THE JOURNAL OF PHYSICAL CHEMISTRY Letters

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Stochastic Mechanisms of Cell-Size Regulation in Bacteria

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Cite This: J. Phys. Chem. Lett. 2020, 11, 8777−8782 Read Online

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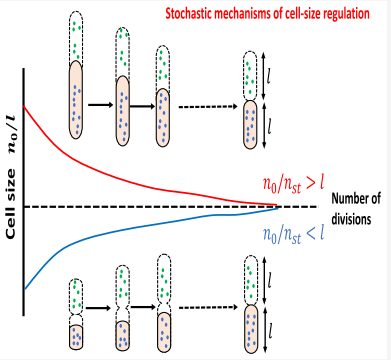
ABSTRACT: How bacteria are able to maintain their sizes remains an open question. It is believed that cells have narrow distributions of sizes as a consequence of a homeostasis that allows bacteria to function at the optimal conditions. Several phenomenological approaches to explain these observations have been presented, but the microscopic origins of the cell-size regulation are still not understood. Here, we propose a new stochastic approach to investigate the molecular mechanisms of maintaining the cell sizes in bacteria. It is argued that the cell-size regulation is a result of coupling of two stochastic processes, cell growth and division, which eliminates the need for introducing the thresholds. Dynamic properties of the system are explicitly evaluated, and it is shown that the model is consistent with the experimentally supported adder principle of the cell-size regulation. In addition, theoretical predictions agree with experimental observations on *E. coli* bacteria. Theoretical analysis clarifies some important features of bacterial cell growth.



While for different bacteria cell sizes and shapes might strongly differ, for a given organism cells have remarkably reproducible shapes and strikingly narrow distributions of sizes.[1−6] It has been suggested that this is a consequence of a homeostasis, a dynamic state of the living matter at which the most optimal functioning of organisms is achieved by keeping their physiological properties as constant as possible.[1] It is assumed that to support the homeostasis the sizes and shapes of bacterial cells of the same type must also be very similar. However, the microscopic mechanisms of how such tight control might be realized are still not well-understood.[2,3,5,7,8] Unlike eukaryotes, bacteria lack the so-called cell-cycle checkpoints, biochemical pathways that regulate the cell division and size.[4,8] However, they must overlap the DNA replication with the division machinery. This poses a challenge for the bacterial cells to coordinate division with growth in the dynamically changing environment. In recent years, some progress has been made to elucidate the details of the correlation between the cell division and growth in bacteria.[3,5,7,8] However, many microscopic aspects of the cell-size control are still not clarified.[2]

Several theoretical ideas to explain the uniformity and narrow distribution of cell sizes have been proposed, and two main directions are dominating the discussions in the field: the so-called sizer and adder models.[2,8,9] The sizer concept assumes that the constant cell size is a consequence of the regulation mechanism that selectively restricts the growth of large cells and promotes the growth of small cells. As a result, the cell size converges to a specific average value. At the same time, the adder concept assumes that all types of cells, small or large, between the divisions accumulate approximately the same amount of mass; i.e., they grow by the same length, assuming that the growth is effectively a one-dimensional process, as frequently observed in real biological systems. After the division, the originally large cells decrease their lengths, while the originally small cells increase their length, and this leads to the limitations in the cell-size variations.

Significant experimental efforts have been devoted to clarifying the mechanisms that control the cell sizes.[4,8,10] Recent advances in single-cell microfluidic techniques provided substantial amounts of quantitative data for various bacteria.[2,5] These investigations clearly showed that the cell-size regulation in prokaryotic cells follows the adder principle. It was also suggested that the adder mechanism is a consequence of two general processes: (1) a balanced biosynthesis, which is viewed as always keeping the numbers of protein molecules relevant for the growth and division to be proportional to the cell volume; and (2) a threshold accumulation of division initiators and precursors to a fixed number. However, the molecular picture that leads to the adder mechanism remains undetermined.[3,5,7,11] One of the weakest points of all deterministic phenomenological approaches is the assumption of existence of thresholds that direct the processes in the desired direction. A specific set of molecular biochemical and biophysical processes must be responsible for the appearance of such thresholds, but none of them have been clearly identified so far despite extensive experimental studies.[2]

In this paper, we present a new theoretical approach to investigate the mechanisms of the cell-size regulation in bacteria.

