# Supplementary Information

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## A. Comparison between our model and others

In Ref. [1], Hausser et al. assumed that the fitness cost of the translation cost of expressing the exogenous gene to be $C_{\rm tl} = p_{\rm u}/p$, and the transcription cost to be $C_{\rm tx} = m_{\rm u}/m$, where $p$ and $m$ are the copy numbers of all endogenous mRNAs and proteins.

In Ref. [2], Lo et al. proposed a concept called the effective total metabolic load: $L_{\rm eff} = p + \lambda m'$, where $\lambda$ is a factor calibrating the load per mRNA produced to the load per protein produced. $m' = \frac{T}{\tau \ln 2} m$ is the mRNA number produced per cell cycle. The authors assumed that the proteins are non-degradable; therefore, $p$ is the protein number produced per cell cycle. The translation cost of the exogenous gene is $C_{\rm tl} = \frac{p_{\rm u}}{L_{\rm eff}}$, and the transcription cost is $C_{\rm tx} = \frac{\lambda m'_{\rm u}}{L_{\rm eff}}$.

In Ref. [3], Scott et al. assumed that the growth rate $\mu$ is proportional to $1-\phi_{\rm Q}-\phi_{r,0}-\phi_{\rm u}$, where $\phi_{\rm Q}$ is a constant proteome fraction of the housekeeping sector $Q$, $\phi_{r,0}$ is a constant proteome fraction of ribosomal proteins that do not contribute to growth, and $\phi_{\rm u}$ is the unnecessary protein proteome fraction. The fitness cost comes from the dilution of ribosome fraction due to the expression of the exogenous genes, which is $C = -\frac{\Delta\mu}{\mu} = \frac{\phi_{\rm u}}{1-\phi_{\rm Q}-\phi_{r,0}}$.

In Ref. [4], Calabrese et al., assumed that the growth rate $\mu$ is proportional to $\phi_r f_{{\rm b},r}$, where $f_{{\rm b},r} = 1 - f_r = \frac{\phi_n f_{{\rm b},n}}{\phi_n f_{{\rm b},n} + K_{\rm eff}}$ is the fraction of bound ribosomes, with $f_{{\rm b},n} = 1 - f_n$ the fraction of bound RNAPs. The expression of unnecessary genes leads to a proteome fraction $\phi_{\rm u}$, which influences $\mu$ by changing $\phi_r$, $\phi_n$, and $f_{{\rm b},n}$. The fitness cost $C = -\frac{\Delta\mu}{\mu} = -[\frac{\Delta\phi_r}{\phi_r} + f_r(\frac{\Delta\phi_n}{\phi_n} + \frac{\Delta f_{{\rm b},n}}{f_{{\rm b},n}})]$. Assuming a constant proteome fraction ($\phi_{\rm Q}$) of the housekeeping sector $Q$, they have $\frac{\Delta\phi_r}{\phi_r} = -\frac{\phi_{\rm u}}{1-\phi_{\rm Q}}$ due to dilution effects; $\frac{\Delta\phi_n}{\phi_n} = -\frac{\phi_{\rm u}}{1-\phi_{\rm Q}}$ due to dilution effects if $n \notin Q$ or $\frac{\Delta\phi_n}{\phi_n} = 0$ if $n \in Q$; $\frac{\Delta f_{{\rm b},n}}{f_{{\rm b},n}} = f_n \frac{\phi_{\rm u}}{1-\phi_{\rm Q}}$ because the insertion of unnecessary genes increases the fraction of bound RNAPs (see the details of derivation in the supporting information of [4]). According to the above information, we have $\frac{C}{\phi_{\rm u}} = \frac{1}{1-\phi_{\rm Q}}[1+f_r(1-f_n)]$ ($n \notin$ Q) or $\frac{C}{\phi_{\rm u}} = \frac{1}{1-\phi_{\rm Q}}[1 - f_r f_n]$ ($n \in$ Q).

We remark that in [1] and [2], the fitness costs essentially come from the processes of gene expression where various resources are consumed; in [3] and [4], the fitness costs primarily arise from the dilution effects of protein products expressed. A summary of the above four models is presented in Table S1. A quantitative comparison between models and experiments is presented in Table S2.

