Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
International Journal of Food Microbiology 91 (2004) 261–277
INTERNATIONAL JOURNAL OF Food Microbiology
www.elsevier.com/locate/ijfoodmicro

Estimating the bacterial lag time: which model, which precision?

Florent Baty[a,*], Marie-Laure Delignette-Muller[b]

[a] CNRS UMR 5558, Biométrie-Biologie Évolutive, Laboratoire de Bactériologie, Faculté de Médecine Lyon-Sud, BP 12, 69921 Oullins Cedex, France
[b] Unité de Microbiologie Alimentaire et Prévisionnelle, École Nationale Vétérinaire de Lyon, BP 83, 69280 Marcy l'Étoile, France

Received 21 March 2003; received in revised form 23 July 2003; accepted 29 July 2003

Abstract

The objective of this work was to explore the large number of bacterial growth models recently proposed in the field of predictive microbiology, concerning their capacity to give reliable estimates of the lag phase duration (λ). We compared these models on the basis of their underlying biological explanations of the lag phenomenon, their mathematical formulation and their statistical fitting properties. Results show that a variety of biological interpretations of the lag phase exists, although different biological hypotheses sometimes converge to give identical mathematical equations. The fit of the different models provides relatively close λ estimates, especially if we consider that the imprecision of the λ estimates is generally larger than the differences between the models. In addition, the consistency of the λ estimates closely depends on the quality of the dataset on which models were fitted.

Keywords: Bacterial growth models; Lag time; Estimate precision

1. Introduction

Microbiologists classically use two main parameters to characterize the bacterial growth curve: the lag phase duration (λ) and the maximum specific growth rate (μ_{max}). Both parameters need to be accurately estimated in various fields, notably in food microbiology. In order to assess these parameters thoroughly and objectively, many growth models have been proposed since 1980. Models can be classified according to diverse criteria. They generally differ on how precisely they describe the successive growth phases. In a scale of increasing complexity, many empirical sigmoid curves were initially used to describe bacterial growth. Then, some new less empirical deterministic models were developed in the field of predictive microbiology. Finally, some authors recently proposed new more complex models including those based on stochastic phenomena. These models usually differ in their number of parameters and in the biological significance of their parameters.

In practice, deterministic models with parameters having a biological meaning prove to be very interesting. They are generally easy to fit to data and, thus, growth parameter estimates can be more conveniently assessed. Models that only have few parameters, each of them being microbiologically relevant, are prefer-

* Corresponding author. Tel.: +33-478-863-167; fax: +33-478-863-149.
E-mail address: baty@biomserv.univ-lyon1.fr (F. Baty).

0168-1605/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijfoodmicro.2003.07.002

able as they can be more easily validated by the microbiologist (Ratkowsky, 1983; VanGerwen and Zwietering, 1998; Schepers et al., 2000).

Nevertheless, many authors emphasized the particular difficulties in estimating λ (McKellar, 1997; Baranyi, 2002). Two reasons may explain those difficulties. The first reason is the lack of physiological understanding of the lag phenomenon. In actual fact, little knowledge is available concerning this physiological stage and only few authors were able to put some biological information about λ into model equations. The second reason is related to the first one and comes from the fact that the actual definition of λ is either purely geometric or purely mathematic. If we refer to the classical definition, λ is the time when a horizontal tangent to the curve at t_0 intersects the linear extrapolation of the exponential phase. Now, if we refer to the Buchanan and Cygnarowicz (1990) definition, λ is the time when growth acceleration is at its maximum. In order to mitigate this problem and improve knowledge of the lag phase, various authors have recently proposed new stochastic models based on the study of individual cell behavior. Baranyi (1997, 1998, 2002) proposed remarkable works in this field. Within this framework, several interesting concepts were developed such as the relationship between the cell lag and the population lag, the inter-individual cell lag variability, etc. Works of McKellar and colleagues (McKellar, 1997, 2001; McKellar and Knight, 2000) also brought insights in the capability of stochastic models to estimate growth parameters. They developed models describing the lag phase which combine stochastic and deterministic parameters. McKellar and coworkers mentioned some limits in the use of these models. For example, validating the biological variability of growth parameters among the cells of a population requires very precise growth monitoring at the cell level. So far, technical limits prevent us obtaining such data. Eventually, although stochastic models are powerful theoretical tools enabling to improve our understanding on the complex lag phenomenon, they remain practically difficult to handle for growth parameters estimations.

In a previous study, Baty et al. (2002) pointed out that both the technique used to monitor bacterial growth and the model fitted to estimate parameters influence significantly the estimates of λ. They specified that even though among different deterministic growth models none consistently gave the best fit, it was important to take into account the inter-model variations in the λ estimates.

In the present study, we compiled an inventory of several different deterministic models among those recently proposed in the literature. We compared them in terms of biological meaning, mathematical definition and statistical fitting properties. We fitted models on two kinds of dataset mainly differing in the number of points per growth curve.

In the first section of this work, we discussed biological hypotheses of the lag time. We also studied the mathematical formulation of these hypotheses, we compared them from one model to one another and we classified them.

In the second section of this work, we focused on the goodness-of-fit of some of these models on different datasets. We paid a particular attention in the precision of the estimates provided by the different models. Our objective was mainly to evaluate how reliable the λ estimates between models are and, if possible, to decide which model should be preferentially used.

2. Description and mathematical comparison of models

When one plots the logarithm of the bacterial density in a batch culture as a function of time, one usually divides the growth kinetics into three distinct phases. Cells newly inoculated in a fresh medium typically show a lag time prior to their first division. This ‘‘adaptation period’’ is classically followed by an exponential growing phase, where the bacterial population doubles at each doubling time. Afterwards, the bacterial density reaches a maximum. Growth is partly inhibited because of the lack of nutritive resources. From an idealized bacterial growth kinetics, one can estimate four characteristic parameters:

- $y_0 = \ln(x_0)$, x_0 being the initial bacterial density (cells/ml)
- λ, the lag phase duration (h)
- $\mu_{max} = \ln(2)/t_d$, the maximum specific growth rate (h^{-1}) and t_d the doubling time (h)
- $y_{max} = \ln(x_{max})$, x_{max} being the maximum bacterial density (cells/ml).

2.1. Sigmoid models

Sigmoid models were historically used to describe the increase in the logarithm of the bacterial cell density with time. Among them, one should mention the Logistic model and the modified Gompertz model. In their initial formulation, these two models were not intended to describe growth of microorganisms. They were adapted for bacterial growth description and were reparameterized so they contain parameters that are microbiologically relevant (Gibson et al., 1988; Zwietering et al., 1990). Zwietering et al. (1990) evaluated similarities and differences between five sigmoid models and dealt with the question of which models can be used on the basis of statistical reasoning. They concluded that, in many cases, the modified Gompertz model could be regarded as the best sigmoid model to describe growth data. As a matter of fact, these reparameterized models, and namely the modified Gompertz model, have been broadly used. However, during the 1990s, limits in the use of sigmoid curves to model bacterial growth curves were highlighted. The main drawback related to sigmoid curves comes from the very fact that, by definition, a sigmoid curve has an inflection point. Consequently, sigmoid curves are inappropriate for describing the exponential growth phase. Indeed, the relationship between the logarithm of the cell density and the time is by definition linear. The limitations in the use of the modified Gompertz model have been widely discussed, attention being particularly paid to the overestimation of μ_{max} and λ (Whiting and Cygnarowicz-Provost, 1992; Dalgaard, 1995; Membre et al., 1999; McKellar and Knight, 2000).

2.2. Models with an adjustment function

Since 1993, a new family of less empirical growth models was proposed by Baranyi et al. (1993). These models are based on the differential equation:

$$\frac{dx}{xdt} = \mu_{max}\alpha(t)f(x) \text{ with } x(t=0) = x_0 \quad (1)$$

where x is the cell density, μ_{max} is the maximum specific growth rate (h^{-1}), $\alpha(t)$ is an adjustment function describing the adaptation of the bacterial population to its new environment and $f(x)$ is an inhibition function describing the end-of-growth inhibition. As in many dynamic population models, $f(x)$ is usually described by a logistic inhibition function ($f(x) = 1 - (x/x_{max})$), where x_{max} is the maximal population density. On the other hand, authors proposed various adjustment functions ($\alpha(t)$) describing the lag phase and the transition to the exponential growth phase. Mathematically, $\alpha(t)$ is a monotone function increasing from a value close or equal to 0 to 1 as t tends to ∞. The role of this function is to delay the exponential growth. At first, we will focus on the initial growth phase without taking into account the inhibition phase.

