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Microbial Growth and Decay: A Commented Review of the Model

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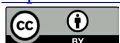

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Abstract

The paper reviews previous publications and reports some comments about a semi empirical model of the growth and decay process of a planktonic microbial culture. After summarizing and reshaping some fundamental mathematical expressions, the paper highlights the reasons for the choice of a suitable time origin that makes the parameters of the model self-consistent. Besides the potential applications to predictive microbiology studies and to effects of bactericidal drugs, the model allows a suitable proxy of the fitness of the microbial culture, which can be of interest for the studies on the evolution across some thousand generations of a Long Term Evolution Experiment.

Keywords

Microbial Cultures, Model, Time Scale, Growth and Decay, Evolution

1. Introduction

Every microbial culture behaves like a factory where substrates become living organisms [1]. This transformation seems a peculiar property of the living cells (either pro-, or eukaryotic), since it does not occur if they are absent. The cells trigger the process, but are themselves accelerators of the evolution.

In such perspective, the microbial growth looks like an auto-catalyzed process. However, this is not what really happens, since the growth rate rises up to a maximum and then declines toward zero, in spite of the largely increased number of the cells.

Such a behavior is reflected by the so-called growth curve, log (N)-vs-t, that describes the trend of the population density, N, as function of the time, t.

Since the first decades of the last century, many authors, including the Nobel laureate Jaques Monod [2], described the "macroscopic" evidence of the growth

curve through models ([3] and therein quoted authors) that include some best fit adjustable parameters, like maximum specific growth rate, lag phase, etc., which were also given some biological meaning.

Recent investigations addressed the attention to the underlying biochemical mechanism and to the molecular peculiarities that characterize the growth of various microbial species in different mediums [4] [5], as well as to some collective effects, like quorum sensing and mechanosensing [6] [7].

Finally, the awareness of possible genomic mutations that can either enhance or depress the fitness of a given microbial culture, led to a vast specialized literature on the evolution of the microbes and the related effects, like the emergence of resistance to antibiotic drugs, or the improved fitness after thousand generations in Long Term Evolution Experiments (LTEE) [8] [9].

These approaches could mislead to the conclusion that the early models are just naïve descriptions of the microbial growth. However, in spite of the wide variability of biochemical cycles within the cells and chemical composition of the surrounding medium, all the microbial cultures show the same kind of "macroscopic" behavior, namely, the growth curve, which therefore must obey to laws that prevail biological and biochemical differences and still deserves a reliable interpretation [10].

The present paper is a review of previous works [11]-[17] that suggest a new approach to the growth curve, looking at the microbial culture as at an overall system (medium + cells) that is thermodynamically unstable and evolves irreversibly. A major novelty of this approach is that it includes the decay phase that follows the growth phase. This extension can be of interest for predictive microbiology applied to food preservation and pharmaceutical investigations. The quantitative traits of the approach come from the description of an ideal planktonic microbial culture that may be a reference for every microbial culture. The empirical parameters that come from the log (N)-vs-t data are interconnected with one another theoretically, showing a self-consistency that is a common feature of every microbial culture.

2. The Growth Phase

The present paper summarizes the fundamental aspects of the model, the details being reported elsewhere [11]-[17]. The model deals with a planktonic culture with cells evenly dispersed in the medium. The progress of the growth is synchronic for all the duplication lines stemmed from the starting N_o cells. No cell dies during the growth progress. The basic assumption of the model is a variable generation time, τ, that allows reproduction of the sigmoid trend of the growth curve as the best fit of the experimental log (N) data that significantly (confidence > 95%) differ from the log (N_o) starting population. Such empirical basis therefore reflects a duplication process in action and does not directly concern any earlier adjustment of the cells.

