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*Report TW 315, January 2001*



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## **Abstract**

Bacterial growth is characterised by an initial lag phase, followed by an exponential growth phase with saturation. In this paper, several mathematical models are developed which describe bacterial growth under constant environmental conditions. These models are inspired by the widely used model by Baranyi and Roberts, and they are described by ordinary differential equations or by delay differential equations. We discuss the identification of the models using experimental data for *Escherichia coli* K12. The new models give fitting errors comparable to the model of Baranyi and Roberts.

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## Abstract

Bacterial growth is characterised by an initial lag phase, followed by an exponential growth phase with saturation. In this paper, several mathematical models are developed which describe bacterial growth under constant environmental conditions. These models are inspired by the widely used model by Baranyi and Roberts, and they are described by ordinary differential equations or by delay differential equations. We discuss the identification of the models using experimental data for *Escherichia coli* K12. The new models give fitting errors comparable to the model of Baranyi and Roberts.

## 1 Introduction

This research can be situated in the field of predictive food microbiology, the objective of which is the mathematical modelling of microbial dynamics in foods. Microbial growth under constant environmental conditions shows a sigmoidal evolution of the cell density in time, with three different phases: a lag phase, caused by environmental and/or physiological changes at inoculation of the bacterial culture, an exponential growth phase and a stationary phase, see Fig. 1. Several models have been developed in the past decennia to describe this behaviour (see, e.g. [7, 6] for an overview). The standard way to describe the evolution of the cell density  $N(t)$  (colony forming units per mL) in time is

$$\frac{dN(t)}{dt} = \mu(N(t))N(t),$$

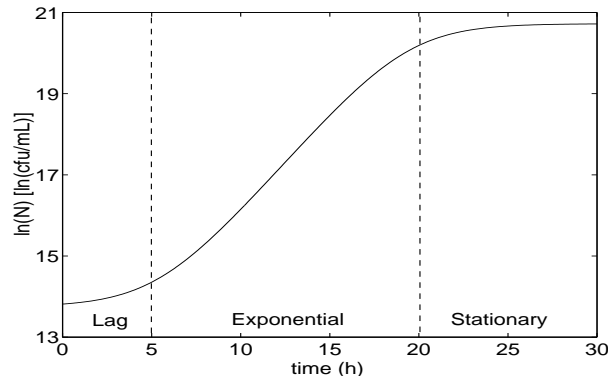


Figure 1: A typical bacterial growth curve under constant environmental conditions showing a lag phase, an exponential growth phase and a stationary phase.

where  $\mu(t)$  is the specific growth rate. In the widely used model by Baranyi and Roberts [3],  $\mu(t)$  is taken to be a product of three factors:

$$\mu(t) = \mu_{\max} \left( \frac{Q(t)}{1+Q(t)} \right) \left( 1 - \frac{N(t)}{N_{\max}} \right), \quad (1)$$

where

- $\mu_{\max}$  is the maximum specific growth rate ( $\text{h}^{-1}$ ),
- $Q(t)$  (-) is the solution of

$$\frac{dQ(t)}{dt} = \nu Q(t).$$

The factor  $\frac{Q(t)}{1+Q(t)}$ , the so-called adjustment function, enables to model the initial lag phase. Hereto  $Q(0)$  should be small. As time evolves,  $Q(t)$  grows exponentially and the value of the adjustment function approaches 1, having no influence anymore on  $\mu(t)$ .

- $N_{\max}$  is the maximum cell density (colony forming units per mL). The factor  $(1 - N(t)/N_{\max})$  induces cessation of the growth when  $N(t)$  approaches  $N_{\max}$ .

A drawback of this model (already noted by Baranyi and Roberts in [4]) is that  $Q(t) = Q(0)e^{\nu t}$  grows without bound as time proceeds.

In this paper, a different way of modelling the lag phase is introduced. The presented models are inspired by the model of Baranyi and Roberts in the sense that the factor  $\mu_{\max} \left( \frac{Q(t)}{1+Q(t)} \right)$  in (1) is replaced by other factors which allow the description of the lag phase at the beginning of the experiment.

The paper is structured as follows. In Sect. 2 we outline the model situation. We identify the assumptions made and a general format for new mathematical

models is proposed. Here, we allow not only ordinary differential equations (ODEs), but also delay differential equations (DDEs) which allow to take into account the previous history of cell growth. In Sect. 3 the experiments with *Escherichia coli* K12 which we use for the parameter estimation procedure are described. We also consider the initial value problem and the parameter estimation problem for DDEs in the context of the models we develop. In Sect. 4, we introduce three new mathematical models for bacterial growth. The results on the parameter estimation, using data on *E. coli*, are discussed and compared to results obtained with the model by Baranyi and Roberts. Sect. 5 contains conclusions.

