Sensitivity analysis of mathematical models for bacterial growth

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Report TW 327, August 2001

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Abstract

We briefly review some new models for bacterial growth under constant environmental conditions. These models are described by a system of ODEs or DDEs parameterized by four parameters. For the growth of *E. coli* K12, optimal values for the parameters have been determined using experimental data. In this report, we study the sensitivity of these models, by analysing both the sensitivity of the solution with respect to the parameters and the sensitivity of the parameters with respect to the experimental data, using a procedure introduced by Baker and Rihan.

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Abstract

We briefly review some new models for bacterial growth under constant environmental conditions. These models are described by a system of ODEs or DDEs parameterized by four parameters. For the growth of *E. coli* K12, optimal values for the parameters have been determined using experimental data. In this report, we study the sensitivity of these models, by analysing both the sensitivity of the solution with respect to the parameters and the sensitivity of the parameters with respect to the experimental data, using a procedure introduced by Baker and Rihan [1].

1 Introduction

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. If the inoculation is done from the stationary phase of the preculture growth, a lag phase occurs. This delayed response is due to the adjustment of the cells to the new environment. When the environmental conditions (e.g. temperature) do not further change, the population grows exponentially with rate $\mu_{\max}$ after the lag phase. When the cell density $N(t)$ increases, the amount of nutrient available decreases, causing a stagnation of the growth, leading to a steady state (stationary phase).

In [3] and [2] we have introduced three mathematical models to describe bacterial growth under constant environmental conditions. They are of the form

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = M(t)L(t)N(t), \tag{1}$$

with $N(0) = N_0$ the cell density at inoculation. The factor $L(t)$, the limiting factor causes the transition from exponential growth to the stationary phase. 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. The following dynamical behaviour for $M(t)$ is aimed at:

(a) When inoculation is done from the stationary phase, $M(0)$ is set to zero, which corresponds to the state of non-active cells. The low value of $M(t)$ for small t causes the initial lag.

(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.

The three models are described by a system of ODEs or DDEs with four parameters.

Model 1.

$$\left\{ \begin{array}{l} \frac{\mathrm{d}N(t)}{\mathrm{d}t} = M(t)(1 - \frac{N(t)}{N_{\max}})N(t) \\ \frac{\mathrm{d}M(t)}{\mathrm{d}t} = \rho\left(\mu_{\max}(1 - \frac{N(t)}{N_{\max}}) - M(t)\right), \end{array} \right. \tag{2}$$

with initial conditions $N(0) = N_0$ and $M(0) = 0$. N_0, ρ, $\mu_{\max}$ and $N_{\max}$ are parameters.

Model 2.

$$\left\{ \begin{array}{l} \frac{\mathrm{d}N(t)}{\mathrm{d}t} = M(t)(1 - \frac{N(t)}{N_{\max}})N(t) \\ M(t) = \mu_{\max}(1 - \frac{N(t-\tau)}{N_{\max}}). \end{array} \right. \tag{3}$$

This model is a scalar DDE in $N(t)$ (substituting $M(t)$ in the first equation of (3)). The initial function $N(t),\ t \in [-\tau, 0],\ \tau > 0$, is defined by

$$N(t) = N_{\max},\ t \in [-\tau, 0),\ N(0) = N_0. \tag{4}$$

The parameters are N_0, τ, $\mu_{\max}$ and $N_{\max}$.

Model 3.

$$\left\{ \begin{array}{l} \frac{\mathrm{d}N(t)}{\mathrm{d}t} = M(t)(1 - \frac{N(t)}{N_{\max}})N(t) \\ M(t) = \frac{1}{\tau}\mu_{\max}\int_{t-\tau}^{t}(1 - \frac{N(s)}{N_{\max}})ds. \end{array} \right. \tag{5}$$

This is a DDE with distributed delay. However, we can reformulate the model as a DDE with discrete delay by differentiation of the second equation in (5). The resulting model is

$$\left\{ \begin{array}{l} \frac{\mathrm{d}N(t)}{\mathrm{d}t} = M(t)(1 - \frac{N(t)}{N_{\max}})N(t) \\ \frac{\mathrm{d}M(t)}{\mathrm{d}t} = \frac{1}{\tau}\mu_{\max}\left((1 - \frac{N(t)}{N_{\max}}) - (1 - \frac{N(t-\tau)}{N_{\max}})\right). \end{array} \right. \tag{6}$$

The initial function $N(t),\ t \in [-\tau, 0],\ \tau > 0$, is defined as for model 2 and $M(0)$ is defined by (5), evaluated at $t = 0$. The parameters are N_0, τ, $\mu_{\max}$ and $N_{\max}$.

2 Parameter estimation for the growth of E. coli

Parameter estimation for the three models, using experimental data for *Escherichia coli* K12, is described in [3]. Here we only mention those results which are important for the sensitivity analysis, described in the next section. The strain was grown at constant temperature, 23.1°C, after inoculation from the stationary phase and the cell density during the growth process was measured at 15 time points. Best fit values for the parameters in the three models can be found in Table 1. In this table, the MSE (mean sum of squared errors) equals $\frac{\Phi(\mathbf{p}^*)}{K-q}$, with Φ the objective function to be minimized, defined as

$$\Phi(\mathbf{p}) := \sum_{i=1}^{K} (\ln(N(t_i;\mathbf{p})) - \ln(N_i))^2, \tag{7}$$

with $\mathbf{p}^*$ the best fit parameters, K and q the number of experimental data and estimated parameters, respectively. The experimental data $\{t_j; N_j\}_{j=1}^{15}$ and the model solutions $N(t)$, $M(t)$ are shown in Figs. 1-3 for models 1, 2 and 3, respectively. Clearly, for the three models, $M(t)$ has the desired behaviour, described in Section 1.

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

Model	$\ln N(0)$	$\ln N_{\max}$	$\mu_{\max}$	ρ	τ	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

For model 2, we observe (Fig. 2) 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 τ, see Fig. 4. 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 (4). In Fig. 5 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). Contour lines are depicted for $\Phi(\mathbf{p})$ varying from 0.42 to 0.81 with a constant step. The observed discontinuity in $\Phi(\mathbf{p})$ does not give any problems in the optimisation procedure.

