Mathematical Biology and Bioinformatics
2015. V. 10. № Suppl. P. t20–t28. doi: 10.17537/2015.10.t20

The translation of the original article
2015 Likhoshvai V. A., Khlebodarova T. M. Matematicheskaya biologiya i bioinformatika. 2015. V. 10. № 1. P. 154-163. doi: 10.17537/2015.10.154

========== MATHEMATICAL MODELING ==========

UDC: 577.213:576.362:579.23

On the types of bacterial growth laws

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***Abstract*:** Volume, mass and envelope surface area of a bacterium are significant parameters of cell development during one bacterial cell cycle. In our previous studies it was shown that during one division cycle cells can encounter the problem of unlimited size growth. Two fundamental types of bacterial growth laws, which were called “exponential” and “linear”, have been identified. Under certain conditions exponentially growing cells encounter the problem of unlimited growth, whereas lineally growing cells don’t [1]. In this study the laws of bacterial size growth were shown to belong exclusively to the linear type. It was demonstrated that this phenomenon is a consequence of the universal principle of storage and transmission of genetic information essential to all living organisms. The bacterial growth laws of exponential type could exist only at the very early stages of cell evolution, when the genetic machinery had not evolved yet into its modern form.

***Key words*:** *modeling, prokaryotes, cell cycle, exponential and linear types of cell growth laws.*

INTRODUCTION

Coupling between the growth of different cellular structures during one cell cycle in prokaryotes has been under extensive investigation for a long time, starting with the pioneer works by Pritchard et.al [2], Donachie [3] and Cooper&Helmsteter [4]. Theoretically the problem of coupling between cell volume growth and replication rates was first considered in Pritchard et al. [2]. The authors introduced a model of cell cycle with a repressor-controlled initiation of genomic DNA replication. In the model the rate of repressor synthesis was set proportional to the number of copies of its structural gene while the repressing activity was a function of concentration of the repressor’s functional form responsible for the coupling between growth and replication processes.

Experimental data on the constancy of cellular mass/volume per replication origin at the moment of genome DNA replication are presented in Donachie [3]. This ratio called “initiation mass” also makes it possible to couple the processes of replication and growth.

In 1968, Cooper&Helmsteter [4] suggested that cell cycle is regulated by the replication rates. Assuming that C-period (the time for a round of DNA replication) and D-period (the time between termination of DNA replication and cell division) are constants, the authors elaborated a model of coordinated cell growth, division and replication. Subsequently it was demonstrated that the constancy of C- and D-periods holds only in the cells of *Escherichia coli* with the cell cycle shorter than one hour [5].

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Since no global replication initiation repressor has been discovered in *E. coli* yet (see reviews [6, 7]), the model of Pritchardt et al. [2] has been abandoned, whereas the ideas of Cooper&Helmsteter [4] and Donachi [3] continue to serve as a base for developing modern models of cell cycle in *E. coli* [8–10].

Notably, the above-mentioned studies took the coupling problem for granted. Despite the fact that the existence of the coupling problem is reflected in the titles of the subsequent studies [10–13], it has not been solved to date even for a model organism such as *E. coli*. The theoretical aspects of the coupling problem have not been addressed in the previous studies.

For instance, we could not find answers to some questions such as whether a cell always encounters the problem of coupling between growth rate and replication. Or whether there are certain conditions in which the coupling problem just does not exist. To find answers to these questions we carried out a theoretical analysis of the problem of coupling between cell growth and DNA replication [1, 14].

According to our results, under assumption of Cooper&Helmsteter [4] (cell cycle duration depends on replication initiation rates) in cell cycle models no coupling problem arises for the processes of replication initiation. This is evidently an expectable result: under the assumption of Cooper&Helmsteter [4] replication is the driving cell cycle process that sets its duration and ensures automatic coupling in the once-cycle replication model. At the same time under the assumption of Cooper&Helmsteter [4] and in the models of cell volume growing according to a phenomenological function with fixed parameters a modeled cell encounters the problem of coupling of cell volume growth and replication rates. The analysis performed in [1] demonstrated that the existence/nonexistence of the coupling problem directly depends on the phenomenological law of growth accepted in the model. For instance, if the volume growth is described by function $V(t) = V_0 \exp(kt)$ or $V(t) = V_0 (1 + kt)$, then the "cell" encounters a problem of unlimited growth of its volume. On the contrary, laws $V(t) = V_0 + kV_1 t$ and $V(t) = V_0 + V_1 (\exp(kt) - 1)$ do not generate the coupling problem [1]. Therefore, the coupling problem in the models under consideration depends on the growth law, on the one hand, and manifests itself as a tendency to unlimited growth of volume in the cell progeny, on the other hand. Based on the studies performed in [1] "exponential" and "linear" types of cell growth laws were identified. The growth laws generating the problem of unlimited growth were referred to the exponential type and the growth laws not generating this problem were referred to the linear type. The types of growth laws were named by their typical representatives: phenomenological exponential law $V(t) = V_0 \exp(kt)$ and phenomenological linear law $V(t) = V_0 + V_1 kt$, respectively [1, 14].