This selection of the experimental data differentiates the present model from

all the previous others, which propose best fits that gather data that clearly reflect a no-growth condition together with data that indicate the increase of the cell population. This apparent contradiction comes from the common opinion that the microbes must first "self-adjust" to the medium at the beginning of any plate count experiment [18], namely, that the growth process would actually start before the onset of the cell duplication. However, such reasonable opinion does not justify the use of a single function to fit data that deal with the increase of the cell population, namely, the experimental evidence of a change of the population density, together with data that indicate that no duplication is occurring. The two conditions (increase and no-increase of N) require two different mathematical approaches, while the description of the whole growth process should come from side constraints imposed by the model used.

The present model takes into account such a gap between no-duplication and duplication phases through a wider vision of the issue, stating that the time origin of the whole process (thus including the self-adjustment phase) does not necessarily coincide with the start of the experiment. This statement rises the problem of defining an ideal time origin of the growth. It was noticed that the condition $N = 1$ is the lowest requirement to obey the constraint that the system has to host a trigger, without which no duplication is possible. For this reason, the "ideal" time origin, $\theta = 0$, for the growth process should comply with such requirement.

In order to single out the "ideal" time origin using the available experimental data, one has to address the attention to the best evidence of the duplication process, namely, the fastest duplication rate. This corresponds to the largest specific growth rate, $\dot{N}/N$, namely the flex point of the growth curve. This condition, dubbed "balanced growth" [5], reflects the perfect synchronism of the biochemical activities underlying the cell duplication, namely, with no "self -adjustment" delay: the process is purely cell duplication. This means that the extrapolation of the straight- line tangent to the growth curve at its flex point down to the level log (N) = 0 allows singling out the ideal time origin, $\theta = 0$. It is also worth noticing that the condition log (N) = 0 (namely, $N = 1$) holds for any log base used for the growth curve. Furthermore, since the argument of the logarithm must be a pure number, a correct expression would indeed be log ($N/[N]$), where $[N]$ stands for the units used for the microbial population (e.g., CFU, CFU/mL, CFU/g, etc.). This means that the extrapolation process mentioned above can single out the time origin, no matter the units of N and the log base, which can be helpful in many practical applications. **Figure 1** clarifies this conclusion.

This choice creates a self-consistency between the time scale and the progress of the cell duplication. Now the experimental data to treat must be those that actually reflect the increase of N, neglecting those that do not significantly differ from the starting value, N_o. These data enter the best-fit routine based on the equation for the cell duplication,

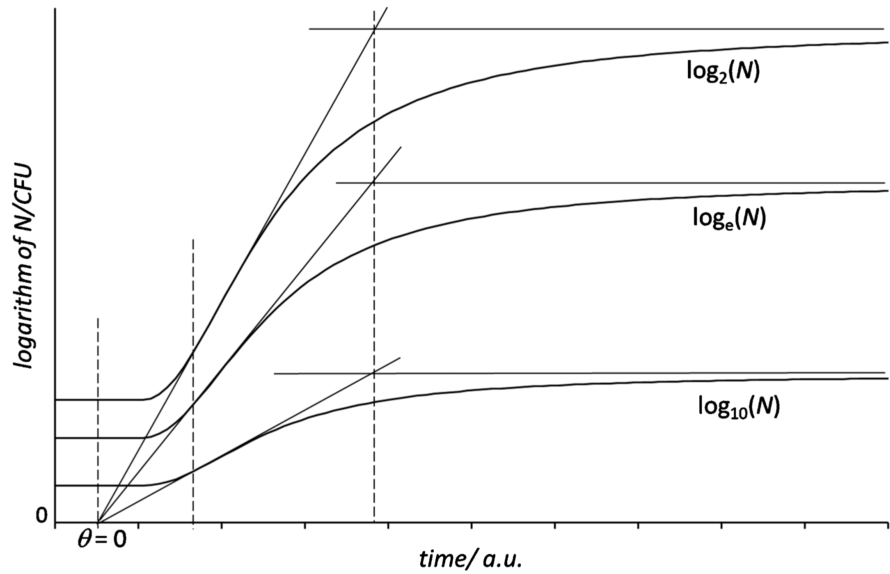

Figure 1. No matter the units for the cell population, N, and the log base used to plot the growth curve, the time origin, $\theta = 0$, is unequivocally singled out through the condition $\log(N) = 0$. The plot refers to the same N_o starting level.

$$N = N_o 2^{(\theta - \theta_o)/\tau(\theta)} \tag{1}$$

where τ is the variable generation time and θ_o is the time lapse that precedes the onset of the duplication process. The experimental evidence indicates that the duplication rate, $1/\tau$, is null for $\theta = \theta_o$ and for $\theta \to \infty$.

