

Study of Proteome Partition Model

An Annotated Bibliography

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Experimental Studies

- [1] M. Basan, S. Hui, H. Okano, Z. Zhang, Y. Shen, J. R. Williamson, and T. Hwa, “Overflow metabolism in escherichia coli results from efficient proteome allocation,” *Nature*, vol. 528, no. 7580, pp. 99–104, 2015.

Basan et al. show that *E. coli*’s aerobic acetate ”overflow” is not wasteful mishandling of carbon but a global strategy driven by proteome allocation. The work reframes overflow metabolism as an optimal allocation outcome under proteome constraints rather than a regulatory failure.

- [2] S. Hui, J. M. Silverman, S. S. Chen, D. W. Erickson, M. Basan, J. Wang, T. Hwa, and J. R. Williamson, “Quantitative proteomic analysis reveals a simple strategy of global resource allocation in bacteria,” *Molecular Systems Biology*, vol. 11, no. 1, p. 784, 2015.

Hui et al. use quantitative mass-spectrometry across controlled carbon, anabolic, and ribosomal limitations in *E. coli* to show that the proteome partitions into coarse-grained sectors whose mass fractions vary linearly with growth rate. Roughly half of the proteome follows these growth-rate-dependent trends, which are captured by a minimal flux model with only two effective parameters, linking proteome partitioning tightly to metabolic throughput. The results reveal a simple, global resource-allocation strategy underpinning complex gene-expression responses and provide a phenomenological

framework for predicting cellular physiology without detailed molecular regulation, with implications for systems biology and synthetic circuit design.

- [3] M. Jahn, V. Vialas, J. Karlsen, G. Maddalo, F. Edfors, B. Forsström, M. Uhlén, L. Käll, and E. P. Hudson, “Growth of cyanobacteria is constrained by the abundance of light and carbon assimilation proteins,” *Cell Reports*, vol. 25, no. 2, pp. 478–486.e8, 2018.

Using shotgun proteomics in *Synechocystis* PCC 6803 across light- and inorganic-carbon-limited regimes, Jahn et al. partition the proteome into functional sectors and show several sector sizes vary roughly linearly with growth rate. Compared with *E. coli*, the ribosomal sector is smaller, consistent with a lower maximal growth rate in cyanobacteria. Light limitation reshapes multiple sectors strongly, whereas Ci limitation has a weaker impact; notably, carbon-assimilation proteins track light more than external Ci.

- [4] Y. Korem Kohanim, D. Levi, G. Jona, B. D. Towbin, A. Bren, and U. Alon, “A bacterial growth law out of steady state,” *Cell Reports*, vol. 23, no. 10, pp. 2891–2900, 2018.

Kohanim et al. extend bacterial ”growth laws” to dynamically changing environments by deriving and testing a law for nutritional upshifts: immediately after an upshift, the growth rate equals the geometric mean of the pre-shift growth rate and the growth rate on saturating carbon. Using chemostat and batch experiments, they show that this relation holds robustly.

- [5] A. Lourenço, S. Carneiro, J. P. Pinto, M. Rocha, E. C. Ferreira, and I. Rocha, “A study of the short and long-term regulation of *E. coli* metabolic pathways,” *Journal of Integrative Bioinformatics*, vol. 8, no. 3, p. 183, 2011.

This paper surveys how *E. coli* metabolism is controlled across two timescales: ”long-term” transcriptional regulation that adjusts enzyme levels via transcription factors, and ”short-term” enzymatic (allosteric/metabolic) regulation that can override expression programs. The review offers a global view of the regulatory network and highlights implications for modeling and control of bacterial metabolism.

- [6] E. Metzl-Raz, M. Kafri, G. Yaakov, I. Soifer, Y. Gurvich, and N. Barkai, “Principles of cellular resource allocation revealed by condition-dependent proteome profiling,” *eLife*, vol. 6, p. e28034, 2017.

Cells maintain a substantial pool of excess ribosomal proteins (about 8% of the proteome), implying that about 25% of ribosomes in fast growth are idle and that this reserve increases as growth slows. This “spare ribosome” strategy trades off steady-state efficiency for rapid responsiveness.

- [7] M. Mori, Z. Zhang, A. Banaei Esfahani, J. Lalanne, H. Okano, B. C. Collins, A. Schmidt, O. T. Schubert, D. Lee, G. Li, R. Aebersold, T. Hwa, and C. Ludwig, “From coarse to fine: the absolute *Escherichia coli* proteome under diverse growth conditions,” *Molecular Systems Biology*, vol. 17, no. 5, p. e9536, 2021.