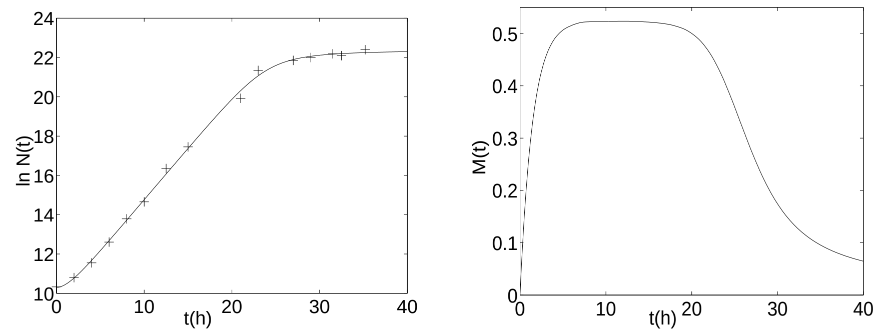

Figure 1: Model 1. Left: The experimental data for *E. coli* K12 are denoted by +; $\ln(N(t))$ with $N(t)$ the model solution with best fit parameters is given by a solid line. Right: Evolution of the function $M(t)$.

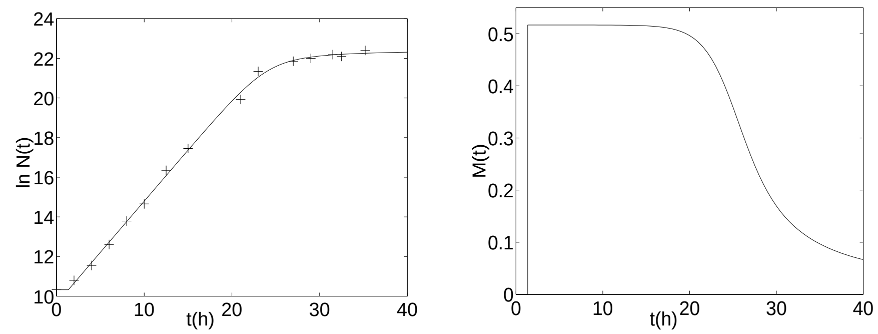

Figure 2: Model 2. Left: The experimental data for *E. coli* K12 are denoted by +; $\ln(N(t))$ with $N(t)$ the model solution with best fit parameters is given by a solid line. Right: Evolution of the function $M(t)$.

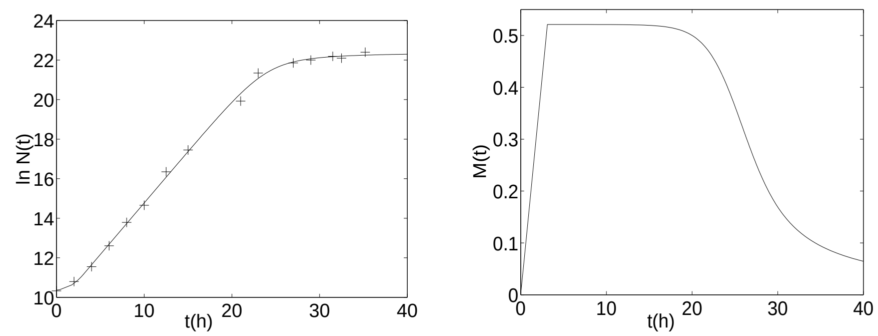

Figure 3: Model 3. Left: The experimental data for *E. coli* K12 are denoted by +; $\ln(N(t))$ with $N(t)$ the model solution with best fit parameters is given by a solid line. Right: Evolution of the function $M(t)$.

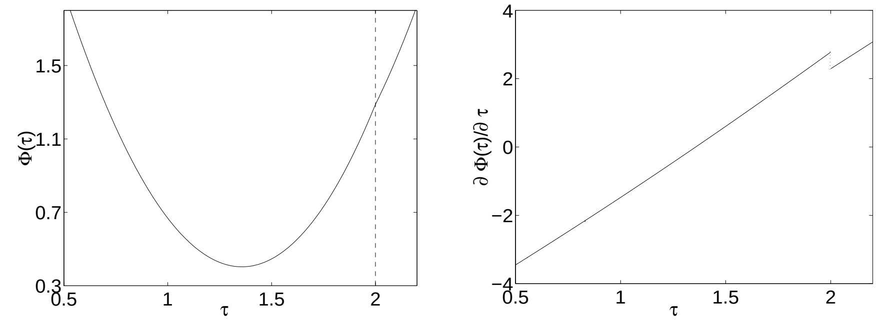

Figure 4: Model 2. The objective function $\Phi(\tau)$ (left) and $\partial\Phi(\tau)/\partial\tau$ (right) as functions of τ. $\partial\Phi(\tau)/\partial\tau$ has a discontinuity at $\tau = 2$.

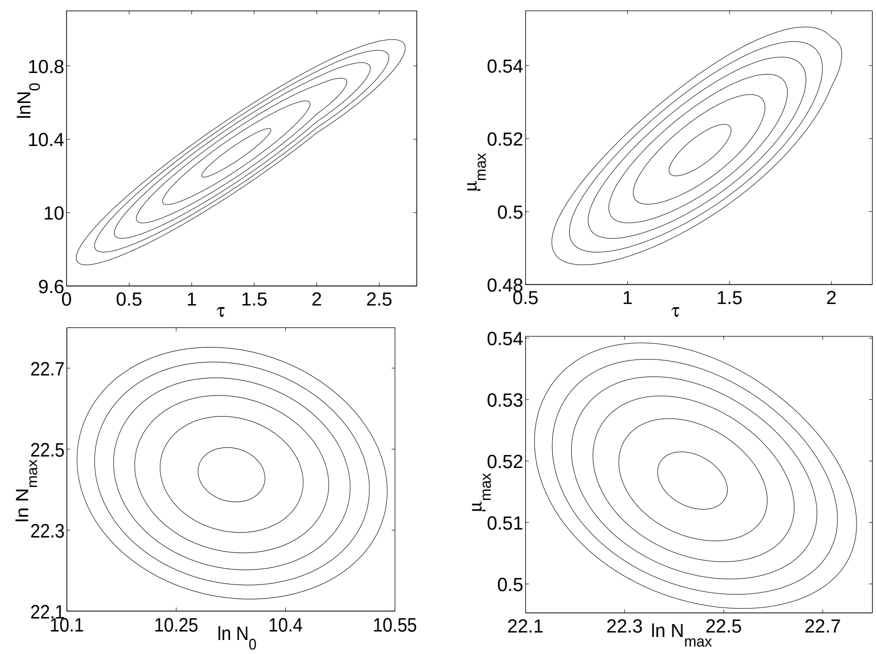

Figure 5: Model 2. Dependence of the function $\Phi(\mathbf{p})$ on the model parameters. Contour plots correspond to $\Phi(\mathbf{p})$ varying from 0.42 to 0.81 with a constant step.

Note that the results in Fig. 5 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. In the next section we perform a detailed sensitivity analysis for models 1 and 2.

3 Sensitivity analysis

In this section, we compute the sensitivity of the state variables to the parameter estimates for model 1 and model 2 and the sensitivity of the parameter estimates to the experimental data for model 1. We follow the procedure described by Baker and Rihan in [1]. From now on we will use the logarithm of $N(t)$, namely $n(t) = \ln N(t)$.