## 2 Model situation

Commonly, in batch culture experiments, the bacterial population is first cultured under optimal conditions. Part of this precultured population is then taken, inoculated at time  $t = 0$ , and grown in the actual (new) environment of the experiment. The inoculation can be done from the exponential growth phase or from the stationary phase of the preculture growth. After inoculation, a lag phase commonly occurs. This delayed response is caused by the process of adjustment of the cells to the new environment. Under constant environmental conditions, after this lag phase the population grows exponentially with rate  $\mu_{\max}$ . As the cell density increases, the amount of nutrient available decreases, causing a stagnation of the growth, leading to a steady state. We do not deal here with the situation of a non-steady behaviour at the end of the experiment, due to death of or stress on the bacteria.

In this paper, we develop new mathematical models to describe bacterial growth (and lag-phases) under constant environmental conditions. The following general expression for the evolution of the cell density  $N(t)$  is used,

$$\frac{dN(t)}{dt} = M(t)L(t)N(t), \quad (2)$$

with  $N(0) = N_0$  the cell density at inoculation. Generally,  $L(t)$ , as the limiting factor, which causes the transition from exponential growth to the stationary phase, is taken to be

$$L(t) = \left(1 - \frac{N(t)}{N_{\max}}\right). \quad (3)$$

If  $M(t)$  is constant,  $M(t) \equiv \mu_{\max}$ , equation (2) gives rise to the well-known logistic growth model. Note that the model of Baranyi and Roberts (1) is of the form (2), with  $M(t) = \mu_{\max} \left(\frac{Q(t)}{1+Q(t)}\right)$ .

The function  $M(t)$  is designed to take into account adaptations of the cells to changes in the environment. Hypothetically,  $M(t)$  can be related to the metabolic state of the cells. In order to model the general sigmoidal growth dynamics, the following dynamical behaviour for  $M(t)$  is aimed at:

- (a)  $M(0)$  is (approximately) zero in case the cells have reached an equilibrium before inoculation. This low initial value of  $M(t)$  causes the initial lag. When inoculation is done from the exponential phase in the preculture,  $M(0)$  should be higher, as a shorter lag or no lag is observed in that case.
- (b)  $M(t)$  grows during the lag phase and becomes (almost) constant,  $M(t) \simeq \mu_{\max}$ , during the exponential growth phase.
- (c) when approaching the equilibrium for  $N(t)$ ,  $M(t)$  decreases to a low value since it is plausible that the lack of nutrient also leads to a decrease in the metabolic state of the cells. Note that this situation contrasts with the situation of model (1) where  $\mu_{\max} \left( \frac{Q(t)}{1+Q(t)} \right)$  becomes constant as time proceeds.

We wish to model  $M(t)$  in terms of the cell density  $N(t)$ . To fulfil conditions (b) and (c),  $M(t)$  can be approximated by  $m(t)$ , with

$$m(t) = \mu_{\max} L(t). \quad (4)$$

Indeed, during the exponential growth phase,  $N(t)$  is small compared to  $N_{\max}$ , hence  $L(t) \simeq 1$  and  $m(t) \simeq \mu_{\max}$ , while near the equilibrium  $N(t) \simeq N_{\max}$ , hence  $L(t) \simeq 0$  and  $m(t) \simeq 0$ .

In order to introduce the lag phenomenon, i.e. to fulfil condition (a), it is necessary that  $M(t)$  does not change immediately. We model the adaptation of cells to the new environmental state in three different ways.

- (i) First,  $M(t)$  can approach  $m(t)$  in a way that is governed by the ordinary differential equation,

$$\frac{dM(t)}{dt} = \rho(m(t) - M(t)), \quad (5)$$

where  $\rho$  is a constant adaptation rate.

We can also assume that cells need a fixed amount of time to adapt. In this case,  $M(t)$  depends on the cell density in the past. One way to model this is to introduce a delay in the function  $m(t)$ .

- (ii) When we assume that this lag is the same for all cells, this results in a discrete delay for  $M(t)$ , modelled by

$$M(t) = m(t - \tau), \quad \tau > 0. \quad (6)$$

- (iii) However, when we assume a distribution in the lag over the cell population, we can use a distributed delay,

$$M(t) = \frac{1}{\tau} \int_{t-\tau}^t m(s) ds, \quad (7)$$

averaging  $m(s)$  over the interval  $[t - \tau, t]$ .