The study develops a DIA/SWATH mass-spectrometry workflow and a new protein-inference algorithm (xTop) to quantify absolute abundances for over 2,000 *E. coli* proteins across over 60 conditions. The resource offers high-quality mass-fraction measurements for systems biology and multi-omics modeling of bacterial physiology.

- [8] A. Schmidt, K. Kochanowski, S. Vedelaar, E. Ahrné, B. Volkmer, L. Callico, K. Knoops, M. Bauer, R. Aebersold, and M. Heinemann, “The quantitative and condition-dependent *Escherichia coli* proteome,” *Nature Biotechnology*, vol. 34, no. 1, pp. 104–110, 2016.

The study quantified absolute abundances for about 2,300 *E. coli* proteins (about 55% of genes) across 22 growth conditions using streamlined fractionation and high-resolution mass spectrometry. The dataset reveals how protein mass redistributes among cellular functions with growth rate and environment, uncovers widespread post-translational modifications, and highlights system-wide allocation.

Theoretical Models

- [9] E. Bosdriesz, D. Molenaar, B. Teusink, and F. J. Bruggeman, “How fast-growing bacteria robustly tune their ribosome concentration to approximate growth-rate maximization,” *FEBS Journal*, vol. 282, no. 10, pp. 2029–2044, 2015.

Bosdriesz et al. develop a coarse-grained kinetic model for *E. coli* that links ppGpp-mediated regulation of ribosome synthesis to near-optimal growth across conditions. They show that the native control logic keeps ribosomes saturated with charged tRNAs, preventing costly overproduction of ribosomal proteins and reallocating proteome to other growth-promoting enzymes; in this scheme, the fraction of inactive ribosomes acts as an intracellular signal of nutrient status. The model demonstrates that basic biochemical interactions are sufficient to achieve robust protein partitioning and growth-rate maximization, offering a mechanistic basis for bacterial “growth laws.”

- [10] D. W. Erickson, S. J. Schink, V. Patsalo, J. R. Williamson, U. Gerland, and T. Hwa, “A global resource allocation strategy governs growth transition kinetics of *escherichia coli*,” *Nature*, vol. 551, no. 7678, pp. 119–123, 2017.

Erickson et al. develop a top-down, parameter-free kinetic model that extends coarse-grained proteome allocation theory from steady state to transients and shows that a single flux-controlled resource-allocation strategy can predict how *E. coli* reprograms gene expression and biomass accumulation during nutrient upshifts and downshifts (including diauxic shifts). Using only qualitative regulatory knowledge plus a flux-balance constraint, the model quantitatively captures the time courses of ribosomal and catabolic sectors without adjustable kinetic parameters and explains why cells often recover suboptimally after shifts: protein-synthesis resources are reallocated according to a rigid global rule rather than to relieve specific bottlenecks. Quantitative proteomics validates the predicted trajectories, pointing to a general framework for describing growth-transition kinetics without detailed biochemical rate constants.

- [11] A. Goyal and G. Chure, “Paradox of the sub-plankton: Plausible mechanisms and open problems underlying strain-level diversity in microbial communities,” *Environmental Microbiology*, vol. 27, no. 4, p. e70094, 2025.

The authors synthesize candidate mechanisms for maintaining “microdiversity,” covering niche-based processes (e.g., resource

partitioning and cross-feeding), neutral processes (e.g., migration and drift), and evolutionary processes (e.g., horizontal gene transfer).

- [12] X.-P. Hu and M. J. Lercher, “An optimal growth law for rna composition and its partial implementation through ribosomal and trna gene locations in bacterial genomes,” *PLOS Genetics*, vol. 17, no. 11, p. e1009939, 2021.

The paper derives a growth law for bacterial RNA composition by minimizing the combined mass of ribosomes (rRNA) and ternary complexes (largely EF-Tu-GTP-tRNA) at a required protein production rate. They predict that the optimal tRNA/rRNA ratio decreases monotonically with growth rate, which matches measurements across *E. coli* and other fast-growing microbes. The authors further show that genomes may help realize this law, since in many bacteria, rRNA operons are positioned closer to the replication origin than tRNA genes, so replication-associated effects drive lower tRNA/rRNA expression ratios at higher growth.