TABLE S1. **A summary of the four other models on the fitness cost of gene expression.**

| | **Hausser et al. [1]** | **Lo et al. [2]** | **Scott et al. [3]** | **Calabrese et al. [4]** |
|---|---|---|---|---|
| Primary origin of cost | Processes | Processes | Products | Products |
| $C$ | $\frac{p_{\rm u}}{p} + \frac{m_{\rm u}}{m}$ | $\frac{p_{\rm u}+\lambda m'_{\rm u}}{p+\lambda m'}$ | $\frac{\phi_{\rm u}}{1-\phi_{\rm Q}-\phi_{r,0}}$ | $\frac{1+f_r(1-f_n)}{1-\phi_{\rm Q}}\phi_{\rm u}$ |
| $\frac{C_{\rm tl}}{p_{\rm u}}$ | $\frac{1}{p}$ | $\frac{1}{p+\lambda m'}$ | —— | —— |
| $\frac{C_{\rm tx}}{m_{\rm u}}$ | $\frac{1}{m}$ | $\frac{\lambda T}{\tau_{\rm u}\ln 2}\frac{1}{p+\lambda m'}$ | —— | —— |

TABLE S2. **A quantitative comparison among theories and experimental results.** Here, we analyze the data of TDH3 promoter in the standard culture. Details on the calculations of a-b are explained in Table I and Methods B in the maintext. Values of c-f are calculated according to expressions in Table S1. Here, all values are kept to one decimal place for the convenience of comparison. The parameter values we use are as follows (if present): $a_{\rm u} = 27$ kDa [5], $a = 50$ kDa [6, 7], $M = 4.0 \times 10^{-12}$ g [8, 9], $\phi_{\rm u}/g_{\rm u} = 1.7\%$, $p_{\rm u}/g_{\rm u} = 1.5 \times 10^6$, $m_{\rm u}/g_{\rm u} = 6 \times 10^2$ (Methods B in the maintext), $p = M/a = 5 \times 10^7$, $m = 3 \times 10^4$ [10, 11], $T = 1.7$ h [12], $\tau = \tau_{\rm u} = 16$ min [13, 14], $\phi_{\rm Q} = 0.2$ [4], $\phi_{r,0} = 0.08$ [15], $f_r = 0.3$ [15], $f_n = 0.9$ [11]. The corresponding expressions of (c) and (d) are multiplied by $a_{\rm u}/a = 0.54$, taking account of the shorter mRNA(protein) length of a mCherry gene compared to an average endogenous gene. $\lambda$ is set to be 100 or 10 in (d) [2]. The two values in (f) represent the cases $n \notin {\rm Q}$ and $n \in {\rm Q}$, respectively.

| **Value** | $\frac{C}{\phi_{\rm u}}$ | $\frac{C_{\rm tl}}{p_{\rm u}}$ $(10^{-8})$ | $\frac{C_{\rm tx}}{m_{\rm u}}$ $(10^{-5})$ | $\frac{C_{\rm RNAP}}{m_{\rm u}}$ $(10^{-7})$ | $\frac{C_{\rm TF}}{g_{\rm u}}$ $(10^{-3})$ |
|---|---|---|---|---|---|
| **(a) Experiment** | 0.9 | 0.6 | 1.0 | —— | —— |
| **(b) This article** | 1.1 | 0.9 | 0.8 | 3.1 | 4.5 |
| **(c) Hausser et al. [1]** | 1.6 | 1.1 | 1.8 | —— | —— |
| **(d) Lo et al. [2]** | 0.8 or 0.9 | 0.7 or 1.0 | 0.6 or 0.1 | —— | —— |
| **(e) Scott et al. [3]** | 1.4 | —— | —— | —— | —— |
| **(f) Calabrese et al. [4]** | 1.3 or 0.9 | —— | —— | —— | —— |

### B. The fitness cost per proteome fraction

To calculate the fitness cost per proteome fraction, we use the relationship between the gene copy number and the proteome fraction:

$$\phi_{\rm u} = p_{\rm u}\frac{a_{\rm u}}{M_{\rm tot}} = m_{\rm u}\frac{\beta_{p,{\rm u}}a_{\rm u}}{\gamma_{\rm u}M_{\rm tot}} = g_{\rm u}\frac{\beta_{m,{\rm u}}\tau_{\rm u}\beta_{p,{\rm u}}a_{\rm u}}{\gamma_{\rm u}M_{\rm tot}}, \tag{S1}$$

where $M_{\rm tot}$ is the cellular protein mass, including the exogenous proteins. If we have two gene constructs denoted as "1" and "2", the ratio between $\phi_1/g_1$ and $\phi_2/g_2$ satisfies the following relationship:

$$\frac{\phi_2/g_2}{\phi_1/g_1} = \frac{\beta_{m,2}\tau_2\beta_{p,2}a_2/\gamma_2}{\beta_{m,1}\tau_1\beta_{p,1}a_1/\gamma_1}. \tag{S2}$$

The experimental data from Ref. [12] agree well with Eq. [S2] (Figure S1), where the two gene constructs only differ in the lifetimes of mRNA.