Therefore, the problem of coupling between size growth rates and one cell cycle duration appears to be directly dependent on the type of growth law. The available experimental data on the dynamics of bacterial length/mass/volume during a cell cycle on the level of populations and individual cells are often approximated by exponential or linear, or bilinear, or even trilinear functions [15–26] belonging to both linear and exponential types. Since the resulting approximations are essentially the phenomenological functions, they cannot serve as a base for determining the true type of growth laws implemented in natural unicellular organisms.

Information essential for establishing the type of the law governing bacterial growth during a cell cycle can be derived only from the analysis of molecular mechanisms of cellular processes. In the recent studies of some aspects of the cell growth/division coupling problem the authors emphasized the necessity to search for new theoretical approaches to its solution [27].

In this work we consider the exponential mechanism of cell surface area growth and investigate the conditions under which a cell employs exponential or linear types of growth laws. The fundamental principles of genetic information storage and transmission underlying

the functioning of all known living organisms were shown to entail the fact that all cell growth laws belong to one type - linear. This peculiarity of a cell as a self-reproducing system does not depend on specific control mechanisms for cell volume/envelope surface area growth, which may differ in different species. This means that in modern bacterial species the growth laws of exponential type *do not exist*. Exponential growth laws (including the classical exponential law $F(t)=F_0\exp(kt)$) could exist at the very early (pregenetic and early genetic) stages of evolution of a cell as a self-reproducing system, however, the emergence of a modern-type molecular-genetic machinery resulted in the elimination of exponential growth laws or their transformation into linear growth laws.

RESULTS

1. Formulation of the problem of unlimited growth

Let us consider a typical bacterium with a classical cell cycle scenario: …→ {birth of a cell as a result of the parent cell division → cell growth → cell division into two daughter cells } → …. The cell cycle of an individual bacterium starts at the moment of its birth and ends at the moment of its division. During the time interval between the onset and end of the cell cycle the bacterium actively consumes nutrients to synthesize substances in the quantities sufficient to produce two daughter cells at the end of the cell cycle. In a cell, some structural components are represented by sufficiently large macrosystems. Such macrosystems include cell envelope whose growth is a complex molecular process. Under the assumption of symmetric division at the moment of division the envelope surface is distributed equally between the two daughter cells. This means that at birth the surface of the daughter cell envelope becomes half the surface of the parent cell envelope at the moment of division. In the successive cell generations the process of cell envelope growth is represented by a cyclic reproducible sequence of events: … → {surface area growth during cell cycle → surface area halving at the moment of division} → ….

Then if at the current moment of cell cycle bacterial surface area is denoted by $S(t)$, the sequence of surface area values for successively descending cells can be put down as

$$S\big|_1(0)=S_0, S\big|_2(0)=\frac{1}{2}S\big|_l(T_D\big|_1),...,S\big|_{l+1}(0)=\frac{1}{2}S\big|_l(T_D\big|_l),\ ....\qquad(1)$$

Where l is the number of the cell cycle resulting in the birth of a daughter cell of the (l+1)-th generation (only one cell is under consideration as under the symmetric division assumption all daughter cells are identical), $T_D|l$ is the duration of the l-th cell cycle, $S|l$ is the function of surface area growth for the l-th cell, $S|_l(0)$ is the surface area of the l-th cell, $S|_l(T_D|_l)$ is the surface area at the moment of the l-th cell division.

If the behavior of a succession of cells (1) generated in a real experiment is observed, the surface area value turns out to be bounded above. Therefore, in a real system cell growth is coupled with cell cycle duration. In this case there arises the question on the nature of coupling maintenance.

A priori there are two options. First, a cell can restrain itself from unlimited growth using a special molecular mechanism. Therefore, if this mechanism fails, the cells become incapable of coordinating the growth rates and cell cycle duration and potentially can maximally increase their sizes. In this case the maximum possible size serves as the limiting factor and exceeding this size results in the loss of viability.

