UNIVERSIDAD CARLOS III DE MADRID working papers

Working Paper 10-21 (09)
Statistics and Econometrics Series
April 2010

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BAYESIAN HIERARCHICAL MODELLING OF BACTERIA GROWTH

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Abstract

Bacterial growth models are commonly used in food safety. Such models permit the prediction of microbial safety and the shelf life of perishable foods. In this paper, we study the problem of modelling bacterial growth when we observe multiple experimental results under identical environmental conditions. We develop a hierarchical version of the Gompertz equation to take into account the possibility of replicated experiments and we show how it can be fitted using a fully Bayesian approach. This approach is illustrated using experimental data from *Listeria monocytogenes* growth and the results are compared with alternative models. Model selection is undertaken throughout using an appropriate version of the deviance information criterion and the posterior predictive loss criterion. Models are fitted using WinBUGS via R2WinBUGS.

Keywords: Predictive microbiology, growth models, Gompertz curve, Bayesian hierarchical modelling.

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1 Introduction

Bacterial growth is the division of one bacterium into two identical, daughter cells during a process called *binary fission*. Both daughter cells do not necessarily survive, but if, on average, at least half of the daughter cells survive, then the bacterial population grows exponentially. In food safety experiments, bacteria are commonly grown in petri dishes and in such experiments, bacterial growth can be divided in four different phases. Firstly, in the *lag phase* the initial colony of bacteria is adapting to the growth conditions and are not yet able to divide. Secondly, in the *exponential phase*, that is the cell doubling period - the number of new bacteria created per unit time is approximately proportional to the present population. Thirdly in the *stationary phase*, reached as the bacteria begin to exhaust the limited resources available to them, the growth rate slows down as a consequence of nutrient depletion and accumulation of waste. Finally, in the *death phase*, there are no nutrients left and the bacteria die.

Given this type of behaviour we can model the first three phases of bacteria growth using a sigmoidal type function. Many such models have been developed, see e.g. Zwietering et al. (1990) for a good review and in particular, one of the first and most popular models, which we consider in this article is the Gompertz curve, see Gompertz (1825).

Several empirical studies of bacterial growth, such as Grijspeerdt and Vanrolleghem (1999), estimate the parameters by nonlinear least square procedures. Nevertheless, most of these models do not recognize explicitly that there are two sources of indeterminacy. The first, called *variability*, reflects the intrinsic heterogeneity of the phenomenon. The second, called *uncertainty*, comes from the lack of knowledge and can be reduced by additional data from further experiments. Pouillot et al. (2003) and Delignette-Muller et al. (2006) propose the use of a Bayesian approach to the estimation of uncertainty and variability in microbial growth. In this paper, we shall also consider a Bayesian approach to Gompertz modeling.

One of the main characteristic of bacterial growth experiments is that researchers often replicate bacterial growth experiments under equal, or different, temperature, acidity and salt levels. Up to now, however, there has been little research on incorporating multiple experimental results into the prediction of bacterial growth curves. In this paper, we shall consider the case where that we observe the growth of $r > 1$ bacteria populations under identical environmental conditions. To model this process, one possible approach is to assume that the growth curve has the same nature for every experiment. We can represent this by assuming a common model for each growth curve. A disadvantage of this approach is that it does not take into account any specific, unobserved, characteristics of each petri dish experiment which may influence bacteria growth in that case. A second possibility is to estimate each growth curve independently, but this does not take the fact that we should expect the different bacterial populations to grow in a similar way under the same conditions. An alternative, intermediate approach is to use hierarchical modeling. Under this approach each experiment follows its own growth process that is characterized by its own

growth parameters but these parameters are considered as a sample from a common distribution. This approach will be followed here.

The paper is organized as follows. In Section 2, we introduce the Gompertz model for bacterial growth and develop a hierarchical version of this model to take into account the possibility of replicated experiments. In Section 3, we show how to undertake Bayesian inference for this model using the `WinBUGS` software through the `R2WinBUGS` interface. In Section 4, we apply our approach to the analysis of listeria growth curves and in Section 5, we finish with some conclusions and possible extensions.