3.1 Model 1

3.1.1 The sensitivity of the model solution with respect to the parameters

Taking $n(t) = \ln N(t)$, system (2) can be written as

$$\begin{cases} \frac{dn(t)}{dt} & = M(t)(1 - e^{n(t)-n_{\max}}) \\ \frac{dM(t)}{dt} & = \rho(\mu_{\max}\,(1 - e^{n(t)-n_{\max}}) - M(t)) \end{cases} \tag{8}$$

with $n(0) = n_0$ and $M(0) = 0$. The parameters in this model are $\rho,\ \mu_{\max},\ n_{\max},\ n_0$. The partial derivatives $\frac{\partial n(t)}{\partial p_i}$ and $\frac{\partial M(t)}{\partial p_i}$ measure the local sensitivity of the solution with respect to changes in the parameters p_i. The functions $s_{p_i}(t,\mathbf{p}) = \{\frac{\partial}{\partial p_i}\}n(t,\mathbf{p})$ and $u_{p_i}(t,\mathbf{p}) = \{\frac{\partial}{\partial p_i}\}M(t,\mathbf{p})$ are called the *first order sensitivity coefficients* [1]. To determine these functions, we first differentiate (8) with respect to p_i. The two ODEs obtained in this way, together with the two original equations, can be solved for $s_{p_i}(t,\mathbf{p})$ and $u_{p_i}(t,\mathbf{p})$. Evaluation of these four equations at $\mathbf{p}^*$ gives us $s_{p_i}(t,\mathbf{p}^*)$ and $u_{p_i}(t,\mathbf{p}^*)$.

Differentiation of (8) with respect to ρ, $\mu_{\max}$, n_0 and $n_{\max}$ leads to

$$\begin{cases} \frac{ds_\rho(t,\mathbf{p})}{dt} & = u_\rho(t,\mathbf{p}) - u_\rho(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}} - M(t,\mathbf{p})s_\rho(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}} \\ \frac{du_\rho(t,\mathbf{p})}{dt} & = (1 - e^{n(t,\mathbf{p})-n_{\max}})\mu_{\max} - M(t,\mathbf{p}) + \rho\{-\mu_{\max}s_\rho(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}} \\ & \quad -u_\rho(t,\mathbf{p})\} \end{cases} \tag{9}$$

with $s_\rho(0,\mathbf{p}) = 0$ and $u_\rho(0,\mathbf{p}) = 0$,

$$\begin{cases} \frac{ds_{\mu_{\max}}(t,\mathbf{p})}{dt} & = u_{\mu_{\max}}(t,\mathbf{p}) - u_{\mu_{\max}}(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}} - M(t,\mathbf{p})s_{\mu_{\max}}(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}} \\ \frac{du_{\mu_{\max}}(t,\mathbf{p})}{dt} & = \rho\{-s_{\mu_{\max}}(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}}\mu_{\max} + (1-e^{n(t,\mathbf{p})-n_{\max}}) - u_{\mu_{\max}}(t,\mathbf{p})\} \end{cases} \tag{10}$$

with $s_{\mu_{\max}}(0,\mathbf{p}) = 0$ and $u_{\mu_{\max}}(0,\mathbf{p}) = 0$,

$$\begin{cases} \frac{ds_{n_0}(t,\mathbf{p})}{dt} & = u_{n_0}(t,\mathbf{p}) - u_{n_0}(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}} - M(t,\mathbf{p})s_{n_0}(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}} \\ \frac{du_{n_0}(t,\mathbf{p})}{dt} & = \rho(-s_{n_0}(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}}\mu_{\max} - u_{n_0}(t,\mathbf{p})) \end{cases} \tag{11}$$

with $s_{n_0}(0,\mathbf{p}) = 1$ and $u_{n_0}(0,\mathbf{p}) = 0$,

$$\begin{cases} \frac{ds_{n_{\max}}(t,\mathbf{p})}{dt} & = u_{n_{\max}}(t,\mathbf{p}) - u_{n_{\max}}(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}} - s_{n_{\max}}(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}}M(t,\mathbf{p}) \\ & \quad +e^{n(t,\mathbf{p})-n_{\max}}M(t,\mathbf{p}) \\ \frac{du_{n_{\max}}(t,\mathbf{p})}{dt} & = \rho\{-(s_{n_{\max}}(t,\mathbf{p})-1)e^{n(t,\mathbf{p})-n_{\max}}\mu_{\max} - u_{n_{\max}}(t,\mathbf{p})\} \end{cases} \tag{12}$$

with $s_{n_{\max}}(0,\mathbf{p}) = 0$ and $u_{n_{\max}}(0,\mathbf{p}) = 0$.

We solved each of the systems (9), (10), (11) and (12) together with (8) (evaluated at the optimal parameter values $\mathbf{p} := \mathbf{p}^* = [\rho^*,\ \mu^*_{\max},\ n^*_0,\ n^*_{\max}]$), by using the Matlab package ode23 [4]. Figs. 6 and 7 show the behaviour of the sensitivity of $n(t)$ and $M(t)$ with respect to the parameters (see Table 1).

From the behaviour of $s_{n_0}(t,\mathbf{p}^*)$ we see that, as expected, the influence of n_0 on the solution $n(t)$ is large in the beginning, decreases after the exponential phase and goes to zero. The influence of $n_{\max}$ behaves just in the opposite way, it is small in the beginning and increases to 1. Further, $s_\rho(t,\mathbf{p}^*)$ is large during the exponential phase and $s_{\mu_{\max}}(t,\mathbf{p}^*)$ attains its maximum value at the end of the exponential phase.

3.1.2 The sensitivity of the parameters with respect to the data

The sensitivity of (the optimal value of) a parameter p_l with respect to an experimental data point η_j can be defined as $\frac{\partial p^*_l}{\partial \eta_j}$. To calculate the sensitivity of each parameter with respect to the data point η_j, we must solve the following system of four equations and four unknowns $\frac{\partial p^*_l}{\partial \eta_j}$ (see Eq. (2.8) in [1]),