Baranyi et al. (1993) initially proposed an adjustment function of the form:

$$\alpha(t) = \frac{t^n}{\lambda^n + t^n} \quad (2)$$

where n is a positive number that characterizes the curvature of the growth curve at the transition between the lag and the exponential phase (for convenience, the authors arbitrarily fixed n to 4). Then, Baranyi et al. (1993) proposed a biological interpretation of $\alpha(t)$ which could model the accumulation of a substrate required to ensure the growth in the new environment and that follows Michaelis–Menten kinetics. In practice, the explicit solution of Eq. (1) using the adjustment function (Eq. (2)) leads to an expression which is not convenient to handle for standard fitting procedures.

A new version of this model was developed later by Baranyi and Roberts (1994). The new adjustment function is of the form:

$$\alpha(t) = \frac{q(t)}{1 + q(t)} \quad (3a)$$

where $q(t)$ represents the physiological state of the bacterial population. In this case, the physiological state is proportional to the concentration of a critical substance that follows a first-order kinetics:

$$\frac{dq}{dt} = vq \text{ with } q(0) = q_0 \quad (3b)$$

where q_0 represents the physiological state of the inoculum. For convenience, Baranyi and Roberts

(1994) proposed a simplification by fixing v equal to μ_{max}. In a constant environment, the adjustment function which results from this simplification is described as follows:

$$\alpha(t) = \frac{q_0}{q_0 + e^{-\mu_{max} t}}$$

In this model, $\alpha(t)$ varies from $\alpha_0 = (q_0)/(q_0 + 1)$ at t_0 to 1 when t tends to ∞.

The explicit solution of $dx/x dt = \mu_{max}\alpha(t)$ is

$$y(t) = y_0 + \mu_{max}\left(t - \frac{1}{\mu_{max}} \ln\left(\frac{1 + q_0}{e^{-\mu_{max} t} + q_0}\right)\right) \qquad (4)$$

where $y(t) = \ln(x(t))$ and $y_0 = \ln(x_0)$.

From this equation, one can define the lag time parameter:

$$\lambda = \frac{\ln(1 + 1/q_0)}{\mu_{max}}.$$

Indeed, when time converges to infinity, $y(t)$ converges to $y_0 + \mu_{max}(t - \lambda)$. This definition of λ is coherent with the classical definition of the lag phase duration.

Another model that belongs to the same family describes $\alpha(t)$ as a step function:

$$\alpha(t) = \begin{cases} 0 & (t \le \lambda) \\ 1 & (t > \lambda) \end{cases}.$$

Many authors used this model and named it in different ways (see, for example, Buchanan et al., 1997; Baranyi, 1998; VanGerwen and Zwietering, 1998). The resulting model, simple in its form, is purely empirical. However, it proves to be consistent with some aspects of bacterial physiology. Buchanan et al. (1997) discussed the fact that a progressive transition between the lag phase and the exponential phase is due to the inter-cell variability of λ. They assumed that this variability is small and proposed this model with an abrupt transition from the lag phase to the exponential phase. In this model, the definition of λ is in total conformity with the classical definition.

2.3. Compartmental models

Numerous compartmental models were developed in order to model the lag phase. We will examine those which are based on simple biological hypotheses and which possess a limited number of parameters.

Hills and Wright (1994) developed a structured cell model with two compartments. It is rather complex in its biological presentation. The first compartment describes the evolution of all chromosomal material against time and the second compartment describes the evolution of all nonchromosomal material against time. The authors postulate that a minimal biomass per unit of cell is necessary for survival. When the conditions are acceptable for growth, the excess of biomass is used by the cell for initiating chromosomal replication. The rate of chromosome replication (v) and the rate of nonchromosomal synthesis (μ_{max}) are both considered constant. The two-compartment model of Hills and Wright (1994) is defined by the system of equations:

$$\begin{cases} \dfrac{dm}{dt} = \mu_{max} m & \text{with } m(t = 0) = x_0 \\ \dfrac{dx}{dt} = vx\left(\dfrac{m - x}{x}\right) & \text{with } x(t = 0) = x_0 \end{cases} \qquad (5)$$

where m is the total biomass concentration of the bacterial batch culture measured in units of minimal biomass per cell, x is the cell concentration, x_0 is the initial value of this cell concentration and t is the time. In their model, Hills and Wright (1994) assumed that at the beginning of the lag phase, the amount of biomass per cell is minimal ($m(t = 0) = x_0$ in unit of minimal biomass per cell), and that during the lag phase, the cells increase their average biomass by absorbing nutrients form the surrounding medium and by converting them into nonchromosomal material. A lag time arises in this two-compartment model because the chromosome replication is delayed during the lag phase until the excess of cell biomass has reached its maximum value for a particular growth environment. It is then assumed that a constant rate v relates the rate of the chromosome replication $dx/x dt$ to the excess of cell biomass $(m - x)/x$. The authors finally gave a simple solution

for the previous system of Eq. (5) when μ_{max} and v are constant:

$$x(t) = \frac{x_0}{\mu_{max} + v}\left(v e^{\mu_{max} t} + \mu_{max} e^{-vt}\right). \quad (6)$$

If we use the logarithm transformation, we obtain:

$$y(t) = y_0 + \mu_{max}\left(t + \frac{1}{\mu_{max}} \ln\left(\frac{v}{\mu_{max} + v} + \frac{\mu_{max}}{\mu_{max} + v} e^{-(\mu_{max}+v)t}\right)\right).$$

If time converges to infinity, $y(t)$ converges to $y_0 + \mu_{max}(t - \lambda)$. Therefore, one can define the parameter λ as follows:

$$\lambda = \ln\left(1 + \frac{\mu_{max}}{v}\right) \Big/ \mu_{max}$$

This definition of λ is consistent with the classical definition of the lag phase duration.

The Hills and Wright (1994) model is defined as a structured-cell model. In that case, the lag phase is a consequence of an intracellular phenomenon. On the other hand, structured-population models have also been developed.

The model proposed in McKellar (1997) is a two-compartment model that is reasonably easy to handle. It is based on the assumption that within a bacterial population freshly inoculated in a rich medium, some cells will grow exponentially without any delay (G compartment) and some will never grow (NG compartment). The mathematical formulation of the model is described below by the two following differential equations:

$$\begin{cases} \dfrac{dx_G}{dt} = x_G \mu_{max} & \text{with } x_G(t=0) = x_{G0} = \alpha_0 x_0 \\ \dfrac{dx_{NG}}{dt} = 0 & \text{with } x_{NG}(t=0) = x_{NG0} = (1-\alpha_0)x_0 \end{cases} \quad (7)$$

with x_G the number of immediate growing cells, x_{NG} the number of nongrowing cells, x_0 the initial total cell concentration and α_0 the proportion of growing cells in the population. The total number of cells at time t is $x(t) = x_G(t) + x_{NG}(t)$. Consequently, we obtain:

$$x(t) = (1 - \alpha_0)x_0 + \alpha_0(x_0 e^{\mu_{max} t})$$

or in its logarithm transformation:

$$y(t) = y_0 + \ln(1 - \alpha_0 + \alpha_0 e^{\mu_{max} t})$$

one can rewrite:

$$y(t) = y_0 + \mu_{max}\left(t + \frac{\ln((1-\alpha_0)e^{-\mu_{max} t} + \alpha_0)}{\mu_{max}}\right) \quad (8)$$

Now, if we take $\alpha_0 = q_0/(q_0 + 1)$, it clearly appears that Eq. (8) is identical to Eq. (4) proposed by Baranyi and Roberts (1994). It is interesting to note that McKellar (1997) only mentioned strong similarities between the two models without demonstrating the exact mathematical equivalence of the two models. More generally, we can show that the model of McKellar defined by the differential equations (Eq. (7)) is equivalent to the model of Baranyi and Roberts (1994) defined by the Eqs. (1), (3a) and (3b). We will not detail the demonstration in this paper, but it is easy to perform this by defining $x_G = \alpha(t)x$ and $x_{NG} = (1 - \alpha(t))x$, then by calculating dx_G/dt and dx_{NG}/dt from the equation $dx/xdt = \mu_{max}\alpha(t)$ combined with Eqs. (3a) and (3b) to finally obtain Eq. (7).

McKellar and colleagues also recently developed two other more mechanistic models (McKellar and Knight, 2000; McKellar, 2001). Because they both incorporate stochastic phenomena, this makes them less adapted for fitting procedures. So we will not detail them any further.

