A coarse-grained, mechanistic model of cellular growth

Andrea Y. Weiße, Diego A. Oyarzún, Vincent Danos, Peter S. Swain

Contents

1 Overview

We consider a mechanistic model of the cell. It combines nutrient import and its conversion to cellular energy with the biosynthetic processes of transcription and translation. In its basic form, the model includes 14 intracellular variables: internal nutrient s_i; energy, a, such as ATP[1]; and four types of proteins along with their corresponding free and ribosome-bound mRNAs. The four types of proteins we consider are (1) ribosomes r, (2) a transporter enzyme e_t and (3) a metabolic enzyme e_m, and (4) a class of house-keeping proteins q. We denote the corresponding free mRNAs by m_x and ribosome-bound mRNA by c_x with $x \in \{r, t, m, q\}$.

Table 1: List of reactions considered.

	dilution	transcription	dilution/degradation	ribosome binding	dilution	translation
ribosomes	$r \xrightarrow{\lambda} \varnothing$	$\varnothing \xrightarrow{\omega_r} m_r$	$m_r \xrightarrow{\lambda+d_m} \varnothing$	$r + m_r \underset{k_u}{\overset{k_b}{\longleftrightarrow}} c_r$	$c_r \xrightarrow{\lambda} \varnothing$	$n_r\, a + c_r \xrightarrow{\nu_r} r + m_r + r$
transporter enzyme	$e_t \xrightarrow{\lambda} \varnothing$	$\varnothing \xrightarrow{\omega_t} m_t$	$m_t \xrightarrow{\lambda+d_m} \varnothing$	$r + m_t \underset{k_u}{\overset{k_b}{\longleftrightarrow}} c_t$	$c_t \xrightarrow{\lambda} \varnothing$	$n_t\, a + c_t \xrightarrow{\nu_t} r + m_t + e_t$
metabolic enzyme	$e_m \xrightarrow{\lambda} \varnothing$	$\varnothing \xrightarrow{\omega_m} m_m$	$m_m \xrightarrow{\lambda+d_m} \varnothing$	$r + m_m \underset{k_u}{\overset{k_b}{\longleftrightarrow}} c_m$	$c_m \xrightarrow{\lambda} \varnothing$	$n_m\, a + c_m \xrightarrow{\nu_m} r + m_m + e_m$
growth-independent proteins	$q \xrightarrow{\lambda} \varnothing$	$\varnothing \xrightarrow{\omega_q} m_q$	$m_q \xrightarrow{\lambda+d_m} \varnothing$	$r + m_q \underset{k_u}{\overset{k_b}{\longleftrightarrow}} c_q$	$c_q \xrightarrow{\lambda} \varnothing$	$n_q\, a + c_q \xrightarrow{\nu_q} r + m_q + q$
internal nutrient	$s_i \xrightarrow{\lambda} \varnothing$	$s \xrightarrow{\nu_{\mathrm{imp}}} s_i$	$s_i \xrightarrow{\nu_{\mathrm{cat}}} n_s\, a$			
ATP	$a \xrightarrow{\lambda} \varnothing$	nutrient import	metabolism			

We model the cell as a system of ordinary differential equations derived from the

[1] Similarly a can also be interpreted as amino acids, or any other essential resource for biosynthetic reactions.

reactions listed in Table 1:

$$\dot{s}_i = \nu_{\text{imp}}(e_t, s) - \nu_{\text{cat}}(e_m, s_i) - \lambda s_i, \tag{1}$$

$$\dot{a} = n_s \cdot \nu_{\text{cat}}(e_m, s_i) - \sum_{\substack{x\in \\ \{r,t,m,q\}}} n_x \nu_x(c_x, a) - \lambda a, \tag{2}$$

$$\dot{r} = \nu_r(c_r, a) - \lambda r + \sum_{\substack{x\in \\ \{r,t,m,q\}}} (\nu_x(c_x, a) - k_b r m_x + k_u c_x), \tag{3}$$

$$\begin{aligned} \dot{e}_t &= \nu_t(c_t, a) - \lambda e_t, \\ \dot{e}_m &= \nu_m(c_m, a) - \lambda e_m, \\ \dot{q} &= \nu_q(c_q, a) - \lambda q, \end{aligned} \tag{4}$$

$$\dot{m}_x = \omega_x(a) - (\lambda + d_m) m_x + \nu_x(c_x, a) - k_b r m_x + k_u c_x, \tag{5}$$

$$\dot{c}_x = -\lambda c_x + k_b r m_x - k_u c_x - \nu_x(c_x, a), \qquad x \in \{r, t, m, q\}. \tag{6}$$