$$\begin{cases} \sum_{i=1}^{15}\sum_{l=1}^{4}[s_\rho(t_i,\mathbf{p}^*)s_{p_l}(t_i,\mathbf{p}^*) + [n(t_i,\mathbf{p}^*)-\eta_i]r_{p_l,\rho}(t_i,\mathbf{p}^*)]\frac{\partial p^*_l}{\partial \eta_j} & = & s_\rho(t_j,\mathbf{p}^*) \\ \sum_{i=1}^{15}\sum_{l=1}^{4}[s_{\mu_{\max}}(t_i,\mathbf{p}^*)s_{p_l}(t_i,\mathbf{p}^*) + [n(t_i,\mathbf{p}^*)-\eta_i]r_{p_l,\mu_{\max}}(t_i,\mathbf{p}^*)]\frac{\partial p^*_l}{\partial \eta_j} & = & s_{\mu_{\max}}(t_j,\mathbf{p}^*) \\ \sum_{i=1}^{15}\sum_{l=1}^{4}[s_{n_0}(t_i,\mathbf{p}^*)s_{p_l}(t_i,\mathbf{p}^*) + [n(t_i,\mathbf{p}^*)-\eta_i]r_{p_l,n_0}(t_i,\mathbf{p}^*)]\frac{\partial p^*_l}{\partial \eta_j} & = & s_{n_0}(t_j,\mathbf{p}^*) \\ \sum_{i=1}^{15}\sum_{l=1}^{4}[s_{n_{\max}}(t_i,\mathbf{p}^*)s_{p_l}(t_i,\mathbf{p}^*) + [n(t_i,\mathbf{p}^*)-\eta_i]r_{p_l,n_{\max}}(t_i,\mathbf{p}^*)]\frac{\partial p^*_l}{\partial \eta_j} & = & s_{n_{\max}}(t_j,\mathbf{p}^*), \end{cases} \tag{13}$$

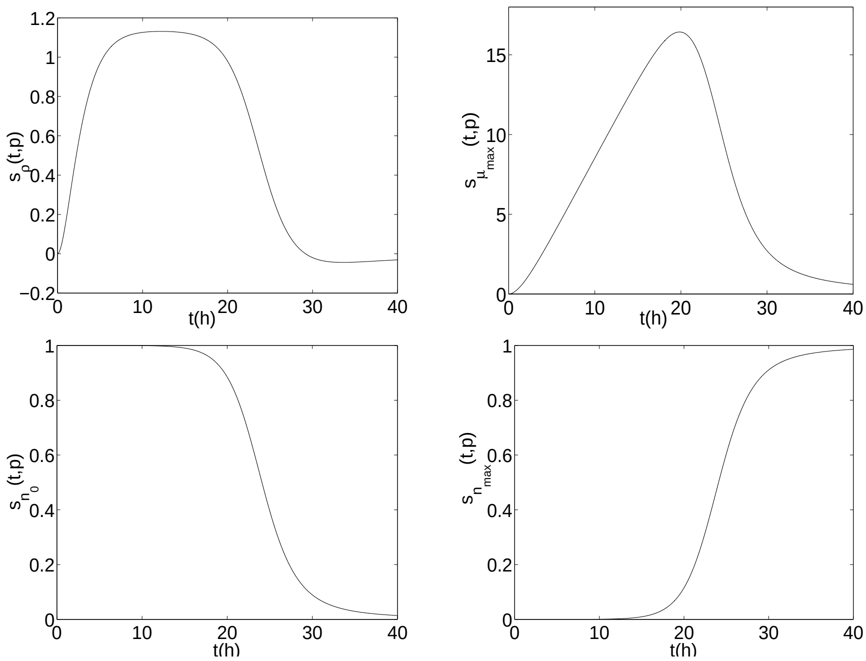

Figure 6: Model 1. The first-order sensitivity coefficients for $n(t)$ with respect to ρ, $\mu_{\max}$, n_0 and $n_{\max}$.

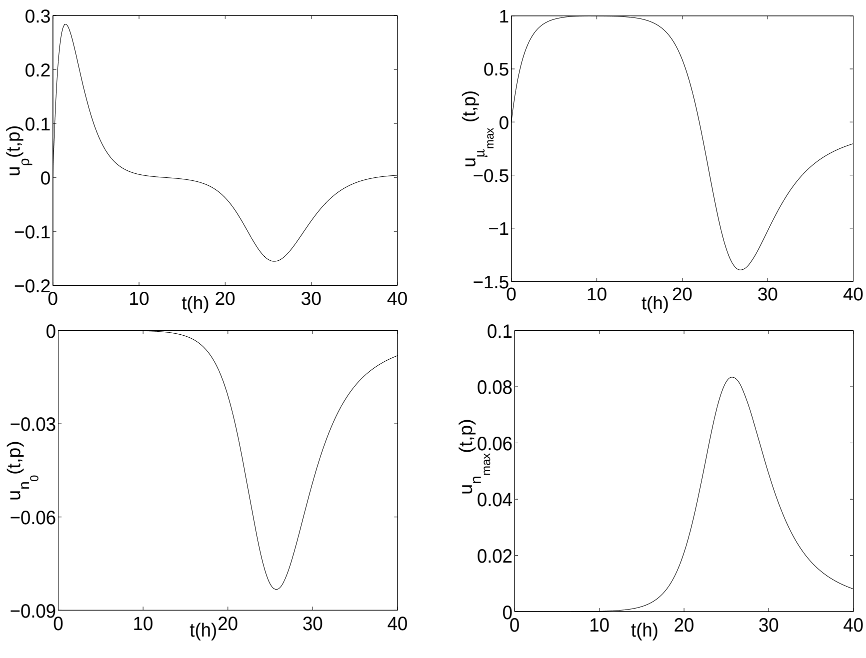

Figure 7: Model 1. The first-order sensitivity coefficients for $M(t)$ with respect to ρ, $\mu_{\max}$, n_0 and $n_{\max}$.