Received: August 27, 2020
Accepted: September 25, 2020
Published: October 1, 2020

https://dx.doi.org/10.1021/acs.jpclett.0c02627
J. Phys. Chem. Lett. 2020, 11, 8777−8782

Our main idea is that it is governed by two stochastic processes, cell growth and cell division, which are coupled together in such a way that leads to the efficient regulation of the cell sizes. Importantly, the stochasticity of involved cellular processes eliminates the necessity of using the thresholds, which is the weakest point of the existing theoretical approaches. The analysis of our minimal theoretical model allows us to perform explicit calculations of dynamic features in the system, and theoretical predictions agree with available experimental observations. It also clarifies the role of stochasticity in the regulation of cell sizes in bacteria.

Let us present a discrete-state stochastic model of the cell-size regulation in bacteria as illustrated in Figure 1. Because the

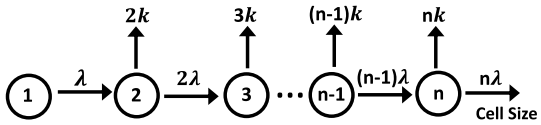


Figure 1. Schematic view of a discrete-state stochastic model of the cell-size regulation. The cell size is described by a discrete variable n that corresponds to the number of proteins responsible for growth.

bacterial cells mostly change their lengths while the widths are kept almost constant,[2,8] a one-dimensional description of the cell growth is justified as a first approach. We introduce a discrete variable n, which corresponds to a number of proteins responsible for the growth and for the division, as a measure of the length of the cell. At typical proliferating conditions, when the nutrients are sufficiently available, it is reasonable to assume that the proteins responsible for cell growth and division are formed much faster than the rates of growth and division events. Thus, the numbers of division and growth protein precursors are always proportional to the cell size, which is consistent with experimental findings pointing to the balanced biosynthesis in bacteria.[5] For this reason, as a simplest approximation, one can use a single discrete parameter n to quantify the length of the cell. It is a discrete variable because the changes in the amounts of proteins responsible for growth and division are obviously also quantized. For example, we can associate the variable n with the number of FtsZ proteins, which is a primary component of membrane constriction during the cell division.[12−17]

In our minimal theoretical model, only two processes might happen: growth and division. For the cell of size n, it is assumed that the growth rate is equal to λn where λ is a rate constant for the growth: see Figure 1. This reflects the fact that the cell growth is proportional to the number of proteins that support the increase in the cell size. Similarly, we assume that the division can happen at any cell size with the rate proportional to the cell size. This means that the cell of size n can divide with a rate kn (where k is a rate constant for the division), as shown in Figure 1. In our approach, the growth and division processes are viewed as effective chemical "reactions" (although real processes, of course, are much more complex). This allows us to naturally introduce the stochasticity in the system while keeping theoretical calculations of dynamic properties relatively simple. The main advantage of our theoretical method is the assumption that the division can take place for the cells of any size. However, because of the coupling with the growth, the division happens preferably at a relatively narrow range of cell sizes. This eliminates the need for introducing and explaining the appearance of the thresholds, which is the weakest point in the current phenomenological approaches.[5]

If the number of proteins responsible for growth and division is very high ($n \gg 1$), we can present simple mean-field arguments to describe the dynamics of the cell size using an effectively continuous approach. At these conditions, the temporal evolution of the average cell length $\langle n(t)\rangle$ can be written as

$$\frac{\mathrm{d}\langle n\rangle}{\mathrm{d}t} = \lambda\langle n\rangle - 2k\langle n\rangle\frac{\langle n\rangle}{2} \tag{1}$$