We consider all variables in molecules per cell. For the rates of those bimolecular reactions that depend on concentrations of molecular species, we assume a fixed volume of 1 μm^3 (approximately matching the volume of *E. coli*) to convert to numbers of molecules. The units of the parameters and their default values are listed in Table 2. The growth rate $\lambda = \lambda(\sum_x c_x, a)$ is a function of the number of translating ribosomes and energy. Below we elaborate on the main assumptions of the model and on the derivation of the reaction rates in Eqs. 1-6.

2 Derivation of reaction rates

2.1 Main assumptions

Apart from the three main trade-offs elaborated in the main text (finite energy, finite ribosomes and finite proteome) we base our model on the following assumptions:

1. First-order dilution of the intracellular species;
2. No degradation of proteins (although it can be included) and first-order degradation of mRNA;
3. Mass action kinetics for the binding and unbinding of mRNAs with free ribosomes;
4. Energy consumption within the cell is from translation only and we neglect the consumption from transcription [9, 13].

2.2 Nutrient import and metabolism

We assume the enzymatically catalyzed reactions, nutrient import and metabolism, to be saturable and use Michaelis-Menten kinetics with maximal rates v_t and v_m and

Table 2: Model parameters. Default values were used unless otherwise stated. ★Obtained by parameter optimization (see §**??** for details). †Chosen relative to K_t; ‡chosen such that maximal growth rate matches that of *E. coli*; §*E. coli*'s average; ♯for steep auto-inhibition; *near the diffusion limit; ♢order of magnitude; aa denotes number of amino acids.

	description	default value	unit	source
s	external nutrient	10^4	[molecs]	†
d_m	mRNA-degradation rate	0.1	$[\text{min}^{-1}]$	[12]
n_s	nutrient efficiency	0.5	none	‡
n_r	ribosome length	7459	$[^{\text{aa}}/_{\text{molecs}}]$	[7]
n_x, $x \in \{t, m, q\}$	length of non-ribosomal proteins	300	$[^{\text{aa}}/_{\text{molecs}}]$	[2]§
$\gamma_{\max}$	max. transl. elongation rate	1260	$[^{\text{aa}}/_{\text{min molecs}}]$	[3]
K_γ	transl. elongation threshold	7	$[^{\text{molecs}}/_{\text{cell}}]$	★
v_t	max. nutrient import rate	726	$[\text{min}^{-1}]$	[5]
K_t	nutrient import threshold	1000	[molecs]	
v_m	max. enzymatic rate	5800	$[\text{min}^{-1}]$	[1]
K_m	enzymatic threshold	1000	$[^{\text{molecs}}/_{\text{cell}}]$	
w_r	max. ribosome transcription rate	930	$[^{\text{molecs}}/_{\text{min cell}}]$	★
$w_e = w_t = w_m$	max. enzyme transcription rate	4.14	$[^{\text{molecs}}/_{\text{min cell}}]$	★
w_q	max. q-transcription rate	948.93	$[^{\text{molecs}}/_{\text{min cell}}]$	★
θ_r	ribosome transcription threshold	426.87	$[^{\text{molecs}}/_{\text{cell}}]$	★
θ_{nr}	non-ribosomal transcription threshold	4.38	$[^{\text{molecs}}/_{\text{cell}}]$	★
K_q	q-autoinhibition threshold	152 219	$[^{\text{molecs}}/_{\text{cell}}]$	★
h_q	q-autoinhibition Hill coeff.	4	none	♯
k_b	mRNA-ribosome binding rate	1	$[^{\text{cell}}/_{\text{min molecs}}]$	*
k_u	mRNA-ribosome unbinding rate	1	$[\text{min}^{-1}]$	
M	total cell mass	10^8	[aa]	[3]♢
k_{cm}	chloramphenicol-binding rate	0.00599	$[(\text{min}\,\mu M)^{-1}]$	★

half-maximal thresholds K_t and K_m, such that

$$\nu_{\text{imp}}(e_t, s) = e_t \frac{v_t s}{K_t + s}, \qquad \nu_{\text{cat}}(e_m, s_i) = e_m \frac{v_m s_i}{K_m + s_i}. \tag{7}$$

In the basic cell model, we consider a constant environment, and so the external nutrient s is a constant parameter. In §**??** we show how to extend the basic model to include a dynamic environment. The nutrient efficiency parameter, n_s, determines energy yield per molecule of s_i.