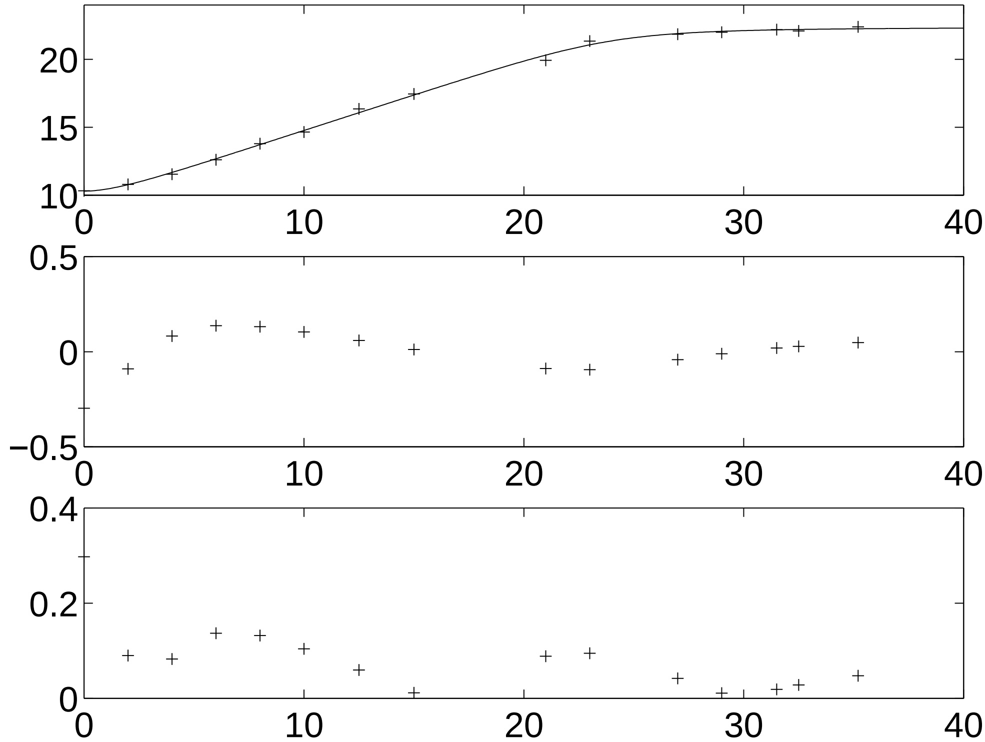

Figure 8: Model 1. (top) The model solution and the experimental data, (middle) the sensitivity of ρ with respect to the data, $\frac{\partial \rho^*}{\partial \eta_j}, j = 1, \ldots, 15$, (bottom) the absolute value of the sensitivity of ρ with respect to the data.

where

$$r_{p_i,p_j}(t, \mathbf{p}^*) = \frac{\partial}{\partial p_j} s_{p_i}(t, \mathbf{p}^*) = \frac{\partial^2}{\partial p_j \partial p_i} n(t, \mathbf{p}^*) \quad (i, j = 1, \ldots, 4)$$

are the *second order sensitivity coefficients*. To obtain equations for r_{p_i,p_j} we must differentiate equations (9), (10), (11) and (12) with respect to each parameter. Since $r_{p_i,p_j} = r_{p_j,p_i}$, we have to calculate 10 coefficients and solve the resulting ODEs.

In Figures 8, 9, 10 and 11, the sensitivity of the parameters ρ, $\mu_{\max}$, n_0 and $n_{\max}$ in model 1 with respect to the 15 data points is shown.

Because $n(t_i, \mathbf{p}^*) - \eta_i$ is small, we can neglect the term $[n(t_i, \mathbf{p}^*) - \eta_i] r_{p_l,p_j}$ $(j = 1, \ldots, 4)$ as is done in [1]. This makes the calculations for $\frac{\partial p_l^*}{\partial \eta_j}$ easier because in that case, the second order sensitivity coefficients don't have to be calculated. In Figure 12 the results for this approach for the calculations of the sensitivity of ρ can be found.

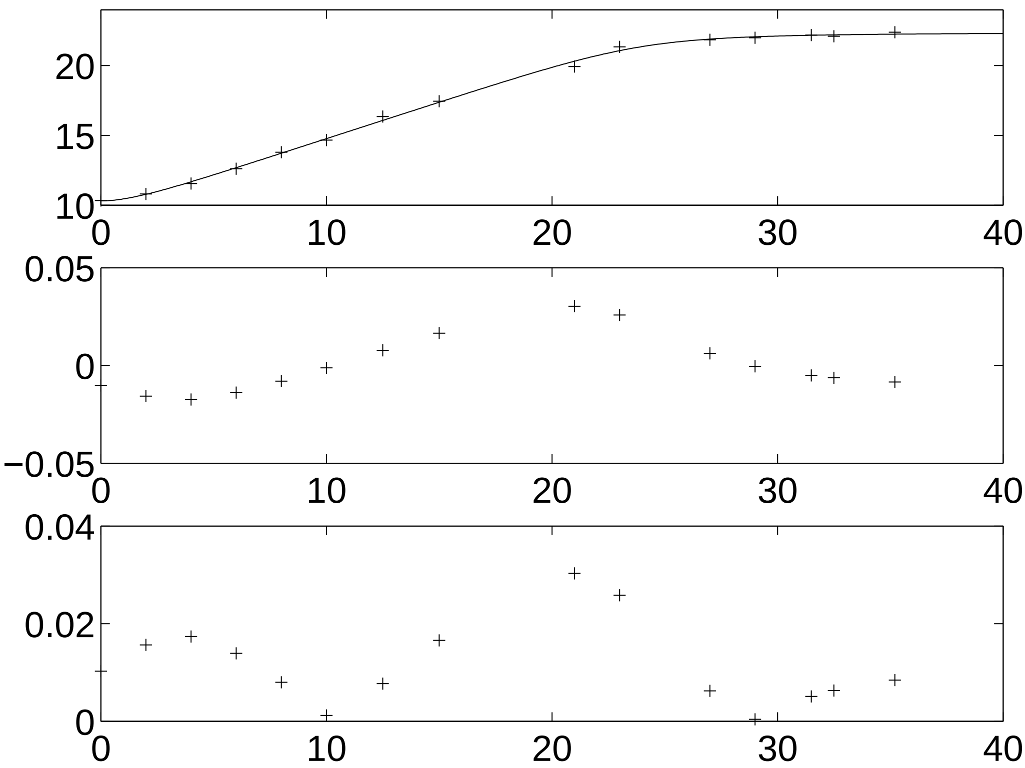

Figure 9: Model 1. (top) The model solution and the experimental data, (middle) the sensitivity of $\mu_{\max}$ with respect to the data, $\frac{\partial \mu^*_{\max}}{\partial \eta_j}$, $j = 1, \ldots, 15$, (bottom) the absolute value of the sensitivity of $\mu_{\max}$ with respect to the data.