A simple function that obeys this condition [16] [17] is:

$$\tau = \frac{\alpha}{\vartheta - \theta_o} + \frac{\vartheta - \theta_o}{\beta} \tag{2}$$

Equation (2) allows rewriting Equation (1) in the $\log_2$ scale,

$$\log_2\left(\frac{N}{N_o}\right) = \frac{\beta(\vartheta - \theta_o)^2}{\alpha\beta + (\vartheta - \theta_o)^2} \tag{3}$$

Equation (3) states that the largest extent of the cell duplication (for $\theta \to \infty$) is $N_{max} = N_o 2^{\beta}$, which identifies β as the number of duplication steps experienced by each of the N_o duplication lines. A straightforward algebra [13] shows that the specific duplication rate goes through a maximum, $\mu = \left(\dot{N}/N\right)_{max}$, at $\left(\theta^* - \theta_o\right) = (\alpha\beta/3)^{1/2}$, when $\log_2\left(\frac{N}{N_o}\right)^* = \frac{\beta}{4}$. The value of μ is

$$\mu = \frac{3\sqrt{3}}{8}\sqrt{\frac{\beta}{\alpha}} \tag{4}$$

This means that the straight line tangent to the growth curve in the plot $\log_2(N)$-vs-θ corresponds to the equation

$$\log_2(N) = \left(\log_e(2)\frac{3\sqrt{3}}{8}\sqrt{\frac{\beta}{\alpha}}\right)\theta = \log_e(2)\mu\theta \tag{5}$$

This straight line goes through $\log_2(N) = [\log_2(N_o) - \beta/8]$ for $\theta = \theta_o$, while crosses the $\log_2(N_o)$ and the $\log_2(N_{max})$ levels at $\theta(0)$ and θ_{end}, respectively (Figure 2), with $(\theta_{end} - \theta_o) = 3(\theta^* - \theta_o)$ and $[\theta(0) - \theta_o] = (\theta^* - \theta_o)/2$.

For $\theta < 0$, any cellular activity does not directly aim at the duplication. This is another main difference from all the other models reported in the literature.

It is important to remind that the above parameters are properties of the whole system (cells + medium). This means that microbial cultures prepared pouring a given microbial population in different mediums will show different values of the parameters. All the above relationships hold for the growth curves of every prokaryotic microbial culture so far checked by the author, including those quite far from planktonic conditions, once the time scale of the experiment is reported to their own time origin $\theta = 0$.

When so, one can use the reduced variables $\theta_R = (\theta - \theta_o)/(\theta^* - \theta_o)$ and $\xi = \log_2(N/N_o)/\beta$ to gather all the growth curves in a single ξ-vs-θ_R master plot [13] that corresponds to the equation

$$\xi = \frac{\theta_R^2}{3 + \theta_R^2} \tag{6}$$

Such master plot reflects the collective self-consistent behavior underlying the shape of the growth curve of every microbial culture, in spite of the physical, chemical, biochemical and biological peculiarities of the system.