2 Hierarchical Gompertz model

The modified Gompertz equation is a well known model for bacterial growth over time. This model has a sigmoidal shape which reflects the three stages that characterize the bacterial growth process. Firstly, the lag stage reflects the adaptation of cells inoculated in a new medium. Secondly, the exponential stage represents the bacterial growth by binary fission and, finally, the stationary stage which describes the decay of the growth rate as a consequence of nutrient depletion and accumulation of waste. If N_t represents population size of bacteria cultivated in a Petri dish experiment at time $t \geq 0$, then the modified Gompertz function is:

$$E[N_t|N0, D, \mu, \lambda] = N0 + D \exp\left(-\exp\left(1 + \frac{\mu e(\lambda - t)}{D}\right)\right) \equiv g(t, D, N0, \mu, \lambda) \quad \text{say.} \tag{1}$$

where e is the Euler's number, $N0$ is the initial bacterial density, D is the difference between the maximum bacterial density and $N0$, μ is the maximum growth rate and λ is the time lag.

Here we wish to extend the Gompertz model to the case of hierarchial models which take into account the case of several experiments carried out under equal, controlled environmental conditions. Thus, we consider r bacterial populations under the same environmental conditions. Then the hierarchical Gompertz model can be expressed as

$$\begin{aligned} E[N_{ij}|N0_i, D_i, \mu_i, \lambda_i] &= N0_i + D_i \exp\left(-\exp\left(1 + \frac{\mu_i e(\lambda_i - t_{ij})}{D_i}\right)\right) \\ &= g(t_{ij}, D_i, N0_i, \mu_i, \lambda_i). \end{aligned} \tag{2}$$

where $i = 1, \ldots, r$ and the i'th bacterial density is measured at time points t_{ij} for $j = 1, \ldots, n_i$ where n_i represents the total number of times that population i is observed. Here, each particular experiment grows according to its own

Gompertz curve. Now, we suppose the hierarchical formulation:

$$\begin{aligned} N_{ij}|N0_i, D_i, \mu_i, \lambda_i, \sigma &\sim \mathcal{N}\left(g(t_j, D_i, N0_i, \mu_i, \lambda_i), \sigma^2\right) \\ N0_i|m_0, s_0 &\sim \mathcal{N}\left(m_0, s_0^2\right) \\ \log D_i|\alpha_D, \tau_D &\sim \mathcal{N}\left(\alpha_D, \tau_D^2\right) \\ log(\mu_i)|\alpha_\mu, \tau_\mu &\sim \mathcal{N}\left(\alpha_\mu, \tau_\mu^2\right) \\ log(\lambda_i)|\alpha_\lambda, \tau_\lambda &\sim \mathcal{N}\left(\alpha_\lambda, \tau_\lambda^2\right) \end{aligned}$$

where σ^2 is an unknown variance assumed to be common for each growth curve and $\alpha_D, \tau_D, m_0, s_0, \alpha_\mu, \tau_\mu, \alpha_\lambda, \tau_\lambda$ are unknown hyperparameters.

2.1 Alternative models

Alternative models can be used for the case of multiple experiments under equal conditions. As a submodel of the previous one, it is possible to consider some of the model parameters with individual variations and others to be equal for all the individuals. When observing several growth curves under equal environmental conditions, lag parameter seems to be very similar among them. So, we will consider a second model with λ assumed to be a fixed effect and μ and D are modelled as random effects with hierarchical structure. As this kind of models incorporate both random and fixed effects they are called mixed effects models. Our mixed model is

$$\begin{aligned} E[N_{ij}|N0_i, D_i, \mu_i, \lambda] &= N0_i + D_i \exp\left(-\exp\left(1 + \frac{\mu_i e(\lambda - t_{ij})}{D_i}\right)\right) \\ &= g(t_{ij}, D_i, N0_i, \mu_i, \lambda). \end{aligned} \tag{3}$$

Another approach is to assume that the growth curve has the same nature for every experiment. That means that, when environmental conditions are equal, each curve is described by the same growth process assuming a common Gompertz curve for all of them. We call this a pooled model and express it in the following form

$$E[N_{ij}|N0, D, \mu, \lambda] = g(t, D, N0, \mu, \lambda). \tag{4}$$

Finally, the simplest model can be considered assuming that each growth curve is independent. In such case, each curve is described by its own Gompertz function with different parameters' values as expressed in Equation 1.

3 Bayesian inference

In order to fit the hierarchical model described in the previous section, one possibility would be to use classical, random effects techniques, but here, we prefer to use a fully Bayesian approach. In order to implement Bayesian inference, we must define prior distributions for the model variance and for the unknown

hyperparameters. Firstly, we suppose little prior knowledge concerning the variance σ^2 and hence propose a vague, inverse-gamma, prior distribution.