In this equation, the first term on the right side describes the increase in the cell length due to the growth, while the second term corresponds to the shortening due to the cell division. In this shortening process, every division removes the $\langle n\rangle/2$ length from the original average cell length, and it happens with the rate $k\langle n\rangle$. The coefficient 2 in the rate reflects the fact that for every single cell of the size $\langle n\rangle$ two shorter cells of the size $\langle n\rangle/2$ are created after division. eq 1 can be solved at all times with an initial condition $\langle n(t=0)\rangle = n_0$, yielding

$$\langle n(t)\rangle = \frac{c\lambda \mathrm{e}^{\lambda t}}{1 + kc\mathrm{e}^{\lambda t}} \tag{2}$$

where $c = \frac{n_0}{\lambda - kn_0}$. At the steady state ($t \to \infty$), we obtain $n_{\mathrm{st}} = \frac{\lambda}{k}$, which is the average cell size in the population. Then, eq 2 can be rewritten in the dimensionless form as

$$\frac{\langle n(t)\rangle}{n_{\mathrm{st}}} = \frac{\mathrm{e}^{\lambda t}}{\frac{n_{\mathrm{st}}}{n_0} - 1 + \mathrm{e}^{\lambda t}} \tag{3}$$

The results of our theoretical calculations and comparisons with experimental data for *E. coli* bacteria[2] are presented in Figure 2.

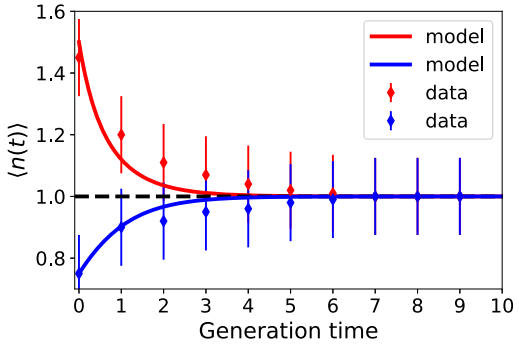


Figure 2. Normalized cell length as a function of the time in units of interdivision generation time. Solid lines are theoretical predictions (without fitting parameters) from eq 3, and symbols are from experimental observations for *E. coli* bacteria as given in ref 2.

The model predicts that the average cell size reaches a homeostasis value, and this fully agrees with experimental observations. The cells longer than the homeostasis cell length reduce in length after each division, while cells shorter than the homeostasis cell length increase in length after each division. One can see that for typical conditions in *E. coli* bacteria[2] 4−5 divisions are enough to reach the stationary length even when the original cell lengths deviate as much as ∼50%.

Now let us consider the growth and division dynamics in bacterial cells without mean-field assumptions, but only for the stationary-state regime. Because two processes (growth and division) are independent of each other, the probability to divide at the length n is given by

https://dx.doi.org/10.1021/acs.jpclett.0c02627
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$$p_n = p = \frac{kn}{kn + \lambda n} = \frac{1}{1 + \frac{\lambda}{k}} \tag{4}$$

This is an important result since it shows that in our stochastic model the probability of division is always constant and independent of the cell size. Now let us assume that we have a cell with the size n_0 at some initial time. The probability that the cell will divide after increasing its size by exactly n units can be written as

$$Q_n = p(1 - p)^n \tag{5}$$

The physical meaning of this expression is simple: there are no divisions after n events (only cell growth), but the $(n + 1)$-th event leads to the division. In Figure 3, the probabilities to divide

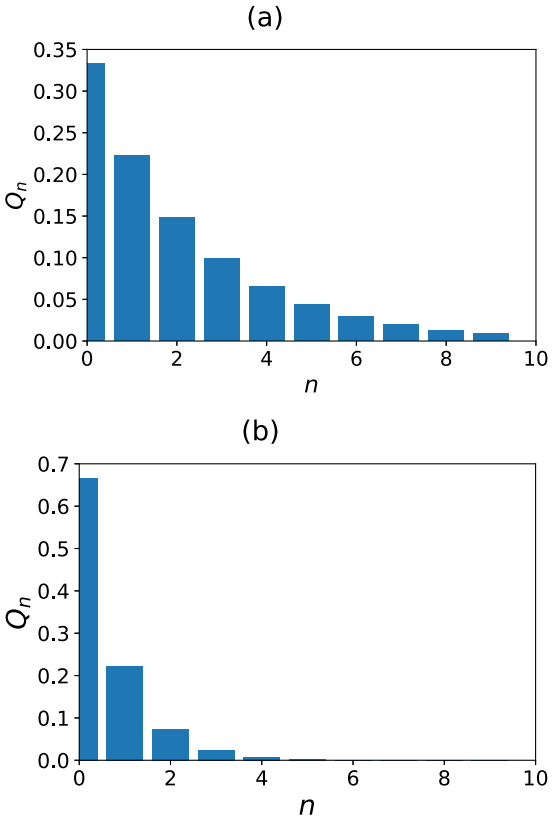

Figure 3. Probability to divide Q_n as a function of cell size n for (a) $\lambda/k = 2$ and (b) $\lambda/k = 0.5$.