Another population-structured model found in the literature is the one proposed by Baranyi (1998). In this model, the author postulated that a bacterial population could be divided into two compartments: cells which are still in the lag phase (x_{NG}) and cells which are in the exponential phase (x_G). The author assumed that cells transform from the lag to the exponential phase at a constant rate (v). Cells in the exponential phase are growing at a constant rate (μ_{max}). The hypotheses made by Baranyi (1998) are close to those made by McKellar (1997). The only difference concerns the transfer between the two compartments which is not taken into

account by McKellar. The Baranyi (1998) model can be described by a system of two linear equations with two initial values:

$$\begin{cases} \dfrac{dx_{NG}}{dt} = -vx_{NG} & \text{with } x_{NG}(t=0) = x_0 \\ \dfrac{dx_G}{dt} = \mu_{max}x_G + vx_{NG} & \text{with } x_G(t=0) = 0 \end{cases} \quad (9)$$

where x_0 is the initial cell density of the bacterial batch culture. The explicit solution of this system can be written:

$$x(t) = x_{NG}(t) + x_G(t) = \frac{x_0}{\mu_{max} + v}\left(ve^{\mu_{max}t} + \mu_{max}e^{-vt}\right) \quad (10)$$

Now, if we compare the explicit solution of both the model of Hills and Wright (1994) (Eq. (6)) and the model of Baranyi (1998) (Eq. (10)), one notices that the two equations are identical. In fact, if we define $m = x + \mu_{max}x_G/v$ with $x = x_G + x_{NG}$, we can easily find the equations system (Eq. (5)) by calculating dm/dt and dx/dt from Eq. (9).

2.4. Unified formulation of models

Among various deterministic growth models proposed in the literature, some regrouping shall be considered. The underlying biological hypotheses modeled by the authors lead to diverse mathematical formulations. Nevertheless, it appears that models built on totally different biological hypotheses may actually be mathematically equivalent. Thus, McKellar (1997) compared his model with the one proposed by Baranyi and Roberts (1994). He only noticed that these two models had strong similarities despite fundamentally different assumptions. As a matter of fact, Baranyi and Roberts (1994) assumed that the cell population is homogeneous while McKellar (1997) assumed that the cell population is heterogeneous. In spite of this dissimilarity, the two models are mathematically equivalent. The same conclusions can be drawn if we compare the equations of the Hills and Wright (1994) model with the equations of Baranyi (1998). The two models do not rely on the same biological hypotheses but they are mathematically equivalent.

Finally, from all the models presented above (except for the sigmoid models), we distinguish three mathematically different models:

- the Baranyi model (Baranyi and Roberts, 1994) which is mathematically equivalent to McKellar model (McKellar, 1997)
- the Hills model (Hills and Wright, 1994) which is equivalent to the compartmental model proposed by Baranyi (1998)
- the Lag-exponential model (Buchanan et al., 1997).

These three models can be written in a similar form:

$$\frac{dx}{xdt} = \mu_{max}\alpha(t)f(x) \text{ with } x(t=0) = x_0$$

where x is the cell density of bacterial batch culture, x_0 is the initial cell density, t is the time, μ_{max} is the maximum specific growth rate, $f(x)$ is the inhibition function describing the transition of the growth curve to the stationary phase which may be fixed to 1 if no inhibition is modeled, $\alpha(t)$ is the adjustment function describing the adjustment of the culture to its new environment, differently defined for the three models.

(i) For the Baranyi model,

$$\alpha(t) = \frac{q(t)}{1 + q(t)}$$

and

$$\frac{dq}{dt} = vq \text{ with } q(0) = q_0.$$

(ii) For the Hills model,

$$\alpha(t) = v\left(\frac{m-x}{x}\right) \text{ or } \alpha(t) = \frac{\mu_{max}}{e^{\mu_{max}\lambda} - 1}\left(\frac{m-x}{x}\right)$$

and

$$\frac{dm}{dt} = \mu_{max}m \text{ with } m(t=0) = x_0.$$

(iii) For the lag exponential model,

$$\alpha(t) = \begin{cases} 0 & (t \le \lambda) \\ 1 & (t > \lambda) \end{cases}.$$

3. Statistical comparison of models

3.1. Models and fitting procedures

In the fitting analysis, we only considered three models: the modified Gompertz model (for simplicity, we will name it later Gompertz), the Baranyi model (Baranyi and Roberts, 1994) and the Lag-exponential model. These models describe the whole bacterial growth kinetics from the lag phase to the saturation phase. For the Baranyi and Lag-exponential models, we chose the logistic inhibition function ($f(x) = 1 - (x/x_{max})$) to model the end-of-growth saturation. We removed the Hills model from our analysis because there is no explicit solution when integrating the differential equation including the logistic inhibition function. This prevented us using the usual nonlinear fitting routines.

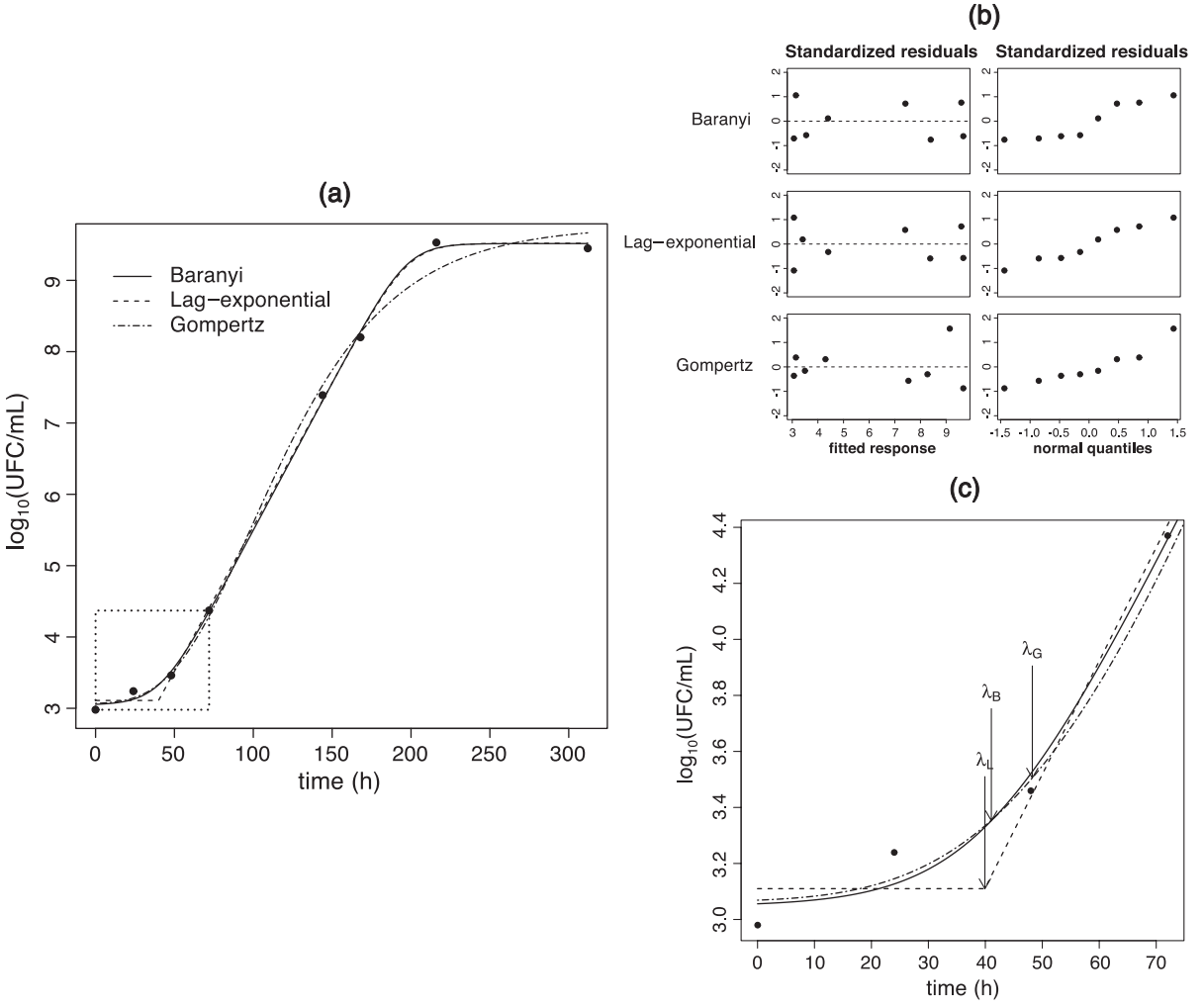

Fig. 1. Fit of a typical G-I dataset (G-I 02) with the Baranyi, Lag-exponential and Gompertz models (a). Standardized residuals are plotted for the three models as a function of the fitted response and the normal quantiles (b). Detail of lag phase (enlarging corresponding to dotted line box in (a)) and position of the λ estimates are plotted for the Baranyi (λ_B), the Lag-exponential (λ_L) and the Gompertz (λ_G) models (c).

