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, some organisms might double only 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 logarithmic relationship between the total cellular protein content and the cellular 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 reexamined this relationship with single-cell and single-protein resolution using modern methods of video microscopy (***Si et al., 2017***; ***Harris and Theriot, 2018***) and through advances in mass spectrometry and sequencing technologies (***Schmidt et al., 2016***; ***Li et al., 2014***). This has permitted quantitative insight into how bacteria like *E. coli* allocate their cellular resources under nutrient-limitation, and following genomic and pharmacological perturbations (***Scott et al., 2010***; ***Hui et al., 2015***; ***Basan et al., 2015***). This body of experimental data places us in the auspicious position to explore how the abundance of essential 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 (***Valgepea et al., 2013***; ***Li et al., 2014***; ***Peebo et al., 2015***; ***Hui et al., 2015***; ***Schmidt et al., 2016***) 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 hy-

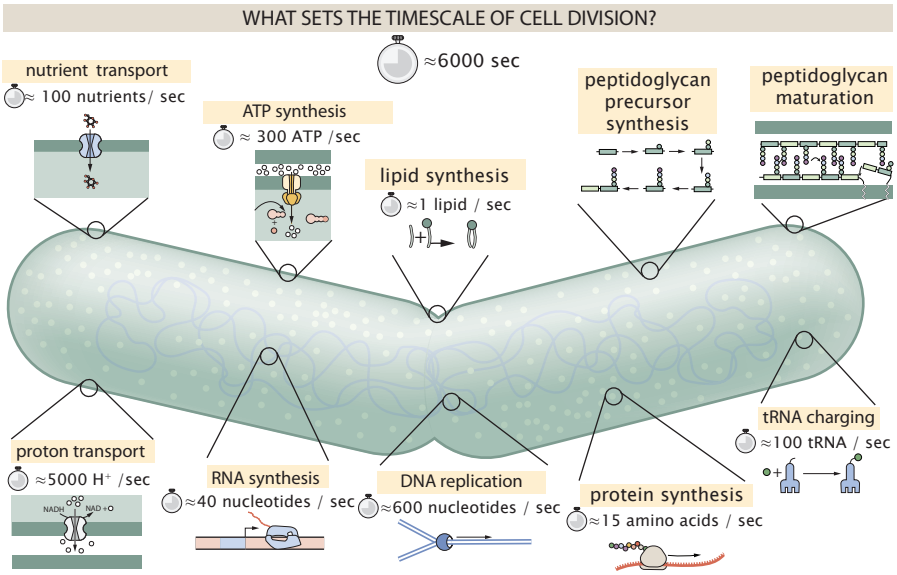

Figure 1. Transport and synthesis processes necessary for cell division. We consider an array of processes necessary for a cell to double its molecular components. Such processes include the transport of carbon across the cell membrane, the production of ATP, and fundamental processes of the central 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.

pothesis 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 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. 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 in line with 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 (usually quantified through the ratio of RNA to protein) for fast growing cells (***Scott et al., 2010***), but suggests a more prominant 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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