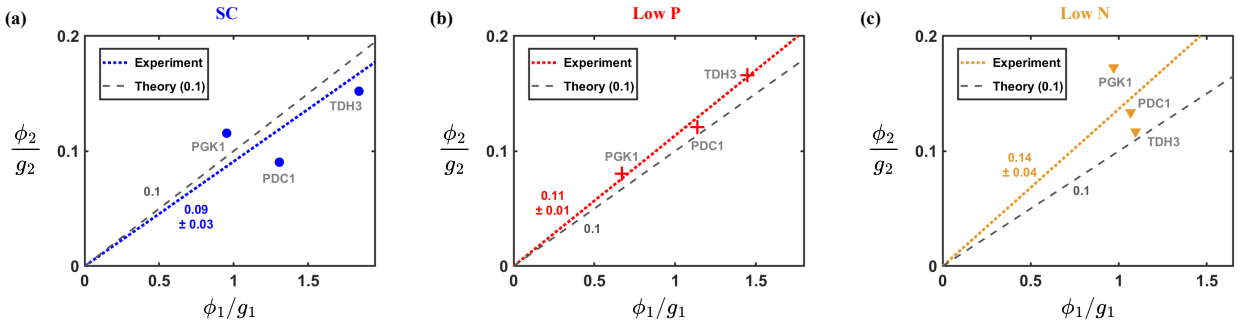


FIG. S1. **Ratio between gene copy number and proteome fraction.** The proteome fraction per gene of the wild-type and DAmP constructs (denoted as "1" and "2", respectively) in the standard culture (a), low phosphate condition (b), and low nitrogen condition (c). The mRNA lifetime of DAmP is about 0.1 that of the wild-type construct; therefore, the slope (gray dashed line) is predicted to be $\tau_2/\tau_1 = 0.1$ by Eq. [S2]. The slope of the dotted line marks the experimental average of three different promoters (TDH3, PGK1, PDC1), which agrees well with our prediction.

Therefore, combining Eq. [S2] and Eq. [14] in the maintext, we derive the fitness cost per proteome fraction as

$$\frac{C}{\phi_{\rm u}} = \frac{\gamma_{\rm u}M_{\rm tot}}{a_{\rm u}}\left[\frac{1}{\tau_{\rm u}\beta_{p,{\rm u}}}\left(\frac{c_g}{\beta_{m,{\rm u}}} + \frac{T_{{\rm tx},{\rm u}}}{N_n}f_r\right) + \frac{T_{{\rm tl},{\rm u}}}{N_r}\right], \tag{S3}$$

which is Eq. [15] in the maintext. Applying $M_{\rm tot} = M/(1-\phi_{\rm u})$, $M = g\beta_m\tau\beta_p a/\gamma$ ($\gamma = \mu + d$), $N_n(1-f_n) = gP_n\Lambda_n = g\beta_m T_{\rm tx}$, $N_r(1-f_r) = mP_r\Lambda_r = m\beta_p T_{\rm tl}$ (see Eqs. [1, 3, 7, 26, 27] in the maintext for details) to Eq. [S3], we get

$$\frac{C}{\phi_{\rm u}} = \frac{\gamma_{\rm u}}{\gamma(1-\phi_{\rm u})}\frac{g\beta_m\tau\beta_p a}{a_{\rm u}}\left\{\frac{1}{\tau_{\rm u}\beta_{p,{\rm u}}}\left[\frac{c_g}{\beta_{m,{\rm u}}} + \frac{T_{{\rm tx},{\rm u}}}{g\beta_m T_{\rm tx}}(1-f_n)f_r\right] + \frac{T_{{\rm tl},{\rm u}}}{m\beta_p T_{\rm tl}}(1-f_r)\right\}. \tag{S4}$$