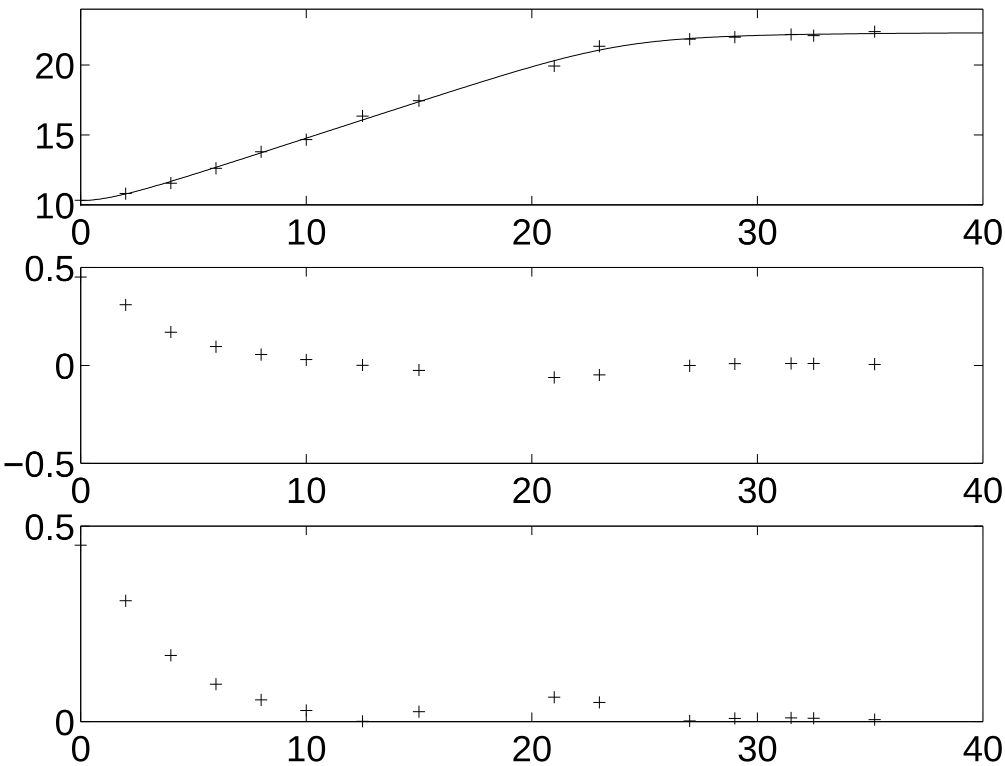

Figure 10: Model 1. (top) The model solution and the experimental data, (middle) the sensitivity of n_0 with respect to the data, $\frac{\partial n_0^*}{\partial \eta_j}, j = 1, \ldots, 15$, (bottom) the absolute value of the sensitivity of n_0 with respect to the data.

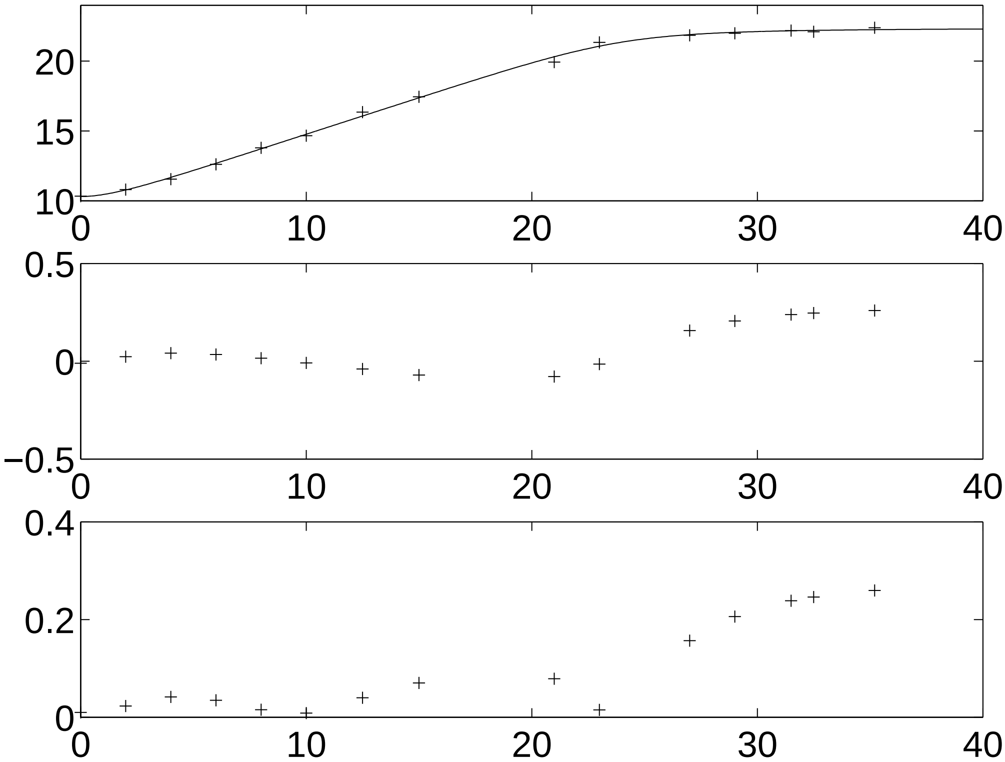

Figure 11: Model 1. (top) The model solution and the experimental data, (middle) the sensitivity of $n_{\max}$ with respect to the data, $\frac{\partial n^*_{\max}}{\partial \eta_j}, j = 1, \ldots, 15$, (bottom) the absolute value of the sensitivity of $n_{\max}$ with respect to the data.

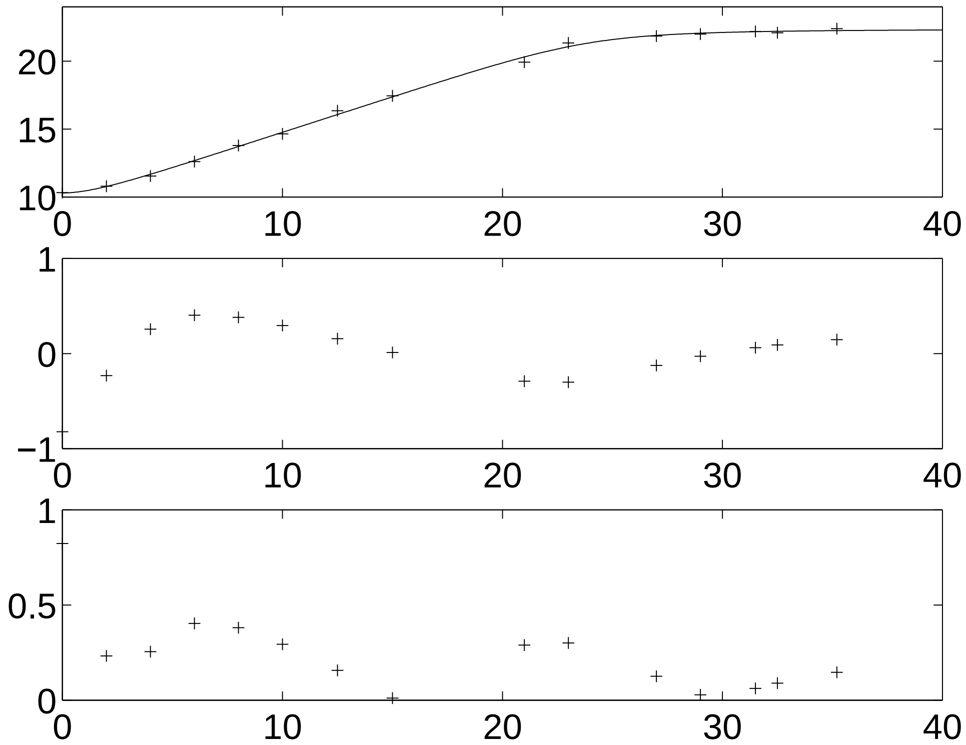

Figure 12: Model 1. (top) The model solution and the experimental data, (middle) the sensitivity of ρ with respect to the data calculated by neglecting the term $n(t_i, \mathbf{p}^*) - \eta_i$ in (13), (bottom) the absolute value of the sensitivity of ρ with respect to the data.

