Mechanistic links between cellular trade-offs, gene expression, and growth

Andrea Y. Weiße et al., *PNAS* vol. 112 no. 9

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Outline of the presentation

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A coarse-grained, ODE model

- Describes intracellular levels of energy, nutrients, mRNAs and proteins
- Only 14 different variables, obeying simple differential equations obtained from chemical reactions
- Much simpler than whole-cell models, and thus simpler to reason about

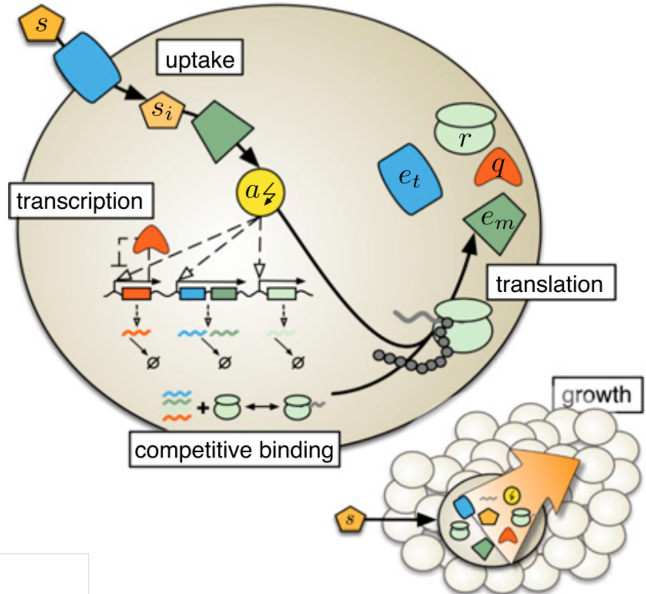
Goal of the model

- Main goal: be able to study the trade-offs that cells have to make when growing
- Simplicity: allows us to tweak it easily and add extensions

3 cellular trade-offs

- Finite energy levels: mRNA-ribosome complexes compete for energy to translate
- Finite ribosome levels: mRNAs compete for ribosomes to bind to
- Finite cell mass: proteins compete for proportion of cell mass

Description



Differential equations

$$
\begin{cases}
\dot{s}_i & = \nu_{imp}(e_t, s) - \nu_{cat}(e_m, s_i) - \lambda s_i \\
\dot{a} & = n_s \nu_{cat}(e_m, s_i) - \sum\limits_{x \in \{r, e_t, e_m, q\}} n_x \nu_x(c_x, a) - \lambda a \quad (1) \\
\dot{r} & = \nu_r(c_r, a) - \lambda r + \sum(\nu_x(c_x, a) - k_b r m_x + k_u c_x) \\
\dot{e}_t & = \nu_t(c_t, a) - \lambda e_t \\
\dot{e}_m & = \nu_e(c_e, a) - \lambda e_m \\
\dot{q} & = \nu_q(c_q, a) - \lambda q \\
\dot{m}_x & = \omega_x(a) - (\lambda + d_m) m_x + \nu_x(c_x, a) - k_b r m_x + k_u c_x \quad (2) \\
\dot{c}_x & = -\lambda c_x + k_b r m_x - k_u c_x - \nu_x(c_x, a)
\end{cases}
$$