Further using Eqs. [5, 13] in the maintext, the fitness cost per proteome fraction can be expressed as

$$\frac{C}{\phi_{\rm u}} = \frac{\gamma_{\rm u}}{\gamma(1-\phi_{\rm u})}\left\{\frac{\tau\beta_p}{\tau_{\rm u}\beta_{p,{\rm u}}}\left[\frac{a}{a_{\rm u}}(1-f_t)f_n + \frac{v_{\rm tx}}{v_{{\rm tx},{\rm u}}}(1-f_n)\right]f_r + \frac{v_{\rm tl}}{v_{{\rm tl},{\rm u}}}(1-f_r)\right\}. \tag{S5}$$

The following approximations are used for Eq. [S5]: (1) $a_{\rm u}/a = L_{{\rm tl},{\rm u}}/L_{\rm tl} = L_{{\rm tx},{\rm u}}/L_{\rm tx}$, where we assume that the protein mass is proportional to both the length of the mRNA translated and the length of the gene transcribed; (2) $T_{\rm tx} \approx L_{\rm tx}/v_{\rm tx}$ and $T_{\rm tl} \approx L_{\rm tl}/v_{\rm tl}$ where the initiation durations are neglected because both transcription and translation primarily involve elongation as the most time-consuming process. We notice that for an "average" gene whose properties represent the average genome ($\frac{\gamma_{\rm u}}{\gamma} = \frac{\tau_{\rm u}\beta_{p,{\rm u}}}{\tau\beta_p} = \frac{a_{\rm u}}{a} = \frac{v_{{\rm tl},{\rm u}}}{v_{\rm tl}} = \frac{v_{{\rm tx},{\rm u}}}{v_{\rm tx}} = 1$), the cost per proteome fraction is simplified as

$$\frac{C}{\phi_{\rm u}} = \frac{1-f_r+f_r[1-f_n+f_n(1-f_t)]}{1-\phi_{\rm u}} = \frac{1-f_r f_n f_t}{1-\phi_{\rm u}} \approx 1, \tag{S6}$$

where we use the approximation $\phi_{\rm u} \ll 1$ and $f_r f_n f_t \ll 1$. A numerical comparison between our model and four other models is summarized in Table S3. Intriguingly, despite distinct mechanisms behind each model, the numerical predictions for an "average" gene are close. This implies that, on average, the fitness cost due to resource competition is similar to dilution. The differences only appear when we consider a gene with distinct properties (e.g., mRNA lifetime, protein degradation rate as in Figure 4b in the maintext) since a dilution mechanism (e.g., Scott et al. [3]) always gives the same $C/\phi_{\rm u}$ for all gene constructs. The linear relationship between the fitness cost and the proteome fraction also exists in *E. coli* where the slopes are also condition-dependent (Table S4) [3, 16, 17].

TABLE S3. **A comparison of the five models on the cost per proteome fraction in both** *S. cerevisiae* **and** *E. coli*. Here, the numerical values represent an "average" gene in the corresponding model. We notice that an "average" gene satisfies $p_{\rm u}/p = m_{\rm u}/m = m'_{\rm u}/m' = \phi_{\rm u}$ where $m'$ is the mRNA number produced per cell cycle, such that (2) and (3) can be easily calculated from Table S1. The parameters used for (4) and (5) are (if present): *S. cerevisiae*: $\phi_{\rm Q} = 0.2$, $\phi_{r,0} = 0.08$, $f_r = 0.3$, $f_n = 0.9$; *E. coli*: $\phi_{\rm Q} = 0.45$, $\phi_{r,0} = 0.07$, $f_r = 0.3$ [3], $f_n = 0.5$ (including nonspecifically DNA-bound RNAPs which effectively enlarge the free RNAP pool [18]). The two possibilities in *S. cerevisiae* of (5) represent the cases $n \notin {\rm Q}$ and $n \in {\rm Q}$, respectively. $n \notin {\rm Q}$ for *E. coli* [18]. For experimental values of various gene constructs, please refer to Figure 4b in the maintext (*S. cerevisiae*) and Table S4 (*E. coli*).

| $\frac{C}{\phi_{\rm u}}$ | **(1) This article** | **(2) Hausser et al.** | **(3) Lo et al.** | **(4) Scott et al.** | **(5) Calabrese et al.** |
|---|---|---|---|---|---|
| *S. cerevisiae* | 1.0 | 2.0 | 1.0 | 1.4 | 1.3 or 0.9 |
| *E. coli* | 1.0 | 2.0 | 1.0 | 2.1 | 2.1 |