2.3 Translation

In exponentially growing microbes, protein synthesis, in particular translation-associated processes, accounts for a major part of the energy budget [9, 13, 14]. Here we assume a simplified mechanism, illustrated in Fig. 1, to derive the dependence of the translation rates on the energy levels of the cell. Using the rate constants in Fig. 1 and defining

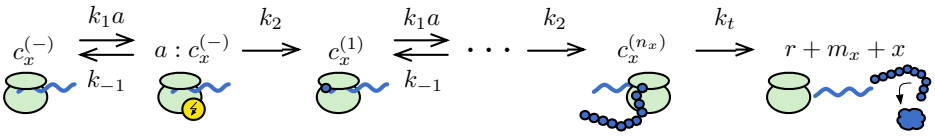

Figure 1: A simplified mechanism of translation. In a reversible reaction, the mRNA-ribosome complex, c_x, binds energy. In a second step, the nascent peptide chain elongates by one amino acid consuming energy. The two steps are repeated n_x times, where n_x is the length in amino acids of protein x. Finally, termination of translation releases the ribosome, the mRNA and the newly synthesised protein.

$K_p := \frac{k_1 k_2}{k_{-1}+k_2}$, we can derive the net rate [4] of translating a protein x as

$$\nu_x(c_x, a) = c_x \left(n_x \left(\frac{1}{K_p a} + \frac{1}{k_2} \right) + \frac{1}{k_t} \right)^{-1}. \tag{8}$$

Assuming that the final termination step is fast, $\frac{1}{k_t} \ll n_x \left(\frac{1}{K_p a} + \frac{1}{k_2} \right)$, we write ν_x as

$$\nu_x(c_x, a) \approx c_x \frac{\gamma(a)}{n_x}, \qquad \gamma(a) := \frac{\gamma_{\max} a}{K_\gamma + a}, \tag{9}$$

where n_x is the length of protein x (in amino acids) and γ is the rate of translational elongation with maximal rate $\gamma_{\max} = k_2$ and threshold $K_\gamma = {}^{k_2}/_{K_p}$ for half-maximal elongation.

2.4 Transcription

The contribution of transcription-associated processes to the overall consumption of energy is small compared to that of translation (less than 10% in rapidly growing *E. coli* and *S. cerevisiae* [9, 13]), and so we neglect this contribution to energy consumption.

We do, however, let transcription be an energy-dependent process that ceases when the cell runs out of energy. Analogous to translation (see Fig. 1), transcription involves repeated steps of elongation that each depend on energy. If we assume that the energy consumed in each elongation step is constant, it follows that the effective transcription rate has the form

$$\omega_x(a) = w_x \frac{a}{\theta_x + a}, \qquad x \in \{r, t, m\}. \tag{10}$$

Unlike the translational elongation thresholds, the transcriptional thresholds θ_x depend on the gene x. We distinguish two transcriptional thresholds, $\theta_x = \theta_{\mathrm{nr}}$ for all non-ribosomal genes $x \in \{t, m, q\}$ and $\theta_r \neq \theta_{\mathrm{nr}}$ for ribosomal genes, because ribosomal expression may have a different sensitivity to physiological changes within the cell. The maximal rate of transcription, w_x, is a lumped description of the speed of transcriptional elongation and gene-related information such as copy number, induction and length. We assume that the transporter and the metabolic enzymes, e_t and e_m, are co-expressed and so $w_t = w_m = w_e$.

We further assume that all but the q-proteins have a transcription rate that solely depends on energy levels. The q-proteins, we assume, are auto-regulated to sustain stable protein levels across different growth conditions. Following [8], we thus model the effective rate of q-transcription by

$$\omega_q(q, a) = w_q \frac{a}{\theta_x + a} \mathcal{I}(q), \quad \text{with} \quad \mathcal{I}(q) := \frac{1}{1 + (q/K_q)^{h_q}}, \tag{11}$$

where $\mathcal{I}$ is the auto-inhibition function with threshold K_q and Hill-coefficient h_q.