For each dataset, we fitted the log-transformed equation of the following models:

Gompertz model:

$$y(t) = y_0 + (y_{\max} - y_0)\exp\left(-e^{\left(1+\mu_{\max}e^{1}\frac{(\lambda-t)}{(y_{\max}-y_0)}\right)}\right).$$

Baranyi model:

$$y(t) = y_{\max} + \ln\left(\frac{-1+e^{\mu_{\max}\lambda}+e^{\mu_{\max}t}}{(-1+e^{\mu_{\max}t})+e^{(\mu_{\max}\lambda+y_{\max}-y_0)}}\right).$$

Lag-exponential model:

$$y(t) = \begin{cases} y_0 & t \le \lambda \\ y_{\max} + \mu_{\max}(t-\lambda) - \ln(e^{(y_{\max}-y_0)} - 1 + e^{\mu_{\max}(t-\lambda)}) & t > \lambda \end{cases}$$

For reasons of visibility, graphics were plotted using the decimal logarithm transformation.

The three models were fitted by nonlinear regression by using the least-squares criterion (Bates and Watts, 1988). Estimates for parameters ($\hat{\theta}$) were obtained by minimizing the residual sum of squares (RSS):

$$\mathrm{RSS} = \sum_{i=1}^{n}(y_i - \hat{y}_i)^2$$

where n is the number of data points, y_i is the ith observed value and $\hat{y}_i$ is the ith fitted value. All the statistical calculations were computed using R Software version 1.6.1 (Ihaka and Gentleman, 1996). Nonlinear regression was computed with the *nls* package available with R. We used the Gauss–Newton algorithm of minimization which is the default algorithm in *nls*. The performance of models was evaluated by using a comparison of residual standard error ($\mathrm{RSE} = \sqrt{\mathrm{RSS}/(n-p)}$), where RSS is the residual sum of squares, n is the number of data points and p is the number of parameters. We compared the precision of the estimates by calculating the asymptotic and jackknife (Duncan, 1978) confidence intervals (see Appendixes A and B). We checked for the structural dependences of the models' parameters by calculating and plotting the Beale's confidence regions (Beale, 1960) (see Appendix C).

Table 1
λ estimates obtained by the fit of the Baranyi, Lag-exponential and Gompertz models on the G-I datasets and the coefficients of variation (asymptotic standard error divided by λ estimate) associated to these estimates

	λ Baranyi	CV (%)	λ Lag-exponential	CV (%)	λ Gompertz	CV (%)	Inter-model CV (%)
G-I 01	28.73	4	29.72	10	33.45	13	7
G-I 02	41.05	10	39.92	8	48.25	18	9
G-I 03	4.12	18	3.42	6	5.34	35	18
G-I 04	5.78	21	5.60	16	7.09	19	11
G-I 05	3.25	27	2.87	18	4.24	13	17
G-I 06	2.57	16	2.52	12	2.63	24	2
G-I 07	0.92	43	1.04	34	1.34	45	16
G-I 08	1.49	35	1.46	32	1.87	38	12
G-I 09	1.36	30	1.22	30	1.99	23	22
G-I 10	1.58	10	1.55	8	2.01	14	12
G-I 11	13.34	60	12.21	65	16.13	84	12
G-I 12	12.95	51	10.23	60	14.99	112	15
G-I 13	113.60	31	117.30	25	62.43	67	26
G-I 14	43.35	24	35.84	28	48.27	22	12
G-I 15	14.61	52	11.76	57	18.07	70	17
Mean		28.8		27.3		39.8	13.9

Last column gives the inter-model coefficients of variation of the estimates.

3.2. Data

In order to evaluate the fitting properties of the three models, we collected 32 datasets belonging to two distinct groups. The first group (G-I) corresponds to 15 datasets tabulated in Buchanan et al. (1997). These 15 datasets concern the growth of a cocktail of three *Escherichia coli* O157:H7 strains at diverse conditions of temperature (5–42 °C), pH (4.5–8.5), nitrite concentration (0–200 μg/ml), sodium chloride concentration (5–50 g/l) and oxygen availability (aerobic versus anaerobic). These datasets have on average only few points per curve (from 6 to 13 points). On the other hand, the second group (G-II) is made of 17 growth curves of three *Listeria monocytogenes* strains. These data were kindly placed at our disposal by H. Bergis (LERAC, AFSSA, Maisons-Alfort, France). Growth of these strains was monitored by viable count enumeration at various conditions of temperature (2–30 °C) in trypticase soy broth supplemented with yeast extract. These datasets are more substantial as they have on average

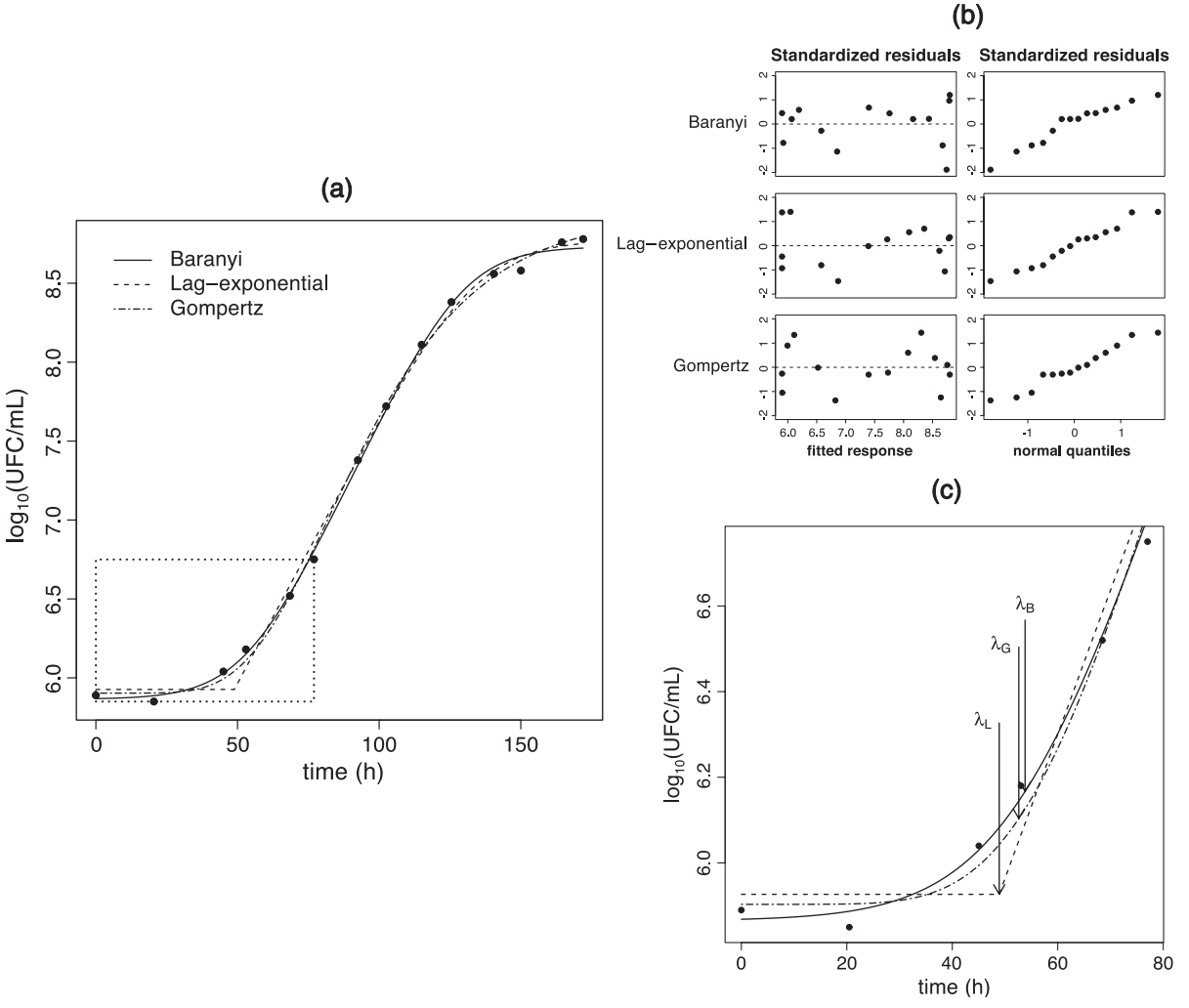

Fig. 2. Fit of a typical G-II dataset (G-II 14) with the Baranyi, Lag-exponential and Gompertz models (a). Standardized residuals are plotted for the three models as a function of the fitted response and the normal quantiles (b). Detail of lag phase (enlarging corresponding to dotted line box in (a)) and position of the λ estimates are plotted for the Baranyi (λ_B), the Lag-exponential (λ_L) and the Gompertz (λ_G) models (c).

a greater number of points per curve (from 12 to 24 points).