TABLE S4. **Experimental measurements of the fitness cost per proteome fraction for** *E. coli*.

| | $C/\phi_{\rm u}$ | Unnecessary Protein | Promoter | Medium | Growth Rate ($h^{-1}$) | Ref |
|---|---|---|---|---|---|---|
| 1 | $1.4 \pm 0.2$ | $\beta$-lactamase | *bla* | LB | 1.29 | [16] |
| 2 | $2.0 \pm 1.0$ | $\beta$-lactamase | *bla* | M9CA | 0.99 | [16] |
| 3 | $0.9 \pm 0.6$ | $\beta$-lactamase | *bla* | M9 | 0.51 | [16] |
| 4 | $2.2 \pm 0.3$ | $\beta$-galactosidase | *lacUV5* | M9-glycerol | 0.86 | [17] |
| 5 | $2.1 \pm 0.1$ | truncated EF-Tu | *tac* | M9-glycerol | 0.97 | [17] |
| 6 | $2.0 \pm 0.5$ | $\beta$-galactosidase | P*u* | RDM | 1.70 | [3] |
| 7 | $1.9 \pm 0.6$ | $\beta$-galactosidase | P*u* | cAA | 0.87 | [3] |
| 8 | $2.0 \pm 0.8$ | $\beta$-galactosidase | P*u* | M63 | 0.60 | [3] |

### C. The extended model where the levels of endogenous proteins and the cell volume are changeable

In the maintext, we mostly consider a simplified scenario in which the levels of the endogenous proteins and the cell volume are unaffected by the produced exogenous protein. In this section, we justify the simplification by taking into account all possible changes in resources ($N_r$, $N_n$, and $N_t$), endogenous proteome mass ($M$), volumes ($V_\mathrm{c}$, $V_\mathrm{n}$), and mRNA lifetime ($\tau$). For a specific kind of resources $j$, where $j$ can be $r$ (ribosome), $n$ (RNAP), or $t$ (TF), by differentiating $P_j = \frac{N_j f_j}{N_j f_j + K_j V_j}$ we have

$$Z_{P_j} = (1 - P_j)(Z_{f_j} + Z_{N_j} - Z_{V_j}), \tag{S7}$$

where $Z_y$ is an abbreviation for $\frac{\mathrm{d}y}{y \mathrm{d}g_\mathrm{u}}$ for any variable $y$ of interest. One should note that the corresponding $V_j$ volumes for TF, RNAP, and ribosome are $V_\mathrm{n}$ (nuclear volume), $V_\mathrm{n}$, and $V_\mathrm{c}$ (cytoplasmic volume), respectively.

Differentiating the partition equation of each resources $N_j = N_{j,\mathrm{f}} + N_{j,\mathrm{endo}} + N_{j,\mathrm{u}}$ and taking $N_{j,\mathrm{u}} \to 0$ (Eqs. [17, 19, 29] in the maintext), where $N_{j,\mathrm{endo}}$ is the number of resources $j$ consumed by the endogenous genes, we get the following three equations:

$$Z_{f_t} = \frac{1}{1 - P_t(1 - f_t)}[-\frac{\mathrm{d}N_{t,\mathrm{u}}}{N_t \mathrm{d}g_\mathrm{u}} + (1 - f_t)(P_t Z_{N_t} + (1 - P_t) Z_{V_n})], \tag{S8}$$

$$Z_{f_n} = \frac{1}{1 - P_n(1 - f_n)}[-\frac{\mathrm{d}N_{n,\mathrm{u}}}{N_n \mathrm{d}g_\mathrm{u}} + (1 - f_n)(P_n Z_{N_n} + (1 - P_n) Z_{V_n} - Z_{P_t})], \tag{S9}$$

$$Z_{f_r} = \frac{1}{1 - P_r(1 - f_r)}[-\frac{\mathrm{d}N_{r,\mathrm{u}}}{N_r \mathrm{d}g_\mathrm{u}} + (1 - f_r)(P_r Z_{N_r} + (1 - P_r) Z_{V_c} - (Z_{P_t} + Z_{P_n} + Z_\tau))]. \tag{S10}$$