2.5 Growth and dilution

The growth rate λ is crucial to connect the cellular processes with growth, as it dilutes all intracellular species by redistributing the cellular content between mother and daughter cells (Table 1). We define the total mass of the cell as the total protein mass (including bound ribosomes):

$$M = \sum_x n_x x + n_r \sum_x c_x. \tag{12}$$

Defining the number of translating ribosomes $\sum_x c_x$ to be R_t, we can show that

$$\frac{dM}{dt} = \gamma(a) R_t - \lambda M. \tag{13}$$

At steady-state, the growth rate

$$\lambda = \frac{\gamma(a) R_t}{M}, \tag{14}$$

is therefore proportional to the rate of protein synthesis, which agrees with other definitions of growth rate in the literature [6, 10, 11]. Here M is the the mass of a mid-log cell.

We emphasize that specifying a value for M at steady-state (M_s), the typical mass in numbers of amino acids of the proteins of a mid-log cell, is necessary to fully parameterize our model and by doing so we impose the constraint Eq. 12, and so the trade-off in levels of proteins. For the simulations, we assume that Eq. (14), with $M = M_s$, also holds away from steady-state.

Supplementary References

[1] K. R. Albe, M. H. Butler, and B. E. Wright. Cellular concentrations of enzymes and their substrates. *J Theor Biol*, 143(2):163–195, 1990.

[2] F. Brandt, S. A. Etchells, J. O. Ortiz, A. H. Elcock, F. U. Hartl, and W. Baumeister. The native 3D organization of bacterial polysomes. *Cell*, 136(2):261–271, 2009.

[3] H. Bremer and P. Dennis. Modulation of chemical composition and other parameters of the cell by growth rate. In C. Neidhardt, editor, Escherichia coli *and* Salmonella, pages 1553–1569. ASM Press, Washington, DC, 1996.

[4] W. Cleland. Partition analysis and concept of net rate constants as tools in enzyme kinetics. *Biochemistry*, 14(14):3220–3224, 1975.

[5] K. Dornmair, P. Overath, and F. Jähnig. Fast measurement of galactoside transport by lactose permease. *J Biol Chem*, 264(1):342–346, 1989.

[6] M. Ehrenberg and C. Kurland. Costs of accuracy determined by a maximal growth rate constraint. *Q Rev Biophys*, 17(01):45–82, 1984.

[7] I. M. Keseler, J. Collado-Vides, A. Santos-Zavaleta, M. Peralta-Gil, S. Gama-Castro, L. Muñiz Rascado, C. Bonavides-Martinez, S. Paley, M. Krummenacker, T. Altman, P. Kaipa, A. Spaulding, J. Pacheco, M. Latendresse, C. Fulcher, M. Sarker, A. G. Shearer, A. Mackie, I. Paulsen, R. P. Gunsalus, and P. D. Karp. Ecocyc: a comprehensive database of escherichia coli biology. *Nucleic Acids Research*, 39(suppl 1):D583–D590, 2011.

[8] S. Klumpp, Z. Zhang, and T. Hwa. Growth rate-dependent global effects on gene expression in bacteria. *Cell*, 139(7):1366–1375, 2009.

[9] J. B. Russell and G. M. Cook. Energetics of bacterial growth: balance of anabolic and catabolic reactions. *Microbiol Rev*, 59(1):48–62, 1995.

[10] M. Scott, C. W. Gunderson, E. M. Mateescu, Z. Zhang, and T. Hwa. Interdependence of cell growth and gene expression: origins and consequences. *Science*, 330(6007):1099–1102, Nov. 2010.

[11] M. Scott and T. Hwa. Bacterial growth laws and their applications. *Curr Opin Biotech*, 22(4):559–565, Aug. 2011.

[12] Y. Taniguchi, P. J. Choi, G.-W. Li, H. Chen, M. Babu, J. Hearn, A. Emili, and X. S. Xie. Quantifying e. coli proteome and transcriptome with single-molecule sensitivity in single cells. *Science*, 329(5991):533–538, 2010.

[13] A. Wagner. Energy constraints on the evolution of gene expression. *Mol Biol Evol*, 22(6):1365–1374, 2005.

[14] J. R. Warner. The economics of ribosome biosynthesis in yeast. *Trends Biochem Sci*, 24(11):437–440, 1999.