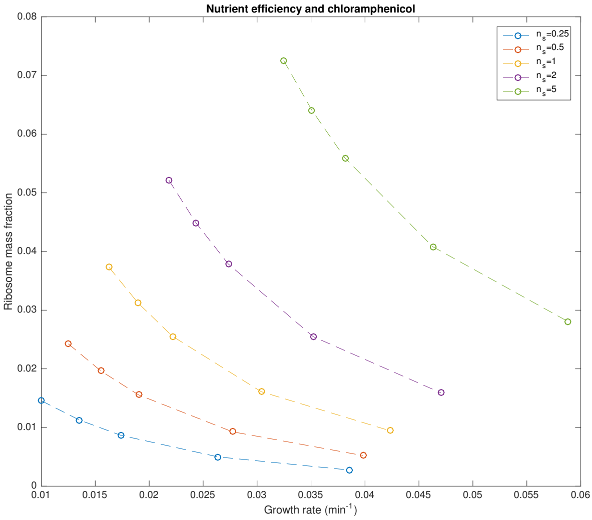
Differential equations

$$
\begin{cases}
\nu_{imp}(e_t, s) & = e_t \frac{v_t s}{K_t + s} \\
\nu_{cat}(e_m, s_i) & = e_m \frac{v_m s_i}{K_m + s_i} \\
\nu_x(c_x, a) & = c_x \frac{\gamma(a)}{n_x} \qquad (1) \\
\gamma(a) & = \gamma_{max} \frac{a}{K_\gamma + a} \\
\omega_x(a) & = w_x \frac{a}{\theta_x + a} \\
\omega_q(a) & = w_x \frac{a}{\theta_x + a} I(q) \\
I(q) & = \frac{1}{1 + (\frac{q}{K_q})^{h_q}} \\
R_t & = \sum_x c_x \\
M & = \sum_x n_x x + R_t \quad (3, constant) \\
\lambda & = \gamma(a) \frac{R_t}{M}
\end{cases}
$$

Nutrient efficiency and chloramphenicol

- Varying nutrient efficiency changes the level of available energy in the cell, impacting the 1st tradeoff
- Chloramphenicol: antibiotic that inhibits translation, affects the 2nd tradeoff

Experimental results



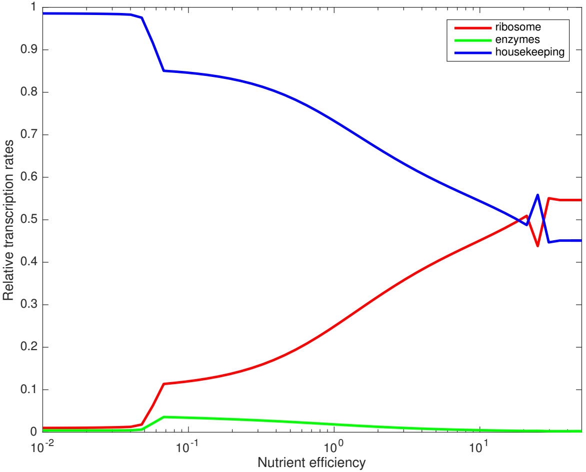


Figure: Evolution of transcription rates with nutrient efficiency.

The cell chooses what to transcribe depending on the available energy level

- At low energy: make more enzymes to increase energy levels
- At high energy: make more ribosomes to increase protein production

Gene dosage compensation

- Delete one of two paralogous genes
- Observe the change in the expression rate
- Responsiveness: $R(x) = \log(\frac{x^{\Delta_y}}{\delta(x,y)x^{wt}})$

Experiments

- Wild-type strain: with a gratuitous protein
- Protein deletion strain: halve the protein transcription
- Enzyme deletion strain: halve enzyme transcription

Enzyme deletion strain

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Description of the model

Varying the external medium

Relative transcription rates and energy levels

Gene dosage compensation

Adding a synthetic circuit

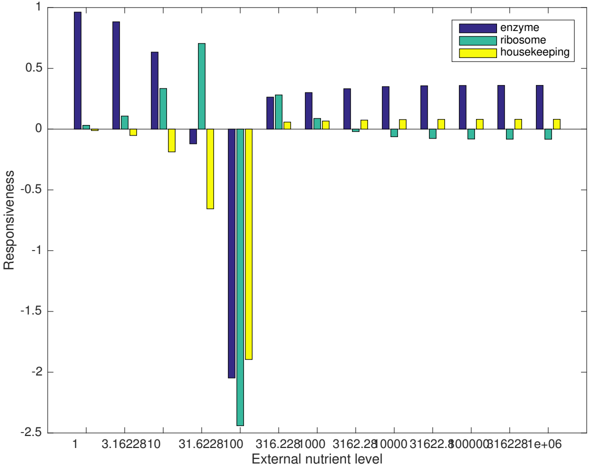


Figure: Responsiveness in the enzyme deletion strain.