$$\sigma^2 \sim \mathcal{IG}(a, b)$$

Usually, we will have good prior knowledge about the average initial population density, $m_0 = E[N0_i|m_0, s_0]$ and the variance, s_0, as typically, petri dishes are seeded with very similar quantities of bacteria close to a known, theoretical level, so we shall typically assume that these are known. Otherwise, a simple non-informative prior distribution $f(m_0, t_0) \propto 1/t_0$, where $t_0 = 1/s_0^2$ can be used when, immediately, we have that given the observed set of initial densities, $\mathbf{N0} = (N0_1, \ldots, N0_r)$,

$$\begin{aligned} m_0|\mathbf{N0}, s_0 &\sim \mathcal{N}\left(\overline{N0}, \frac{s_0^2}{r}\right) \\ s_0^2|\mathbf{N0} &\sim \mathcal{IG}\left(r-1, \sum_{i=1}^{r}(N0_i - \overline{N0})^2\right) \end{aligned}$$

where $\overline{N0} = \frac{1}{r}\sum_{i=1}^{r} N0_i$ is the average initial density.

The model is completed by vague, but proper prior distributions for the remaining hyperparameters.

$$\begin{aligned} \alpha_D &\sim \mathcal{N}(m_D, s_D) & \tau_D^2 &\sim \mathcal{IG}(r_D, v_D) \\ \alpha_\lambda &\sim \mathcal{N}(m_\lambda, s_\lambda) & \tau_\lambda^2 &\sim \mathcal{IG}(r_\lambda, v_\lambda) \\ \alpha_\mu &\sim \mathcal{N}(m_\mu, s_\mu) & \tau_\mu^2 &\sim \mathcal{IG}(r_\mu, v_\mu) \end{aligned}$$

Unfortunately, given the full sample of data, (N_{ij}, t_{ij}) for $i = 1, \ldots, r$, $j = 0, \ldots, n_i$, exact Bayesian inference for the unknown model parameters is impossible. However, Markov-Chain Monte-Carlo (MCMC) techniques can be employed to allow us to generate an approximate Monte Carlo sample from the posterior parameter distributions. In this case, we propose to use the generic MCMC sampler, `WinBUGS`, as developed by Spiegelhalter et al. (1999), which is appropriate for hierarchical modeling situations, programmed in combination with `R`, via `R2WinBUGS`. Figure 1 illustrates the dependence structure of the model in WinBUGS style (although `WinBUGS` code cannot be constructed directly from this diagram).

In the figure, random and logical nodes are represented by ellipses and fixed nodes (independent variables) are represented by rectangles. The arrows represent dependence relationships with the single arrows showing stochastic dependence and the double arrows representing logical dependence. For more details see `http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml`, the WinBUGS homepage. As WinBUGS is a generic approach to MCMC sampling, it is important to check on the convergence of the sampler. Various tools

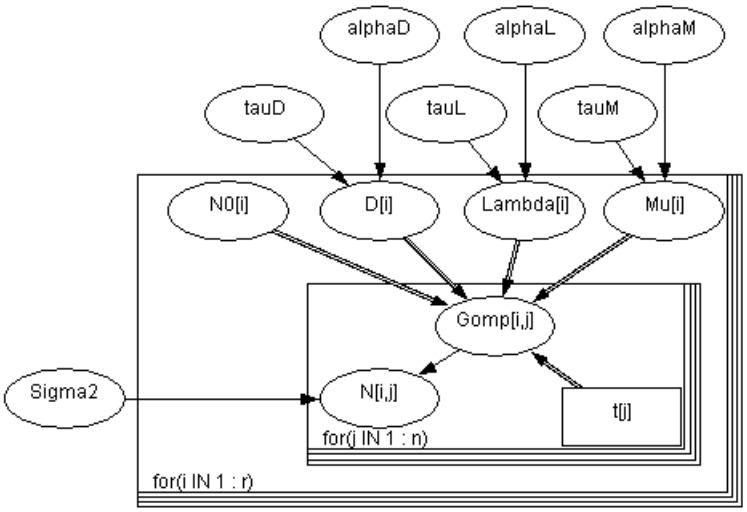


Figure 1: Dependence structure of the hierarchical Gompertz model

can be used to check the convergence. In particular, as well as standard graphical techniques such as looking at the trace, the evolution of the mean and the autocorrelations of the sampled output, we also use formal diagnostic techniques such as the modified Gelman-Rubin statistic, as in Brooks and Gelman (1998)

Inference for the mixed model can be carried out in an analogous way. All prior and hyperprior distributions are the same as in the hierarchical model, except for the lag parameter because it is assumed to be equal amongst all the curves and therefore it has not a hierarchical structure. A vague log-normal prior distribution is assigned to the lag parameter, $\lambda|m_\lambda, s_\lambda \sim \mathcal{LN}(m_\lambda, s_\lambda^2)$, where m_λ and s_λ^2 are constants. For the pooled and the independent models we follow the same approach as before, assuming relatively uninformative log-normal prior distributions for the non-negative Gompertz parameters D, λ and μ, and a vague inverse-gamma prior distribution for σ^2. For the alternative models exact Bayesian inference for the unknown model parameters is also impossible as in the case of the hierarchical model, therefore, we propose to use WinBUGS.