as a function of the cell size n for two different cases $\lambda > k$ (growth is faster) and $\lambda < k$ (division is faster) are presented. One can see that for fast growth rates the probability to divide is slowly decreasing with n, while for the situation when the division rates are fast the probability is decreasing much faster with n. This can be explained by the fact that for $\lambda > k$ (growth is faster) the cells of various sizes might exist, while for $\lambda < k$ (division is faster) only relatively short length cells can be found.

The average length l added between consecutive divisions can now be explicitly calculated as

$$\langle l \rangle \equiv l = \sum_{n=0}^{\infty} nQ_n = \frac{1 - p}{p} = \lambda/k \tag{6}$$

This is another important result because it shows that, independent of the initial cell size, on average the same length is added to the growing cells between two divisions. The ratio of the growth and division rate constants specifies this length. It also shows that the average added length is equal to the average cell length. This result fully agrees with the adder principle, and it indicates that our stochastic model is consistent with major experimental observations in bacteria.[2,5]

While the average length added to the cell between two consecutive divisions is the same, due to stochasticity of the growth and division processes there is a distribution of added lengths. In our model, we can quantify these fluctuations by calculating (as shown in the Supporting Information) the normalized variance [also known as the coefficient of variance (CV)] of the added size

$$\bar{\sigma} = \frac{\sqrt{\langle l^2 \rangle - \langle l \rangle^2}}{\langle l \rangle} = \sqrt{\frac{1 + \lambda/k}{\lambda/k}} \tag{7}$$

The results of theoretical calculations are presented in Figure 4, and they suggest that increasing the added length between the

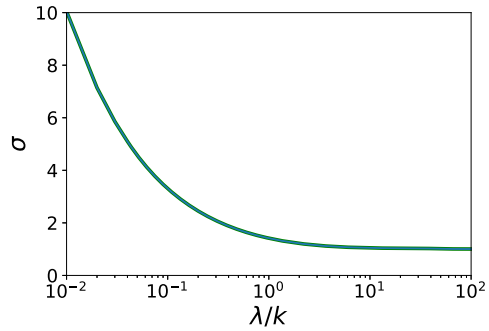

Figure 4. Normalized variance $\bar{\sigma}$ of the added average cell size as a function of λ/k.

divisions should lower the relative fluctuations around the average added cell length. For typical cellular conditions in bacteria, we could estimate that $\lambda/k \gg 1$, and our model predicts $\bar{\sigma} \equiv CV \sim 1$. However, experimental observations on *E. coli* bacteria at variable growth conditions reported $CV \sim 0.2-0.3$.[2] The distribution of added lengths is more narrow than predicted in our theoretical approach. This indicates that a more detailed biochemical description of the growth and division processes might be required to explain smaller fluctuations for the added length in the cell-size regulation in bacteria. However, our minimal theoretical model is already capable of explaining some important physical observations.

The presented discrete-state stochastic approach allows us also to understand better the microscopic details of bacterial cell division. It can be done by utilizing a method of first-passage processes, which is a powerful theoretical tool that was successfully used in analyzing various problems in chemistry, physics, and biology.[18,19] Our goal is to evaluate the distribution of the cell division times for the system that starts from the cell size n_0, and with the added size before the next division to be equal, exactly $l = \langle l \rangle$ (see eq 6). The cell growth in the system is proceeding, and the process is stopped immediately as soon as the division happens *exactly* at the location $n_0 + l$. There could be other situations when the division happens earlier at the site m ($m < n_0 + l$) or later ($m > n_0 + l$), but we consider such events to be unsuccessful. One can define a function $F_m(t)$ as the probability density of dissociating exactly at the size $n_0 + l$ (see Figure 1) for the first time at time t if at $t = 0$ the cell size was

https://dx.doi.org/10.1021/acs.jpclett.0c02627
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equal to m. The temporal evolution of such first-passage probability functions is governed by a set of backward master equations[18,19]

