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 $x_i = x_j = m \Rightarrow A_{mm}(t)$.

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

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

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

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

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

Take $t=0$, we get Note that $I_{mp(A)}(t) = 0$ when $t<0$.

$$\eta_{mp} = \int_{-\infty}^{0} A_{mm}(t')\, I_{mp(A)}(-t')\, dt'$$
$$= \int_0^{\infty} A_{mm}(-t')\, I_{mp(A)}(t')\, dt'$$
$$= \int_0^{\infty} A_{mm}(t')\, I_{mp(A)}(t')\, dt' \quad \text{(stationary)} \quad (30)$$

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

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

Oh nein. Schade. There is $\delta(t)$ in this ODE... Non ti preoccupare, let's use Laplace Transform.

$$\mathcal{L}[f(t)] = \int_0^{\infty} f(t) e^{-st} dt := \bar{f}(s)$$

$$s \bar{I}_{mp(A)}(s) - 0 = \frac{1}{\tau_p} \cdot 1 - \frac{1}{\tau_p} \bar{I}_{mp(A)}(s)$$

$$\bar{I}_{mp(A)}(s) = \frac{\beta_p}{s+\beta_p}$$

Look up the $\mathcal{L}^{-1}[\bar{f}(s)]$ form, we get $I_{mp(A)}(t) = \frac{1}{\tau_p} e^{-\frac{t}{\tau_p}}$

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

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 $\hat{A}(t) = \hat{\eta}\, Exp(\hat{M}t)$

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 $\hat{M}$.

$\hat{A}(t) = \hat{\eta} \hat{P}^{-1} Exp(\hat{\Lambda}t) \hat{P} = \hat{\eta} \hat{P}^{-1} \begin{pmatrix} e^{\lambda_1 t} & 0 & 0 \\ 0 & e^{\lambda_2 t} & 0 \\ 0 & 0 & e^{\lambda_3 t} \end{pmatrix} \hat{P}$. 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.

$m \xrightarrow{\lambda z(t)} m+1 \quad p \xrightarrow{\alpha m} p+1$

$m \xrightarrow{\beta_m m} m-1 \quad p \xrightarrow{\beta_p p} p-1$ 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 <u>the unsynchronized ensemble averages and (co) variances</u> as

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

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

Time-averaged signal

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

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

Again, use Laplace Transform to solve $I_{zm}(t)$.

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

$$s \bar{I}_{zm}(s) = \lambda - \beta_m \bar{I}_{zm}(s)$$

$$\bar{I}_{zm}(s) = \frac{\lambda}{s+\beta_m}$$

$$I_{zm}(t) = \lambda e^{-\beta_m t}$$

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

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

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

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

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

$$\begin{aligned}
\eta_{mz} &= \frac{Cov(m,z)}{\langle m \rangle \langle z \rangle} = \frac{\beta_m}{\lambda A^2} Cov(m,z) = \frac{1}{2} \frac{\beta_m^2}{\beta_m^2 + w^2} \\
&= \frac{1}{2} \frac{1}{1 + w^2 \tau_m^2} \qquad (58)
\end{aligned}$$