Another important relationship easily achievable through a straightforward algebra is:

$$\mu\theta_o = \frac{\log_2(N_o) - \beta/8}{\log_e(2)} \tag{7}$$

that interconnects three fundamental parameters of the model, namely, μ, β and θ_o. In particular, Equation (7) states that, for given N_o and β, the shorter the

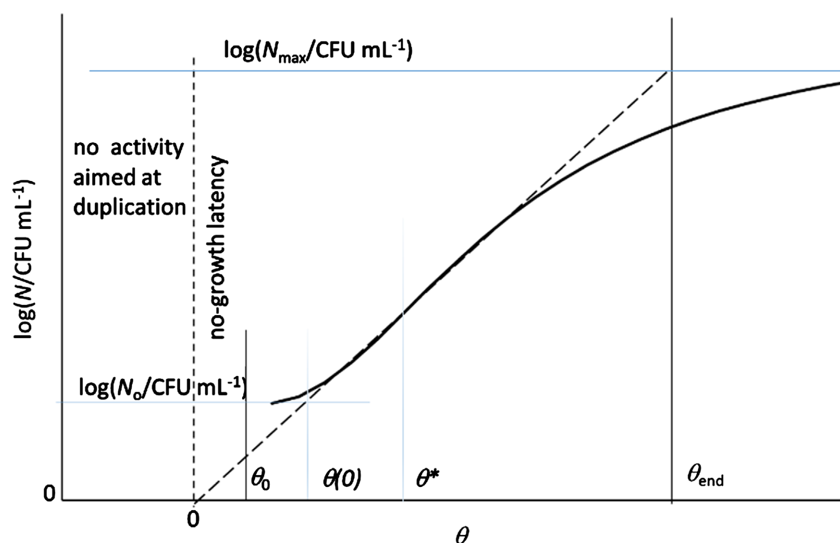

Figure 2. The growth curve goes through crucial milestones identified with peculiar values of the time, θ, namely, θ_o, $\theta(0)$, θ^* and θ_{end}.

latency phase that precedes the duplication onset, the faster the specific duplication rate. This makes sense as long as θ_o indicates the promptness of the cells to duplicate in the surrounding medium. Finally, since $(\mu\theta_o) > 0$, $\beta < 8\log_2(N_o)$.

Finally, it can be of some interest to notice that the formal treatment used to describe the duplication process that is typical of prokaryotic microbes holds also for eukaryotic yeasts and molds that show a sigmoid growth curve with a flex point. What one needs to do is just to put

$$\log_e(N) = \log_e(N_o) + \left[(\theta - \theta_o)/t\right]\log_e(n) \tag{8}$$

with $n > 1$, and replace β and $\log_2$ with $\nu\beta$, where $\nu = \log_e(n)$, and $\log_e$, respectively, in the above equations.

3. The Decay Phase

The experimental evidence shows that most microbial cultures undergo a decline once they have attained a maximum level of the population density. Between ascending and descending trends of N, a steady intermediate phase or a broad maximum can occur. Literature reports either kind of trends. Since the relationship between growth and decay could be of some relevance in food predictive microbiology as well as in the antibiotic pharmacology, an overall description seemed of some interest.

The above growth model finds a natural extension to the decay phase through the assumption of a basic principle. In the absence of any external adverse agent, death primarily hits the oldest cells [16].

The N_o starting cell of the model planktonic culture have the same age, but, after few duplication steps, the population hosts cells of different age: the newest born represent 50% of the whole population (no cell death occurs during the growth process) and soon overwhelm the starting N_o ancestors.

For this reason, if one accepts the above principle for the cell death, the first to dye will be just the N_o ancestors, namely a negligible fraction of the population. Small fractions will follow, until death hits the younger generations that correspond to major fractions of N_{max}.

Once reported in a log scale, the start of the decay is almost undetectable and remains so for some while, giving the impression of a culture in a steady condition if the average life span of the cells is large compared to the duplication time, τ. Conversely, if the life span is comparable or lower than τ, the observed trend of N shows a broad maximum between ascending and descending branches. This approach justifies the "cascade" effect of the decay trend that shows an increasingly downward slope [16] [17].

Formally, one can describe such a behavior through a pseudo exponential function of the time, t, elapsed after the attainment of the N_{max} threshold,

$$N_{surv} = N_{max}\exp\left(-\frac{t^2}{d}\right) \tag{9}$$

where d is a constant.