Stabilization of the variance of data was done using the usual logarithmic transformation.

3.3. Fitting results

We fitted systematically the three models on each of the 32 datasets from the G-I and the G-II groups. The fit of the three models on a typical dataset from the G-I group is presented in Fig. 1a. This dataset is made of eight points and we notice that the three models fit it correctly. The graphical analysis of the standardized residuals shows that in every case residuals are approximately independent and identically normally distributed (Fig. 1b). Now, if we examine the estimates of λ (Fig. 1c), we notice that some apparent differences exist between the three models. Overall, results presented in Table 1 show that in 14/15 datasets, the Gompertz model gives the biggest λ estimates, whereas in 12/15 datasets, the Lag-exponential model gives the smallest λ estimates.

The fit of the three models on a typical dataset from the G-II group is presented in Fig. 2a. This dataset is made of 14 points and the three models fit it correctly. Standardized residuals are approximately independent and identically normally distributed (Fig. 2b). Differences exist between the λ estimates provided by the three models (Fig. 2c). In Table 2, we notice that in 14/17 datasets, the Baranyi model gives the biggest λ estimates, whereas in 14/17 datasets, the Lag-exponential model gives the smallest λ estimates. It is interesting to remark that the biggest λ estimates are not given by the same model in G-I as in G-II.

Tables 3 and 4 provide the residual standard errors (RSE) obtained after the fit of the three models. Although the Baranyi model fits the best (in terms of RSE) in 9/15 datasets for the G-I group and in 12/17 datasets for the G-II group, none of the models consistently produced the best fit to all the growth curves. In Fig. 3, we clearly notice that the fits of the G-I group gives on average larger RSE than the fits of the G-II group.

If we globally compare the λ estimates provided by the three models on the datasets of both groups (Fig. 4), we find that the inter-model variations of λ estimates are more important within the G-I group (CV = 13.9%) than within the G-II group (CV = 4.1%). Another interesting point resulting from this analysis concerns the orientation and the amplitude of the bias

Table 2
λ estimates obtained by the fit of the Baranyi, Lag-exponential and Gompertz models on the G-II datasets and the coefficients of variation (asymptotic standard error divided by λ estimate) associated to these estimates

	λ Baranyi	CV (%)	λ Lag-exponential	CV (%)	λ Gompertz	CV (%)	Inter-model CV %
G-II 01	188.3	4	174.78	3	177.3	3	3
G-II 02	79.56	5	76.751	6	75.43	7	2
G-II 03	30.462	11	27.493	5	31.53	11	6
G-II 04	7.731	6	7.518	6	7.78	11	1
G-II 05	1.623	14	1.655	10	1.85	16	6
G-II 06	278	2	249.2	2	258.9	2	5
G-II 07	141.5	4	125.7	5	128.5	4	5
G-II 08	49.38	5	45.31	6	47.5	6	4
G-II 09	26.751	2	25.29	4	25.67	2	2
G-II 10	12.18	8	11.27	5	12.166	7	4
G-II 11	4.57	3	4.41	4	4.51	5	2
G-II 12	205.7	3	198.1	3	199.125	3	2
G-II 13	151.3	2	137.4	2	142.1	2	4
G-II 14	53.81	4	48.90	5	52.62	4	4
G-II 15	22.32	5	19.21	2	22.07	4	7
G-II 16	16.19	3	14.21	5	12.17	7	12
G-II 17	4.36	5	4.238	6	4.29	6	1
Mean		5.1		4.7		5.9	4.1

Last column gives the inter-model coefficients of variation of the estimates.

Table 3
Residual standard errors (RSE) obtained after the fit of the Baranyi, Lag-exponential and Gompertz models on the G-I datasets

	RSE Baranyi	RSE Lag-exponential	RSE Gompertz	*df*
G-I 01	0.037[a]	0.109	0.109	2
G-I 02	0.107[a]	0.120	0.248	4
G-I 03	0.061	0.026[a]	0.091	5
G-I 04	0.113	0.139	0.106[a]	6
G-I 05	0.179	0.152	0.143[a]	6
G-I 06	0.100	0.089[a]	0.126	3
G-I 07	0.246[a]	0.266	0.332	6
G-I 08	0.242[a]	0.244	0.317	4
G-I 09	0.211[a]	0.220	0.257	3
G-I 10	0.123	0.120[a]	0.238	7
G-I 11	0.557[a]	0.563	0.577	5
G-I 12	0.192[a]	0.201	0.264	6
G-I 13	0.086[a]	0.102	0.095	5
G-I 14	0.262	0.296	0.214[a]	9
G-I 15	0.225[a]	0.233	0.275	5
Mean	0.183	0.192	0.23	

Last column gives the degrees of freedom (*df*) of each dataset.
[a] Lower RSE.

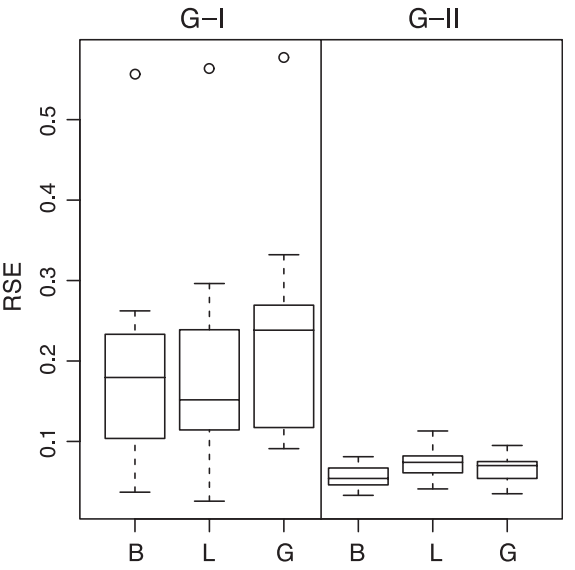

Fig. 3. Box plot representations of the residual standard error (RSE) obtained by fitting the Baranyi (B), Lag-exponential (L) and Gompertz (G) models on the G-I and G-II datasets. The 25th, 50th and 75th percentiles and extreme values are shown.

of λ estimates between the three models. In 2000, Augustin and Carlier collected a large number of growth kinetics from the literature and fitted various growth models to these data. They studied the inter-model bias on λ estimates and proposed a method to correct the bias between λ estimated with the Lag-exponential model and other growth models (Baranyi, Gompertz, Logistic). The authors emphasized the existence of a systematic bias between the three models we studied. In our analysis, we did not find any comparable variations. In the box plot presented in Fig. 4, we notice that the divergence of the λ estimates from the Baranyi model (λ_B) and the Gompertz model (λ_G) compared to the Lag-exponential model (λ_L) varies from one group to one another. We also notice that the ratios λ_B/λ_L and λ_G/λ_L are much more variable within the G-I group ($SD_{\lambda_B/\lambda_L}=0.11$ and $SD_{\lambda_G/\lambda_L}=0.27$) compared to the G-II group ($SD_{\lambda_B/\lambda_L}=0.05$ and $SD_{\lambda_G/\lambda_L}=0.07$). In the G-I group, λ_B and λ_G are on average respectively 1.03 and 1.3 times larger than the λ_L. In the G-II group, the λ_B and λ_G are on average respectively 1.08 and 1.03 times larger than the λL. On the other hand, Augustin and Carlier (2000) determined a median ratio λ_B/λ_L equals to 1.05 and a median ratio λ_G/λ_L equals to 1.22. Our results suggest that the inter-model bias closely depends on the quality of the dataset. Consequently,

Table 4
Residual standard errors (RSE) obtained after the fit of the Baranyi, Lag-exponential and Gompertz models on the G-II datasets

	RSE Baranyi	RSE Lag-exponential	RSE Gompertz	*df*
G-II 01	0.069	0.074	0.063[a]	18
G-II 02	0.058[a]	0.098	0.066	17
G-II 03	0.081	0.052[a]	0.086	8
G-II 04	0.044[a]	0.061	0.076	12
G-II 05	0.056[a]	0.063	0.070	11
G-II 06	0.046[a]	0.056	0.054	20
G-II 07	0.073[a]	0.113	0.080	16
G-II 08	0.053[a]	0.087	0.071	11
G-II 09	0.035[a]	0.072	0.035	16
G-II 10	0.080	0.079	0.075[a]	12
G-II 11	0.048[a]	0.081	0.074	9
G-II 12	0.067	0.070	0.058[a]	18
G-II 13	0.043[a]	0.057	0.047	15
G-II 14	0.048[a]	0.082	0.052	10
G-II 15	0.054	0.041[a]	0.049	16
G-II 16	0.033[a]	0.081	0.075	9
G-II 17	0.065[a]	0.096	0.095	9
Mean	0.056	0.074	0.066	

Last column gives the degrees of freedom (*df*) of each dataset.
[a] Lower RSE.

