Fundamental limits on the rate of bacterial cell division

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Abstract

Introduction

The range of bacterial growth rates can be enormous where in natural environments, some microbial organisms might double only once per year while 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 and has remained a major topic of inquiry in bacterial physiology for over a century (***Jun et al., 2018***). As was noted by Jacques Monod, "the study of the growth of bacterial cultures does not constitute a specialized subject or branch of research, it is the basic method of Microbiology." Those words ring as true today as they did when they were written 70 years ago. Indeed, the study of bacterial growth has undergone a molecular resurgence since many of the key questions addressed by the pioneering efforts in the middle of the last century can be revisited by examining them through the lens of the increasingly refined molecular census that is available for bacteria such as the microbial workhorse *Escherichia coli*. Several of the outstanding questions that can now be studied about bacterial growth include: what sets the fastest time scale that bacteria can divide, and how is growth rate tied to the quality of the carbon source. In this paper, we address these two questions from two distinct angles. First, as a result of an array of high-quality proteome-wide measurements of the *E. coli* proteome under a myriad of different growth conditions, we have a census that allows us to explore how the number of key molecular players change as a function of growth rate. This census provides a window onto whether the processes they mediate such as molecular transport into the cells and molecular synthesis within cells can run faster. Second, because of our understanding of the molecular pathways responsible for many of the steps in bacterial' growth, we can also make order of magnitude estimates to infer the copy numbers that would be needed to achieve a given growth rate. In this paper, we pass back and forth between the analysis of a variety of different proteomic datasets and order-of-magnitude estimations to determine possible molecular bottlenecks that limit bacterial growth and to see how

the growth rate varies in different carbon sources.

Specifically, we leverage a combination of *E. coli* proteomic data sets collected over the past decade using either mass spectrometry (***Schmidt et al., 2016***; ***Peebo et al., 2015***; ***Valgepea et al., 2013***) or ribosomal profiling (***Li et al., 2014***) across 31 unique growth conditions. 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, phosphorous, and sulfur atoms are needed to facilitate this requirement given a 5000 second division time. As a second hypothesis, we consider the possibility that 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 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. A third class of estimates considers the need to maintain the size and shape of the cell through the construction of new lipids for the cell membranes as well as the glycan polymers which make up the rigid peptidoglycan. Our 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.

In broad terms, we find that the majority of these estimates are in close agreement with the experimental observations, with protein copy numbers apparently well-tuned for the task of cell doubling. This allows us to systematically scratch off the hypotheses diagrammed in ***Figure 1*** as setting possible speed limits. Ultimately, we find that protein translation (particularly the generation of new ribosomes) acts as 1) a rate limiting step for the *fastest* bacterial division, and 2) the major determinant of bacterial growth across all nutrient conditions we have considered under steady state, exponential growth. This perspective is in line with the linear correlation observed between growth rate and ribosomal content (typically quantified through the ratio of RNA to protein) for fast growing cells (***Scott et al., 2010***), but suggests a more prominent role for ribosomes in setting the doubling time across all conditions of nutrient limitation. Here 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 growth rate.

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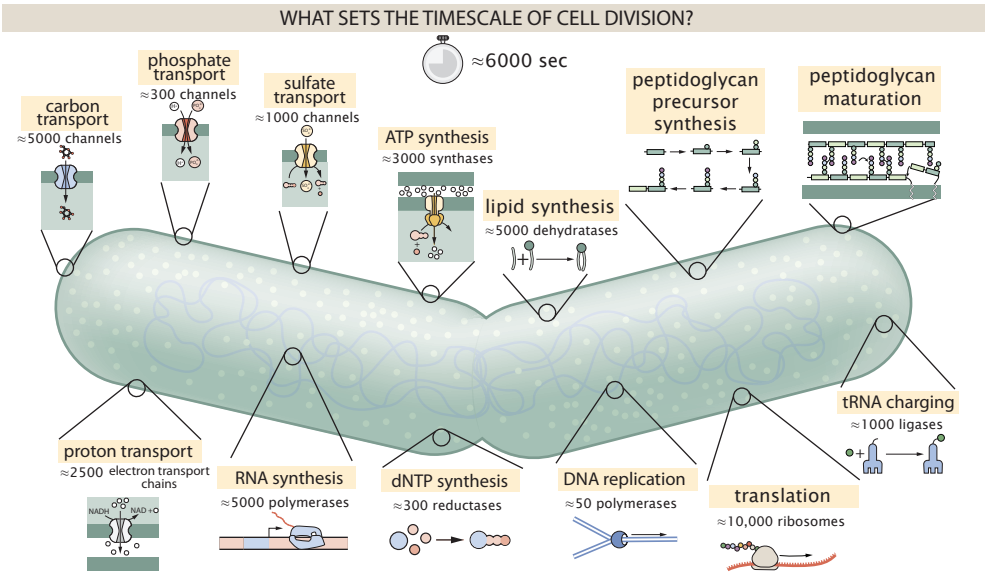

Figure 1. Transport and synthesis processes necessary for cell division. We consider an array of processes necessary for a cell to double its molecular components. Such processes include the transport of carbon across the cell membrane, the production of ATP, and fundamental processes of the central dogma namely RNA, DNA, and protein synthesis. A schematic of each synthetic or transport category is shown with an approximate measure of the complex abundance at a growth rate of 0.5 per hour. In this work, we consider a standard bacterial division time of ≈ 5000 sec.