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Towards a novel class of predictive microbial growth models

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Abstract

Food safety and quality are influenced by the presence (and possible proliferation) of pathogenic and spoilage microorganisms during the life cycle of the product (i.e., from the raw ingredients at the start of the production process until the moment of consumption). In order to simulate and predict microbial evolution in foods, mathematical models are developed in the field of predictive microbiology. In general, microbial growth is a self-limiting process, principally due to either (i) the exhaustion of one of the essential nutrients, and/or (ii) the accumulation of toxic products that inhibit growth. Nowadays, most mathematical models used in predictive microbiology do not explicitly incorporate this basic microbial knowledge. In this paper, a novel class of microbial growth models is proposed. In contrast with the currently used logistic type models, e.g., the model of Baranyi and Roberts [Baranyi, J., Roberts, T.A., 1994. A dynamic approach to predicting bacterial growth in food. International Journal of Food Microbiology 23, 277–294], the novel model class explicitly incorporates nutrient exhaustion and/or metabolic waste product effects. As such, this novel model prototype constitutes an elementary building block to be extended in a natural way towards, e.g., microbial interactions in co-cultures (mediated by metabolic products) and microbial growth in structured foods (influenced by, e.g., local substrate concentrations). While under certain conditions the mathematical equivalence with classical logistic type models is clear and results in equal fitting capacities and parameter estimation quality (see Poschet et al. [Poschet, F., Vereecken, K.M., Geeraerd, A.H., Nicolaï, B.M., Van Impe, J.F., 2004. Analysis of a novel class of predictive microbial growth models and application to co-culture growth. International Journal of Food Microbiology, this issue] for a more elaborated analysis in this respect), the biological interpretability and extendability represent the main added value.

Keywords: Predictive microbiology; Mechanistic modelling; Product inhibition; Substrate depletion; Primary modelling; Microbial growth

1. Introduction

Both the safety and quality of a food product are determined by the presence (and possible proliferation) of pathogenic and spoilage microorganisms during its life cycle (i.e., from the raw ingredients at the start of

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the production process until the moment of consumption). In the context of a global process model (see Fig. 1), the mathematical modelling of the evolution of microorganisms is, next to the mathematical modelling of quality influencing factors, an important step in quantitatively describing the influence of processing conditions on food safety. The evolution of the microbial population and the quality attributes are affected by the local environmental conditions. For food products homogeneous in temperature, for example, after a few hours in the refrigerator, the local temperature corresponds to the global one. However, during heating up gradients in temperature exist. Other environmental conditions may be spatially distributed as well (e.g., microbial load, water activity and pH) and are to be measured or calculated with appropriate model types (Valdramidis et al., 2004).

Predictive microbiology deals with the development of accurate and at the same time versatile mathematical models, able to describe the microbial evolution in food products as function of environmental conditions, which are assumed to be known or measurable (i.e., being the input in the right rectangle of Fig. 1). The modelling process aims at *condensing* existing microbiological knowledge about the patterns of the microbial behaviour and the microbial physiology into mathematical models (Ross, 1999).

Within each model building process, a complexity trade-off has to be made between *model accuracy* and *model manageability*: the model should be complex enough to cover the main dynamics but should also be user friendly (not too demanding with respect to computational aspects) and parsimonious.

A part of the results and main achievements of this paper is also presented in Van Impe et al. (2003).

2. General aspects of microbial growth modelling

The most elementary model building block describing microbial evolution is the following first order differential equation:

$$\frac{dN(t)}{dt} = \mu(\cdot) \cdot N(t) \tag{1}$$

in which $N(t)$ [CFU/mL] represents the concentration of microorganisms at time instant t and $\mu(\cdot)$ [1/h] the specific growth rate. $\mu(\cdot)$ can depend on process conditions (e.g., temperature), atmospheric conditions, food properties (e.g., pH, concentration of available substrate(s) and/or metabolites) and components governing interspecies/intraspecies interactions. $\mu(\cdot)$ is positive in the case of microbial growth and negative in the case of microbial inactivation. In this paper, we focus on microbial growth.

