Atlas of Science
another view on science
https://atlasofscience.org

How do spaghetti-like bacteria regulate their size?

Why is your thumb longer than your pinky? Answering this question and, more in general, to understand how tissues/organs regulate their size and proportions, requires to understand how individual cells control their size. Bacteria are probably the simplest organism to address this question. Bacteria typically grow to double their size and divide around the middle. By repeating this process, the bacterial population reaches a cell size distribution that is narrow and stable, i.e., size homeostasis is achieved. You might now think "OK! problem solved". However, the devil is in the details…how does a bacterium "know" that it has grown enough to divide?

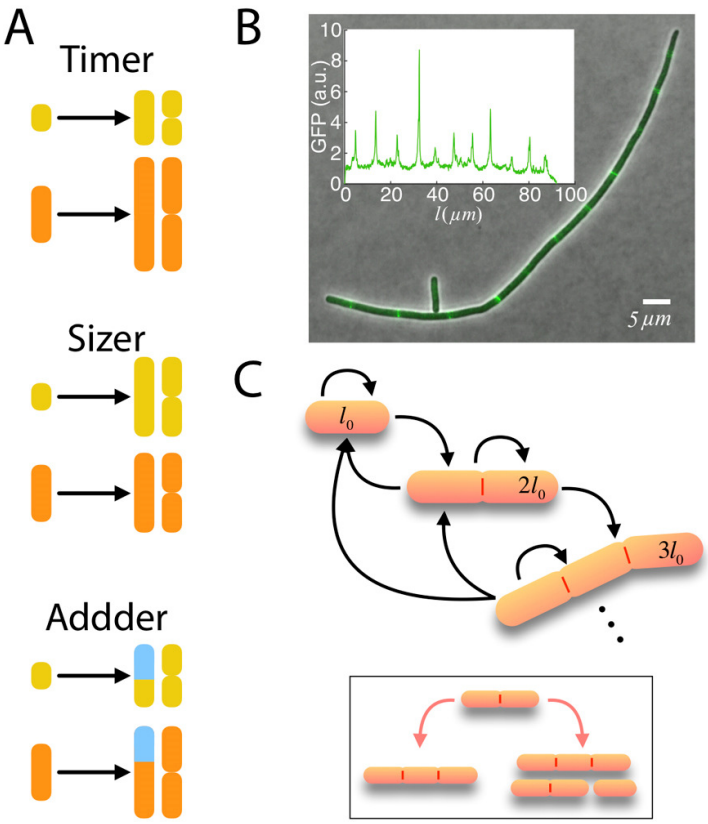

Fig. 1. A: When the timer rule applies, cells grow for a specific amount of time (regardless of their size at birth) and then divide. If the growth speed is independent of their initial size, then size convergence cannot be achieved. In the sizer model, cells grow until they reach a given length and then divide: size homeostasis is attained. In the adder rule, cells accumulate the same amount of mass (blue portion) independently of their size at birth, and then divide. This rule leads to size convergence after a number of generations. B: When bacteria develop a filamentous morphology, their division machinery (green signal, FtsZ:GFP) assembles at several locations regularly spaced. Inset: readout of the intensity of signal as a function of the length coordinate that illustrates the aforementioned regularity of the spacing. C: Our mathematical model to understand cell growth/division during filamentation considers that cells can be represented as sets of rods with a given length (l0) and explore the possible length configurations probabilistically and depending on the division pattern: the red segment indicate possible division sites. Inset: after growing by one l0 unit, cells either continue elongating of divide.

Experiments have revealed different relations between the size at birth and the size when a cell divide. Thus, cells follow one of the following rules: *timer*, *sizer*, or *adder* (Fig. 1A). The *timer* implies that cells, regardless of their size at birth, follow an internal clock, grow during a specific amount of time, and then divide. This mechanism suggests that cells, after growth and division, maintain their birth sizes and size convergence cannot be cannot achieved. The *sizer* implies that cells can measure distances, they grow until reaching a critical size, and then divide. This mechanism can certainly correct fluctuations of the size at birth and convergence is achieved. Finally, the *adder* means that cells accumulate the same amount of mass from birth to division. As shown in Figure 1A, the *adder,* combined with a symmetric division (division at the middle), also leads to size convergence and homeostasis after a number of generations. Most bacterial species, e.g., *E. coli*, follow this latter size control mechanism. Problem solved? No…again, the devil is in the details. As we just insinuated, the cleavage location is key: how does a bacterium "know" where is the middle? To cut a long story short, bacteria are able to assemble a division machinery at *regular* intervals along the cell. If cells have "normal" sizes, only one division site is formed by the middle and a symmetric division occurs. However, if cells grow longer, multiple division sites are created and, consequently, a cell can divide at different locations (Fig. 1B). How is this possibly relevant to us? Well, nature is full of exceptions and under stress, e.g., antibiotic treatment, cells develop a filamentous morphology (spaghetti-like). Can filamentous cells still achieve size homeostasis/convergence?

Recent studies have suggested that the adder rule is satisfied during filamentation. And yet, how can *adder* be compatible with a sizer property that "quantizes" multiple division locations with regular spacing? Moreover, since there are several possible cleavage sites, how important is this election? To understand the elongation/division of cells that undergo anomalous growth we proposed a mathematical model (Fig. 1C). Cells are modeled as sets of rods with different potential division sites. Upon growth/division, cells probabilistically explore different size configurations. Interestingly, we showed that a sizer property of individual cells can be reconciled with *adder* at a population level, and that the observed correlation between the sizes at birth and division is independent of the division pattern (e.g., division close to middle, close to poles, etc.) and size convergence is achieved. We also analyzed experimental data and concluded that *E. coli* cells during filamentation more likely follow a division pattern that favors cleavage close to the poles. In summary, our research clarifies how anomalously growing cells are able to achieve size homeostasis and paves the way to understand phenotypic diversity in bacterial colonies under stress conditions.

Yanyan Chen [1], ***Javier Buceta*** [1,2]
[1]*Department of Bioengineering, Lehigh University, Iacocca Hall, 111 Research Dr., Bethlehem, PA, USA*
[2]*Department of Chemical and Biomolecular Engineering, Lehigh University, Iacocca Hall, 111 Research Dr., Bethlehem, PA, USA*

Publication

A Markovian Approach towards Bacterial Size Control and Homeostasis in Anomalous Growth Processes.
Chen Y, Baños R, Buceta J
Sci Rep. 2018 Jun 25