Impact of the cell division cycle on the dynamics of gene expression

Supporting Information

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S1. Consistency of protein synthesis with exponential growth

In this section, we demonstrate that the cell cycle dependence of protein synthesis rate is consistent with exponential volume growth. To this end, we consider stable proteins ($\beta = 0$) that are all transcribed with the same synthesis rate α. The protein content $P(t)$ is then given by

$$P(t) = \begin{cases} \alpha(t + 2T - t_x) & t < t_x \\ \alpha(2(t - t_x) + 2T) & t > t_x, \end{cases} \tag{1}$$

where t_x is the replication time and T the duration of the cell division cycle. The protein content $P(t)$ obeys the boundary conditions for $P(T) = 2P(0)$, and hence implicitly incorporates cell division. We now assume that genes are distributed homogeneously over the chromosome. Integration over all replication times then results in the overall protein content per cell,

$$P_{\text{all}}(t) = \frac{N_g}{T} \int_0^T P(t)dt_x = \frac{N_g \alpha}{2T} \left(t^2 + 2tT + 3T^2\right), \tag{2}$$

where N_g is the number of genes. Fig. S1 shows the relative deviation $\bar{P}_{\text{all}}/f(t) - 1$ of $\bar{P}_{\text{all}} = P_{\text{all}}(t)/P_{\text{all}}(t = 0)$ from the exponential (growth) function $f(t) = \exp(\ln(2)t/T)$, as a function of t. Here, we have rescaled $P_{\text{all}}(t)$ with $P_{\text{all}}(0) = 3/2\, \alpha N_g T$ for comparison with $f(t)$. The deviation is $< 0.5\%$, and remains the same irrespective of the value of T.

S1. Analytical form of the concentration $p(t)$

In the case without any repression, the concentration $p(t)$ in the interval $[0, T]$ reads

$$p(t) = \begin{cases} -\frac{\alpha e^{-\beta t} 2^{-\frac{t}{T}} \left(-2e^{\beta(t+T)} + e^{\beta t} + e^{\beta t_x}\right)}{\beta V_0 \left(2e^{\beta T} - 1\right)} & \text{for } t < t_x \\ -\frac{\alpha e^{-\beta t} 2^{1-\frac{t}{T}} \left(-2e^{\beta(t+T)} + e^{\beta t} + e^{\beta(T+t_x)}\right)}{\beta V_0 \left(2e^{\beta T} - 1\right)} & \text{for } t > t_x. \end{cases} \tag{3}$$

Here, α is the synthesis rate, β is the degradation rate, V_0 the volume at the beginning of the cell cycle, t_x is the replication time, and T the cell division time. $p(t)$ obeys the boundary conditions $p(0) = p(T)$.
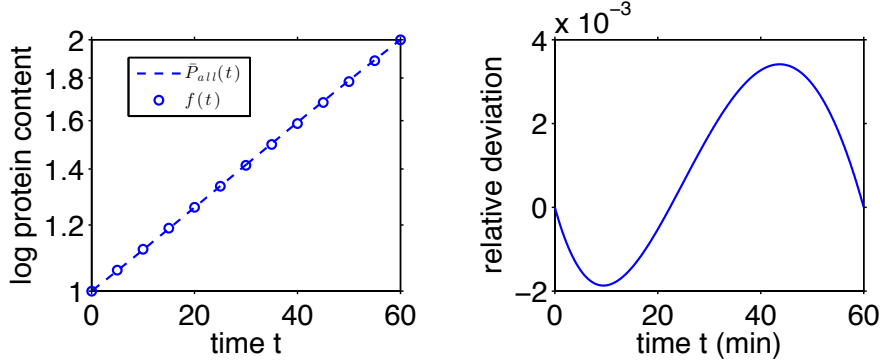
Figure S 1: Left panel: comparison between scaled protein content with homogeneous replication time distribution, $\bar{P}_{\text{all}}(t)$ (dashed line), and exponential growth $f(t)$, (symbols). Right panel: relative deviation between exponential growth and overall protein content, $\bar{P}_{\text{all}}(t)/f(t) - 1$. The relative deviation between the exponential function $f(t)$ and $P_{\text{all}}(t)/P_{\text{all}}(0)$ is less than 0.5%. Here, we have set $T = 60$ min.
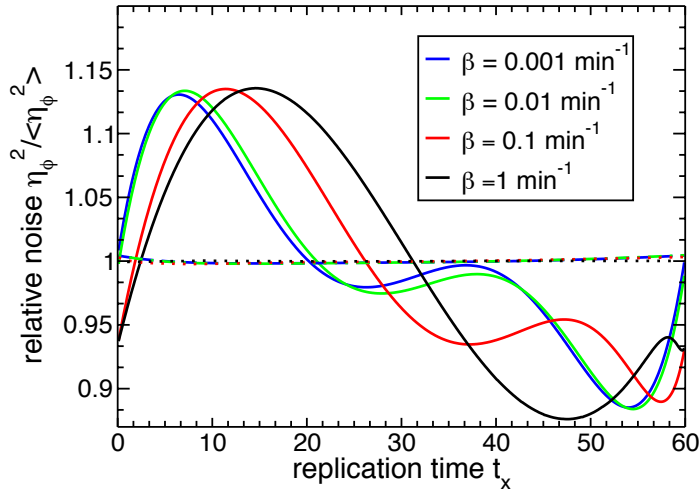