$$\frac{dF_m(t)}{dt} = m\lambda F_{m+1}(t) - m(k+\lambda)F_m(t) \tag{8}$$

for $n_0 \le m < n_0 + l$, and

$$\frac{dF_{n_0+l}(t)}{dt} = k(n_0+l)F_d(t) - (\lambda+k)(n_0+l)F_{n_0+l}(t) \tag{9}$$

for $m = n_0 + l$. In this equation, $F_d(t)$ is the probability to be found in the state immediately after the division at $n_0 + l$, and we can assume that $F_d(t) = \delta(t)$. This means that if the system is in this state at $t = 0$, the process is immediately accomplished.

These master equations can be solved analytically using Laplace transformations (see Supporting Information), producing explicit expressions for $\tilde{F}_{n_0}(s) \equiv \int_0^\infty e^{-st}F_{n_0}(t)dt$. An alternative propagator method to calculate the same functions is also presented in the Supporting Information. This allows us to obtain explicitly all dynamic properties in the system. For example, the overall probability that the cell starting with the size n_0 will divide at the size $n_0 + l$ is given by

$$\Pi_{n_0} \equiv \int_0^\infty e^{-st}F_{n_0}(t)dt = \tilde{F}_{n_0}(s=0) = p(1-p)^l \tag{10}$$

in agreement with eq 5 obtained using different arguments. Similarly, we can estimate the mean interdivision time, which in our approach is viewed as a mean-first-passage time for the system to divide at exactly the size $n_0 + l$

$$T_{n_0} \equiv -\frac{1}{\Pi_{n_0}}\frac{\partial \tilde{F}_{n_0}}{\partial s}(s=0) = \frac{1}{k+\lambda}\sum_{j=0}^{l}\frac{1}{n_0+j} \tag{11}$$

We can define also a rescaled dimensionless generation time by multiplying both sides of eq 11 by the rate λ, yielding

$$\overline{T}_{n_0} = \lambda T_{n_0} = \frac{1}{1+\frac{k}{\lambda}}\sum_{j=0}^{l}\frac{1}{n_0+j} = \frac{1}{1+\frac{1}{l}}\sum_{j=0}^{l}\frac{1}{n_0+j} \tag{12}$$

For $l \to \infty$, we can convert summation to integration, obtaining a simple approximate expression

$$\overline{T}_{n_0} \simeq \frac{1}{1+\frac{1}{l}}\ln\left(1+\frac{l}{n_0}\right) \tag{13}$$

To compare our theoretical predictions with experimental data, we must also rescale the newborn size, n_0. To do so we divide n_0 by the average newborn cell size $\langle n_0\rangle$, where

$$\langle n_0\rangle = \frac{1}{l-l_0}\sum_{i=l_0}^{l} n_0^{(i)} \tag{14}$$

Here we assumed that $l_0 \le n_0 \le l$. Thus, the rescaled generation time as a function of the rescaled newborn size reads as

$$\overline{T}_{n_0} = \frac{1}{1+\frac{1}{l}}\sum_{j=0}^{l}\frac{1}{\frac{n_0}{\langle n_0\rangle}+j} \tag{15}$$

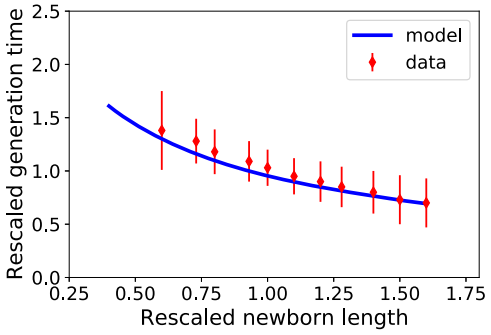

Figure 5. Rescaled mean generation times between consecutive divisions as a function of the rescaled starting cell size. The details of calculations are presented in the text, and data are from ref 2.

Figure 5 shows theoretically calculated $\overline{T}_{n_0}$ as a function of rescaled newborn cell length $\frac{n_0}{\langle n_0\rangle}$ along with experimental data on *E. coli* bacteria adapted from ref 2. We are predicting that the generation time decreases with newborn length of the cell, and this fully agrees with experimental observations. This can be easily explained using our theoretical model. Increasing the starting length n_0 leads to faster growth and division rates, and this means that the same average length l between two consecutive divisions can be added faster at these conditions than for the smaller starting lengths n_0. Excellent agreement with experimental data is giving additional support to our theoretical model based only on the stochastic mechanisms.