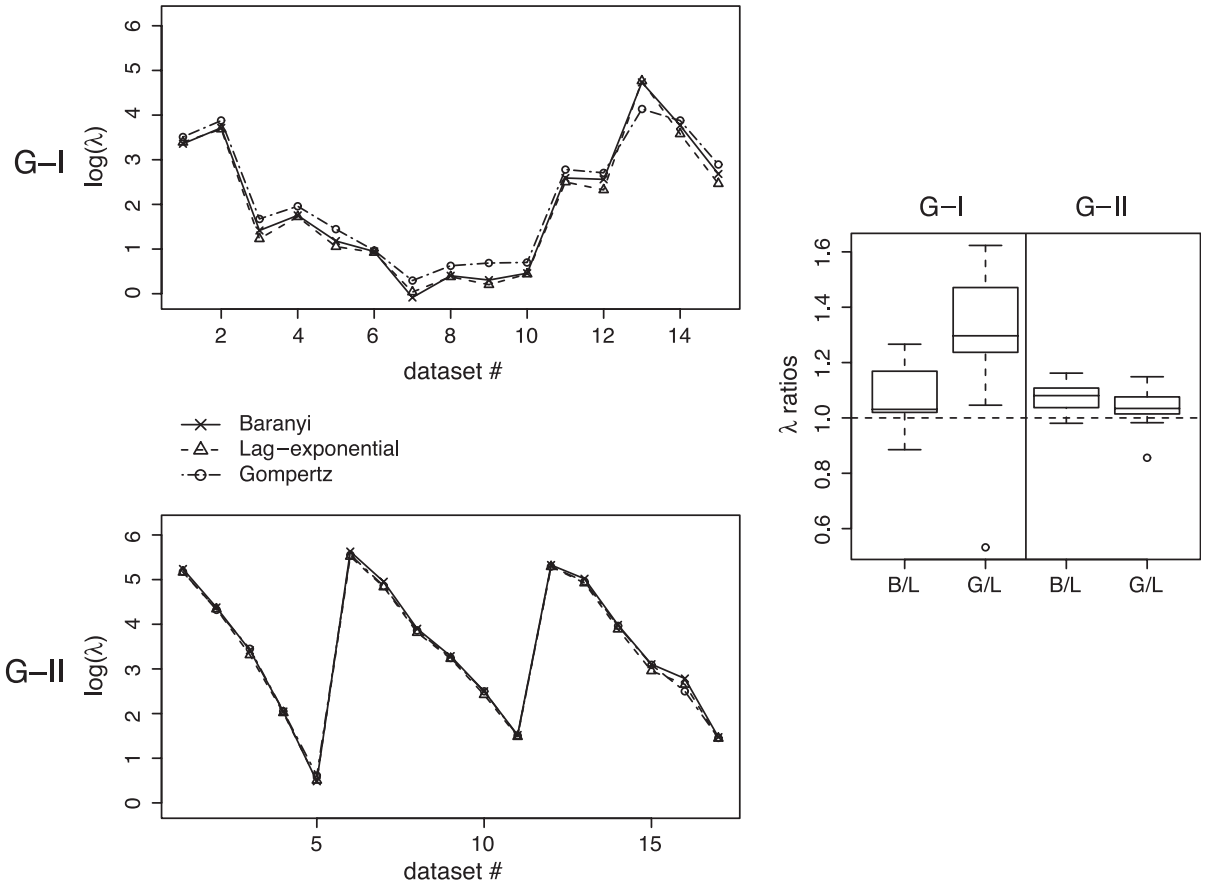

Fig. 4. Plot of the logarithm of the λ estimates obtained after the fit of the Baranyi, Lag-exponential and Gompertz models on the G-I and G-II datasets. On the right side is plotted the box plot representation of the ratios between the Baranyi λ estimates and the Lag-exponential λ estimates (B/L) and between the Gompertz λ estimates and the Lag-exponential λ estimates (G/L) for the G-I and G-II groups.

we recommend not using a systematic correcting factor to convert a λ estimate from one model to one another.

3.4. Precision of the λ estimates

In the previous section, we were dealing with the inter-model variations of the λ estimates. Now, we focus on the variations around every single estimate. Several methods provide a means to calculate a confidence interval that has a given probability of containing the true value of λ. A first way to assess a confidence interval is to calculate the standard deviation associated to λ by making the assumption that the linear approximation of the model is true at $\hat{\theta}$. This is a strong assumption and it is preferable to use cautiously these estimations of the standard deviation (Tomassone et al., 1992). However, these confidence intervals are easy to obtain from any classical non-linear regression routine. We plotted the asymptotic confidence intervals in the case of the two previous examples (Fig. 5). We notice that the deviation is much more important for the typical G-I dataset than for the typical G-II dataset. More generally, the box plot in Fig. 6 shows the distribution of the relative asymptotic intervals obtained within the two groups by the three models. We immediately notice that these intervals are huge for the G-I datasets and rather reasonable for the G-II group. As a matter of fact, it appears sometimes quite impossible to give an estimation of λ considering the imprecision associated to the estimate. This is particularly true concerning

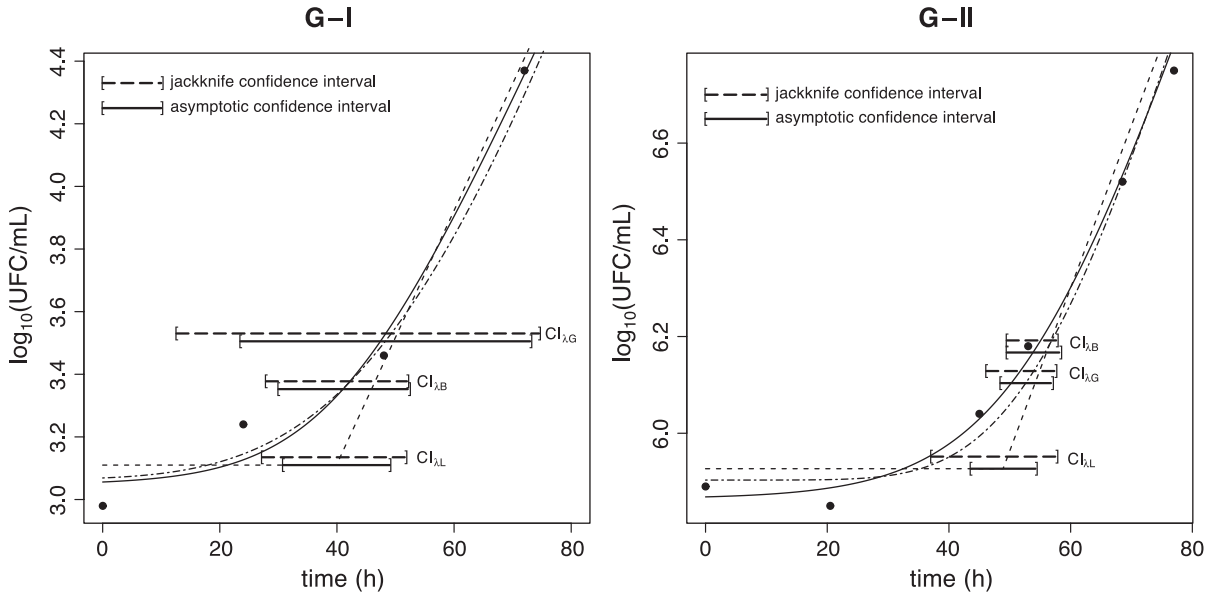

Fig. 5. Detail of the lag phase with a representation of the asymptotic and the jackknife 95% confidence intervals of the λ estimates obtained with the Baranyi (CI_{λ_B}), Lag-exponential (CI_{λ_L}) and Gompertz (CI_{λ_G}) models on a typical G-I dataset (G-I 02) and a typical G-II dataset (G-II 14).