Figure S 2: Variation of rescaled deterministic noise $\eta_\phi^2/\langle\eta_\phi^2\rangle$ as a function of replication time t_x, for different protein degradation rates. The solid curves show the variation of $\eta_\phi^2(t_x)/\langle\eta_\phi^2(t_x)\rangle$ as a function of t_x with β as indicated in the legend. The maximal deviation from the mean is very similar for all values of β and does not exceed 15% . The dashed lines correspond to the values of $\eta_\phi^2/\langle\eta_\phi^2\rangle$ computed with an effective synthesis rate $\alpha_{\text{eff}}(t_x) = \alpha(2 - t_x/T)$, which deviate from the mean by less than 0.3 %.
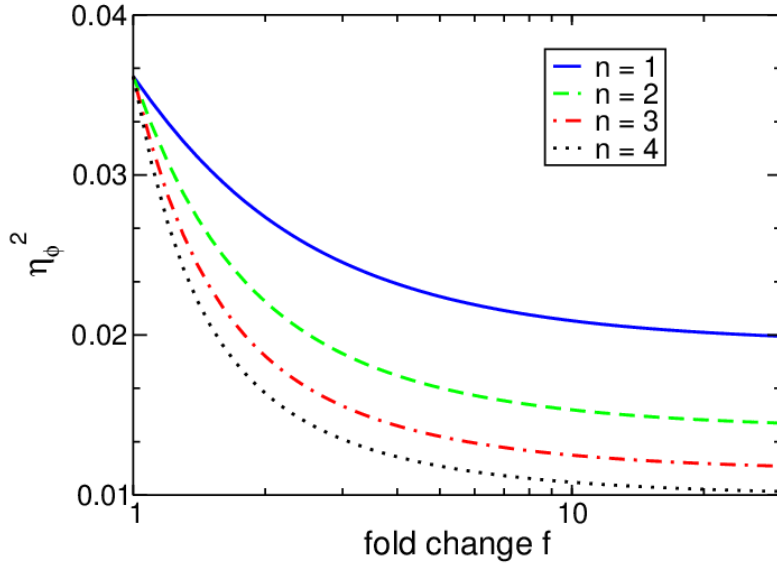
Figure S 3: Dependence on the Hill coefficient n of the deterministic noise η_ϕ^2 with regulatory concentration $\bar{K} = 1$ as a function of the fold change f, for negative autoregulation.
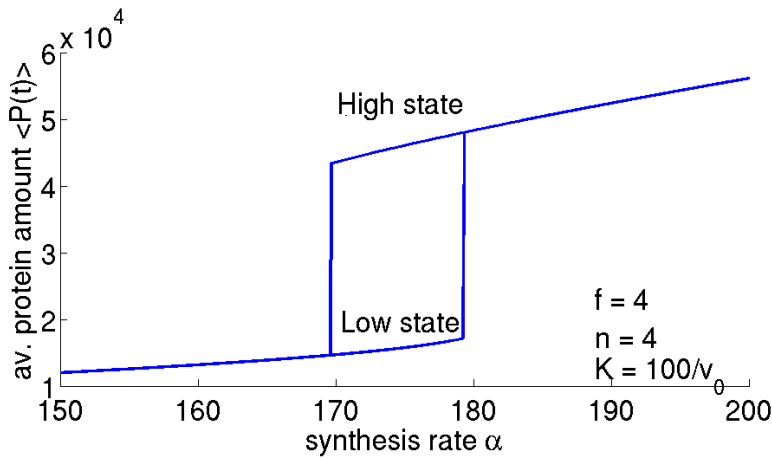

