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Supporting Material

Interplay between Intrinsic Noise and the Stochasticity of the Cell Cycle in Bacterial Colonies

Oriol Canela-Xandri, Francesc Sagues, and Javier Buceta

Supplementary Material: Interplay between Intrinsic Noise and the Stochasticity of the Cell Cycle in Bacterial Colonies, by Canela-Xandri et al.

Parameters calibration

Note that if $\Lambda_R = 0$ then protein production equals K. In our modeling, this regime corresponds to the operator at state $O_{\varnothing\varnothing}$ when $\left\langle c_{O_{\varnothing\varnothing}} \right\rangle = \Lambda_O$. Thus, the following must be satisfied,

$$K = \left\langle \dot{c}_P \right\rangle = \left\langle k_P^+ c_{O_{\varnothing\varnothing}} \right\rangle = \left\langle k_P^+ \right\rangle \left\langle c_{O_{\varnothing\varnothing}} \right\rangle = \frac{k_0}{\ln 2} \Lambda_O.$$

By considering one gene copy, $\Lambda_O \simeq 1.1\text{nM}$, then $k_0 \simeq 152.8\,\text{min}^{-1}$. On the other hand, protein production is reduced by half when $\Lambda_R = \beta = 55\text{nM}$. In our modeling this corresponds when $\left\langle c_{O_{\varnothing\varnothing}} \right\rangle = \Lambda_O/2 = 0.55\text{nM}$. In order to use this condition we notice that at time scales of the order of the cell cycle binding-unbinding reactions reach equilibrium (adiabatic elimination). Thus, the following relations hold[1],

$$\begin{aligned}
\mathcal{K}_{R_2} &= \frac{\left\langle c_{R_2} \right\rangle}{\left\langle c_R \right\rangle^2}, \\
\mathcal{K}_{O_{\varnothing *}} &= \frac{\left\langle c_{O_{\varnothing *}} \right\rangle}{\left\langle c_{O_{\varnothing\varnothing}} \right\rangle \left\langle c_{R_2} \right\rangle}, \\
\mathcal{K}_{O_{*\varnothing}} &= \frac{\left\langle c_{O_{*\varnothing}} \right\rangle}{\left\langle c_{O_{\varnothing\varnothing}} \right\rangle \left\langle c_{R_2} \right\rangle}, \\
\mathcal{K}_{O_{**}} &= \frac{\left\langle c_{O_{**}} \right\rangle}{\left\langle c_{O_{\varnothing\varnothing}} \right\rangle \left\langle c_{R_2} \right\rangle^2},
\end{aligned}$$

where $\mathcal{K}_X$ stands for the reaction equilibrium constant. We point out that only $\mathcal{K}_{R_2} \simeq 10^{-1}\text{nM}^{-1}$ has been characterized experimentally. If we further assume that $\mathcal{K}_{O_{\varnothing *}} = \mathcal{K}_{O_{*\varnothing}}$, i.e. a repressor dimmer indistinctly binds to any of the operator sites, and $\mathcal{K}_{O_{**}}/\mathcal{K}_{O_{*\varnothing}} = \alpha \gg \text{nM}^{-1}$, i.e. the two binding sites

[1]Here we assume that when averaging over cell lineages the deterministic description is accurate and correlations can be neglected, e.g. $\langle c_Z^m \rangle \simeq \langle c_Z \rangle^m$.

interact cooperatively favoring the two sites to be occupied at low repressor concentration[2], then the conservations laws for the total concentration of repressor and genetic material can be written as a function of the set of equilibrium constants and the concentrations $\langle c_{O_{\varnothing\varnothing}} \rangle$ and $\langle c_R \rangle$:

$$\Lambda_R = \langle c_R \rangle \left[1 + 2\mathcal{K}_{R_2} \langle c_R \rangle \left(1 + 2\mathcal{K}_{O_{\varnothing *}} \langle c_{O_{\varnothing\varnothing}} \rangle \left(1 + \alpha \mathcal{K}_{R_2} \langle c_R \rangle^2\right)\right)\right], \quad (1)$$
$$\Lambda_O = \langle c_{O_{\varnothing\varnothing}} \rangle \left[1 + \mathcal{K}_{R_2}\mathcal{K}_{O_{\varnothing *}} \langle c_R \rangle^2 \left(2 + \alpha \mathcal{K}_{R_2} \langle c_R \rangle^2\right)\right].$$

By imposing in Eqs.(1) that if $\Lambda_R = \beta = 55\text{nM}$ then $\langle c_{O_{\varnothing\varnothing}} \rangle = \Lambda_O/2 = 0.55\text{nM}$, and that $\mathcal{K}_{O_{**}}/\mathcal{K}_{O_{*\varnothing}} = \alpha$, we are able to obtain the value of the unknown equilibrium constants as a function of α. In our *in silico* experiments we find that an optimal fit to the experimental gene regulatory function is obtained when $\alpha \simeq 10^2 \text{nM}^{-1}$ leading to:

$$\mathcal{K}_{O_{\varnothing *}} = \mathcal{K}_{O_{*\varnothing}} \simeq 2.7 \cdot 10^{-5} \text{nM}^{-1},$$
$$\mathcal{K}_{O_{**}} \simeq 2.7 \cdot 10^{-3} \text{nM}^{-2}.$$

We finally notice that $\mathcal{K}_Z = k_Z^+/k_Z^-$ and that the unbinding rates, k_Z^-, are typically of order $\sim 10^2 \,\text{min}^{-1}$. Thus, by supposing, $k_{R_2}^- \simeq 10^2 \,\text{min}^{-1}$ and $k_{O_{\varnothing *}}^- = k_{O_{*\varnothing}}^- = k_{O_{**}}^- \simeq 6 \cdot 10^2 \,\text{min}^{-1}$, we finally obtain $k_{R_2}^+ \simeq 10 \,\text{min}^{-1}\,\text{nM}^{-1}$, $k_{O_{**}}^+ \simeq 1.6 \,\text{min}^{-1}\,\text{nM}^{-2}$, and $k_{O_{\varnothing *}}^+ = k_{O_{*\varnothing}}^+ \simeq 1.6 \cdot 10^{-2} \,\text{min}^{-1}\,\text{nM}^{-1}$.

