Appendix A : Protein variability for constant transcription

$$m \xrightarrow{\lambda} m+1 \qquad (m,c) \xrightarrow{\delta m} (m-1,\, c+1) \qquad c \xrightarrow{\varphi c} c-1 \qquad p \xrightarrow{\alpha m} p+1$$

$$m \xrightarrow{\beta_m m} m-1 \qquad (m,c) \xrightarrow{\gamma c} (m+1,\, c-1) \qquad p \xrightarrow{\beta_p p} p-1$$

The standard linear noise approach is described in detail in [2].

Note that in this article the authors defined $M_{ij} = \frac{\langle x_j \rangle}{\langle x_i \rangle} K_{ij}$ instead of $M_{ij} = -\frac{\langle x_j \rangle}{\langle x_i \rangle} K_{ij}$ in [2].

Now we have

$$\hat{K} = \begin{pmatrix} -\beta_m - \delta & \gamma & 0 \\ \delta & -(\gamma+\varphi) & 0 \\ \alpha & 0 & -\beta_p \end{pmatrix} \xrightarrow[\text{with flux balance}]{\text{normalize}} \hat{M} = \begin{pmatrix} -\frac{1}{\tau_m} & \frac{R}{\tau_m} & 0 \\ \frac{1}{\tau_c} & -\frac{1}{\tau_c} & 0 \\ \frac{1}{\tau_p} & 0 & -\frac{1}{\tau_p} \end{pmatrix} \quad (25)$$

$$D_{ij} = \frac{\sum_k S_i^k S_j^k r_k(\vec{x})}{\langle x_i \rangle \langle x_j \rangle}$$

$$\hat{D} = \begin{pmatrix} \frac{2}{\tau_m \langle m \rangle} & -\frac{R}{\tau_m \langle c \rangle} - \frac{1}{\tau_c \langle m \rangle} & 0 \\ -\frac{R}{\tau_m \langle c \rangle} - \frac{1}{\tau_c \langle m \rangle} & \frac{2}{\tau_c \langle c \rangle} & 0 \\ 0 & 0 & \frac{2}{\tau_p \langle p \rangle} \end{pmatrix} \quad (25)$$

$$\eta_{ij} = \frac{\mathrm{Cov}(x_i, x_j)}{\langle x_i \rangle \langle x_j \rangle}$$

Lyapunov equation $\hat{M}\hat{\eta} + \hat{\eta}\hat{M}^T + \hat{D} = \hat{0}$ (24)

Plug (25) into (24), we can get (26).

A.2 mRNA autocorrelations

$$A_{ij}(t) = \frac{\langle x_i(t)\, x_j(0) \rangle - \langle x_i(t) \rangle \langle x_j(0) \rangle}{\langle x_i \rangle \langle x_j \rangle}$$

Note that $A_{ij}(t)$ is normalized, where $x_i = x_j = m \Rightarrow A_{mm}(t)$.

In Eq.(30), $A_m(t) = \frac{\langle m(0)m(t) \rangle - \langle m \rangle^2}{\mathrm{Var}(m)}$ is not my $A_{mm}(t)$!

$$\frac{\partial}{\partial t} \hat{A}(t) = \hat{M}\hat{A}(t), \quad \hat{A}(t) = \hat{\eta}\, \mathrm{Exp}(\hat{M}t)$$

$$\frac{\partial}{\partial t} \begin{pmatrix} A_{mm}(t) & A_{mc}(t) & A_{mp}(t) \\ A_{cm}(t) & A_{cc}(t) & A_{cp}(t) \\ A_{pm}(t) & A_{pc}(t) & A_{pp}(t) \end{pmatrix} = \begin{pmatrix} -\frac{1}{\tau_m} & \frac{R}{\tau_m} & 0 \\ \frac{1}{\tau_c} & -\frac{1}{\tau_c} & 0 \\ \frac{1}{\tau_p} & 0 & -\frac{1}{\tau_p} \end{pmatrix} \begin{pmatrix} A_{mm}(t) & A_{mc}(t) & A_{mp}(t) \\ A_{cm}(t) & A_{cc}(t) & A_{cp}(t) \\ A_{pm}(t) & A_{pc}(t) & A_{pp}(t) \end{pmatrix}$$

$$\frac{d}{dt} A_{pm}(t) = \frac{1}{\tau_p} A_{mm}(t) - \frac{1}{\tau_p} A_{pm}(t)$$

Denote the linear relationship $A_{mp}(t) = \mathbb{L}_1[A_{mm}(t)]$

Use linear response, if $A_{mp}(t) = \int_{-\infty}^{t} A_{mm}(t')\, \mathrm{Imp}_{(A)}(t-t')\, dt'$, then $\mathrm{Imp}_{(A)}(t) = \mathbb{L}_1[\delta(t)]$.