Single species microbial growth, whether in a bioreactor or in a (liquid) food product, normally passes three phases: first a lag phase during which the microbial cells adapt to their new environment, followed by an exponential growth phase during which the cells multiply exponentially, and finally a stationary phase during which the maximum popula-

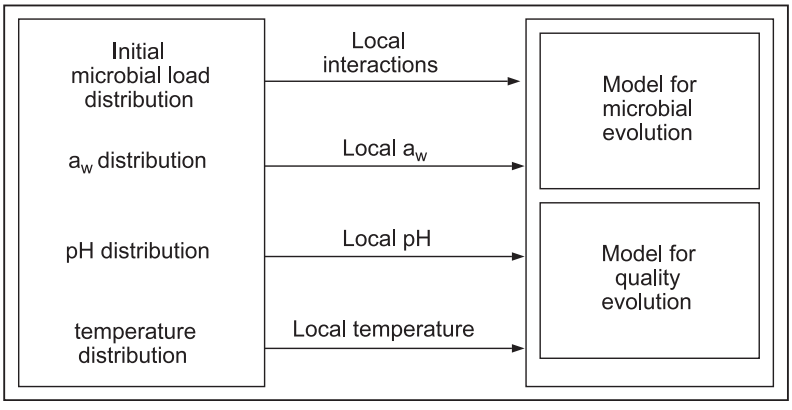

Fig. 1. The global process model. The large rectangle represents a food product revealing (possibly) a number of environmental factors distributions (left rectangle). These local environmental conditions are the input for the modelling of the microbial evolution and the food quality (right rectangle).

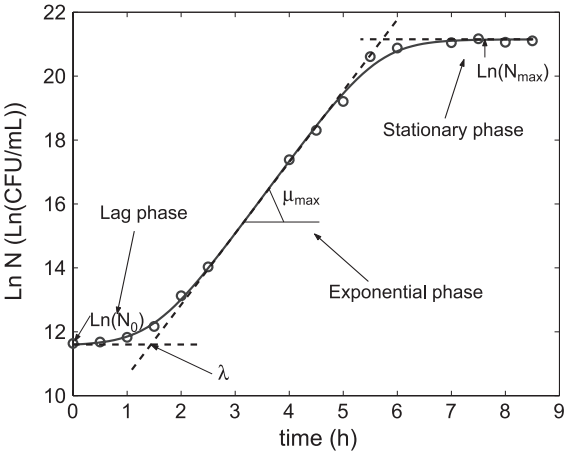

Fig. 2. Description of the model of Baranyi and Roberts on a typical growth curve in monoculture: growth of *E. coli* K12 at 35 °C.

tion density is reached (as shown in Fig. 2). More details on the exemplary experimental data shown can be found in Bernaerts et al. (2000).

Most models used in predictive microbiology are of the logistic type and do not *explicitly* reflect microbiological (mechanistic) knowledge on the self-limiting growth process when reaching the stationary phase (Lynch and Poole, 1979). This is illustrated with the nowadays widely used growth model of Baranyi and Roberts (George et al., 1996; Fernández et al., 1997; McClure et al., 1997; van Gerwen and Zwietering, 1998; Rodríguez et al., 2000; Coleman et al., 2003; Cornu et al., 2003; McKellar and Lu, 2003; Panagou et al., 2003), which can be considered as a prototype of logistic type microbial growth models.