The phenomenological growth laws with the above-stated characteristics are represented by exponential

$$Z(t)=Z_0\exp(kt),\qquad(2)$$

and linear

$$Z(t) = Z_0(1+kt), \quad (3)$$

laws [1]. There is strong evidence that these laws provide accurate approximation of the cell growth kinetics [15–26]. In line with [1], let us describe the properties of series (1) after substituting exponential function (2). Simple transformations give the series

$$Z\big|_1 = \frac{1}{2} Z_0 \exp(k\, T_D\big|_1), Z\big|_2 = Z_0\left(\frac{1}{2}\exp(k\frac{T_D\big|_1 + T_D\big|_2}{2})\right)^2, ..., Z\big|_l = Z_0\left(\frac{1}{2}\exp(k\frac{T_D\big|_1 + ... + T_D\big|_l}{l})\right)^l, ... \quad (4)$$

Then if $\lim\limits_{l\to\infty}\frac{T_D\big|_1 + ... + T_D\big|_l}{l} > \frac{\ln 2}{k}$, series (4) is unbounded above and if $\lim\limits_{l\to\infty}\frac{T_D\big|_1 + ... + T_D\big|_l}{l} < \frac{\ln 2}{k}$, this series is infinitely close to zero. There is only one limit value, $\lim\limits_{l\to\infty}\frac{T_D\big|_1 + ... + T_D\big|_l}{l} = \frac{\ln 2}{k}$, at which series (4) can be maintained in a finite range. To maintain the surface area of a cell as a self-reproducing system within a certain range, it is necessary for the cell to have a specific control mechanism. We proposed to call all the laws demonstrating a potential for unlimited size growth the laws of exponential type [1].

Another option that cannot be excluded is that the bacterial envelope growth is controlled by a mechanism with an *immanence* of limited surface area. In this case a cell is not required to employ a growth-restraining mechanism as unlimited growth is just impossible. This holds, for instance, for the linear

$$Z(t) = Z_0 + kZ_c t, \quad (5)$$

and exponential

$$Z(t) = Z_0 + Z_c(\exp(kt) - 1) \quad (6)$$

laws. If these laws are substituted into series (1), one gets the series bound above (the proof is given in [1]). These are the so-called laws of the linear type.

There arises a question about the conditions under which the laws of the exponential type can be implemented. It is quite evident that under the conditions of unlimited resources for cell envelope growth and in the absence of limiting factors all growth laws (2), (3), (5), (6) can be implemented under realistic assumptions on the molecular mechanisms of bacterial envelope construction.

For example, assume that the number of elements required for cell envelope growth is proportional to the envelope surface and that each newly constructed envelope element is an independent growth element. Therefore, the rate of growth can be described by the following differential equation

$$\frac{dS}{dt} = k_{GR}S, S(0) = S_0. \quad (7)$$

In (7) k_{GR} is a constant of surface area growth rate, S_0 – surface area at the moment of cell birth. Equation (7) has an obvious analytical solution (2). Therefore, one gets an exponential law of the exponential type.

Assume that for all cells growing under equivalent conditions at birth the number of growth elements is the same and does not depend on the surface area at birth, but all newly constructed envelope elements are the growth sites. Then the growth rate is described by the following equation

$$\frac{dS}{dt} = k_{GR}(S + S_1 - S_0), S(0) = S_0. \quad (8)$$

In (8) k_{GR} and S_0 mean the same as analogous parameters in (7), S_1 is cell surface area at birth of a cell capable of growing. In this case we obtain equation (6) describing the exponential law of the linear type.

Laws (3) and (5) are implemented under the following assumptions. Law (3) is valid under the assumption that at birth the number of constructive elements is proportional to the surface area and remains constant during the cell cycle. For law (5) to be valid assume that all cells growing under equivalent conditions independently of the size have the same number of constructive elements during the entire cell cycle.

Therefore, under the unlimited resource conditions different molecular mechanisms lead to the growth laws of both exponential and linear types. This result is based on the simplified assumption on unlimited resources and absence of other limiting factors. Therefore, at this level of simplification the existence of bacteria implementing different growth laws is not forbidden. Moreover, some molecular mechanisms generate the laws of the exponential type, other mechanisms – the laws of the liner type. Nonetheless, it could be important that there are molecular mechanisms which on this level of elaboration of envelope growth processes finally lead to the laws of the linear type. It is quite evident that a more elaborated description of the growth mechanism is not longer significant for such mechanisms since additional details make it possible to clarify the type of the law rather than to change it from linear to exponential. On this basis in the context of the coupling problem of special interest is the analysis of growth mechanisms (2) and (3) with inclusion into the model of a larger number of details inherent in modern cells. In the next section the exponential mechanism of cell growth (2) is analyzed. The results of the analysis of the molecular mechanism (3) are omitted as the analysis is carried out in a similar way and the results are qualitatively analogous.

