a^{n_a-1} z_b^{n_b} P(n_a-1,n_b) \\
&= z_a \sum_{n'_a=-1}\sum_{n_b} z_a^{n'_a} z_b^{n_b} P(n'_a,n_b) \\
&= z_a \sum_{n'_a=0}\sum_{n_b} z_a^{n'_a} z_b^{n_b} P(n'_a,n_b) \\
&= z_a F(z_a,z_b)
\end{aligned}$$

where I used the fact that $P(n_a<0,n_b)=0$. Also:

$$\begin{aligned}
\sum_{n_a}\sum_{n_b} n_a z_a^{n_a} z_b^{n_b} P(n_a,n_b) &= z_a \sum_{n_a}\sum_{n_b} n_a z_a^{n_a-1} z_b^{n_b} P(n_a,n_b) \\
&= z_a \frac{\partial F}{\partial z_a}
\end{aligned}$$

$$\begin{aligned}
\sum_{n_a}\sum_{n_b} (n_a+1) z_a^{n_a} z_b^{n_b} P(n_a+1,n_b) &= \sum_{n'_a=1}\sum_{n_b} n'_a z_a^{n'_a-1} z_b^{n_b} P(n'_a,n_b) \\
&\approx \frac{\partial F}{\partial z_a}
\end{aligned}$$

$$\begin{aligned}
\sum_{n_a}\sum_{n_b}\sum_{n_f} n_f z_a^{n_a} z_b^{n_b} z_f^{n_f} P(n_a-1,n_b,n_f) &= z_a z_f \sum_{n_a}\sum_{n_b}\sum_{n_f} z_a^{n_a-1} z_b^{n_b} n_f z_f^{n_f-1} P(n_a-1,n_b,n_f) \\
&= z_a z_f \sum_{n'_a}\sum_{n_b}\sum_{n_f} z_a^{n'_a} z_b^{n_b} n_f z_f^{n_f-1} P(n'_a,n_b,n_f) \\
&= z_a z_f \frac{\partial F}{\partial z_f}
\end{aligned}$$

$$\begin{aligned}
\sum_{n_a}\sum_{n_b} (n_a+1) z_a^{n_a} z_b^{n_b} P(n_a+1,n_b-1) &= z_b \sum_{n'_a=1}\sum_{n'_b=-1} n'_a z_a^{n'_a-1} z_b^{n'_b} P(n'_a,n'_b) \\
&\approx z_b \frac{\partial F}{\partial z_a}
\end{aligned}$$