Plasmid distribution as a source of noise in the gene regulatory function

Once the model parameters have been calibrated with the experimental results, we perform similar *in silico* protein dilution experiments but considering several copies (plasmids) of our gene of interest encoding for protein P in order to test the effect of plasmid distributions in the noise of the GRF. Thus, we suppose that the initial replicating cell harbors 25 copies ($\Lambda_O \simeq 27.8\text{nM}$): a typical concentration of plasmids due to transformation. In this case we implement the simulations using both the modified Gillespie and the Langevin methods and two different plasmid distribution schemes: equally vs. binomially distributed. Our results show that the fitting parameters coincide for

[2]Note that the ratio between the probabilities of finding either two or one occupied sites of the operator read $\mathcal{P}_{O_{**}}/\mathcal{P}_{O_{*\varnothing}} = \alpha c_{R_2}$.

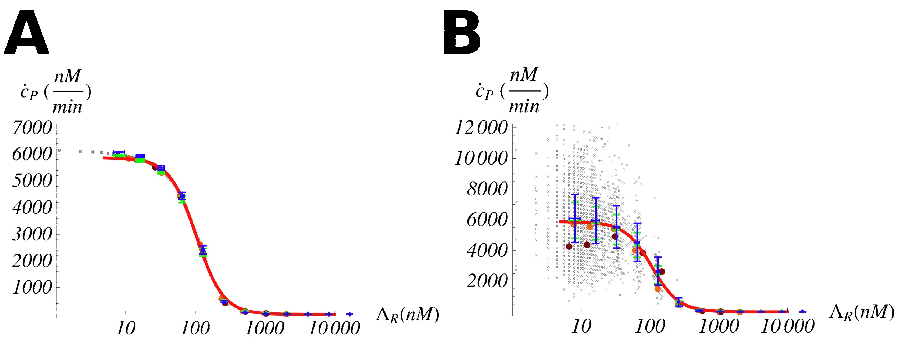

Figure 1: Gene regulatory function in *in silico* dilution experiments. **A:** Gene regulatory function (GRF) for the protein dilution process (25 gene copies equally distributed after division events): individual cells (gray crosses), average among cells (green/blue points with error bars indicate Gillespie/Langevin dynamics) and fit to Hill function (red solid line). The GRF for two cell lineages (orange and brown circles) have been highlighted. **B:** GRF for the protein dilution process when 25 gene copies following a binomial distribution after division is considered. Color and symbol codes as in **A**.

the partition schemes,

$$\text{Equally distributed}: \begin{cases} \hat{K} = (6106 \pm 1)\,\text{nM}/\,\text{min} \\ \hat{\beta} = (102.8 \pm 0.1)\,\text{nM} \\ \hat{n} = 2.034 \pm 0.004 \end{cases}$$

$$\text{Binomially distributed}: \begin{cases} \hat{K} = (6100 \pm 60)\,\text{nM}/\,\text{min} \\ \hat{\beta} = (107 \pm 6)\,\text{nM} \\ \hat{n} = 2.0 \pm 0.2 \end{cases} ,$$

however, the dispersion in the equally distributed case is largely reduded with respect to the binomial one (see Fig. 1).

Numerical implementation of intrinsic and extrinsic noise averages

In order to calculate numerically the statistical averages with respect to intrinsic and extrinsic noise terms we implement *in silico* two copies, P_1 and P_2, of our gene of interest in every cell. We average over $N_{\text{cells}} = 5000$ cells

and refer all cellular clocks to a common laboratory time such that at the laboratory time t_j,

$$\overline{\langle c_P\left(t_j\right)\rangle}^2 = \left(\frac{1}{N_{\text{cells}}}\sum_{i=1}^{N_{\text{cells}}} c^i_{P_1}\left(t_j\right)\right)^2 = \left(\frac{1}{N_{\text{cells}}}\sum_{i=1}^{N_{\text{cells}}} c^i_{P_2}\left(t_j\right)\right)^2,$$

$$\overline{\langle c^2_P\left(t_j\right)\rangle} = \frac{1}{N_{\text{cells}}}\sum_{i=1}^{N_{\text{cells}}} \left(c^i_{P_1}\left(t_j\right)\right)^2 = \frac{1}{N_{\text{cells}}}\sum_{i=1}^{N_{\text{cells}}} \left(c^i_{P_2}\left(t_j\right)\right)^2,$$

$$\overline{\langle c_P\left(t_j\right)\rangle^2} = \frac{1}{N_{\text{cells}}}\sum_{i=1}^{N_{\text{cells}}} c^i_{P_1}\left(t_j\right) c^i_{P_2}\left(t_j\right).$$