2. Model of a genetically controlled exponential mechanism of cell envelope growth

Let us make model (2) more complex assuming that cell envelope grows under control of a functional protein encoded by a gene belonging to the genome. As a result the envelope surface growth model can be expressed as follows

$$\begin{cases} \frac{dP}{dt} = k_{g,p} g - k_{d,p} P, \\ \frac{dS}{dt} = k_{GR} \frac{P}{V} S, \end{cases} \quad (9)$$

where g is the number of gene copies inside a cell, P is the quantity of protein inside a cell, S is envelope surface area, V is cell volume, function g describes the dynamics of active gene copies during the cell cycle.

Assume that for each cell cycle functions g and V are known and genome doubling rates in a succession of cell generations are coordinated with cell cycle duration. Therefore, by the end of each cell cycle immediately before division a cell has at least two complete genomes and on average the full genome number in a succession of cell generations remains globally bounded. Therefore, on the basis of total cell cycles functions $g\big|_l$ are bounded above by one finite number.

Let us investigate the type of the growth law for envelope surface area S. Notably, it is evident that global boundedness above for function $g(t)$ directly entails global boundedness above for function $P(t)$ for all cell cycles:

$$\exists 0 < B: \ P(t)\big|_i \le B, i = 1, \ldots . \quad (10)$$

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Let us turn to the second equation of system (9). Its right part is the product $k_{GR}P\frac{S}{V}$. The boundedness of function *P* has just been established. Let us consider the surface to volume ratio. Proceeding from the general principles of bacterial structure, it seems there is practically no alternative to the postulate that the surface to volume ratio is a value globally bounded above. Actually, it is difficult to conceive of a cell with the surface to volume ratio growing unrestrictedly during a cell cycle. Therefore, for a finite number *R* for all cell cycles the following inequality holds

$$\left.\frac{S(t)}{V(t)}\right|_l \le R. \tag{11}$$

Assume the restrictions (10) and (11) are satisfied. Then solution $S(t)\big|_l$ of system (9) for the *l*-th descendant is dominated by function $\bar{S}_l(t) = S(0)\big|_l + BRt$. In the division sites

$$S(T_{D,1})\big|_1 \le S_0 + BRT_{D,1} \Rightarrow S_1 = \frac{1}{2}S(T_{D,1})\big|_1 \le \bar{S}_1 = \frac{S_0 + BRT_{D,1}}{2},$$

$$S(T_{D,2})\big|_2 \le \bar{S}_1 + BRT_{D,2} \Rightarrow S_2 = \frac{1}{2}S(T_{D,2})\big|_2 \le \bar{S}_2 = \frac{\bar{S}_1 + BRT_{D,2}}{2} = \frac{S_0}{2^2} + \frac{BRT_{D,1}}{2^2} + \frac{BRT_{D,2}}{2},$$

...

$$S(T_{D,l+1})\big|_{l+1} \le \bar{S}_l + BRT_{D,l+1} \Rightarrow S_{l+1} = \frac{1}{2}S(T_{D,l+1})\big|_{l+1} \le \bar{S}_{l+1} = \frac{\bar{S}_l + BRT_{D,l+1}}{2} = \frac{S_0}{2^{l+1}} + BR\sum_{i=1}^{l+1}\frac{T_{D,i}}{2^{l+1-i}}.$$

Denote the maximum duration of cell cycle in a succession of descendants by T_D. From the biological expedience one can hold that

$$T_D \le \infty. \tag{12}$$

Hence we get global boundedness above for the surface area of all cells in succession of cell generations (1): $\forall l : S(t)\big|_l \le \frac{S_0}{2} + BRT_D$. Therefore, it is concluded that the surface area growth law implemented in model (9) belongs to the linear type.

In conclusion, note that the inclusion into the model of the genetic principle of encoding functional molecules in its explicit form was an essential point of the study. The use of a single functional element in model (9) had no essential impact on the results. It is groundless to presume that the inclusion of more details (ideally all) on cell-cycle molecular-genetic and metabolic processes would change the conclusion qualitatively. It is also worth noting that, in our opinion, conditions (10)–(12) are fulfilled for the overwhelming majority, if not for all, prokaryotic cells. It is difficult to conceive of any cells with an unlimited set of genomes and cells living and growing for an unrestrictedly long time without division. Also it is easy to give examples of cells for which condition (12) is fulfilled, such as cylindrical and spherical cells. Hence, for the living systems implementing the modern genetic principle of information storage and transmission the law of envelope surface area growth can be exclusively of the linear type.