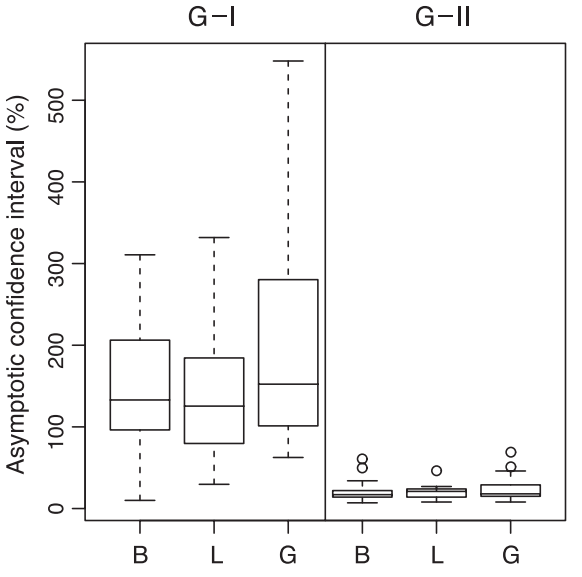

Fig. 6. Box plot representations of the relative asymptotic confidence intervals (in percentage) obtained by fitting the Baranyi (B), Lag-exponential (L) and Gompertz (G) models on the G-I and G-II datasets. The 25th, 50th and 75th percentiles and extreme values are shown.

the G-I group where the confidence interval may reach more than 500% (in the worst case) of the λ estimate.

We used the jackknife procedure as an alternative method to calculate a confidence interval around λ. The jackknife is a ''distribution-free'' procedure which proved to be effective in nonlinear models with small to medium samples (Seber and Wild, 1989). Even though we could not systematically calculate the jackknife confidence intervals on the whole 32 datasets, we were able to calculate them in the two examples (Fig. 5) and for the three models. As we can see, these intervals are quite similar to the asymptotic confidence intervals. As we already shown for the asymptotic confidence intervals, we remark that the jackknife confidence intervals appear considerably larger in the G-I example than in the G-II example.

Beale's confidence regions (Beale, 1960) provide another means to evaluate the precision of the λ estimates. Plots of these confidence regions are presented Fig. 7. We observe that they are much broader with regard to the G-I group compared to the G-II

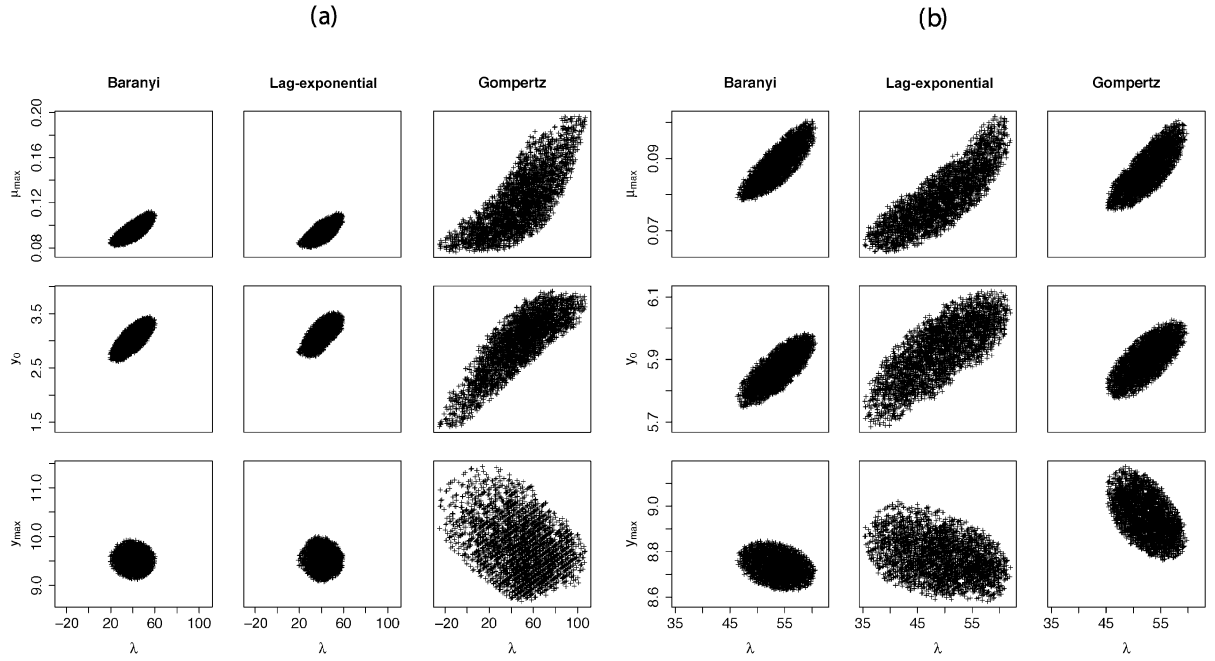

Fig. 7. Plot of 95% confidence regions for the λ estimates compared to the other parameters (μ_{max}, y_0 and y_{max}) obtained after the fit of the Baranyi, Lag-exponential and Gompertz models on a typical G-I dataset (G-I 02) (a) and on a typical G-II dataset (G-II 14) (b).

group. The shape of these regions indicates the existence of structural correlations essentially between λ and y_0 and between λ and μ_{max}. When the number of points per kinetics is minimal (as it is the case for the G-I example), we remark that the regions are particularly large for the Gompertz model. This indicates a lack of confidence in the use of this model in these conditions.

Finally, we must compare the inter-model variability with the uncertainty of the λ estimates. We can see in Tables 1 and 2 that the imprecision of the λ estimates is usually larger than the inter-model variability. This imprecision is even about twice larger than the inter-model variations in the G-I group (CV equals on average 28.8%, 27.3% and 39.8%, respectively, for the Baranyi, Lag-exponential and Gompertz models against 13.9% for the average inter-model CV). In the G-II group, the coefficients of variation are much more reasonable although the imprecision of λ estimates remains on average larger than the inter-model variations (CV equals on average 5.1%, 4.7% and 5.9%, respectively, for the Baranyi, Lag-exponential and Gompertz models against 4.1% for the average inter-model CV).

3.5. Which model, which precision

In the second part of this work, we examined the fitting properties of three growth models corresponding to the three mostly used models in food microbiology. By presenting some typical fits on more or less substantial datasets, we intended to show that reasonable fit could be obtained with any model of the three presented. Although no model consistently provided the best fit for all datasets, we noticed that the Baranyi model fitted the best (in terms of RSE) on a majority of cases whatever the quality of the dataset. We also noticed in Fig. 4 and Tables 1 and 2 that the estimations of λ are much more variable between the models in the first group where the data are more sparse than in the second group where the data are more substantial. In this last group, we showed that the ratio between λ estimated by the Lag-exponential model and λ estimated by the two other models are very close to 1 (cf. box plot, Fig. 4). Thus, the

variations between the estimations of λ provided by the three models closely depend on the quality of the dataset we wanted to model. Furthermore, we should point out that the Baranyi and the Lag-exponential models seem less influenced by the quality of the dataset than the Gompertz model.

However, the most interesting point that arises from our work concerns the confidence intervals associated to the estimations of λ. We clearly showed that, whatever the model used to fit on a growth kinetics, it is crucial to take into account the imprecision of the λ estimates. Thus, in the G-I group, the confidence intervals around λ are on average superior to 100% of the estimated value of λ, whatever the model. These results are confirmed by other methods exposed in the present work (jackknife, Beale's confidence regions).

4. Conclusion

Plethora of growth models has recently been developed in the field of food microbiology and in predictive microbiology. Efforts were made by mathematicians to develop new forms of model that provide more and more reliable estimates of the two parameters which are characteristic of the bacterial growth (λ and μ_{max}). In the recent years, some less empirical models were developed. These models are generally based on diverse biological hypotheses reflecting the authors' interpretation of the different phases of the bacterial growth. The main efforts were directed at studying the lag phase whose physiological meaning is still vague. Among the deterministic models, which are particularly adapted to the fitting procedures, we described three mathematically similar families each containing models that sometimes rely on totally dissimilar biological hypotheses. These models can be written using a unique global formulation describing the evolution of the population growth rate from the lag phase to the stationary phase. The adaptation function, which describes the growth rate increase in the early stage of growth, is the only part of this formulation that differs from one family of models to one another. Many authors compared the capacity of the growth models to provide consistent estimates of λ. It was clearly pointed out that systematic variations exist between the widely used growth models. On the other hand, only few authors compared the inter-model variability with the imprecision related to the estimation of λ. We showed in this work that the inter-model variability is frequently minor comparing to the imprecision of the λ estimates. We clearly correlated this imprecision with the quality of the datasets. Actually, it is really imperative to systematically associate a confidence interval around any estimation of λ. Among the three models studied, we noted that the Baranyi is, if not the definitive, the most constant model because it provides the best fit for a majority of datasets and because it gives reasonably precise λ estimates. On the other hand, the Gompertz is (for the same reasons) possibly the less consistent. However, a modification in the experimental design that enables an increase of the quantity and the quality of the information present in the growth curve is usually necessary for microbiologist to get confident enough λ estimates. Although these recommendations seems trivial, it is extremely common to find reports, notably in predictive microbiology, where the lag phase is modeled with such a huge imprecision that the λ estimates values should never be utilized by the microbiologist (especially in predictive microbiology) whatever the growth model he uses. As previously described by Grijspeerdt and Vanrolleghem (1999), defining a priori an optimal experimental design would help to considerably reduce the uncertainty on the parameter estimates.