The basic equation describing pure exponential growth reads as follows:

$$\frac{dN(t)}{dt} = \mu_{max} N(t) \tag{2}$$

with $N(t)$ [CFU/mL] the microbial load at time instant t and μ_{max} [1/h] the maximum specific growth rate. The logistic type growth model incorporates a logistic type *inhibition function* to describe the stationary phase (Verhulst, 1838; Pearl and Reed, 1920)

$$\frac{dN(t)}{dt} = \mu_{max}\left(1 - \frac{N(t)}{N_{max}}\right)N(t) \tag{3}$$

with N_{max} [CFU/mL] the maximum microbial cell concentration. The inhibition function is a monotonically decreasing function with values between (approximately) one and zero. A typical time behaviour of this inhibition function is presented in the left plot of Fig. 3. Baranyi and Roberts (1994) introduced the following *adjustment function* α as an extra factor to describe the lag phase:

$$\alpha(t) = \frac{Q(t)}{1 + Q(t)} \tag{4}$$

with $Q(t)$ [–] the so-called *physiological state* of the cells, which is assumed to be proportional to the concentration of a (hypothetical) critical substance simulating the bottleneck in the growth process. It is assumed that the physiological state $Q(t)$ is exponentially increasing. The adjustment function $\alpha(t)$ is a monotonically increasing function with values between (approximately) zero and one. A typical time

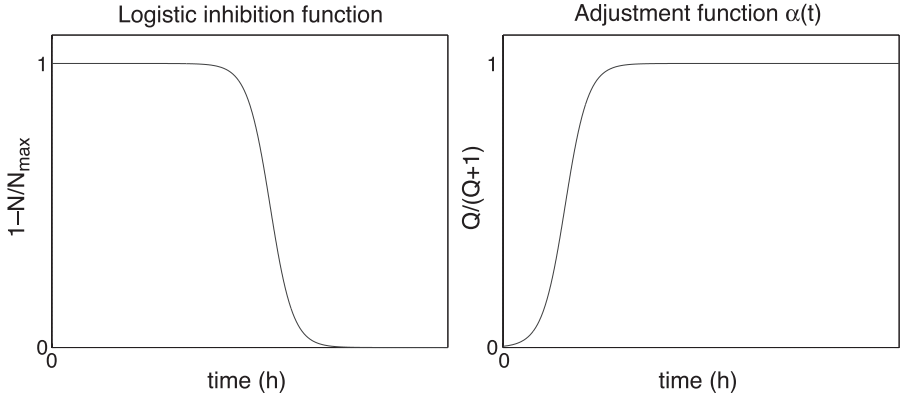

Fig. 3. Typical logistic inhibition function (left plot) and adjustment function (right plot).

Table 1
Model parameter values of the description of the model of Baranyi and Roberts, the P-model, and the S-model on an experimental data set of *E. coli* K12 at 35 °C

Model	$\ln(N_0)$	μ_{max}	$\ln(Q_0)$	$\ln(N_{max})$	$\ln(K_P)$	$\ln(Y_{N/S})$
Baranyi	11.601	2.3045	−3.4316	21.151		
P-model	11.601	2.2995	−3.4300		21.151	
S-model	11.602	2.3030	−3.4357			21.152

behaviour of this adjustment function for a growth curve with lag is presented in the right plot of Fig. 3.

The global implicit formulation valid under dynamic environmental conditions proposed by Baranyi and Roberts (1994) reads then as follows:

$$\frac{dN(t)}{dt} = \mu(\cdot)\cdot N(t) = \mu_{max}\left(\frac{Q(t)}{1+Q(t)}\right)\left(1-\frac{N(t)}{N_{max}}\right)N(t) \quad \text{with } N(t=0)=N_0 \tag{5}$$

$$\frac{dQ(t)}{dt} = \mu_{max}Q(t) \text{ with } Q(t=0)=Q_0 \tag{6}$$

The first differential equation describes the time evolution of the microbial load $N(t)$, as illustrated in Fig. 2. The first factor in the right-hand side of Eq. (5) induces the exponential phase, the second factor is the adjustment function, and the third factor is the inhibition function. The second differential equation (Eq. (6)) describes the time evolution of $Q(t)$, which increases exponentially. Remark that the adjustment function can be regarded as mechanistically inspired, whereas the logistic-type inhibition function is purely empirical as it does not include any cause–effect relationship (Lynch and Poole, 1979). A model description using an exemplary experimental data set with the indication of all model parameters is presented in Fig. 2. The numerical values of the parameter estimations are listed in Table 1, first row.

