

Transient Changes in Intercellular Protein Variability Identify Sources of Noise in Gene Expression

Abhyudai Singh^{1,*}

¹Department of Electrical and Computer Engineering, Department of Biomedical Engineering, and Department of Mathematical Sciences, Center for Bioinformatics and Computational Biology, University of Delaware, Newark, Delaware

Form of functions $\theta(z_1, z_2, m, p)$ and $\delta(z_1, z_2, m, p)$

$$\begin{aligned}
\theta(z_1, z_2, m, p) &= \sum_{i=0}^{\infty} k_1 \alpha_{1i} [\varphi(z_1 + i, z_2, m, p) - \varphi(z_1, z_2, m, p)] \\
&+ \gamma_1 z_1 [\varphi(z_1 - 1, z_2, m, p) - \varphi(z_1, z_2, m, p)] \\
&+ \sum_{i=0}^{\infty} k_2 \alpha_{2i} [\varphi(z_1, z_2 + i, m, p) - \varphi(z_1, z_2, m, p)] \\
&+ \gamma_2 z_2 [\varphi(z_1, z_2 - 1, m, p) - \varphi(z_1, z_2, m, p)] \\
&+ \sum_{i=0}^{\infty} k_m \alpha_i z_1 [\varphi(z_1, z_2, m + i, p) - \varphi(z_1, z_2, m, p)] \\
&+ \gamma_m m [\varphi(z_1, z_2, m - 1, p) - \varphi(z_1, z_2, m, p)] \\
&+ k_p m z_2 [\varphi(z_1, z_2, m, p + 1) - \varphi(z_1, z_2, m, p)] \\
&+ \gamma_p p [\varphi(z_1, z_2, m, p - 1) - \varphi(z_1, z_2, m, p)].
\end{aligned}$$

$$\begin{aligned}
\delta(z_1, z_2, m, p) &= \sum_{i=0}^{\infty} k_1 \alpha_{1i} [\varphi(z_1 + i, z_2, m, p) - \varphi(z_1, z_2, m, p)] \\
&+ \gamma_1 z_1 [\varphi(z_1 - 1, z_2, m, p) - \varphi(z_1, z_2, m, p)] \\
&+ \sum_{i=0}^{\infty} k_2 \alpha_{2i} [\varphi(z_1, z_2 + i, m, p) - \varphi(z_1, z_2, m, p)] \\
&+ \gamma_2 z_2 [\varphi(z_1, z_2 - 1, m, p) - \varphi(z_1, z_2, m, p)] \\
&+ \frac{\partial \varphi(z_1, z_2, m, p)}{\partial m} (k_m \langle B_m \rangle z_1 - \gamma_m m) \\
&+ \frac{\partial \varphi(z_1, z_2, m, p)}{\partial p} (k_p z_2 m - \gamma_p p)
\end{aligned}$$

The case where fluctuations in transcription and translation rates are dependent

Consider the scenario where time-scale of extrinsic fluctuations is much slower than the mRNA and protein half lives ($\gamma_j \ll \gamma_m, \gamma_p$). In this limit, we can think of z_1 and z_2 as two random variables drawn from a static joint distribution. The mRNA transcription and translation rates are given as $k_m z_1$ and $k_p z_2$, respectively. From Eqs. 2 and 3 in the paper, the steady-state mean protein copy number and its second order uncentered moment conditioned on z_1, z_2 are given as

$$\langle p | z_1, z_2 \rangle = \frac{k_p k_m \langle B_m \rangle z_1 z_2}{\gamma_m \gamma_p} \quad (\text{S.1})$$

$$\langle p^2 | z_1, z_2 \rangle = \langle p | z_1, z_2 \rangle^2 + \langle p | z_1, z_1 \rangle + \frac{B_e \langle p | z_1, z_2 \rangle^2 \gamma_p}{\langle m | z_1, z_2 \rangle (\gamma_p + \gamma_m)} \quad (\text{S.2})$$

where

$$\langle m | z_1, z_2 \rangle = \frac{k_m \langle B_m \rangle z_1}{\gamma_m}. \quad (\text{S.3})$$

Unconditioning on z_1 and z_2 we obtain

$$\langle p \rangle = \frac{k_p k_m \langle B_m \rangle}{\gamma_m \gamma_p} \langle z_1 z_2 \rangle \quad (\text{S.4})$$

$$\langle p^2 \rangle = \left(\frac{k_p k_m \langle B_m \rangle}{\gamma_m \gamma_p} \right)^2 \langle z_1^2 z_2^2 \rangle + \langle p \rangle + \left(\frac{k_p}{\gamma_p} \right)^2 \frac{k_m \langle B_m \rangle B_e \langle z_1 z_2^2 \rangle \gamma_p}{\gamma_m (\gamma_p + \gamma_m)} \quad (\text{S.5})$$

which yields

$$CV_p^2 = CV_I^2 + CV_E^2 \quad (\text{S.6})$$

$$CV_E^2 = \frac{\langle z_1^2 z_2^2 \rangle - \langle z_1 z_2 \rangle^2}{\langle z_1 z_2 \rangle^2} \quad (\text{S.7})$$

$$CV_I^2 = \frac{B_e}{\langle m \rangle} \frac{\langle z_1 z_2^2 \rangle \langle z_1 \rangle}{\langle z_1 z_2 \rangle^2} \frac{\gamma_p}{\gamma_p + \gamma_m} + \frac{1}{\langle p \rangle}, \quad \langle m \rangle = \frac{k_m \langle B_m \rangle}{\gamma_p} \langle z_1 \rangle, \quad (\text{S.8})$$

where CV_p^2 , CV_E^2 and CV_I^2 represent the total, intrinsic and extrinsic noise in protein copy numbers.

Next we consider the case of transcription blockage. Using Eq. 24 with $CV_E^2 = 0$, when mRNA production is stopped the conditioned mean and second order moment evolve as

$$\langle p(t) | z_1, z_2 \rangle = \langle p | z_1, z_2 \rangle \frac{\gamma_p \exp(-\gamma_m t) - \gamma_m \exp(-\gamma_p t)}{\gamma_p - \gamma_m} \quad (\text{S.9})$$

$$\langle p^2(t) | z_1, z_2 \rangle = \langle p | z_1, z_2 \rangle^2 + \langle p | z_1, z_1 \rangle + \frac{B_e \langle p(t) | z_1, z_2 \rangle^2 \gamma_p}{\langle m | z_1, z_2 \rangle (\gamma_p + \gamma_m)} f(B_e, \gamma_m, \gamma_p, t). \quad (\text{S.10})$$

Unconditioning as above results in the protein noise level given by (24) in the paper.