Protein deletion strain

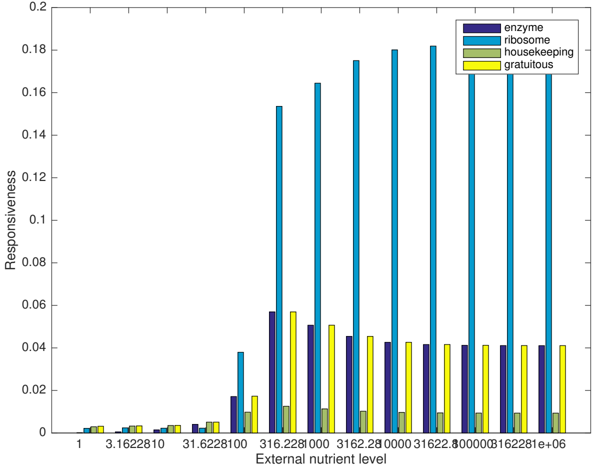


Figure: Responsiveness in the gratuitous protein deletion strain.

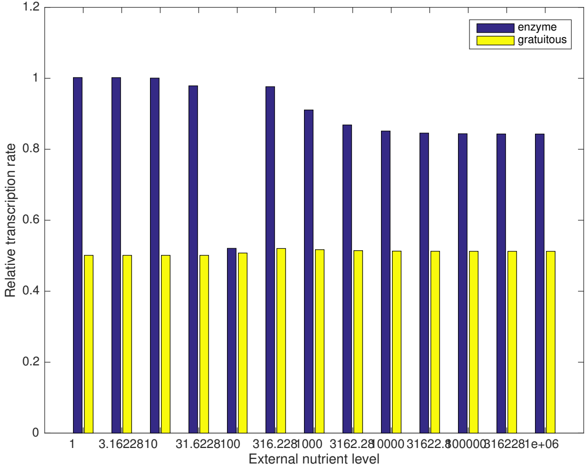
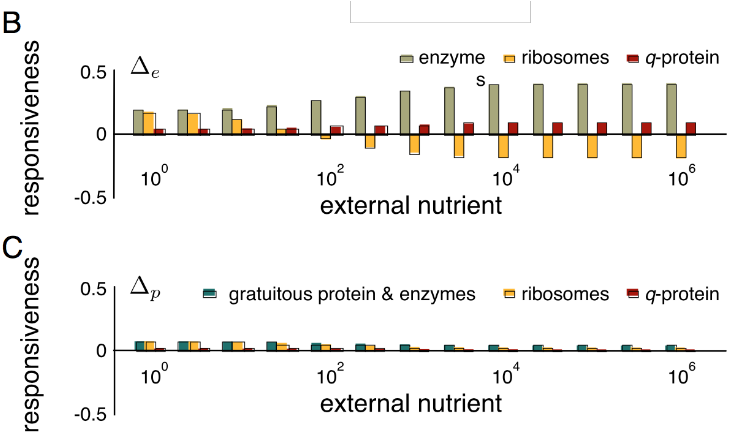


Figure: Relative transcription rates in the deletion strains.

Responsiveness in the paper



The toggle switch

- Two proteins: TetR and LacI
- Inhibit each other's transcription
- Don't interact with the metabolism apart from their use of cell resources

Experiment

- Vary the induction level of the external circuit
- Look at the relative and absolute translation (production) of the proteins involved
- Maximizing induction does not maximize output!

Results

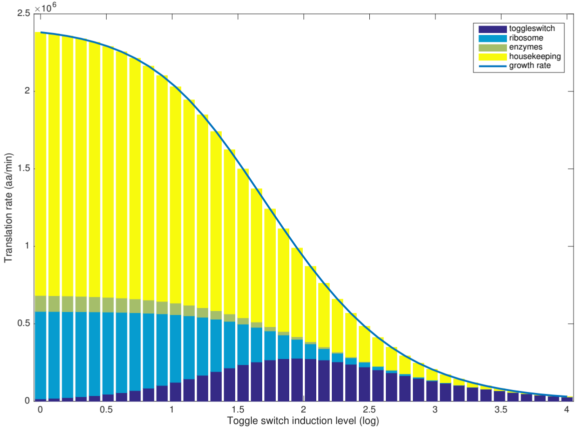


Figure: Protein transcription rates and cell growth rate (in min^{-1}).

Conclusion

- Simple model: experiments are easier to make and to interpret
- The effects of the trade-offs are visible even with a very simple model
- The trade-offs interpretation does help understanding the experimental results