The model of Baranyi and Roberts is widely used for a number of reasons: (i) it is easy to use, (ii) it is applicable under dynamic environmental conditions, (iii) it has a good fitting capacity, and (iv) most of the model parameters are biologically interpretable. Contrary to the adjustment function, the inhibition function is not mechanistically inspired. Although clearly interpretable, this mathematical abstraction, inherited from the logistic model type, lacks a mechanistic base since it does not encapsulate a reason *why* the microbial population stops growing. In other words, it does not reflect any cause–effect relationship. Therefore, the model fails in describing more complex yet more realistic situations (e.g., co-cultural growth, growth in structured media). In the case of growth in structured media, the inhibition of growth because of substrate depletion (due to, e.g., hampered migration of the substrate through the (solid) structure of the medium) cannot be described by a single model parameter N_{max} which is not related with the medium structure and the available substrate concentration. In the case of co-cultural growth, the inhibition of growth because of (i) substrate depletion (which is competitively consumed by all organisms in the medium) and/or (ii) toxic product formation by some organisms cannot be described by means of a (fixed value of) N_{max} which is not related to the toxic product concentration, the initial concentration of all other organisms in the medium,...An example of co-culture growth is presented in Fig. 4, originating from Vereecken (2002). In this figure, the influence of an increasing inoculum size of *Lactococcus lactis* on the evolution of *Listeria innocua* (always with the same inoculum size) is clear: the maximum specific growth rate is unaffected but the maximum population level of *L. innocua* attained is decreasing with increasing *L. lactis* inoculum size. The biological mechanism governing this phenomenon is

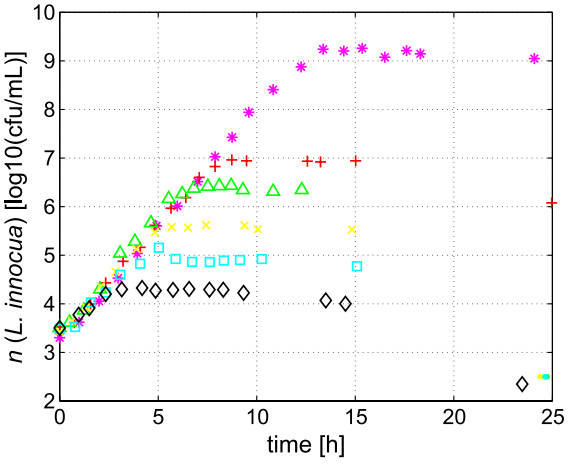

Fig. 4. Cell concentration of *L. innocua* versus time of different *L. innocua* (Li)/*L. lactis* (Ll) co-culture experiments. *: monoculture $N_{0,\,Li}=10^3$, +: $N_{0,\,Li}=10^3$, $N_{0,\,Ll}=10^3$, △: $N_{0,\,Li}=10^3$, $N_{0,\,Ll}=10^4$, ×: $N_{0,\,Li}=10^3$, $N_{0,\,Ll}=10^5$, □: $N_{0,\,Li}=10^3$, $N_{0,\,Ll}=10^6$, ◇: $N_{0,\,Li}=10^3$, $N_{0,\,Ll}=10^7$.

twofold: (i) the production of lactic acid, mainly by the lactic acid bacterium *L. lactis*, and (ii) the inhibition of the *L. innocua* outgrowth by the produced lactic acid. A logistic model type fails to describe this metabolic product mediated phenomenon.

In order to overcome the above drawbacks of logistic model types, a novel class of predictive models is constructed with a more mechanistically inspired description of the stationary phase.