The use of an explicit dependence on the past as in (6) and (7), leads to models described by delay differential equations. We will show how these can be dealt with in the next sections.

### 3 Material and methods

In the first part of this section we describe experiments with *Escherichia coli* K12. Outcomes of these experiments were used for parameter estimation of the developed models (Sect. 4). In the second part, we outline some specific properties of delay differential equations (DDEs) one needs to take into account when dealing with models described by DDEs and we also outline the software packages we use for simulation and parameter estimation.

#### 3.1 Experiments

The strain used was *Escherichia coli* K12 (MG1655) which was stored at  $-80^{\circ}\text{C}$  in Brain Heart Infusion (BHI) broth (Oxoid) supplemented with 25 % glycerol (Merck). Inoculi were prepared by subsequently growing the bacterial strain in 20 ml BHI, incubated at  $18^{\circ}\text{C}$  and placed on a rotary shaker (175 rpm), for 24 and 18 hours, respectively. The growth kinetics were determined in Brain Heart Infusion broth with an initial pH of 7.55.

The experiments have been performed in flasks incubated on a rotary shaker (at 175 rpm) placed in the temperature-controlled incubator (Termaks, model KBP6151). Duplicate flasks containing 200 mL BHI were inoculated. The temperature was measured on-line by a thermometer (Microprocessor Logging Thermometer HI 92840C, Hanna Instruments) inserted in a medium containing flask incubated near the inoculated flask. At regular times, samples were taken aseptically, diluted in a saline peptone solution ( $8\text{ g}\cdot\text{L}^{-1}$  NaCl (Acros) +  $1\text{ g}\cdot\text{L}^{-1}$  Bacteriological peptone (Oxoid)) and surface-plated on Plate Count Agar (PCA) (Oxoid) using a Spiral Plater (Eddy Jet IUL Instruments s.a., Spain). Plates were incubated for 24 h at  $37^{\circ}\text{C}$  and enumerated to determine the number of colony forming units per mL (CFU/mL).

#### 3.2 Numerical analysis of DDE models

##### 3.2.1 Delay differential equations

A delay differential equation (DDE) with one or several *discrete delays*  $\tau_i > 0$ ,  $i = 1, \dots, n$ , has the general form

$$\frac{dN(t)}{dt} = f(N(t), N(t - \tau_1), \dots, N(t - \tau_n)). \quad (8)$$

When the delay effect is averaged over a finite time interval in the past, one obtains a DDE with a finite *distributed delay* of the form

$$\frac{dN(t)}{dt} = f(N(t), \int_{t-\tau}^t w(s-t)N(s)ds), \quad (9)$$

where  $w(t)$  is a weighting function.

Delay differential equations are widely used in modelling population dynamics to incorporate the dependence of the present state of the population on its

past history (see, e.g. [5, 1] and the references therein). In this paper, we only deal with DDEs of the form (8) with one delay. In Sect. 4.1 we show how equation (7) can be reformulated as a DDE with discrete delay.

In order to solve a DDE, the specification of an initial condition  $N(0) = N_0$  (as it is the case for ODEs) is not sufficient. Rather, one must specify an initial function segment  $N(t) = \phi(t)$ ,  $t \in [-\tau, 0]$ , as the representation of the solution over a continuous time-window for the evaluation of the delay arguments.

In the models considered in this paper, the initial function for the cell density  $N(t)$  describes cells preculture growth during the delay interval,  $t \in [-\tau, 0]$ . If inoculation is done from the stationary phase, the initial function segment is given by

$$N(t) = N_{\max}, \quad t \in [-\tau, 0), \quad N(0) = N_0, \quad (10)$$

where  $N_{\max}$  is the maximum cell density in the preculture and  $N_0$  is the cell density at inoculation. Note that this initial function segment is discontinuous at  $t = 0$ . If inoculation is done from the exponential growth phase, we can use

$$N(t) = N_0 e^{\mu_{\max} t}, \quad t \in [-\tau, 0], \quad (11)$$

where  $\mu_{\max}$  is the maximum specific growth rate in the preculture.

For simulation of our DDE models we have used the Matlab package `dde23` [8].

