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Achieving optimal growth: lessons from simple metabolic modules SIDHARTHA GOYAL, Physics, THOMAS CHEN, Applied Mathematics, NED WINGREEN, Molecular Biology, Princeton University — Metabolism is a universal property of living organisms. While the metabolic network itself has been well characterized, the logic of its regulation remains largely mysterious. Recent work has shown that growth rates of microorganisms, including the bacterium *Escherichia coli*, correlate well with optimal growth rates predicted by flux-balance analysis (FBA), a constraint-based computational method. How difficult is it for cells to achieve optimal growth? Our analysis of representative metabolic modules drawn from real metabolism shows that, in all cases, simple feedback inhibition allows nearly optimal growth. Indeed, product-feedback inhibition is found in every biosynthetic pathway and constitutes about 80% of metabolic regulation. However, we find that product-feedback systems designed to approach optimal growth necessarily produce large pool sizes of metabolites, with potentially detrimental effects on cells via toxicity and osmotic imbalance. Interestingly, the sizes of metabolite pools can be strongly restricted if the feedback inhibition is ultrasensitive (*i.e.* with high Hill coefficient). The need for ultrasensitive mechanisms to limit pool sizes may therefore explain some of the ubiquitous, puzzling complexity found in metabolic feedback regulation at both the transcriptional and post-transcriptional levels.

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