3.1 Model comparison

A number of criteria have been proposed for model selection in Bayesian inference. A standard, Bayesian selection criterion which is particularly appropriate when inference is carried out using Markov chain Monte Carlo methods is the deviance information criterion (DIC), as proposed in Spiegelhalter et al. (2002). Many variants of the DIC have also been considered, see e.g. Celeux et al. (2006) and here, for simplicity of calculation, we prefer to use the DIC_3 criterion of

Celeux et al. (2006). For model $\mathcal{M}$ with parameters $\boldsymbol{\theta}$ and observed data $\mathbf{x}$ the DIC_3 is defined as follows:

$$DIC_3 = -4E_{\boldsymbol{\theta}}[\log f(\mathbf{x}|\theta)|\mathbf{x}] + 2\log \prod_{i=1}^{n} E_{\boldsymbol{\theta}}[f(x_i|\boldsymbol{\theta}, \mathbf{x})].$$

Celeux et al. (2006) show that this criterion performs well in number of contexts.

An alternative approach which we also consider is the posterior predictive loss performance (PPLP) as proposed by Gelfand and Ghosh (1998). Based on the posterior predictive distribution, this criterion consists in defining a weight loss function which penalizes actions both for departure from the corresponding observed value as well as for departure from what we expect the replication to be. In this way, the approach is a compromise between the two types of departures, fit and smoothness. It is possible to show that for squared error loss, the criterion becomes

$$PPLP = \frac{k}{k+1} \sum_{i=1}^{n} (\mu_i - x_i)^2 + \sum_{i=1}^{n} \sigma_i^2$$

where $\mu_i = E(x_i^{rep}|\mathbf{x})$ and $\sigma_i^2 = Var(x_i^{rep}|\mathbf{x})$, are respectively the mean and the variance of the predictive distribution of x_i^{rep} given the observed data $\mathbf{x}$ and k is the weight we assign to departures from the observed data. The first term of $PPLP$ is plain goodness-of-fit term, and the second term penalizes the complexity and rewards parsimony.

Although the predictive distribution is useful for prediction, its use for model checking has been criticized because of double use of the data. A preferable approach is to consider the out of sample prediction of a model. In our hierarchial models there are two possible posterior predictive distributions due to the existence of parameters and hyperparameters. Firstly, we can consider the prediction of the growth curve at future times for an existing growth curve and secondly, we can predict the results from a future experiment, that is a future curve under equal conditions, drawn from the same population. Here we examine both.

4 Application: *Listeria monocytogenes*

Listeria is a bacterial genus containing six species. These species are Gram-positive bacilli and are typified by *Listeria monocytogenes*. This bacteria is a well-known food-borne pathogen (rare but fatally infections as listeriosis) and is commonly found in soil, stream water, sewage, plants, and food. The health and economic importance of listeriosis is supported by large amount of studies about this bacteria (see Augustin and Carlier (2000), Delignette-Muller et al. (2006), Pouillot et al. (2003) and Powell et al. (2006) among others). In our application the models are fitted to listeria growth curves. Data come from an experiment in broth monoculture where bacteria growth curves were generated

at fixed temperature, (42 ℃), acidity (pH = 7.4) and salt concentration (2, 5% NaCl) levels and measured as optical density. The data set consists of 18 curves each observed at 16 fixed time intervals of one hour. The data are illustrated in Figure 4 where the circles representing the points for each curve are connected by lines.

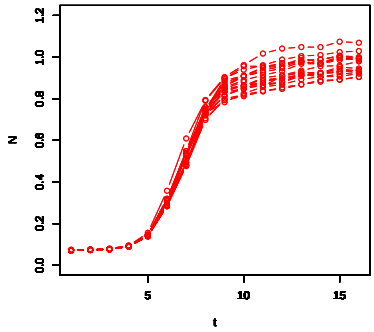


Figure 2: Bacterial growth curves: 42 ℃, pH=7,4 and 2,5% NaCl

We assume that bacteria grows according to the Gompertz function equation expressed in Equation 1 and compare the hierarchical, independent and pooled models described earlier in Section 2. In order to fit the models, in each case we generated two parallel chains using different initial values with 150000 iterations each, including 50000 iterations of burn-in. To diminish autocorrelation between the generated values we also used a thinning rate of 50. Trace plots and autocorrelation functions were used to check convergence and in all cases it was found that the burn-in period of 50000 iterations was reasonable. Figure 3 illustrates these for the population mean lag parameter, α_λ in the hierarchial model. Furthermore, the Gelman-Rubin statistic was equal o very close to 1 after 50000 iterations, giving a good indicator of convergence.