DISCUSSION AND CONCLUSION

Previously we demonstrated that the existence of the problem of coupling between cell growth and replication initiation rates depends on the type of growth law – exponential or linear, each of which can be described both by exponential and linear dependencies [1].

In this study we performed a theoretical analysis of the conditions of the formation of these types of prokaryotic cell growth laws and found that in the models ignoring the genetic

level of cell growth processes control it is possible to specify the molecular mechanisms of envelope growth underlying the growth laws of both exponential and linear types.

We also carried out the analysis of a model describing a molecular-level mechanism ensuring exponential growth and including functional molecules encoding on the gene level. It was found that in a succession of growing and dividing cells the law of envelope surface area growth inevitably belongs to the linear type. Therefore, inclusion into the analysis of the genetic control of the processes of surface area growth automatically ensures that the law of envelope surface area growth belongs to the linear type.

Therefore, it is reasonable to suggest that the linear type of the growth law is a fundamental and universal property of a cell as self-reproducing systems. In evolutionary perspective this property emerged as a consequence of the development by living systems of molecular-genetic principles of information storage and transmission during cell reproduction.

The theoretical data obtained indicate that the exponential type of cell growth, even if such type did exist in nature, could occur in the early stages of life evolution, in the epoch preceding the development of modern principles of information storage and transmission.

It is to be noted that the coupling problem exists as a composition of two problems rather than a separate problem: coordination of the rates of cell growth and replication initiation as separate macroprocesses with the duration of cell cycle.

In this work it was shown that in no circumstances modern bacteria can enlarge their cell size indefinitely. However, as regards the process of replication one cannot assert the same because the replication system is essentially a system of exponential type: one genome generates two genomes and two genomes generate four genomes etc. Therefore, the problem of coordination of the replication initiation rate and the duration of cell cycle can potentially arise. The question on its existence can be answered on the basis of the knowledge about the mechanisms of cell cycle duration control. There are different ways of looking at this problem. For example, under the “sizer” hypothesis the duration of cell cycle depends on the bacterium growth rate [28]. For such cells there arises the problem of unrestricted growth of genome number, i.e. the problem of coordination of replication rates and cell cycle duration.

From a different viewpoint stated in Cooper&Helmsteter back in 1968 the initiation of cell division occurs after replication termination, so the rate of replication initiation actually sets the duration of cell cycle [4]. Evidently, in this case the problem of coupling between replication initiation rates and cell cycle duration does not arise.

While we still lack a complete understanding of the mechanisms for the control of cell cycle duration that could be implemented in natural bacteria, it is, however, reasonable to suggest that in a general case growth or replication initiation rates are not the only factors that set the cell cycle duration. This assumption follows from the concept of limiting factor.

Assume that a parent cell can divide into two daughter cells only when the parameters of a series of macrosystems (M_i) exceed certain minimum critical values ($Z_{i,c}$). In this case a cell cycle length T_D cannot be smaller than the value $T_{D,min}=\max(T_{D,c}, T(Z_{1,c}),...,T(Z_{n,c}))$, where $T_{D,c}$ is the minimum possible cell cycle length, $T(Z_{i,c})$ is the time to achieve the minimum critical value $Z_{i,c}$ for macrosystem M_i.

If in a series of cell cycle lengths for a succession of progeny $T_{D,1},...,T_{D,l},...$ on the basis of above-stated it is assumed that $T_{D,l} \geq T_{D,min}$, then at different moments of time different factors can be limiting.

The results obtained in this work indicate that independently of the nature of limiting factors no problem of unlimited size growth arises for a cell. On the contrary, if the duration of cell cycle is limited by any factor except the replication initiation rate, the latter has to be coupled with the cell cycle duration.

In conclusion, it is necessary to note that our results do not exclude the fact that the bacterial growth curves for *E. coli* and possibly for other bacteria can most accurately be described just by exponential functions [24–26, 29]. However, from our studies it follows that real growth laws approximated by these functions belong to the laws of the linear type, which, in turn, follows from the emergence of the genetic level of cellular organization.

This work was supported by the RFBR (project No. 13-01-00344) and by Siberian Branch of the Russian Academy of Sciences (budget project No. VI.61.1.1). We thank Olga Kharlamova for the translation of an article from Russian to English, and Tatyana Likhoshvai (Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany) for the information support for this study.

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Received April 06, 2015.
Published April 09, 2015.