3. A novel class of predictive growth models

The novel class of growth models should have following model properties:

(i) the kinetics (more specifically the inhibition function to describe the stationary phase) should be more mechanistically inspired,
(ii) as compared to traditional models, the model fitting capacity should be equal under comparable conditions,
(iii) easier to extend to more complex, and more realistic, situations.

Eq. (1) remains the elementary building block of the novel class of predictive growth models. As a matter of fact, this equation is the kernel of a widely applicable, sound model building block database from which the user can retrieve the appropriate building blocks constituting the overall $\mu(\cdot)$. The key ingredients of an elementary building block are the kinetics describing the (micro)biological phenomenon.

Single species growth, whether in a (liquid) food product or in a bioreactor, is a self-limiting process principally due to either (i) the *exhaustion* of *one of the essential nutrients* and/or (ii) the *accumulation* of *metabolic waste products* which inhibit growth (Lynch and Poole, 1979). The effect of both phenomena on the maximum population concentration is depicted in Fig. 5 (Bailey and Ollis, 1986). In order to determine which of both phenomena limits the exponential growth, following reasoning should be performed. If an increase of the initial substrate concentration results in an increase of the maximum microbial population density attained (as depicted in the left-hand side of Fig. 5), then the limiting factor is the substrate availability. If an increase of the initial substrate concentration (whether a C-source, N-source, essential element, a vitamin,...) does not affect the maximum microbial population density (as in the right part of Fig. 5), then the limiting factor is the formation of (a) toxic product(s).

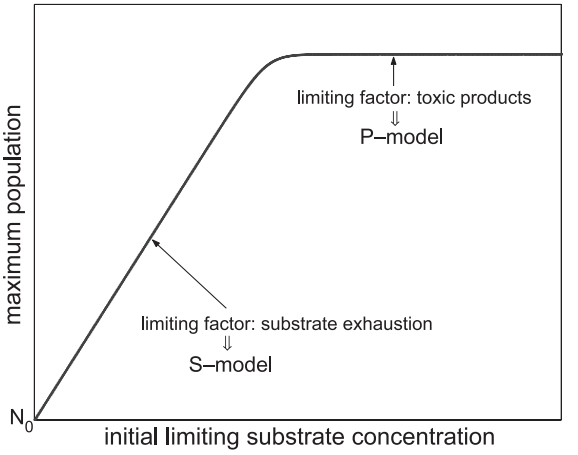

Fig. 5. Influence of the initial substrate concentration on the maximum microbial load population (after Bailey and Ollis, 1986).

The global structure of the novel class of predictive growth models consists of a general expression for the microbial evolution

$$\frac{dN(t)}{dt} = \mu(\cdot)\cdot N(t) = \mu_{max}\mu_Q(Q)\mu_P(P)\mu_S(S)N(t) \quad \text{with } N(t=0)=N_0 \tag{7}$$

together with the appropriate differential equations (and initial conditions) for the physiological state Q [–], the toxic/inhibiting product P [M] and the substrate S [M]. The first factor describes the exponential growth with maximum specific growth rate μ_{max} [1/h]. The second factor $\mu_Q(Q)$ accounts for the lag phase and is (given the scope of this paper) selected equal to the *adjustment function* of the model of Baranyi and Roberts (1994). The third factor $\mu_S(S)$ describes the influence of the phenomenon of exhaustion of a substrate S on the microbial evolution. The fourth factor $\mu_P(P)$ accounts for the inhibition of microbial growth by a toxic product P. Some inhibition functions have been presented in literature. As far as the maximum

population density is concerned, this novel class of predictive models is clearly more mechanistically inspired and is easier to extend in comparison with the existing models. Stationary phase behaviour is induced through an increasing toxic product accumulation and/or substrate exhaustion and can be attained at any population level $N(t)$. This is in contrast with many predictive models that, based on experimental data, impose a mathematical structure that prespecifies a fixed maximum population density N_{max}. Two limiting case studies are further discussed.

