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Bacterial economics: Adaptation to stress conditions via stage-wise changes in the response mechanism

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ABSTRACT

Common features of microbial adaptation are analysed with mathematical models and extended to stress conditions when the bacterial population declines before growing again. A parallel is drawn between bacterial and human communities in terms of non-mutation-based adaptation (acclimation) to stress. For a case study, the behaviour of *Escherichia coli* under osmotic stress, is detailed. It is suggested that stress modelling adaptation should be the focus of further developments in predictive food microbiology.

1. Introduction

Predictive microbiology of foodborne organisms is a relatively young discipline that is still somewhat unsure of its exact identity among other disciplines. Its main tool is mathematical modelling but with an approach that is more pragmatic than those used in biotechnology or medical microbiology. "Black-box" and other (at least semi-) empirical models, primarily (and sometimes purely) based on observed data, are widely used and the implementation and the user-friendliness of their software packages represent the main factors in their success. A consequence of this approach is that significant effort is spent on evaluation of predictive models by assessing their performance when comparing predictions with observations, termed validation, but much less attention has been turned to defining how the models can be embedded in the community of fellow sciences.

We argue, and show with examples, that studying the link to other disciplines by creating analogies between concepts of bacterial and human-built communities, as well as between the respective mechanisms, is useful, not only from an educational point of view, but because these can inspire new developments. Predictive microbiology has not yet explored this idea sufficiently although comparisons between bacterial and economic mechanisms, especially regarding their response to environmental changes, have frequently been quoted in fundamental microbiology literature. Romling (2013) drew a parallel between bacterial communities and capitalist economies; Buescher et al. (2012) emphasized the need of dynamic interactions between the metabolic and regulatory networks to enable the cell to adapt to changing environments, for which Barabási (2003) used network science methods to remind us of analogous interactions between politics and industry. At the other end, the Financial Times Magazine made an extensive analysis on "How bacteria invest for success" (Cookson, 2013).

In this paper further analogies will be described, to show how concepts and models of one field can help the development of another. In the first instance, we show how the concept of physiological state could be extended to take into account cases when a stress divides isogenic inocula into growing and non-growing subpopulations. We report on observed cases of another type of breakdown, termed bistability, which is also induced by stress. Special attention is turned to bacterial responses to osmotic stress as an example. Finally, we describe how approaches from economics can be used to describe stress responses that can be beneficial for the development of predictive microbiology.

2. Mathematics of adaptation

2.1. A mathematical formalism to describe adaptation

A simple mathematical framework to model adaptation is described in the Appendix. The idea can be readily transposed to human economy or society. An example could be a group of immigrants in a new country who need to complete a bottle-neck process (e.g. learning the language) before progressing at a similar rate to the indigenous population. *Lag phase* can be compared to a *culture shock*, which gradually fades away.

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The model of Baranyi and Roberts (1994) is a special case of the generic definition given in the Appendix as follows.

During both inoculation and accidental contamination of food, the environment for the bacterial cells suddenly changes from history ($\mathbf{E_h}$) to current ($\mathbf{E_c}$). If the new environment supports growth, the cells grow exponentially after an adjustment period (not due to a mutation). This transition depends on the difference between $\mathbf{E_h}$ and $\mathbf{E_c}$.

Let μ_{max} be the maximum specific growth rate in $\mathbf{E_c}$ and let the instantaneous specific growth rate be $\alpha(t)\mu_{max}$ for $t > 0$ where t denotes the time. The $\alpha(t)$ adaptation function is monotone increasing with t, from $\alpha_0 > 0$ to 1; see the Appendix. The lag phase is therefore not a single number but a process, characterized by $\alpha(t)$, whose properties are similar to those of a cumulative probability distribution function. Indeed, as Baranyi (1998) pointed out, there is a one-to-one mapping between the probability distribution of single cell lag times and the $\alpha(t)$ adjustment function.

A lag parameter can be defined as the time when the adaptation process is "half-way" i.e. when $\alpha(t)$ reaches the mean between α_0 and 1. This corresponds to a certain mean of the individual cells' lag times (albeit not the arithmetical mean). For example, if the growth rate at the moment of inoculation is considered zero, the end of the lag phase is reached when the instantaneous specific rate

$$\frac{dx/dt}{x} = \frac{d(\ln x)}{dt} = \mu(t)$$

is half of μ_{max}. Baranyi et al. (1993) showed that, in practice, this definition coincides with the traditional definition of the end of the lag phase.