To be reconciled with the ascending trend of N, Equation (9) requires an adjustment of the time scale to align it with the selection of the time origin $\theta = 0$ described above.

The real start of the decay, θ_s, remains rather uncertain and therefore becomes a further parameter to determine through a best-fit routine based on the expression for the surviving population,

$$N_{\text{surv}} = N_{\theta=\theta_s} 2^{\frac{\theta-\theta_s}{\tau_d}} \tag{10}$$

where τ_d is the decay pace. Just like the generation time, τ, τ_d depends on the conditions of the medium that likely worsen for increasing ($\theta - \theta_s$). Putting $\tau_d = d/(\theta-\theta_s)$, one finally obtains the expression

$$N_{\text{surv}} = N_{\theta=\theta_s} 2^{\frac{(\theta-\theta_s)^2}{d}} \tag{11}$$

Equation (11) accounts for the above picture of the decay process through a ranking of the cell ages that parallels, in the reverse direction, the growth process [16] [17].

Finally, if one identifies $N_{(\theta-\theta_s)} = N_{\max}$, the number of viable cells throughout the decay phase is

$$\log_2(N_{\text{surv}}) = \log_2(N_o) + \beta - \frac{(\theta-\theta_s)^2}{d} \tag{12}$$

To define an expression for the overall (growth + decay) profile of N, one can use an expression like

$$\log_2(N) = \log_2(N_o) + \frac{\beta(\theta-\theta_o)^2}{\alpha\beta+(\theta-\theta_o)^2} - \frac{(\theta-\theta_o)^2}{\delta} \tag{13}$$

where $\delta \neq d$ is an adjustable parameter. If $\delta \gg (\theta_s-\theta_o)^2$, Equation (13) leads to practically the same value as Equation (3), for $\theta = \theta_s$, namely, $\log_2(N_{\max})$. Otherwise, the curve bends downward after going through a broad maximum below the level $[\log_2(N_o) + \beta]$. **Figure 3** shows some kinds of expected trends. Applications of Equation 13 to real growth & decay data appeared in previous papers that also report the modified decay trends observed after addition of bactericidal drugs [16].

4. Some Interesting Deviations

When facing adverse conditions, some microorganisms are able to modify their own phenotype or physiological behavior [19], as in the case of sporulation, or even genotype, as in the case of mutants that show resistance to antibiotic drugs [16] [17]. When so, the growth & decay trend significantly deviates from the above model: an easy - to - detect macroscopic signal that something important is occurring.

In other cases, the changes are very subtle, requiring specific approaches to perceive their effects. These approaches deal with observations of the evolution

of a given microbial culture in the course of several thousand generations, as in the Lenski's LTEE [8] [9]. This kind of investigation highlights the previous history of the cells, the memory of which seems related to the so-called fitness (or any suitable proxy of it) of the culture.

As long as β is in relation with μ and θ_o (Equation (7)), which are both representative of the efficiency of the cell in a given surrounding medium, β can be an effective proxy of the fitness. The increase of fitness after some thousand generations in a LTEE [8] (all starting from the same N_o level in the same medium) implies increase of μ and decrease of θ_o (**Figure 4**). These changes take place together with possible genomic mutations, which do not interfere with the growth progress [8] [9].