Take $t=0$, we get

Note that $\mathrm{Imp}_{(A)}(t) = 0$ when $t<0$.

$$\begin{aligned} \eta_{mp} &= \int_{-\infty}^{0} A_{mm}(t')\, \mathrm{Imp}_{(A)}(-t')\, dt' \\ &= \int_0^{\infty} A_{mm}(-t')\, \mathrm{Imp}_{(A)}(t')\, dt' \\ &= \int_0^{\infty} A_{mm}(t')\, \mathrm{Imp}_{(A)}(t')\, dt' \quad (\text{stationary}) \quad (30) \end{aligned}$$

Solve $I_{mp(A)}(t)$.

$$\frac{d}{dt} I_{mp(A)}(t) = \frac{1}{\tau_p} \delta(t) - \frac{1}{\tau_p} I_{mp(A)}(t).$$

For $t>0$, we have $I_{mp(A)}(t) = C_0 e^{-\frac{t_p}{\tau_p}}$, where C_0 should be determined below.

Take $\varepsilon>0$ and $\varepsilon \to 0$, integrate from $-\varepsilon$ to ε.

$$I_{mp(A)}(\varepsilon) - I_{mp(A)}(-\varepsilon) = \frac{1}{\tau_p} - \frac{1}{\tau_p} \int_{-\varepsilon}^{\varepsilon} I_{mp(A)}(t)\, dt$$

From causality, $I_{mp(A)}(t)=0$ for $t<0$. $I_{mp(A)}$ doesn't diverge.

$I_{mp(A)}(\varepsilon) - 0 = \frac{1}{\tau_p} - 0 \Rightarrow I_{mp(A)}(\varepsilon) = \frac{1}{\tau_p} \Rightarrow C_0 = \frac{1}{\tau_p}$, that is, $I_{mp(A)}(t) = \frac{1}{\tau_p} e^{-\frac{t}{\tau_p}}$ for $t>0$.

$$\frac{\mathrm{Cov}(m,p)}{\langle m\rangle\langle p\rangle} = \int_0^\infty \frac{\langle m(0)m(t')\rangle - \langle m\rangle^2}{\langle m\rangle^2} I_{mp(A)}(t')\, dt'$$

In (30), $I(t) = \frac{\langle p\rangle}{\langle m\rangle} I_{mp(A)}(t) = \frac{\langle p\rangle}{\langle m\rangle} \frac{e^{-\frac{t}{\tau_p}}}{\tau_p}$ As (33).

To explain (34), Since we have $\hat{A}(t) = \hat{\eta}\, \mathrm{Exp}(\hat{M} t)$

Diagonalize $\hat{M} = \hat{P}^{-1}\hat{\Lambda}\hat{P}$, $\hat{\Lambda} = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}$, where $\lambda_1, \lambda_2, \lambda_3$ are eigenvalues of $\hat{M}$.

$\hat{A}(t) = \hat{\eta}\hat{P}^{-1}\mathrm{Exp}(\hat{\Lambda}t)\hat{P} = \hat{\eta}\hat{P}^{-1}\begin{pmatrix} e^{\lambda_1 t} & 0 & 0 \\ 0 & e^{\lambda_2 t} & 0 \\ 0 & 0 & e^{\lambda_3 t} \end{pmatrix}\hat{P}$. The weird μ_1 & μ_2 in (36) are just two of those eigenvalues of $\hat{M}$.

Appendix C: Protein variability with periodic upstream transcription rates

I only show the case without mRNA interactions.

$$m \xrightarrow{\lambda z(t)} m+1 \qquad p \xrightarrow{\alpha m} p+1$$
$$m \xrightarrow{\beta_m m} m-1 \qquad p \xrightarrow{\beta_p p} p-1$$

where $z(t) = A[1+\sin(\omega t)]$

Denote the time-dependent ensemble averages conditioned on the history of $z(t)$.

$\tilde{m}(t) := \langle m | z[-\infty, t]\rangle$,

$\tilde{p}(t) := \langle p | z[-\infty, t]\rangle$,

$$\lim_{T\to\infty} \frac{1}{T}\int_0^T \frac{d\tilde{m}(t)}{dt} dt = \lambda\langle z\rangle - \beta_m\langle m\rangle$$

$$\langle m\rangle = \frac{\lambda}{\beta_m}\langle z\rangle = \lambda\tau_m\langle z\rangle$$

$\frac{d\tilde{m}(t)}{dt} = \lambda z(t) - \beta_m \tilde{m}(t) \Rightarrow \tilde{m}(t) = \mathbb{L}_2[z(t)]$. Linear Respond: If $\tilde{m}(t) = \int_{-\infty}^{t} z(t') I_{zm}(t-t')\, dt'$,

then $I_{zm}(t) = \mathbb{L}_2[\delta(t)]$.

