

Suckjoon Jun

Abstract :

How cells control their size and maintain size homeostasis is a fundamental open question. Cell-size homeostasis has been discussed in the context of two major paradigms: “sizer,” in which the cell actively monitors its size and triggers the cell cycle once it reaches a critical size, and “timer,” in which the cell attempts to grow for a specific amount of time before division. These paradigms, in conjunction with the “growth law” and the quantitative bacterial cell-cycle model, inspired numerous theoretical models and experimental investigations, from growth to cell cycle and size control. However, experimental evidence involved difficult-to-verify assumptions or population-averaged data, which allowed different interpretations or limited conclusions.

We extended a microfluidic “mother machine” and monitored hundreds of thousands of Gram-negative *E. coli* and Gram-positive *B. subtilis* cells under a wide range of steady-state growth conditions. We could thus pursue an unprecedented level of quantitative analysis. This revealed an extraordinarily simple mechanism of cell-size control. Specifically, we showed that both *E. coli* and *B. subtilis* cells grow by adding a constant volume each generation, irrespective of their birth sizes. This simple “adder” principle is sufficient for the individual cells to achieve size homeostasis. Furthermore, the adder principle quantitatively explains experimental data at both the population and single-cell levels, and unravels the origin and the hierarchy of variability in growth and division control. Phenomenologically, the adder principle can be generalized to explain size homeostasis of organisms ranging from asymmetrically dividing bacteria to eukaryotes.

E. coli and *B. subtilis* are one billion years divergent and they are textbook examples of how Gram-negative and Gram-positive bacteria are fundamentally different in cell cycle control at the molecular level. The adder principle is thus general and overturns the more than 50-year old “sizer” and “timer” paradigm for cell size control in microorganisms, and represents a higher-level control underlying cellular reproduction.