- [13] I. T. Kleijn, S. Marguerat, and V. Shahrezaei, “A coarse-grained resource allocation model of carbon and nitrogen metabolism in unicellular microbes,” *Journal of the Royal Society Interface*, vol. 20, no. 206, p. 20230206, 2023. [Online]. Available: <https://doi.org/10.1098/rsif.2023.0206>

They formulate a coarse-grained resource allocation model with nitrogen and carbon pathways, describing the effects of the uptake of sugars, and amino acids on the resource allocation towards proteome sectors that maximize the growth rate. It recovers cellular growth laws including the Monod law and the ribosomal growth law. They also find linear correlation between ribosome fraction and the abundance of amino acid equivalents, supporting the view that regulation of translational gene expression can enable cells to achieve an approximately optimal growth state.

- [14] F. Mairet, J.-L. Gouzé, and H. de Jong, “Optimal proteome allocation and the temperature dependence of microbial growth laws,” *npj Systems Biology and Applications*, vol. 7, p. 14, 2021.

A coarse-grained resource-allocation model that explicitly accounts for temperature-dependent protein unfolding and chaperone-assisted refolding, alongside metabolic and ribosomal sectors, and then determine the proteome split that maximizes balanced growth across nutrients and temperatures.

- [15] L. Pacciani-Mori, S. Suweis, A. Maritan, and A. Giometto, “Constrained proteome allocation affects coexistence in models of competitive microbial communities,” *The ISME Journal*, vol. 15, no. 5, pp. 1458–1477, 2021.

extend MacArthur’s consumer–resource framework by embedding proteome-allocation constraints, creating a ”consumer–proteome-resource” model in which species must divide limited protein-synthesis capacity between nutrient uptake and growth. Analytically and numerically, they derive coexistence conditions for many species and resources, showing how time-varying, resource-specific proteome budgeting shapes dynamics. The work links intracellular resource allocation to community-level outcomes and offers tractable criteria to predict when competitors can stably coexist.

- [16] C. J. Russo, K. Husain, and A. Murugan, “Soft modes as a predictive framework for low-dimensional biological systems across scales,” *Annual Review of Biophysics*, vol. 54, no. 1, pp. 401–426, 2025.

Low-dimensional responses observed in many biological systems can be understood through a unifying ”soft modes” dynamical-systems framework. These soft-mode structure can organize data analysis and guide experiments across scales.

- [17] M. Scott, C. W. Gunderson, E. M. Mateescu, Z. Zhang, and T. Hwa, “Interdependence of cell growth and gene expression: origins and consequences,” *Science*, vol. 330, no. 6007, pp. 1099–1102, 2010.

First modern formulation of the three-sector proteome partition model. A phenomenological framework showing that bacterial growth rate and gene expression are tightly coupled by global resource-allocation constraints, especially the share of the proteome devoted to ribosomes. By perturbing *E. coli* with translation-inhibiting antibiotics and by forcing gratuitous protein expression, they derive and validate simple

”growth laws” that quantitatively predict how changes in one dimension (e.g., burdening expression) feed back on the other (cell proliferation) and vice versa.

- [18] M. Scott and T. Hwa, “Bacterial growth laws and their applications,” *Current Opinion in Biotechnology*, vol. 22, no. 4, pp. 559–565, 2011.

The study outlines twin linear laws observed when growth is limited by nutrients versus translation capacity. It proposes emerging ”bacterial growth laws” and shows how these phenomenological constraints can explain diverse physiological behaviors without detailed regulatory models.

- [19] M. Scott, S. Klumpp, E. M. Mateescu, and T. Hwa, “Emergence of robust growth laws from optimal regulation of ribosome synthesis,” *Molecular Systems Biology*, vol. 10, no. 8, p. 747, 2014. [Online]. Available: <https://www.embopress.org/doi/abs/10.1525/msb.20145379>

The study highlights the interplay between phenomenological modeling and molecular mechanisms in uncovering fundamental operating constraints, with implications for endogenous and synthetic design of microorganisms.