3.1. Back to basics: a so-called P-model as a first limiting case study of the novel class of microbial growth models

In a first case study, the stationary phase is assumed to be solely resulting from toxic product inhibition. Mathematically this implies that the factor $\mu_S(S)$ in Eq. (7) is (almost) equal to 1. Other assumptions are that (i) the initial concentration of the toxic product $P(t=0)$ is equal to zero and (ii) there is only one growth inhibiting product. The model consists of the following three differential equations:

$$\frac{dN(t)}{dt} = \mu(\cdot)\cdot N(t) = \mu_{max}\left(\frac{Q(t)}{1+Q(t)}\right)\left(1-\frac{P(t)}{K_P}\right)N(t) \quad \text{with } N(t=0)=N_0 \tag{8}$$

$$\frac{dQ(t)}{dt} = \mu_{max}Q(t) \text{ with } Q(t=0)=Q_0 \tag{9}$$

$$\frac{dP(t)}{dt} = Y_{P/N}\mu_{max}\left(\frac{Q(t)}{1+Q(t)}\right)\left(1-\frac{P(t)}{K_P}\right)N(t) \quad \text{with } P(t=0)=0 \tag{10}$$

Eq. (8) describes the microbial evolution in time, and consists of the *adjustment function* of the model of Baranyi and Roberts (see Eq. (5)). As an example, the inhibition function is chosen to be linear in function of the toxic product concentration P, inspired on Ghose and Tyagi (1979). The larger the concentration of product P, the smaller the increase in microorganisms. Eq. (9) is equal to the second equation of the model of Baranyi and Roberts (Eq. (6)) and describes the exponential evolution of the physiological state. Eq. (10) describes the evolution (i.e., production) of the toxic product concentration P, with $Y_{P/N}$ the yield for product over microorganisms. This equation expresses that, as an example, there is only growth associated production of the toxic product P. The complete model (Eqs. (8)–(10)) has an equal fitting capacity as compared to the model of Baranyi and Roberts, which is illustrated by comparing Fig. 6 with Fig. 2 and comparing the model parameter estimates of both models, listed in Table 1, second and third rows.

3.2. Back to basics: a so-called S-model as a second limiting case study of the novel class of microbial growth models

In a second case study, the stationary phase is assumed to be solely the result of substrate exhaustion, and not of toxic product inhibition. Mathematically this implies that the factor $\mu_P(P)$ in Eq. (7) is assumed to be equal to 1. For this case study, it is also assumed that (i) a linear relation is appropriate to describe the influence of substrate consumption on the microbial growth, (ii) there is no substrate consumption for maintenance, (iii) there is no substrate breakdown in the medium, (iv) no additional substrate is added during the growth process, and (v) there is

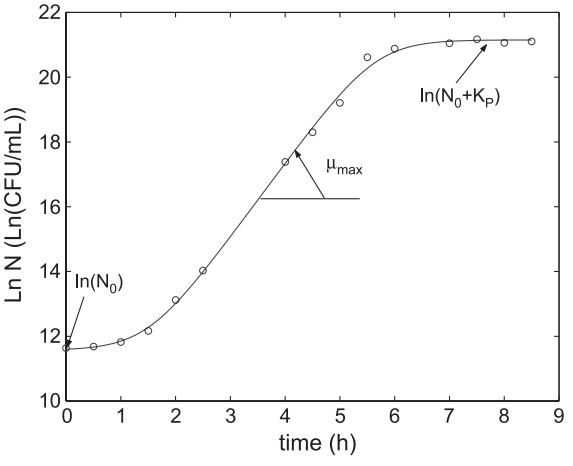

Fig. 6. Description of the basic P-model on an experimental data set of *E. coli* K12 at 35 °C.