### 3.2.2 Parameter estimation problem

In the next section, we introduce ODE and DDE models, containing some parameters, which are estimated using experimental data for *Escherichia coli* growth. Parameter estimation is achieved through minimising the objective function,

$$\Phi(\mathbf{p}) := \sum_{i=1}^K (\ln(N(t_i; \mathbf{p})) - \ln(N_i))^2, \quad (12)$$

where  $N(t; \mathbf{p})$  is the model solution which depends on unknown parameters  $\mathbf{p} \equiv [p_1, p_2, \dots, p_q]$  and  $N_i$  represents the experimental data at time  $t_i$ ,  $i = 1, \dots, K$ . For the DDE models, parameters include the delay  $\tau$  and the parameters of the initial function, i.e.  $N_{\max}, N_0$  in the case (10) and  $\mu_{\max}, N_0$  in the case (11). It is important to note that in both cases, (10) and (11), only a finite number of parameters have to be estimated, and hence the parameter estimation problem is a finite dimensional problem, as in the ODE case.

Parameter estimation in DDE models is discussed in detail in [2, 5]. Here we only discuss the continuity properties of the objective function  $\Phi(\mathbf{p})$ .

Even if the right hand side of a DDE and the initial function are infinitely smooth functions, a discontinuity in the first time derivative of the solution generally appears at time  $t = 0$  and it is propagated through time. The solution operator of a DDE (with constant or distributed delay) smoothes the solution so that discontinuities appear in high derivatives as time increases. In general, the solution of a DDE with one delay  $\tau$  has a discontinuity in the  $k$ -th derivative

at time  $t = (k - 1)\tau$ ,  $k = 1, 2, \dots$ . Additional discontinuities can arise due to discontinuities in the initial function. In the case of the initial function defined by (10), the solution of the DDE has discontinuities in the  $k$ -th derivative at time  $t = k\tau$ ,  $k = 0, 1, 2, \dots$ .

These discontinuities propagate in  $\Phi(\mathbf{p})$  via the solution values  $N(t_i; \mathbf{p})$ . Indeed, from

$$\left(\frac{\partial\Phi(\mathbf{p})}{\partial p_j}\right)_{\pm} = 2 \sum_{i=1}^K (\ln(N(t_i; \mathbf{p})) - \ln(N_i)) \left(\frac{\partial(\ln(N(t_i; \mathbf{p})))}{\partial p_j}\right)_{\pm} \quad (13)$$

it follows that, unless  $N(t_i; \mathbf{p}) = N_i$ , discontinuities can arise in the first (second) partial derivative of  $\Phi(\mathbf{p})$  with respect to  $p_j$ , if the first (second) partial derivative of  $N(t; \mathbf{p})$ , with respect to  $p_j$ , is not continuous at time  $t = t_i$  (i.e. at one of the data points). For instance, derivatives  $\partial\Phi(\mathbf{p})/\partial\tau$  and  $\partial^2\Phi(\mathbf{p})/\partial\tau^2$  are discontinuous at  $\tau = t_i$  when using the initial functions (10), respectively (11). For correct numerical parameter estimation in DDE models, attention has to be given to the differentiability of the solution  $N(t; \mathbf{p})$  with respect to the delay, and the position of the jump discontinuities [2, 5], see the next section.

Note that  $\Phi(\mathbf{p})$  can have several local minima and a good minimisation code and/or good initial parameter values can be important. For the minimisation we use the E04JAF routine from the NAG library, combined with the Matlab packages ode23 (for solving ODEs) and dde23 (for solving DDEs). We use the logarithmic form of the differential equations to avoid computational problems during time integration.

## 4 Modelling bacterial growth

### 4.1 Models

The combination of equation (2) for  $N(t)$  and one of the equations (5), (6), (7) for  $M(t)$  results in three different models, described by a system of ODEs or DDEs with four parameters.

**Model 1.** The combination of (2)-(4) and (5) leads to the model

$$\begin{cases} \frac{dN(t)}{dt} = M(t) \left(1 - \frac{N(t)}{N_{\max}}\right) N(t) \\ \frac{dM(t)}{dt} = \rho \left(\mu_{\max} \left(1 - \frac{N(t)}{N_{\max}}\right) - M(t)\right), \end{cases} \quad (14)$$

with initial conditions  $N(0)$  and  $M(0)$ .  $N(0)$  is an estimated parameter. In our experiments, we assume  $M(0) = 0$ , which corresponds to the state of non-active cells, when inoculation was done from the stationary phase. The use of a small value ( $\ll 1$ ) for  $M(0)$  gives the same quality of fitting of experimental data as when using  $M(0) = 0$ . In the case of inoculation from the exponential phase, we can assume  $M(0) = \mu_{\max}$ , which corresponds to the state of cells dividing at the maximum rate.