3.2 Model 2

The same analysis as in the previous section can be done for model 2. With $n(t) = \ln N(t)$, equation (3) for model 2 becomes:

$$\begin{cases} \frac{dn(t)}{dt} = (1 - e^{n(t)-n_{\max}})M(t) \\ M(t) = (1 - e^{n(t-\tau)-n_{\max}})\mu_{\max} \end{cases} \tag{14}$$

with $n(t) = n_{\max}$ for $t < 0$ and $n(0) = n_0$.

The following equations, obtained by differentiation of (14) with respect to the parameters $\mu_{\max}$, n_0 and $n_{\max}$, must be solved together with (14), to obtain the first order sensitivity coefficients $s_{\mu_{\max}}$, s_{n_0} and $s_{n_{\max}}$:

$$\begin{aligned} \frac{ds_{\mu_{\max}}(t,\mathbf{p})}{dt} = \; & 1 - e^{n(t-\tau,\mathbf{p})-n_{\max}} - \mu_{\max} s_{\mu_{\max}}(t-\tau,\mathbf{p}) e^{n(t-\tau,\mathbf{p})-n_{\max}} - e^{n(t,\mathbf{p})-n_{\max}} \\ & -\mu_{\max} s_{\mu_{\max}}(t,\mathbf{p}) e^{n(t,\mathbf{p})-n_{\max}} + e^{n(t,\mathbf{p})-2n_{\max}+n(t-\tau,\mathbf{p})} \\ & +\mu_{\max}[s_{\mu_{\max}}(t,\mathbf{p}) + s_{\mu_{\max}}(t-\tau,\mathbf{p})] e^{n(t,\mathbf{p})-2n_{\max}+n(t-\tau,\mathbf{p})} \end{aligned} \tag{15}$$

with $s_{\mu_{\max}}(t,\mathbf{p}) = 0$ for $t \leq 0$,

$$\begin{aligned} \frac{ds_{n_0}(t,\mathbf{p})}{dt} = \; & -\mu_{\max} s_{n_0}(t-\tau,\mathbf{p}) e^{n(t-\tau,\mathbf{p})-n_{\max}} - \mu_{\max} s_{n_0}(t,\mathbf{p}) e^{n(t,\mathbf{p})-n_{\max}} \\ & +\mu_{\max}[s_{n_0}(t,\mathbf{p}) + s_{n_0}(t-\tau,\mathbf{p})] e^{n(t,\mathbf{p})-2n_{\max}+n(t-\tau,\mathbf{p})} \end{aligned} \tag{16}$$

with $s_{n_0}(t,\mathbf{p}) = 0$ for $t \leq 0$ and $s_{n_0}(0,\mathbf{p}) = 1$,

$$\begin{aligned} \frac{ds_{n_{\max}}(t,\mathbf{p})}{dt} = \; & -\mu_{\max}[s_{n_{\max}}(t-\tau,\mathbf{p}) - 1] e^{n(t-\tau,\mathbf{p})-n_{\max}} - \mu_{\max} s_{n_{\max}}(t,\mathbf{p}) e^{n(t,\mathbf{p})-n_{\max}} \\ & +\mu_{\max} e^{n(t,\mathbf{p})-n_{\max}} + \mu_{\max}[s_{n_{\max}}(t,\mathbf{p}) - 2] e^{n(t,\mathbf{p})-2n_{\max}+n(t-\tau,\mathbf{p})} \\ & +\mu_{\max} s_{n_{\max}}(t-\tau,\mathbf{p}) e^{n(t,\mathbf{p})-2n_{\max}+n(t-\tau,\mathbf{p})} \end{aligned} \tag{17}$$

with $s_{n_{\max}}(t,\mathbf{p}) = 1$ for $t \leq 0$ and $s_{n_0}(0,\mathbf{p}) = 0$.

Results for these computations (taking $\mathbf{p} = \mathbf{p}^*$) can be found in Figure 13. Time integration is done with dde23 [5].

The calculation of $s_\tau(t,\mathbf{p})$ gives rise to some problems, caused by the fact that the derivative of $n(t)$ is not defined at $t = 0$. Since $n(t) = n_0$ for $0 \leq t < \tau$, $s_\tau(t,\mathbf{p})$ is equal to 0 for $0 \leq t < \tau$. Further, $n(t)$ can be approximated by $n(t) = n_0$ in the lag phase and by $n(t) = \mu_{\max}(t-\tau) + n_0$ in the exponential phase. From

$$\begin{aligned} \lim_{t\to\tau} \frac{\partial n(t)}{\partial \tau} &= 0 && \text{for } t < \tau \\ \lim_{t\to\tau} \frac{\partial n(t)}{\partial \tau} &= -\mu_{\max} && \text{for } t > \tau, \end{aligned} \tag{18}$$

we can assume $s_\tau(\tau,\mathbf{p}) = -\mu_{\max}$. Therefore we did the calculation for $s_\tau(t,\mathbf{p})$ starting from the point $t = \tau$. The equation for $s_\tau(t,\mathbf{p})$ becomes

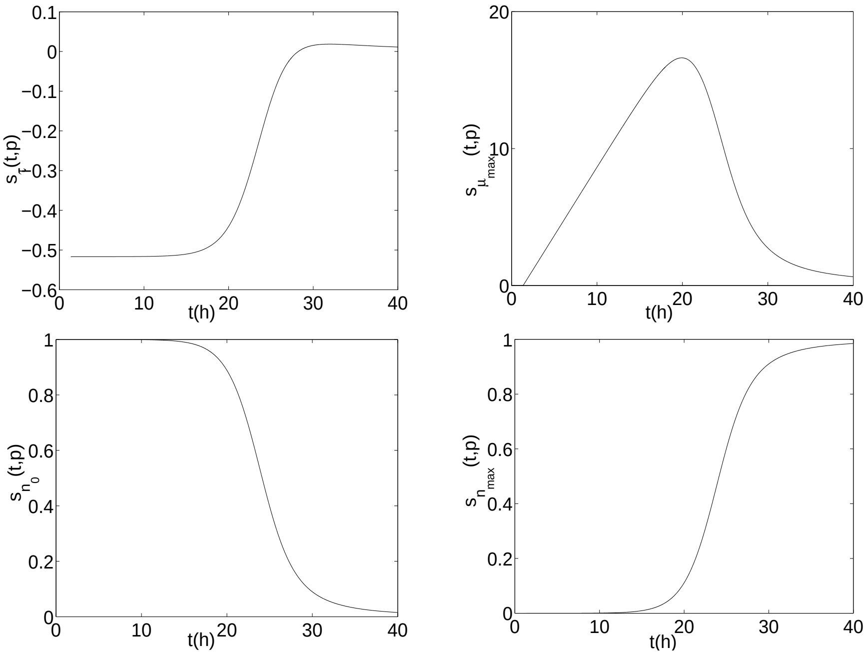

Figure 13: Model 2. The first-order sensitivity coefficients with respect to τ, $\mu_{\max}$, n_0 and $n_{\max}$.