Since the cell division involves multiple biochemical and biophysical processes, it raises a question regarding the level of stochastic noise in the system and how it might affect the generation times. Our theoretical method allows us to evaluate the level of noise in the cell division because exact analytical calculations for all dynamic properties in the system, including the variance of interdivision times, can be performed. As shown in the Supporting Information, the variance is given by

$$\sigma T_{n_0} = \frac{1}{k+\lambda}\sqrt{\sum_{j=0}^{l}\frac{1}{(n_0+j)^2}} \tag{16}$$

Again, for large l we can convert the summation to the integration, yielding a simple approximate expression

$$\sigma T_{n_0} \simeq \frac{1}{k+\lambda}\sqrt{\frac{l}{n_0(l+n_0)}} \tag{17}$$

The normalized variance of the interdivision times as a function of initial size n_0 is presented in Figure 6. We predict that the stochastic noise during the cell division is almost constant and independent from the initial cell size. This trend agrees with experimental observations on *E. coli* bacteria (see Table S3 in ref 2), although the observed noise is slightly higher ($CV \sim 0.1$–0.2). The possible explanation for this difference is the fact that in experiments the divisions after adding the length slightly less ($l_{added} < l$) or slightly more ($l_{added} > l$) than the average length are also reported, increasing the noise. It should be noted that our first-passage approach can take these effects into account too.

The advantage of our stochastic model is that we can explain many aspects of the cell-size regulation mechanisms. The narrow distribution of cell sizes is a result of simultaneous action of two independent stochastic processes: growth and division. For short cell sizes, the division rates are slow, and mostly the growth

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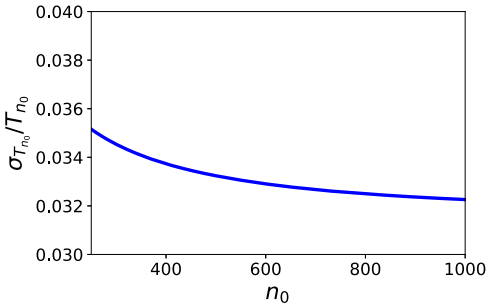

Figure 6. Normalized variance of interdivision times as a function of the initial cell size n_0. The calculations are done using the same parameters as in Figure 5.

processes are observed. For long cell sizes, the division rates are fast, quickly breaking the long cells. This leads to the narrow distribution of cell sizes where the growth and division balance each other. Similar arguments can be presented to explain the robustness of interdivision times.

Stimulated by experimental observations of narrow size distributions and robust cellular divisions in bacteria, a new theoretical method to evaluate cellular growth dynamics is developed. It argues that the cell-size regulation is governed only by two stochastic processes, growth and division. The reliance on stochastic mechanisms allows us to avoid the use of thresholds, which is the weakest point of existing theoretical methods. The proposed discrete-state stochastic model provides explicit calculations of dynamic properties in the system, permitting us to compare theoretical predictions with available experimental observations. It is shown that the model is consistent with the experimentally supported adder principle of the cell-size regulation. The narrow distributions of cell sizes and low stochastic noise in the division dynamics are explained as a result of joint action of two stochastic processes that "cancel" the randomness of each separate process. Good agreements with experimental data suggest that our simple stochastic model is able to capture some important physical−chemical processes taking place during the cell growth in bacteria, and thus, it can be used to extract more information on microscopic mechanisms of these processes.

Although our theoretical approach compares favorably with available experimental observations, it is important to emphasize its limitations. We proposed a minimal theoretical model that lumped complex biochemical and biophysical phenomena during the cell growth and division into two stochastic processes. While it can describe the experimental data, the observations are still quite limited, and some aspects of the data are not fully captured in our approach (see, e.g., our discussions on the degree of fluctuations in the added cell-size lengths). It will be important to extend our theoretical model by taking into account more chemical details of the underlying processes. This will allow us to analyze more recent experimental observations on reprogramming cell-size homeostasis and on the effect of dynamic fluctuations of protein precursors.[5]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpclett.0c02627.