Acknowledgements

We are very grateful to H. Bergis who gave us the G-II datasets on which are based part of our analysis. We are also very thankful to M. Cornu for her helpful critical review of this manuscript.

Appendix A. Asymptotic confidence intervals

The asymptotic variance and covariance matrix of the estimates is built from the linearized model. Let us define

$$F_{ij} = \frac{\partial f(x_i, \hat{\theta})}{\partial \hat{\theta}_j}$$

where $\hat{\theta}$ is the vector the least-squares estimates and $\hat{\theta}_j$ the jth value of this vector. If we define the matrix $\mathbf{F}$ whose terms are F_{ij} ($\mathbf{F}=\{F_{ij}\}$), then the asymptotic variance and covariance matrix of the estimates can be written as follows:

$$\hat{\mathbf{V}}(\hat{\theta}) = \hat{\sigma}^2(\mathbf{F}'\mathbf{F})^{-1}$$

where $\hat{\sigma}^2$ is the estimated error variance. From the matrix $\hat{\mathbf{V}}(\hat{\theta})$, one can define asymptotic confidence intervals that have a given probability to contain the true value of the estimates. These confidence intervals are defined as follow:

$$\hat{\theta}_i - t_{(\alpha/2,n-p)}\sqrt{\hat{\mathbf{V}}_{ii}(\hat{\theta})} \leq \hat{\theta}_i \leq \hat{\theta}_i + t_{(\alpha/2,n-p)}\sqrt{\hat{\mathbf{V}}_{ii}(\hat{\theta})}$$

where $\sqrt{\hat{\mathbf{V}}_{ii}(\hat{\theta})}$ is the standard deviation associated to the ith estimate and $t_{(\alpha/2,n-p)}$ is the $(1-\alpha/2)$th quantile of a Student distribution with $(n-p)$ degrees of freedom.

Appendix B. Jackknife confidence intervals

The jackknife procedure is a resampling method where n new samples are artificially built by removing sequentially one data point from the whole dataset (Seber and Wild, 1989). Let us define $\hat{\theta}_{-i}$ the vector of the least-squares estimates when the ith data point is removed. Then, we define the pseudo-values

$$P_i = n\hat{\theta} - (n-1)\hat{\theta}_{-i}$$

where $i=1,\ldots,n$. The standard jackknife estimate $\hat{\theta}_J$ is defined as the average of the pseudo-values ($\hat{\theta}_J = (1/n)\sum_{i=1}^{n} P_i$). Finally, we construct a variance estimate $\hat{S}_J$ based on the covariance matrix of the pseudo-values:

$$\hat{S}_J = \frac{1}{n(n-1)}\sum_{i=1}^{n}(P_i - \hat{\theta}_J)(P_i - \hat{\theta}_J)'$$

from which we define the jackknife confidence interval around the kth parameter:

$$\hat{\theta}_{J,k} \pm t_{(\alpha/2,n-p)}(\hat{S}_{J,kk})^{1/2}$$

where $t_{(\alpha/2,n-p)}$ is the $(1-\alpha/2)$th quantile of a Student distribution with $(n-p)$ degrees of freedom.

Appendix C. Beale's confidence regions

The approximate confidence regions check the following inequality (Beale, 1960):

$$\mathrm{RSS}(\theta) \leq \mathrm{RSS}(\hat{\theta})\left(1 + \frac{p}{n-p}F^{\alpha}_{p,n-p}\right)$$

where RSS is the residual sum of squares, θ is the vector of parameters values, $\hat{\theta}$ is the vector of least-squares estimates, n is the number of data points, p is the number of parameters and $F^{\alpha}_{p,n-p}$ is the αth quantile of a Fisher distribution with p and $n-p$ degrees of freedom. Random sampling in the values parameters space whose RSS check the inequality constitute an hyperspace whose projection for each couple of parameters gives the 95% confidence regions.

References

Augustin, J.C., Carlier, V., 2000. Mathematical modelling of the growth rate and lag time for *Listeria monocytogenes*. International Journal of Food Microbiology 56, 29–51.

Baranyi, J., 1997. Simple is good as long as it is enough. Food Microbiology 14, 189–192.

Baranyi, J., 1998. Comparison of stochastic and deterministic concepts of bacterial lag. Journal of Theoretical Biology 192, 403–408.

Baranyi, J., 2002. Stochastic modelling of bacterial lag phase. International Journal of Food Microbiology 73, 203–206.

Baranyi, J., Roberts, T.A., 1994. A dynamic approach to predicting bacterial growth in food. International Journal of Food Microbiology 23, 277–294.

Baranyi, J., Roberts, T.A., McClure, P.J., 1993. A non-autonomous differential equation to model bacterial growth. Food Microbiology 10, 43–59.

Bates, D.M., Watts, D.G., 1988. Nonlinear Regression Analysis and Its Applications. Wiley, Chichester, UK.

Baty, F., Flandrois, J.P., Delignette-Muller, M.L., 2002. Modeling the lag time of *Listeria monocytogenes* from viable count enumeration and optical density data. Applied and Environmental Microbiology 68, 5816–5825.

Beale, E.M.L., 1960. Confidence regions in non-linear estimations. Journal of the Royal Statistical Society. Series B 22, 41–88.

Buchanan, R.L., Cygnarowicz, M.L., 1990. A mathematical approach toward defining and calculating the duration of the lag phase. Food Microbiology 7, 237–240.

Buchanan, R.L., Whiting, R.C., Damert, W.C., 1997. When is simple good enough: a comparison of the Gompertz, Baranyi, and three-phase linear models for fitting bacterial growth curves. Food Microbiology 14, 313–326.

Dalgaard, P., 1995. Modelling of microbial activity and prediction of shelf life for packed fresh fish. International Journal of Food Microbiology 26, 305–317.

Duncan, G.T., 1978. An empirical study of jackknife-constructed confidence regions in nonlinear regression. Technometrics 20, 29–33.

Gibson, A.M., Bratchell, N., Roberts, T.A., 1988. Predicting microbial growth: growth responses of salmonellae in a laboratory medium as affected by pH, sodium chloride and storage temperature. International Journal of Food Microbiology 6, 155–178.

Grijspeerdt, K., Vanrolleghem, P., 1999. Estimating the parameters of the Baranyi model for bacterial growth. Food Microbiology 16, 593–605.

Hills, B.P., Wright, K.M., 1994. A new model for bacterial growth in heterogeneous systems. Journal of Theoretical Biology 168, 31–41.

Ihaka, R., Gentleman, R., 1996. R: a language for data analysis and graphics. Journal of Computational and Graphical Statistics 5, 299–314.

McKellar, R.C., 1997. A heterogeneous population model for the analysis of bacterial growth kinetics. International Journal of Food Microbiology 36, 179–186.

McKellar, R.C., 2001. Development of a dynamic continuous-discrete-continuous model describing the lag phase of individual bacterial cells. Journal of Applied Microbiology 90, 407–413.

McKellar, R.C., Knight, K., 2000. A combined discrete-continuous model describing the lag phase of *Listeria monocytogenes*. International Journal of Food Microbiology 54, 171–180.

Membre, J.M., Ross, T., McMeekin, T., 1999. Behaviour of *Listeria monocytogenes* under combined chilling processes. Letters in Applied Microbiology 28, 216–220.

Ratkowsky, D.A., 1983. Nonlinear regression modeling: a unified practical approach. Statistics: Textbooks and Monographs. Marcel Dekker, New York.

Schepers, A.W., Thibault, J., Lacroix, C., 2000. Comparison of simple neural networks and nonlinear regression models for descriptive modeling of *Lactobacillus helveticus* growth in pH-controlled batch cultures. Enzyme and Microbial Technology 26, 431–445.

Seber, G.A.F., Wild, C.J., 1989. Nonlinear Regression. Wiley, New York.

Tomassone, R., Audrain, S., Lesquoy-de Turkheim, E., Millier, C., 1992. La regression. Nouveaux regards sur une ancienne méthode statistique, 2nd ed. Masson, Paris, France.

VanGerwen, S.J., Zwietering, M.H., 1998. Growth and inactivation models to be used in quantitative risk assessments. Journal of Food Protection 61, 1541–1549.

Whiting, R.C., Cygnarowicz-Provost, M., 1992. A quantitative model for bacterial growth and decline. Food Microbiology 9, 269–277.

Zwietering, M.H., Jongenburger, I., Rombouts, F.M., Van'triet, K., 1990. Modeling of the bacterial growth curve. Applied and Environmental Microbiology 56, 1875–1881.