**Model 2.** The combination of (2)-(4) and (6) leads to the model

$$\begin{cases} \frac{dN(t)}{dt} = M(t)\left(1 - \frac{N(t)}{N_{\max}}\right)N(t) \\ M(t) = \mu_{\max}\left(1 - \frac{N(t-\tau)}{N_{\max}}\right). \end{cases} \quad (15)$$

In fact, this model is a scalar DDE in  $N(t)$  (substituting  $M(t)$  in the first equation of (15)). The initial function  $N(t)$ ,  $t \in [-\tau, 0]$ ,  $\tau > 0$ , is defined by (10) or (11) according to the moment of inoculation (stationary or exponential phase).

**Model 3.** Equation (7) can be written as

$$M(t) = \frac{1}{\tau}\mu_{\max} \int_{t-\tau}^t \left(1 - \frac{N(s)}{N_{\max}}\right) ds. \quad (16)$$

Combined with (2)-(4), it yields a DDE with distributed delay. However, we can reformulate the model as a DDE with discrete delay by differentiation of (16). The resulting model is

$$\begin{cases} \frac{dN(t)}{dt} = M(t)\left(1 - \frac{N(t)}{N_{\max}}\right)N(t) \\ \frac{dM(t)}{dt} = \frac{1}{\tau}\mu_{\max} \left( \left(1 - \frac{N(t)}{N_{\max}}\right) - \left(1 - \frac{N(t-\tau)}{N_{\max}}\right) \right). \end{cases} \quad (17)$$

The initial function  $N(t)$ ,  $t \in [-\tau, 0]$ ,  $\tau > 0$ , is defined as for model 2 and  $M(0)$  is defined by (16), evaluated at  $t = 0$ .

## 4.2 Model behaviour and parameter estimation

For each model, parameters are estimated using experimental data for *Escherichia coli* K12. The strain was grown at constant temperature, 23.1°C, after inoculation from the stationary phase and the cell density was measured at 15 time points (see Sect. 3.1). Best fit values for these parameters can be found in Table 1. In this and the following tables, the MSE (mean sum of squared errors) equals  $\frac{\Phi(\mathbf{p}^*)}{K-q}$  with  $\mathbf{p}^*$  the best fit parameters,  $K$  and  $q$  the number of experimental data and estimated parameters, respectively. The experimental data  $\{t_j; N_j\}_{j=1}^{15}$ , the model solutions  $N(t)$ ,  $M(t)$  and the function  $m(t)$  are shown in Figs. 2-4 for models 1, 2 and 3, respectively.

**Model 1.** As can be seen from Fig. 2,  $M(t)$  has the desired behaviour described in Sect. 2. First,  $M(t)$  increases because  $\mu_{\max}\left(1 - \frac{N(t)}{N_{\max}}\right) \approx \mu_{\max} > M(t)$ . Then, when  $N(t) \approx N_{\max}$ , the second equation becomes  $\frac{dM(t)}{dt} \approx -\rho M(t)$  and therefore  $M(t)$  decreases exponentially with speed  $\rho$ . Notice also the lagged behaviour of  $M(t)$  with respect to  $m(t)$ .

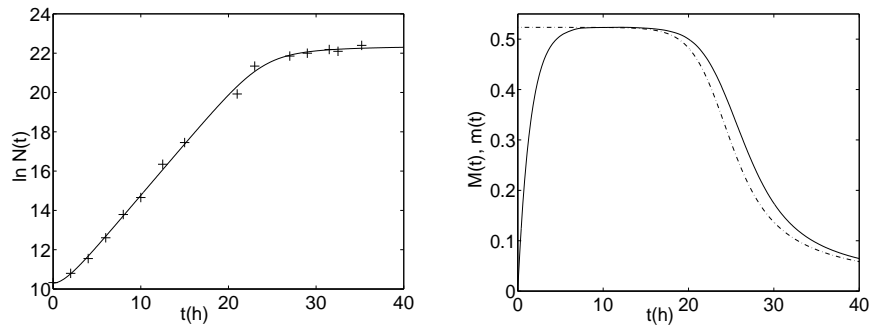


Figure 2: Model 1. Left: The experimental data for *E. coli* K12 are denoted by +;  $\ln(N(t))$  with  $N(t)$  the model solution with best fit parameters is given by a solid line. Right: Evolution of functions  $M(t)$  (solid line) and  $m(t)$  (dashed line).