$$\begin{aligned}\frac{ds_\tau(t,\mathbf{p})}{dt} = & -\mu_{\max}[-\tfrac{dn(t-\tau,\mathbf{p})}{dt} + s_\tau(t-\tau,\mathbf{p})]e^{n(t,\mathbf{p})-n_{\max}} - \mu_{\max}s_\tau(t,\mathbf{p})e^{n(t,\mathbf{p})-n_{\max}} \\ & +\mu_{\max}[s_\tau(t,\mathbf{p}) - \tfrac{dn(t-\tau,\mathbf{p})}{dt} + s_\tau(t-\tau,\mathbf{p})]e^{n(t,\mathbf{p})-2n_{\max}+n(t-\tau,\mathbf{p})}\end{aligned} \tag{19}$$

and $s_\tau(t,\mathbf{p}) = 0$ for $t < \tau$ and $s_\tau(\tau,\mathbf{p}) = -\mu_{\max}$.

By solving (19) together with (14) for $t \geq \tau$ with initial function $n(t,\mathbf{p}) = n_0$, $0 < t \leq \tau$ and taking $\mathbf{p} = \mathbf{p}^*$, $s_\tau(t,\mathbf{p}^*)$ can be calculated. One more problem here is the factor $\frac{dn(t-\tau,\mathbf{p})}{dt}$, which can be replaced by the right hand side of the equation for $n'(t)$ evaluated at time $t-\tau$. The result is depicted in Figure 13.

Alternatively, the functions $s_{p_i}(t,\mathbf{p})$ can be approximated by

$$\bar{s}_{p_i}(t,\mathbf{p}) = \frac{n(t) - \bar{n}(t)}{\Delta p_i}, \tag{20}$$

where $n(t)$ is the solution obtained with the optimal values of the parameters, and $\bar{n}(t)$ is the solution obtained with the optimal values except for the parameter p_i, for which the optimal value is perturbed by a small Δp_i. The result (for $\mathbf{p} = \mathbf{p}^*$) is shown in Figure 14. We took $\Delta p_i = 10^{-4}$ for $p_i = \mu_{\max}$, n_0, $n_{\max}$ and τ. We see that $\bar{s}_{p_i}(t,\mathbf{p}^*) - s_{p_i}(t,\mathbf{p}^*)$ gives an error of 0.1 for $p_i = \tau$, n_0, $n_{\max}$ and an error of 0.01 for $p_i = \mu_{\max}$.

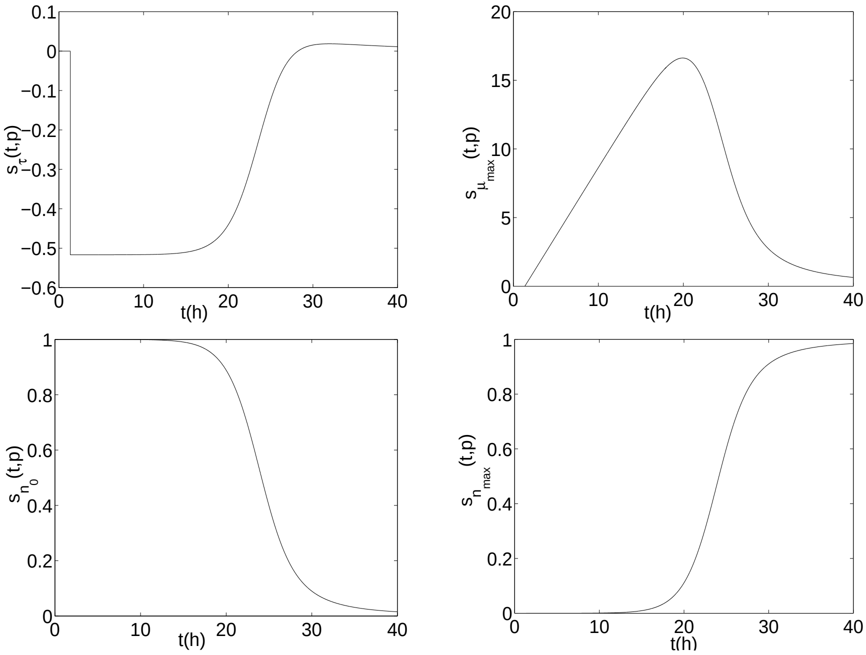

Figure 14: Model 2. Calculation of $\bar{s}_{\mu_{\max}}(t, \mathbf{p}^*)$, $\bar{s}_{n_0}(t, \mathbf{p}^*)$, $\bar{s}_{n_{\max}}(t, \mathbf{p}^*)$ and $\bar{s}_\tau(t, \mathbf{p}^*)$ respectively, based on the difference formula (20).

4 Conclusion

In this paper we analysed the sensitivity of solutions of mathematical models describing bacterial growth to the parameter estimates and the sensitivity of the parameter estimates to the observations, using experimental data for *E. coli* K12. The first model consists of a system of ODEs, while the second model is a delay differential equation.

Each of the parameters of the considered models is designed to have a certain contribution to the solution dynamics: parameters N_0 and $N_{\max}$ determine respectively the initial growth and stationary phase, parameter $\mu_{\max}$ determines the rate of the exponential growth, parameter ρ is an adaptation rate and τ determines the lag phase duration. For this reason, each parameter is more "active" during a certain time interval and has a small or no influence outside of this interval. The obtained results on the sensitivity of the model solutions to the parameter estimates reflect this situation.

The analysis of the sensitivity of the parameter estimates to the experimental data shows that the sensitivity depends on the level of "activity" of the parameter in a time interval and on the number of experimental data in this interval. If there are only a few data points in the time interval, where the influence of a parameter on the solution dynamics is important, then the sensitivity of this parameter to changes in these data is quite high. This case is observed, e.g. for parameters N_0 and $N_{\max}$, respectively in the beginning and at the end of the bacterial growth .

Overall, the obtained results show that the mathematical models are well designed to describe the sigmoidal evolution of bacterial growth and do not contain unnecessary parameters.

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