- [20] S. P. T. H. Stefan Klumpp, Matthew Scott, “Molecular crowding limits translation and cell growth,” *Proceedings of the National Academy of Sciences*, vol. 110, no. 42, pp. 16 754–16 759, 2013. [Online]. Available: <https://www.pnas.org/doi/abs/10.1073/pnas.1310377110>

Klumpp et al. show that a physical transport limit, which is the slow diffusion of ternary complexes in the crowded cytoplasm, constrains translational throughput, and thus bacterial growth. They build a proteome-allocation model coupling ribosome abundance, ternary-complex diffusion, and macromolecular crowding, which predicts an optimal ribosomal fraction and quantitatively accounts for growth-rate-dependent translation speeds and allocation trends. This study reframes growth limits as being diffusion-controlled rather than purely enzymatic-kinetic

- [21] J. Tang and W. J. Riley, “Finding liebig’s law of the minimum,” *Eco-logical Applications*, vol. 31, no. 8, p. e02458, 2021.

Liebig's law of the minimum (LLM) and show it is a coarse approximation of the law of mass action for growth limited by two essential resources. They argue that ecosystem and biogeochemical models should prefer mechanistically grounded formulations.

- [22] A. Vazquez and T. Gedeon, "Geometrically balanced model of cell growth," *Journal of Theoretical Biology*, vol. 604, p. 112085, 2025.

The study argues that growth is limited not only by protein-synthesis capacity but also by surface-area and membrane-lipid demands. Using a reduced metabolic model, they show how this additional constraint reshapes optimal allocation and growth predictions, showing interactions between metabolism and molecular crowding.

Mathematical Background

- [23] M. Feinberg, *Foundations of Chemical Reaction Network Theory*, ser. Applied Mathematical Sciences. Cham: Springer, 2019, vol. 202.

The definitive introduction to chemical reaction network theory (CRNT), developing rigorous links between a network's graphical/algebraic structure and qualitative properties of the nonlinear ODEs it induces.

- [24] J. Gunawardena, "Chemical reaction network theory for *in-silico* biologists," Bauer Center for Genomics Research, Harvard University, 7 Divinity Avenue, Cambridge, MA 02138, USA, Lecture notes, June 2003. [Online]. Available: <https://www.few.vu.nl/rplanque/resources/PapersForProject/gunawardena2003.pdf>
- [25] This lecture note is a self-contained introduction to Chemical Reaction Network Theory for readers in systems biology. Gunawardena formalizes reaction networks, and, using linear-algebraic tools and Perron-Frobenius theory, he develops the pathway to the deficiency-zero theorem, thus establishing conditions for existence, uniqueness, and local asymptotic stability of equilibria. Weak reversibility, terminal strong linkage classes, and examples illustrating when deficiency one admits multistationarity are also discussed. The notes emphasize how much of the nonlinear mass-action dynamics

is constrained by hidden linear structure, making CRNT a powerful qualitative tool even without precise kinetic parameters.

W.-H. Lin, E. Kussell, L.-S. Young, and C. Jacobs-Wagner, “Origin of exponential growth in nonlinear reaction networks,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 117, no. 45, pp. 27 795–27 804, 2020.

Lin et al. proposes a general theoretical framework that explains how exponential growth emerges in complex nonlinear reaction networks by combining two central principles: scalability of flux functions and ergodicity of the rescaled system dynamics. Although many biological networks are highly nonlinear, under the condition of scalability and ergodicity, they will exhibit either a well-defined exponential growth rate or periodic, quasi-periodic, or chaotic growth.

D. Siegel and D. MacLean, “Global stability of complex balanced mechanisms,” *Journal of Mathematical Chemistry*, vol. 27, no. 1, pp. 89–110, 2000.

This paper proves global convergence results for mass-action systems that are complex balanced: for any stoichiometric compatibility class, the omega-limit set of a trajectory consists either of a unique positive complex-balanced equilibrium or of boundary complex-balanced equilibria. The theorem is applied to several enzymatic mechanisms, establishing global asymptotic stability of their interior equilibria. The work extends classical detailed-balance results to the broader complex-balanced class, giving powerful structural criteria for global dynamics without parameter tuning.

E. D. Sontag, “Monotone and near-monotone biochemical networks,” *Systems and Synthetic Biology*, vol. 1, no. 2, pp. 59–87, 2007.

Sontag surveys how monotone systems theory can be used to infer qualitative dynamics of biochemical networks directly from signed interaction graphs, without detailed parameters. In monotone networks, trajectories are order-preserving, ruling out stable oscillations and chaos and enabling powerful decomposition results for large systems. The paper also show how small violations of monotonicity can still yield tractable behaviors, including multistability via positive feedback and robust adaptation motifs.

The review synthesizes graph-theoretic criteria and examples from gene regulation to provide a practical toolkit for reasoning about stability and bistability in complex biochemical networks.