Entropic costs of metabolic regulation

Growth against entropy in bacterial metabolism: the phenotypic trade-off behind empirical growth rate distributions in *E. coli*
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Recommended with a commentary by Kirill Korolev, Boston University

A cell needs to coordinate thousands of chemical reactions in order to replicate. This is not a trivial task for a tiny creature trying to overcome thermal fluctuations with limited computational resources. Yet, bacteria can replicate in mere 20 minutes, which is only a few times longer than the limit imposed by the rate of protein synthesis. How much regulation is necessary to achieve such fast growth rates, and what are the thermodynamic costs of regulation? The featured paper takes a creative approach to answering these questions by quantifying the phase space of metabolic states accessible to a cell.

Bacterial metabolism is very well characterized, and we have a nearly complete list of all chemical reactions within a cell. Most reactions are catalyzed by specific enzymes, so a cell can control its reaction fluxes by tuning the concentration of the required enzymes. To a first approximation, these fluxes define the phase space of metabolic regulation and completely specify the growth rate of a cell. The values of the fluxes are only constrained by stoichiometry and biochemical bounds on the rates of reactions. All this information is available for a number of organisms including *Escherichia coli*, a bacterium commonly used for research in biology. A total of 1075 reactions can take place in *E. coli*, but the constraints reduce the dimensionality of the phase space to 233. Within this space, there is a unique growth optimum, which is commonly used to predict reaction fluxes in metabolic engineering. This flux-based modeling approach makes many simplifying assumptions about the underlying biology. In particular, cells are assumed to grow in a steady state, so that metabolite concentrations remain constant and can be excluded from the analysis. Other important assumptions are that the number of reactants is large enough to neglect fluctuations and that the diffusion is fast enough to neglect spatial correlations.

A key idea in the featured work is that the growth rate of a cell is controlled not only by the growth optimum, but also by the density of metabolic states in its vicinity. The authors directly compute the density of states $q(\lambda)$ for a given growth rate λ and find that it decreases sharply as the maximal growth rate is approached: $q(\lambda) \propto (\lambda_{\max} - \lambda)^{171}$. The large exponent reflects the number of reactions that needs to be tuned to achieve the fastest growth and shows that the localization of metabolic fluxes near the growth optimum must come with a significant entropic cost. Specifically, the results in the paper suggest that the phase space volume needs to be constrained by a factor of 2^{75} in order to achieve a typical growth rate. In other words, the entropic cost of regulation is close to 75 bits. The authors also suggest a very simple mechanism for metabolic regulation: A random walk in the phase space. In a given cell, such regulation of course produces a uniform distribution across the phase space and results in slow growth. In a population of cells, however, faster growing cells leave more offspring, and natural selection concentrates the population near the growth rate optimum. This diffusion-selection mechanism produces metabolic states that are very similar to those obtained by minimizing the entropic costs.

Beyond providing a new perspective on microbial metabolism, the paper also makes testable predictions. In particular, the authors predict the patterns of growth rate variability in a population of identical cells and find excellent agreement with empirical data. In the last 10 years, several groups have measured the distributions of growth rates in *E. coli* and other organisms across different environmental conditions. The distributions have a characteristic unimodal shape with a coefficient of variation of about 10%. These growth rate fluctuations generated a lot of interest, and several hypotheses were proposed to explain them: from evolutionary bet-hedging to noise propagation in auto-catalytic chemical reactions. While more work will be necessary to determine the true origin of growth rate fluctuations, the featured paper provides a compelling explanation that is well grounded in biochemistry and statistical physics. Perhaps the most exciting aspect of this research is that it both connects to empirical data and touches on deep questions about the statistical mechanics of Life.