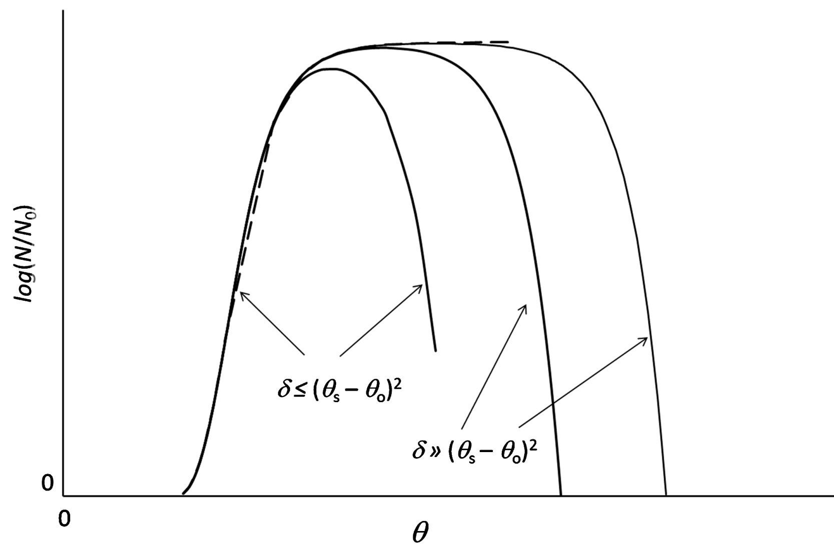

Figure 3. Growth & decay trends, depending on the value of δ compared with $(\theta_s - \theta_o)^2$ (see Equation (13)). The dotted line corresponds to the growth trend according to Equation (3).

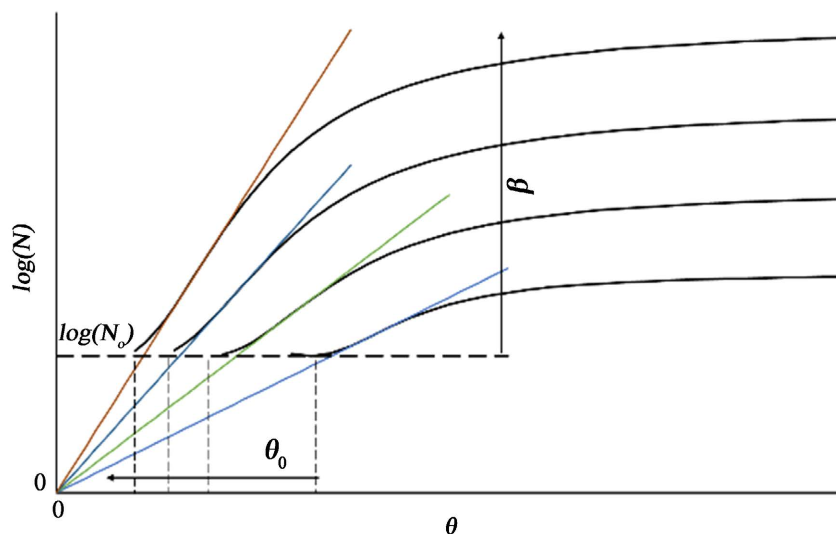

Figure 4. Increase of fitness for a microbial culture undergoing a Lenski's LTEE.

5. Conclusions

In spite of its semi-empirical nature and the assumed idealized conditions, the growth and decay model summarized in the present paper seems rather flexible and adequate to describe the behavior of real microbial cultures. It suggests a vision of the evolution of a given culture, in a given medium, that relates the duplication activity with the preceding no-growth phase, thanks to a suitable choice of a virtual time origin. The phenomenological description of the growth curve, through the assumption of a variable generation time, reveals some important interconnections between the parameters of the model (all determined with best-fit treatments of experimental data). These suggest an overall vision of the growth process as the result of a cooperative behavior of the microbes since the no-growth phase that precedes the duplication onset. Ranking the population fractions according to the respective age allows a naïve, but reasonable, interpretation of the steady plateau, or broad maximum, between rising and declining branches of the population density. The satisfactory check of the model once applied to a number of experimental data leaves me confident about its reliability.

The proposed approach and related model are easy to use thanks to the simple mathematical treatment of the experimental data and have a number of possible applications to microbial spoilage of food, pharmaceutical investigations about the efficacy of bactericidal and bacteriostatic drugs, as well as to studies on the evolution of microbial organisms in chemostat cultures [20].

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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