# Fundamental limits on the rate of bacterial cell division

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## Abstract

## Introduction

The range of bacterial growth rates can be enormous. In natural environments, doublings occur approximately once per year whereas in comfortable laboratory conditions, growth can be rapid with several divisions per hour. This remarkable diversity illustrates the intimate relationship between environmental conditions and the rates at which cells convert nutrients into new cellular material. This relationship between the environment and cellular growth rate has remained a major topic of inquiry in bacterial physiology for over a century (***Jun et al., 2018***). In 1958, Schaecter, Malløe, and Kjeldgaard reported the discovery of a strong, linear dependence of the total cellular protein content on the growth rate, revealing a fundamental relationship between the environment and the composition of the intracellular milieu (***Schaechter et al., 1958***). Over the past decade, a remarkable body of work has examined this relationship with single-protein resolution using modern methods of mass spectrometry (***Valgepea et al., 2013***; ***Peebo et al., 2015***; ***Schmidt et al., 2016***) and ribosomal profiling (***Li et al., 2014***) which permit a quantitative investigation of the relationship between gene expression and growth rate. This body of experimental data places us in the auspicious position to explore how the abundance of fundamental protein complexes are related to the growth rate of the population and interrogate what biological processes may set the speed limit of bacterial growth.

In this work, we seek to leverage a collection of proteomic data sets of *Escherichia coli* across 31 growth conditions to quantitatively explore what biological processes may set the speed limit of bacterial growth. Broadly speaking, we entertain several classes of hypotheses as are illustrated in ***Figure 1***. First, we consider potential limits on the transport of nutrients into the cell. We address this hypothesis by performing an order-of-magnitude estimate for how many carbon atoms needed to facilitate this requirement given a 6000 second division time. As a second hypothesis, we consider there exists a fundamental limit on how quickly the cell can generate ATP. We approach this hypothesis from two angles, considering how many ATP synthase complexes must be needed

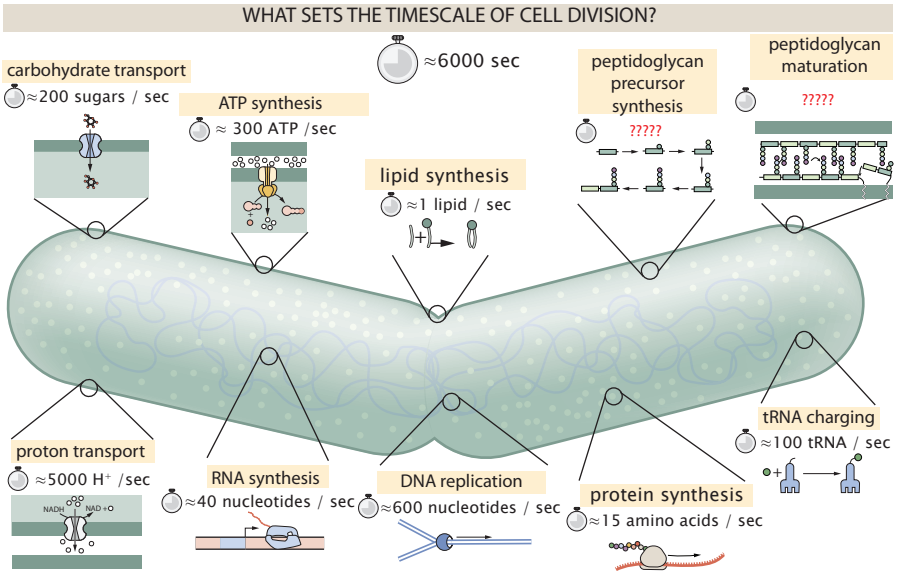


**Figure 1. Transport and synthesis processes necessary for cell division.** We consider an array of processes necessary for a cell to double its molecular components. Such processes include the transport of carbon across the cell membrane, the production of ATP, and fundamental processes of the central dogma namely RNA, DNA, and protein synthesis. A schematic of each synthetic or transport category is shown with an estimate of the rate per macromolecular complex. In this work, we consider a standard bacterial division time of ≈ 6000 sec.

to churn out enough ATP to power protein translation followed by an estimation of how many electron transport complexes must be present to maintain the proton motive force. Our third and final class of hypotheses centers on the synthesis of a variety of biomolecules. Our focus is primarily on the stages of the central dogma as we estimate the number of protein complexes needed for DNA replication, transcription, and protein translation.

With estimates in hand for each of these processes, we turn to our collection of data sets to assess the accuracy of our estimates. In broad terms, we find that the majority of our estimates are exceeded by the experimental observations, allowing us to systematically scratch off the hypotheses diagrammed in ***Figure 1*** as setting the speed limit. Ultimately, we find that protein translation (particularly the generation of new ribosomes) acts as the rate limiting step of bacterial division. We again leverage the quantitative nature of this data set and present a quantitative model of the relationship between the fraction of the proteome devoted to ribosomes and the speed limit of translation, revealing a fundamental tradeoff between the translation capacity of the ribosome pool and the maximal cellular growth rate.

## References

Jun, S., Si, F., Pugatch, R., and Scott, M. (2018). Fundamental principles in bacterial physiology - history, recent progress, and the future with focus on cell size control: A review. *Reports on Progress in Physics*, 81(5):056601.

Li, G.-W., Burkhardt, D., Gross, C., and Weissman, J. S. (2014). Quantifying absolute protein synthesis rates reveals principles underlying allocation of cellular resources. *Cell*, 157(3):624–635.

Peebo, K., Valgepea, K., Maser, A., Nahku, R., Adamberg, K., and Vilu, R. (2015). Proteome reallocation in *Escherichia coli* with increasing specific growth rate. *Molecular BioSystems*, 11(4):1184–1193.

Schaechter, M., Maaløe, O., and Kjeldgaard, N. O. (1958). Dependency on medium and temperature of cell size and chemical composition during balanced growth of *Salmonella typhimurium*. *Microbiology*, 19(3):592–606.

Schmidt, A., Kochanowski, K., Vedelaar, S., Ahrné, E., Volkmer, B., Callipo, L., Knoops, K., Bauer, M., Aebersold, R., and Heinemann, M. (2016). The quantitative and condition-dependent *Escherichia coli* proteome. *Nature Biotechnology*, 34(1):104–110.

68 Valgepea, K., Adamberg, K., Seiman, A., and Vilu, R. (2013). *Escherichia coli* achieves faster growth by increasing
69 catalytic and translation rates of proteins. *Molecular BioSystems*, 9(9):2344.