$$\frac{d\tilde{p}(t)}{dt} = \alpha\tilde{m}(t) - \beta_p(t)\tilde{p}(t)$$

Denote the unsynchronized ensemble averages and (co)variances as

↳ time-averaged time dependent ensemble averages and (co)variances

$\langle m\rangle = \frac{1}{T}\lim_{T\to\infty}\int_0^T \tilde{m}(t)dt$, $\langle p\rangle$, $\mathrm{Var}(m)$, $\mathrm{Var}(p)$, $\mathrm{Cov}(m,p)$

Time-averaged signal

$$\langle z\rangle = \lim_{T\to\infty}\frac{1}{T}\int_0^T z(t)\,dt = A$$

$$\mathrm{Var}(z) = \lim_{T\to\infty}\frac{1}{T}\int_0^T \underbrace{\left(z^2(t) - \langle z\rangle^2\right)}_{A^2\sin^2(\omega t)} dt = \frac{A^2}{2}$$

Solve $I_{zm}(t)$ for $t>0$.

$$\frac{d}{dt} I_{zm}(t) = \lambda \delta(t) - \beta_m I_{zm}(t)$$

$I_{zm}(t) = C_0 e^{-\beta_m t}$, where C_0 to be determined.

Take $\varepsilon>0$ and $\varepsilon \to 0$, integrate from $-\varepsilon$ to ε.

$$I_{zm}(\varepsilon) - I_{zm}(-\varepsilon) = \lambda - \beta_m \int_{-\varepsilon}^{\varepsilon} I_{zm}(t)\, dt$$

$$I_{zm}(\varepsilon) - 0 = \lambda - 0 \Rightarrow C_0 = \lambda \Rightarrow I_{zm}(t) = \lambda e^{-\beta_m t} \text{ for } t>0.$$

Then solve for $Cov(m,z)$.

$$\tilde{m}(t) = \int_{-\infty}^{t} z(t')\, I_{zm}(t-t')\, dt'$$

$$\tilde{m}(t)\, z(t) = \int_{-\infty}^{t} z(t')\, z(t)\, I_{zm}(t-t')\, dt'$$

$$\begin{aligned}
\tilde{m}(t)\, z(t) - \langle z\rangle^2 &= \int_{-\infty}^{t} \left(z(t')z(t) - \langle z\rangle^2\right) I_{zm}(t-t')\, dt' \\
&= \int_{-\infty}^{t} \left(A^2 \sin(\omega t')\sin(\omega t) - A^2\right) I_{zm}(t-t')\, dt' \\
&= \int_{-\infty}^{t} A^2 \left(\sin(\omega t')\sin(\omega t) + \sin(\omega t') + \sin(\omega t)\right) I_{zm}(t-t')\, dt' \\
&\overset{\tau = t-t'}{=} + \int_{0}^{+\infty} A^2 \left(\sin(\omega(t-\tau))\sin(\omega t) + \sin(\omega(t-\tau)) + \sin(\omega t)\right) I_{zm}(\tau)\, d\tau \\
&= \lambda A^2 \int_{0}^{+\infty} \left(\sin(\omega(t-\tau))\sin(\omega t) + \sin(\omega(t-\tau)) + \sin(\omega t)\right) e^{-\beta_m \tau}\, d\tau \\
&= \lambda A^2 \frac{\beta_m}{\beta_m^2 + \omega^2} \sin^2(\omega t) - \frac{\beta_m}{\beta^2+\omega^2} \sin \omega(t-\tau') \Big|_{\tau'=0}^{+\infty}
\end{aligned}$$

$$\begin{aligned}
Cov(m,z) &= \lim_{T\to\infty} \frac{1}{T} \int_0^T \left(\tilde{m}(t)z(t) - \langle z\rangle^2\right) dt \\
&= \lambda A^2 \frac{\beta_m}{\beta_m^2+\omega^2} \frac{1}{T} \lim_{T\to\infty} \left(\int_0^T \sin^2(\omega t)\, dt - \text{finite}\right) = \lambda A^2 \frac{\beta_m}{\beta_m^2+\omega^2} \frac{1}{2}
\end{aligned}$$

$$\eta_{mz} = \frac{Cov(m,z)}{\langle m\rangle \langle z\rangle} = \frac{\beta_m}{\lambda A^2} Cov(m,z) = \frac{1}{2} \frac{\beta_m^2}{\beta_m^2+\omega^2}$$

$$= \frac{1}{2} \frac{1}{1+\omega^2 \tau_m^2} \quad (58)$$