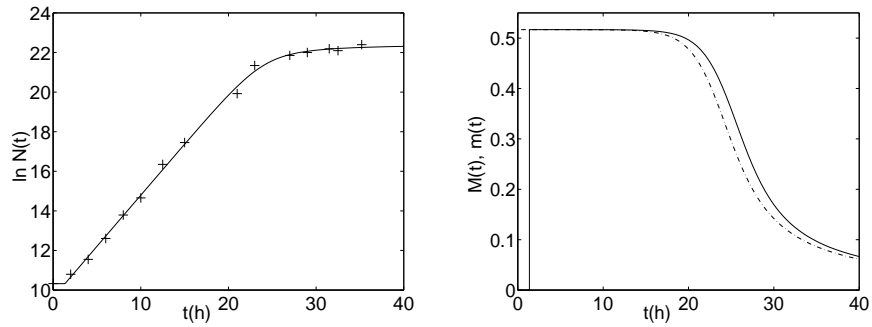


Figure 3: Model 2. Left: The experimental data for *E. coli* K12 are denoted by +;  $\ln(N(t))$  with  $N(t)$  the model solution with best fit parameters is given by a solid line. Right: Evolution of functions  $M(t)$  (solid line) and  $m(t)$  (dashed line).

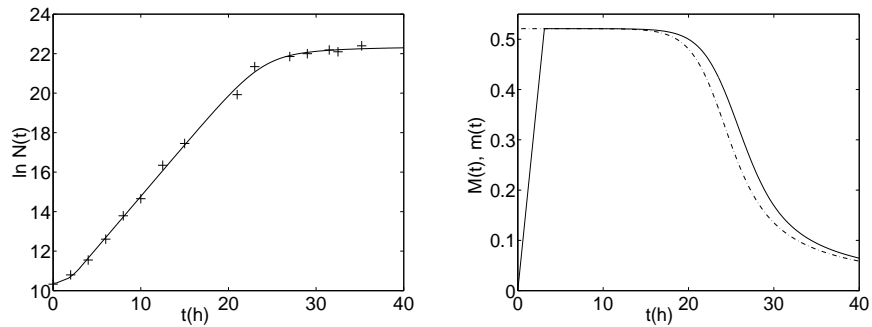


Figure 4: Model 3. Left: The experimental data for *E. coli* K12 are denoted by +;  $\ln(N(t))$  with  $N(t)$  the model solution with best fit parameters is given by a solid line. Right: Evolution of functions  $M(t)$  (solid line) and  $m(t)$  (dashed line).

Table 1: Estimated values of parameters for the three models.

Model	$\ln N(0)$	$\ln N_{\max}$	$\mu_{\max}$	$\rho$	$\tau$	MSE
Model 1	10.303	22.418	0.523	0.679		0.0351
Model 2	10.326	22.437	0.517		1.357	0.0367
Model 3	10.375	22.415	0.521		3.117	0.0350

**Model 2.** We observe (Fig. 3) that for  $t \in [0, \tau)$ ,  $M(t) \equiv 0$  and  $N(t) = N(0)$ , because  $N(t - \tau) = N_{\max}$  for  $t \in [0, \tau)$ . At  $t = \tau$ ,  $N(t - \tau) = N(0) \neq N_{\max}$ . This causes a jump in the function  $M(t)$  at  $t = \tau$ .

For this model, the objective function  $\Phi(\mathbf{p})$  is not continuously differentiable with respect to the delay  $\tau$ , see Fig. 5. Namely,  $\partial\Phi(\tau)/\partial\tau$  has a discontinuity jump at  $\tau = t_2 = 2$  (i.e. at the second data point,  $t_2$ ). This is a consequence of the discontinuity of the solution  $N(t)$  at time  $t = t_1 = 0$  (i.e. at the first data point,  $t_1$ ) caused by using the initial function (10). In Fig. 6, we show the values of the objective function  $\Phi(\mathbf{p})$  where two parameters are altered while the other parameters are kept fixed at their optimal values (cf. Table 1). The origin of the contour plots corresponds to  $\Phi(\mathbf{p}^*) \simeq 0.4$ . Contour lines are depicted for  $\Phi(\mathbf{p})$  varying from 0.42 to 0.81 with a constant step. As it is illustrated in Fig. 6, the observed discontinuity in  $\Phi(\mathbf{p})$  does not give any problems in the optimisation procedure.

**Model 3.** In this model,  $N(t)$  grows linearly during the lag phase, see Fig. 4. Note that the numerical values of  $\tau$  (cf. Table 1) in models 2 and 3 cannot be compared as they have a different meaning.

