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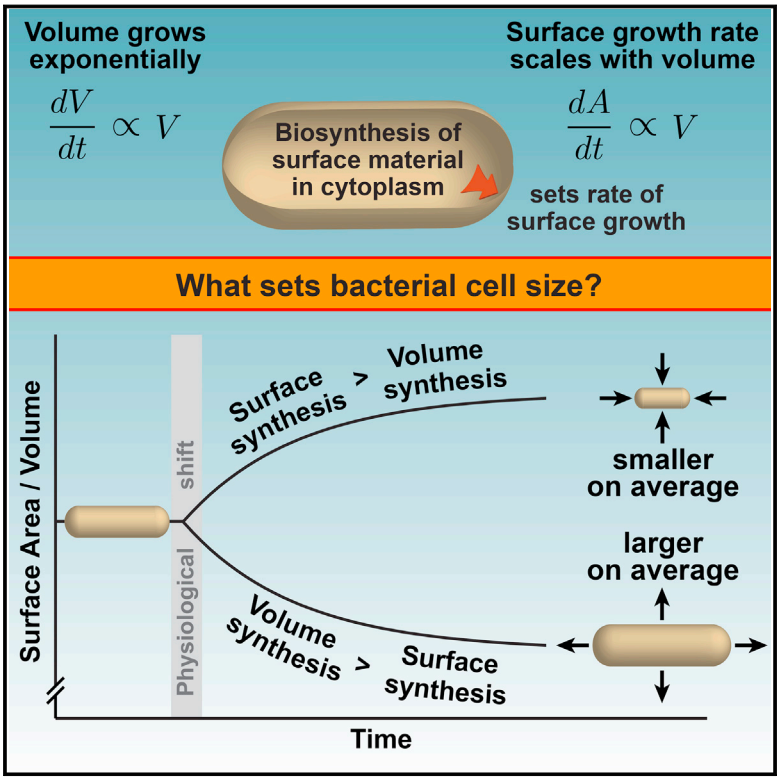
Relative Rates of Surface and Volume Synthesis Set Bacterial Cell Size

Graphical Abstract



Highlights

- Maintenance of a condition-dependent surface area to volume ratio (SA/V) sets bacterial size
- Rates of volume and surface growth both scale with volume, producing SA/V homeostasis
- Biosynthesis of surface material in the cytoplasm links surface growth rate to volume
- A surface material accumulation threshold for division could underlie length control

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In Brief

Rod-shaped bacteria alter both their width and length to achieve a condition-dependent surface area to volume ratio, and this SA/V homeostasis arises because the rates of volume and surface synthesis both scale with cell volume.

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Relative Rates of Surface and Volume Synthesis Set Bacterial Cell Size

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SUMMARY

Many studies have focused on the mechanisms underlying length and width determination in rod-shaped bacteria. Here, we focus instead on cell surface area to volume ratio (SA/V) and demonstrate that SA/V homeostasis underlies size determination. We propose a model whereby the instantaneous rates of surface and volume synthesis both scale with volume. This model predicts that these relative rates dictate SA/V and that cells approach a new steady-state SA/V exponentially, with a decay constant equal to the volume growth rate. To test this, we exposed diverse bacterial species to sublethal concentrations of a cell wall biosynthesis inhibitor and observed dose-dependent decreases in SA/V. Furthermore, this decrease was exponential and had the expected decay constant. The model also quantitatively describes SA/V alterations induced by other chemical, nutritional, and genetic perturbations. We additionally present evidence for a surface material accumulation threshold underlying division, sensitizing cell length to changes in SA/V requirements.

INTRODUCTION

Genetically identical rod-shaped bacterial cells adopt a remarkably narrow range of lengths and widths under constant growth conditions (Schaechter et al., 1962). However, rapidly growing cells in nutrient-rich medium are typically much larger, both in width and length, than isogenic cells growing slowly in minimal medium (Schaechter et al., 1958). These classic observations raise questions that remain open and whose answers will be critical for a thorough understanding of bacterial physiology: what principles set and maintain this narrow range of cellular dimensions, and how are these dimensions modulated in response to a change in the environment?

In most bacteria, the cell wall plays a deterministic role in setting the size and shape of cells (for reviews, see Typas et al. [2012] and Young [2010]). This covalent network is composed of cross-linked peptidoglycan (PG) that surrounds the cell and counteracts turgor pressure. The synthesis of new PG begins in the cytoplasm, where a series of cytosolic enzymes catalyze successive steps in PG precursor biosynthesis, and eventually, precursors are incorporated into the growing cell wall. In rod-shaped bacteria, growth is traditionally divided into two alternating modes, elongation and septation, although these may overlap in time. During elongation, new PG is inserted into the lateral wall and cells become longer while maintaining a relatively constant width; during septation, cells constrict and form two new poles, which eventually resolve to form two daughter cells. Different PG insertion machineries coordinate these two modes of growth and are active at different times during the cell cycle, but both draw from the same pool of PG precursors.

Due to the alternating modes of elongation and division, cell length in rod-shaped cells is primarily determined by how much cells typically elongate before dividing (Typas et al., 2012; Young, 2010). Many models of division timing—and thus length control—have been proposed. Historically, it was thought that cells initiate chromosome replication after reaching a critical mass and divide a fixed amount of time later (Cooper and Helmstetter, 1968). Recently, an "adder" model has been proposed, where cells add a constant amount of volume during each cell cycle before dividing (Amir, 2014; Campos et al., 2014; Deforet et al., 2015; Jun and Taheri-Araghi, 2015; Taheri-Araghi et al., 2015; Tanouchi et al., 2015). How cells are able to "measure" a constant increase in volume, however, remains unknown, and the adder model does not address length differences across different growth rates. Several nutrient-sensing proteins have been tied to changes in cell length in response to the availability of certain nutrients (Hill et al., 2013; Weart et al., 2007; Yao et al., 2012), though these are insufficient to explain how restricting different nutrients leads to similar changes in growth rate and cell size (Schaechter et al., 1958), nor do they address the gradual, growth-rate-dependent nature of this transition (Volkmer and Heinemann, 2011).

In addition to studies based on measurement of cell length, much work has focused on how rod-shaped bacteria adopt a specific width. Several factors have been implicated in this process, including MreB, which is thought to coordinate the insertion of lateral cell wall material (reviewed in Chastanet and Carballido-Lopez, 2012). MreB depletion leads to the loss of rod shape, and mutations in MreB can lead to wider or thinner cells (Dye et al., 2011; Kruse et al., 2003; Monds et al., 2014). These results raise the possibility that MreB can determine bacterial cell width. However, as with length, the fluid modulation of cell width in response to changing physiological conditions (Volkmer and Heinemann, 2011) implies that genetic control cannot be the only force at play. Indeed, when we analyzed the growth patterns of an MreB mutant with a variable-width phenotype (Harris et al., 2014), we found that cell surface area