Using the mathematical theorem shown in the Appendix, we can also define the lag parameter in another way. The solution of the

$$\frac{dx}{dt} = \alpha(t)\cdot\mu_{max}\cdot x$$
$$x(0) = x_0$$

initial value problem converges to the

$$\alpha_0\cdot x_0\cdot\exp(\mu_{max}\cdot t) \;= x_0\cdot\exp(\mu_{max}\cdot t + \ln\alpha_0)$$

function, which is a delayed version of the solution of the original pure growth model (i.e. when the $\alpha(t)$ adjustment function is omitted). Rearranging the model to

$$\alpha_0\cdot x_0\cdot\exp(\mu_{max}\cdot(t-\lambda))$$

the delay term becomes

$$\lambda = -\ln\alpha_0/\mu_{max}$$

which is another definition of the lag parameter. In practical cases, it also provides values very close to other definitions of lag. This latter definition, however, is more suitable for modelling, especially to extend the concept of lag to include the probability of growth.

2.2. Lag phase of bacterial curves exhibiting inactivation and growth

Fig. 1 shows viable count measurements of *Salmonella enterica* Serovar Typhimurium during osmotic stress as analysed by Zhou et al. (2011), where some of the initial cells die, while others manage to build defense against the given stress and proliferate ("*phoenix phenomenon*", see Kelly et al., 2003). It would be desirable to characterize this adaptation process by a single parameter, such as the lag parameter defined above.

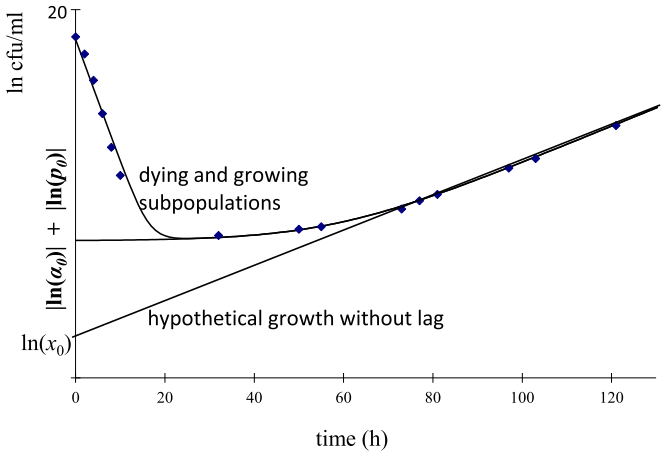

Fig. 1. One of the survival + regrowth curves analysed by Zhou et al. (2011). *Salmonella enterica* Serovar Typhimurium was inoculated in Basic Minimal Medium with 5% added NaCl and the temporal variation of the cell concentration was measured by plate counts. The Ln(cfu/ml) values were fitted by the model described here (upper continuous line). The physiological state parameter is $\beta_0 = p_0\alpha_0$. The $|\ln(\beta_0)|$ value consists of two parts $|\ln(\alpha_0)|$ and $|\ln(p_0)|$ and is the difference between the inoculum and the level where the extension of the exponential phase intercepts the vertical axis. $\beta_0 = p_0\cdot\alpha_0$, is that fraction of the x_0 inoculum that could produce the same exponential phase if these cells divide without lag. Therefore, the new interpretation of the physiological state parameter of the total population includes both the probability of growth and the physiological state of the growing subpopulation.

Inoculation into a stress environment divided the genetically homogeneous cells into two subpopulations; one was non-culturable on agar plates; the other was able to multiply. Note that from a modelling point of view, it does not make any difference whether the non-culturable subpopulation is dead or alive.

A parameter can be defined based on the concept of the initial physiological state, i.e. α_0, a number between 0 and 1. In its original form, α_0 is the fraction of the initial cells that would have been able to generate the observed exponential phase, had they grown instantaneously from the $\alpha_0 x_0$ level at their maximum specific rate μ_{max}, without a lag. In our case, this fraction is the result of both the probability of growth for a single cell in the total initial population, and the initial physiological state of the growing subpopulation. Therefore the convoluted physiological state is

$$\beta_0 = p_0\alpha_0$$

where p_0 is the probability of growth and α_0 is the initial physiological state of the growing subpopulation. From this, the total lag is a delay consisting of two parts:

$$\lambda = -\ln(p_0\alpha_0)/\mu_{max} = -\ln(p_0)/\mu_{max} - \ln(\alpha_0)/\mu_{max}$$

So the delay for the culture to reach exponential phase has two components: the probability of growth and the suitability of the growing cells to the new environment.

This raises the question of whether the division of the initial, genetically homogeneous population into two groups, is based on random selection, or isogenic cells can indeed respond to environmental stress in two ways with totally different outcomes. The occurrence of two stable phenotypes of a genetically identical population was termed bistability by Smits et al. (2006).

3. Bistability as a special case of bimodality of controlling complex systems

Bistability is a special case of what Jia et al. (2013) described as a widespread phenomenon in the control of complex systems, such as regulatory and metabolic networks within a cell, or economy-