Sensitivity analysis of parameters for delay differential models is considered in detail in [2], where methods are proposed to estimate the sensitivity of the state variables to the parameter estimates and the sensitivity of the parameter estimates to the experimental data. Note that the results in Fig. 6 for model 2 and similar ones for the other models indicate a high sensitivity of the objective function (i.e. of the model solution) to the model parameters. Our experiments also showed that there are no other minima of the function  $\Phi(\mathbf{p})$  with  $\mathbf{p}$  in the range of 20% above and below the optimal parameter estimates.

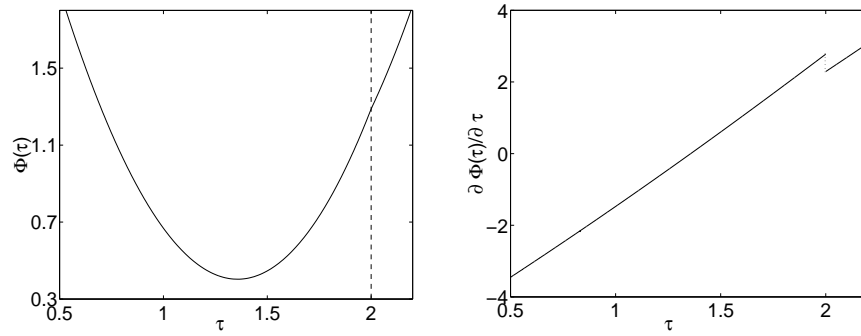


Figure 5: Model 2.  $\Phi(\tau)$  (left) and  $\partial\Phi(\tau)/\partial\tau$  (right) as functions of  $\tau$ .  $\partial\Phi(\tau)/\partial\tau$  has a discontinuity jump at  $\tau = 2$ .

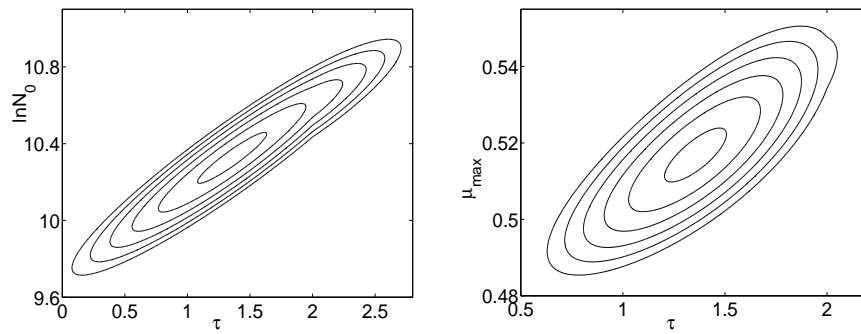


Figure 6: Model 2. Dependence of the function  $\Phi(\mathbf{p})$  on the model parameters. Contour plots correspond to  $\Phi(\mathbf{p})$  varying from 0.42 to 0.81 with a constant step.

### 4.3 Comparison with the model of Baranyi and Roberts

The model of Baranyi and Roberts, introduced in Sect. 1 is given by

$$\begin{cases} \frac{dN(t)}{dt} = \mu_{\max} \left( \frac{Q(t)}{1+Q(t)} \right) \left( 1 - \frac{N(t)}{N_{\max}} \right) N(t) \\ \frac{dQ(t)}{dt} = \nu Q(t). \end{cases} \quad (18)$$

$Q(t)$  is said to represent the physiological state of the cells, being proportional to the per cell concentration of a critical substance produced by the cells. The model (18) has five parameters:  $N(0)$ ,  $Q(0)$ ,  $N_{\max}$ ,  $\mu_{\max}$  and  $\nu$ . In practice, to reduce the number of parameters during identification, one commonly sets  $\nu$  equal to  $\mu_{\max}$ .

This model is of the form (2) with  $M(t) = \mu_{\max} \left( \frac{Q(t)}{1+Q(t)} \right)$ . As time proceeds,  $M(t)$  approaches  $\mu_{\max}$  and cannot decrease again. This behaviour is visualised in Fig. 7. Note that in this case  $M(0)$  is larger than zero and  $M(t)$  remains constant (at the large value of  $\mu_{\max}$ ) when the steady state is reached. Results of estimation of the four parameters (assuming  $\nu = \mu_{\max}$ ) can be found in Table 2.