only one limiting substrate. These assumptions result in the following three differential equations:

$$\frac{dN(t)}{dt} = \mu(\cdot)\cdot N(t) = \mu_{max}\left(\frac{Q(t)}{1+Q(t)}\right)S(t)N(t) \quad \text{with } N(t=0)=N_0 \tag{11}$$

$$\frac{dQ(t)}{dt} = \mu_{max}Q(t) \text{ with } Q(t=0)=Q_0 \tag{12}$$

$$\frac{dS(t)}{dt} = -\mu_{max}\left(\frac{Q(t)}{1+Q(t)}\right)\frac{S(t)}{Y_{N/S}}N(t) \quad \text{with } S(t=0)=1 \tag{13}$$

Eq. (11) describes the microbial evolution in time, and consists of the *adjustment function* of the model of Baranyi and Roberts (see Eq. (5)) and an inhibition function which is (as an example) selected equal to the substrate concentration S. Eq. (12) is equal to the second equation of the model of Baranyi and Roberts (Eq. (6)) and describes the exponential evolution of the physiological state. Eq. (13) describes the evolution (i.e., consumption) of the substrate concentration S. It is assumed that there is only substrate consumption for the growth process, and not for maintenance processes. By consequence, the right-hand side of Eq. (13) is (except for the minus sign and $Y_{N/S}$, the yield coefficient of the concentration of micro-organisms over (scaled) substrate concentration and expressed in CFU/mL) equal to the right-hand side of Eq. (11). The substrate concentration is rescaled in order to have a strictly monotone decreasing inhibition function with values between one and zero (and to obtain a rescaled dimensionless substrate concentration). Also this limiting model has an equal fitting capacity as compared to the model of Baranyi and Roberts, which is illustrated by comparing Fig. 7 with Fig. 2 and comparing the second and fourth rows in Table 1.

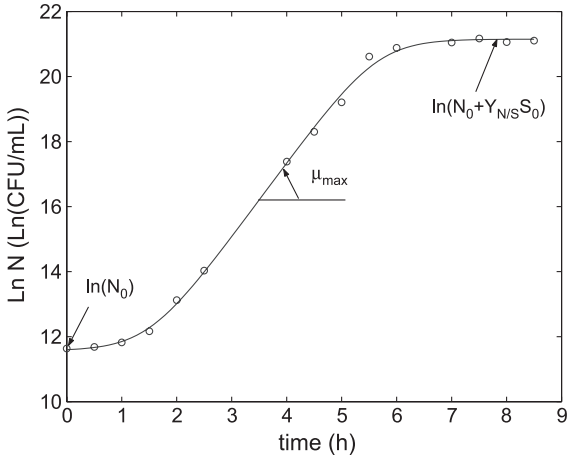

Fig. 7. Description of the basic S-model on an experimental data set of *E. coli* K12 at 35 °C.

4. Conclusions

The main contribution of this paper is the introduction of a novel class of predictive microbial growth models which reflect (micro)biological phenomena governing the microbial growth process. This research particularly focuses on the transition from the exponential growth phase to the stationary phase, which is induced through an increasing toxic product accumulation and/or substrate exhaustion. Contrary to many predictive models that, based on experimental data, impose a mathematical structure that prespecifies a fixed maximum population density, the novel class of predictive levels can cope with any maximum population density induced by toxic product accumulation and/or essential substrate depletion. The novel class of predictive growth models (i) has an equal fitting capacity as the currently used models (see Poschet et al., 2004 for a detailed statistical analysis in this respect), (ii) is applicable to both the macroscopic (i.e., population) as the microscopic (i.e., individual cell) level (see Standaert et al., 2004), and (iii) is easier to extend to more realistic situations. By consequence, in view of the complexity of the microbial phenomena to be described, the following questions need to be addressed: *when is simple good enough*? (free after Buchanan et al., 1997), *what is the model used for*?, *what about a stochastic version of the model*?, *can we include some novel measurements to improve the model*?, . . .In order to deal with the (resulting) increased complexity of the models, *predictive microbiologists* should urgently bridge the gap with *bioinformaticians* as was abundantly illustrated in the presentation of, e.g., Brul et al. (2003) at the PMF4 conference.

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