To calculate the fitness cost $-\Delta C/C$, we differentiate Eq. [7] in the maintext and get

$$Z_\gamma = Z_{P_t} + Z_{P_n} + Z_{P_r} + Z_\tau - Z_M. \tag{S11}$$

Combining Eqs. [S8-S11], approximating $\gamma \approx \mu$ since protein degradation is slow compared to cell growth, and integrating over $g_\mathrm{u}$, we calculate the fitness cost to be

$$\begin{aligned} C = -\frac{\Delta\mu}{\mu} = &(\frac{N_{r,\mathrm{u}}}{N_r} - \frac{\Delta N_r}{N_r} + f_r \frac{\Delta V_\mathrm{c}}{V_\mathrm{c}}) s_r + (\frac{N_{n,\mathrm{u}}}{N_n} - \frac{\Delta N_n}{N_n} + f_n \frac{\Delta V_\mathrm{n}}{V_\mathrm{n}}) s_n \theta_r \\ &+ (\frac{N_{t,\mathrm{u}}}{N_t} - \frac{\Delta N_t}{N_t} + f_t \frac{\Delta V_\mathrm{n}}{V_\mathrm{n}}) s_t \theta_n \theta_r - \theta_r \frac{\Delta\tau}{\tau} + \frac{\Delta M}{M}, \end{aligned} \tag{S12}$$

where the symbol $\Delta$ marks a small change in the corresponding value due to the produced exogenous protein. $s_j$ and $\theta_j$ ($j = r, n, t$) are the sensitivity factor and the downstream factor defined in Methods A and C in the maintext. The difference between this complete version and the version we use in the maintext (Eq. [30]) is

$$C' = \Big(\frac{\Delta M}{M} - \frac{\Delta N_r}{N_r}\Big) + f_r \Big(\frac{\Delta V_\mathrm{c}}{V_\mathrm{c}} - \frac{\Delta N_n}{N_n} + \frac{\Delta V_\mathrm{n}}{V_\mathrm{n}} - \frac{\Delta N_t}{N_t}\Big), \tag{S13}$$

where $C'$ is the cost due to protein product. The following approximations are used for Eq. [S13]: $s_j \approx 1$ and $\theta_j \approx f_j$ ($j = r, n, t$); $f_n \approx 1$ [11]; the terms $-f_r \Delta\tau/\tau$ and $f_r f_n f_t \Delta V_\mathrm{n}/V_\mathrm{n}$ are neglected for simplicity, which are smaller compared to other terms and can cancel out to some extent [19], having minor impacts on the outcome.

We define $\phi'_r = N_r a_r / M$ as the ribosome proteome fraction in the endogenous proteins, $\phi_n = N_n a_n / M_\mathrm{tot}$ as the proteome fraction of RNAP, and $\phi_t = N_t a_t / M_\mathrm{tot}$ as the proteome fraction of transcription initiation associated factors, where $a_r$, $a_n$, and $a_t$ are the corresponding protein molecular masses. We introduce $\eta_\mathrm{nc} = V_\mathrm{n}/V_\mathrm{c}$ as the ratio of the nuclear volume to cytoplasmic volume, and $\rho = M_\mathrm{tot}/(V_\mathrm{c} + V_\mathrm{n})$ as the protein mass density. Then, Eq. [S13] becomes

$$C' = -\frac{\Delta\phi'_r}{\phi'_r} + f_r[-\frac{\Delta\phi_n}{\phi_n} - \frac{\Delta\phi_t}{\phi_t} + \frac{\Delta\eta_\mathrm{nc}}{\eta_\mathrm{nc}} - 2\frac{\Delta\eta_\mathrm{nc}}{1 + \eta_\mathrm{nc}} - 2\frac{\Delta\rho}{\rho}]. \tag{S14}$$

To derive Eq. [16] in the maintext, (1) we assume a constant protein mass density such that $\frac{\Delta\rho}{\rho} = 0$; (2) we assume a constant ratio among transcriptional proteins (i.e., RNAP and TF) such that $\frac{\Delta\phi_n}{\phi_n} = \frac{\Delta\phi_t}{\phi_t} = \frac{\Delta\phi_\mathrm{tx}}{\phi_\mathrm{tx}}$ where $\phi_\mathrm{tx}$ is the proteome fraction of all transcriptional proteins; (3) finally, we notice $\eta_\mathrm{nc} \approx 0.1$ [20–23] such that $\frac{\Delta\eta_\mathrm{nc}}{1+\eta_\mathrm{nc}} \approx 0$.

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