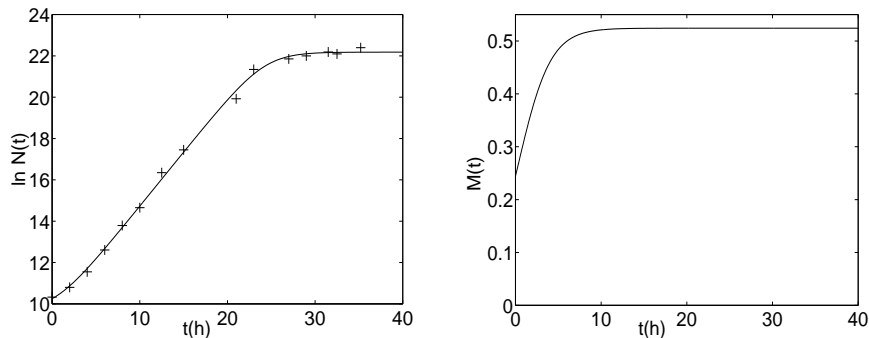


Figure 7: Results for the model of Baranyi and Roberts with 4 parameters. Left: The experimental data for *E. coli* K12 are denoted by +;  $\ln(N(t))$  with  $N(t)$  the model solution with best fit parameters is given by a solid line. Right: Evolution of the function  $M(t)$ .

If  $\nu$  is used as a free parameter, similar results for  $N(0)$ ,  $N_{\max}$  and  $\mu_{\max}$  as in the 4-parameter case are obtained (cf. Table 2). The estimated value for  $\nu$  is quite different from  $\mu_{\max}$  but also  $Q(0)$  differs. We observe (Fig. 8) that  $M(0)$  is much smaller than in the 4-parameter model and  $M(t)$  also increases faster to  $\mu_{\max}$ .

Note that the error values in Table 2 are comparable to (in fact slightly larger than) the error values obtained with the models proposed in this paper (cf. Table 1).

Table 2: Estimated values of parameters for the model of Baranyi and Roberts with four and five parameters.

Model	$\ln N(0)$	$\ln N_{\max}$	$\mu_{\max}$	$Q(0)$	$\nu$	MSE
Model with 4 par.	10.249	22.180	0.524	0.872		0.0414
Model with 5 par.	10.337	22.187	0.519	0.190	1.254	0.0411

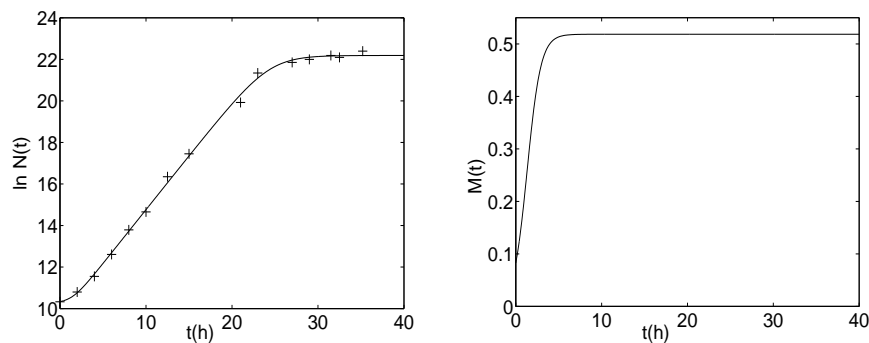


Figure 8: Results for the model of Baranyi and Roberts with 5 parameters. Left: The experimental data for *E. coli* K12 are denoted by +;  $\ln(N(t))$  with  $N(t)$  the model solution with best fit parameters is given by a solid line. Right: Evolution of the function  $M(t)$ .

## 5 Conclusion

In this paper, we have proposed new mathematical models for microbial growth under constant environmental conditions, represented by ordinary differential equations or by delay differential equations. The key element in these models is the function  $M(t)$ , which is designed to take into account the adaptation of cells to environmental changes. Hypothetically,  $M(t)$  can be related to the metabolic state of the cells. When the cells are resting, or are in the stationary phase, the value of  $M(t)$  is low, while cells growing exponentially have a high  $M(t)$  value. All new models show a similar qualitative behaviour for  $M(t)$  which satisfies the expectations.

The developed models are fitted to a set of experimental data. These data describe growth of *Escherichia coli* K12 in a constant environment with fixed temperature. The fitting error after identification of the model parameters, shows for all models an accuracy comparable to the one achieved using the

model by Baranyi and Roberts. The developed models are capable to describe accurately the lag caused by inoculation.

Based on the results, there is no clear reason to give any preference to one of the suggested three models. No delay differential equation is involved in model 1, which may be considered as an advantage. However, due to the availability of efficient and reliable time integration software for delay differential equations, the use of DDE models does not pose computational problems. With model 2 we obtain a larger MSE fitting error, but the duration of the lag is similar as for the other models and it is given directly by the value of the delay  $\tau$ . Model 2 can be considered as an introduction to the more realistic model with distributed delay (model 3).

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