Additional calculations (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work was supported by the Welch Foundation (C-1559), by the NSF (CHE-1664218, CHE-1953453, and MCB-1941106), and by the Center for Theoretical Biological Physics sponsored by the NSF (PHY-2019745).

■ REFERENCES

(1) Alberts, B. *Molecular Biology of the Cell*; Norton, 2018.

(2) Taheri-Araghi, S.; Bradde, S.; Sauls, J. T.; Hill, N. S.; Levin, P. A.; Paulsson, J.; Vergassola, M.; Jun, S. Cell-size control and homeostasis in bacteria. *Curr. Biol.* **2015**, *25*, 385−391.

(3) Amir, A. Cell size regulation in bacteria. *Phys. Rev. Lett.* **2014**, *112*, 208102.

(4) Lloyd, A. C. The regulation of cell size. *Cell* **2013**, *154*, 1194−1205.

(5) Si, F.; Le Treut, G.; Sauls, J. T.; Vadia, S.; Levin, P. A.; Jun, S. Mechanistic origin of cell-size control and homeostasis in bacteria. *Curr. Biol.* **2019**, *29*, 1760−1770.

(6) Ojkic, N.; Serbanescu, D.; Banerjee, S. Surface-to-volume scaling and aspect ratio preservation in rod-shaped bacteria. *eLife* **2019**, *8*, e47033.

(7) Osella, M.; Nugent, E.; Cosentino Lagomarsino, M. Concerted control of Escherichia coli cell division. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, 3431−3435.

(8) Ginzberg, M. B.; Chang, N.; D'Souza, H.; Patel, N.; Kafri, R.; Kirschner, M. W. Cell size sensing in animal cells coordinates anabolic growth rates and cell cycle progression to maintain cell size uniformity. *eLife* **2018**, *7*, No. e26957.

(9) Conlon, I.; Raff, M. Differences in the way a mammalian cell and yeast cells coordinate cell growth and cell-cycle progression. *J. Biol.* **2003**, *2*, 7.

(10) Wood, E.; Nurse, P. Sizing up to divide: mitotic cell-size control in fission yeast. *Annu. Rev. Cell Dev. Biol.* **2015**, *31*, 11−29.

(11) Basan, M.; Zhu, M.; Dai, X.; Warren, M.; Sévin, D.; Wang, Y.-P.; Hwa, T. Inflating bacterial cells by increased protein synthesis. *Mol. Syst. Biol.* **2015**, *11*, 836.

(12) Chien, A.-C.; Hill, N. S.; Levin, P. A. Cell size control in bacteria. *Curr. Biol.* **2012**, *22*, R340−R349.

(13) Loose, M.; Mitchison, T. J. The bacterial cell division proteins FtsA and FtsZ self-organize into dynamic cytoskeletal patterns. *Nat. Cell Biol.* **2014**, *16*, 38−46.

(14) Harry, E.; Monahan, L.; Thompson, L. Bacterial cell division: the mechanism and its precison. *Int. Rev. Cytol.* **2006**, *253*, 27−94.

(15) Haeusser, D. P.; Margolin, W. Splitsville: structural and functional insights into the dynamic bacterial Z ring. *Nat. Rev. Microbiol.* **2016**, *14*, 305.
(16) Palacios, P.; Vicente, M.; Sánchez, M. Dependency of Escherichia coli cell-division size, and independency of nucleoid segregation on the mode and level of ftsZ expression. *Mol. Microbiol.* **1996**, *20*, 1093−1098.
(17) Zheng, H.; Ho, P.-Y.; Jiang, M.; Tang, B.; Liu, W.; Li, D.; Yu, X.; Kleckner, N. E.; Amir, A.; Liu, C. Interrogating the Escherichia coli cell cycle by cell dimension perturbations. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, 15000−15005.
(18) Redner, S. *A Guide to First-Passage Processes*; Cambridge University Press, 2001.
(19) Kolomeisky, A. B. *Motor Proteins and Molecular Motors*; CRC Press, 2015.

https://dx.doi.org/10.1021/acs.jpclett.0c02627
J. Phys. Chem. Lett. 2020, 11, 8777−8782