Figure S 4: Illustration of the transition into a bistable state for a positive autoregulator. The average protein amount $\langle P(t) \rangle$ is shown as a function of the synthesis rate α. For a specific range of α, two stable states exist, indicated as 'High state' and 'Low state'. As parameters, we have used a Hill coefficient $n = 4$, fold change $f = 4$, degradation rate $\beta = 0$, and a regulatory concentration $K = 100/V_0$.
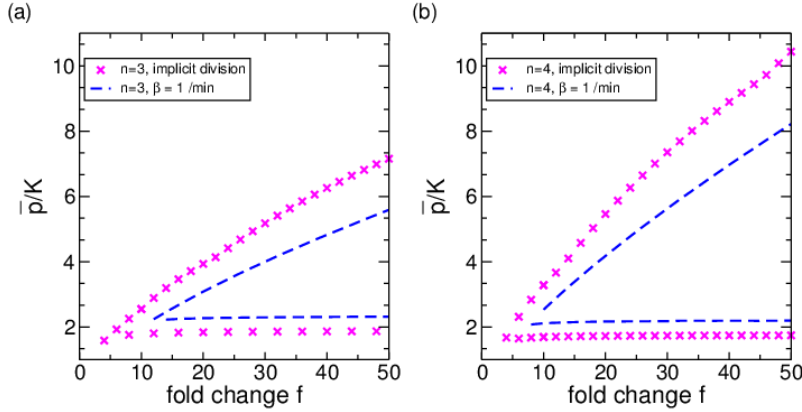
(a)

(b)

Figure S 5: Bistability diagram for the positive autoregulator, for Hill coefficient $n = 3$ (a) and $n = 4$ (b): symbols show the bistable region for implicit cell division and lines show the explicit cell division with a large degradation rate, $\beta = 1\text{min}^{-1}$ as a function of the dimensionless scale $\bar{p}/K$ and the fold change f. As can be infered from comparison of a) and b), the bistable region increases with increasing Hill coefficient. The qualitative behaviour of the parameter region is the same as in the case $n = 2$, see Fig.5b of the main text, for implicit and explicit cell division: for explicit cell division, the parameter region for bistability is diminished as β increases.
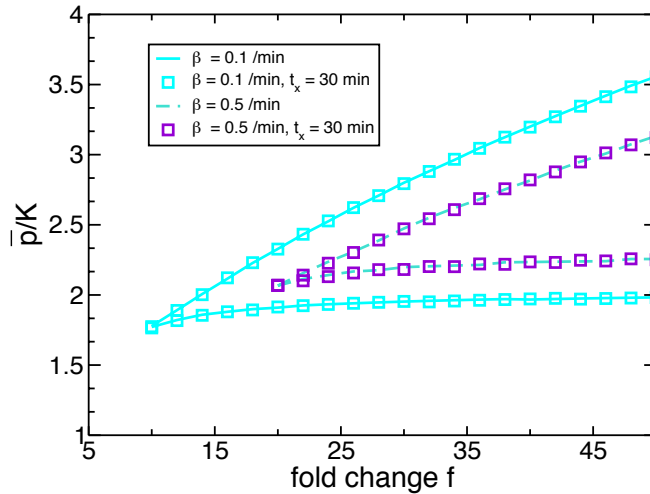

Figure S 6: Comparison of bistability diagrams for the positive autoregulator of explicitly dividing cells with and without gene replication for $t_x = 30$min. The diagrams without gene replication are indicated by solid lines and are obtained by using a synthesis rate α_{eff} that corresponds to the average synthesis rate with a replication time t_x, and those with explicit gene replication are shown as symbols. The bistability diagrams are virtually identical irrespective of the value of β. Hence, using an effective synthesis rate α_{eff} rather than treating gene replication explicitly is sufficient to determine the bistable region.
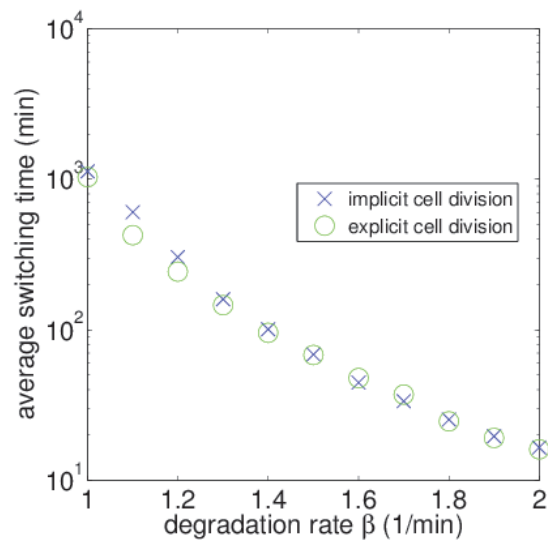
Figure S 7:   Switching times for the toggle switch: average duration of a state (gene X on and Y off or vice versa, due to the symmetry in the parameters, the durations of both states are the same) as a function of degradation rate β. The switching times are not altered when considering explicit cell division. The parameters such that $\bar{p}/K$ is close to the tip of the bistable region, and $\alpha_Y = \alpha_X$.