All models described in Section 2 were fitted to this data. Figure 4 represents the fitting of the pooled, the independent and the full hierarchial models and the 95% credible interval computed through the percentiles of the posterior predictive distribution. The independent model has a good fitting for curve 7, as Figure 5(a) shows, and also for the remainder curves but the 95% credible interval is significantly wider than for the other models. In the pooled model the length of the interval is lower due to the more information available assuming that all the observed curves are samples from the same common distribution. and therefore there is only one estimated curve. Figure 5(b) represents the estimated pooled curve and the 18 observed curves. One can observe that almost all the curves lie inside the 95% credible interval, except for curve number 7. This estimated curve can be interpreted as a mean curve representing the bacterial growth process under the fix environmental conditions. Finally, in the hierarchical model there is one estimated curve for each observed curve as we

can observed in Figure 4. As is expected, the fit of the hierarchial model is more accurate and the credible interval is narrower. For the mixed model very similar results are found and for this reason they are not shown in the graph.

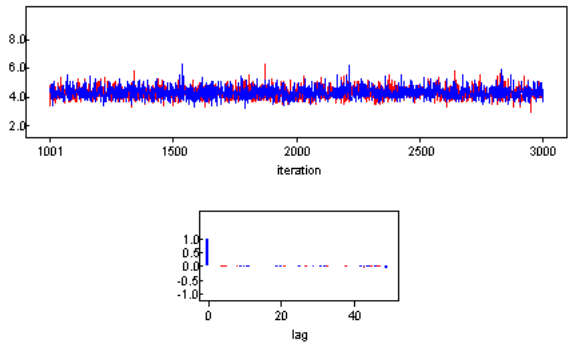
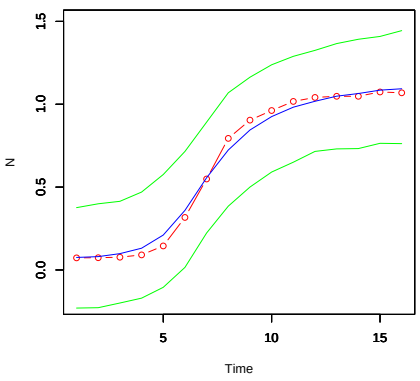


Figure 3: Convergence diagnostic in Hierarchical Gompertz model: α_λ

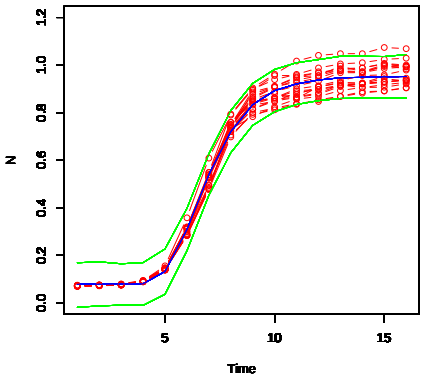
In order to compare the different models, we computed DIC_3 and $PPLP$. The results are summarized in Table 1 where we also include the first term (G) and the second term (P) of $PPLP$, which are given equal weight, that represent the goodness of fit and the complexity respectively. First of all, there is no single model that performs better under both criteria. Regarding the posterior predictive loss criterion, the pooled model has the smallest $PPLP$. The reason is that we have more information to estimate the growth parameters available since data from all the curves are pooled and considered samples from the same population. The uncertainty is considerably smaller than in the other cases as indicates the small value of P. The mixed model is the second best with a value of $PPLP$ equal to 0.43. In this case, looking at the components, we can see that, in contrast to the pooled model, the small value of $PPLP$ is due to a good fit of the model. Comparing the mixed model with the hierarchical model, there is a slightly worse performance for the latter due to higher complexity in the model which is not translated into a better goodness of fit. Thus, variability of lag parameter is not too important among replications. Finally, the smaller variance of the predictive distribution in the hierarchical model compared to the higher variance of the independent model, is explained by the borrowing strength effect - observing one curve we learn about other curves. Regarding DIC_3 indicator, both hierarchical models, the full and the mixed models, have better performance than the pooled model, being the mixed model the best one.

Table 2 shows the population parameter estimations with the standard errors regarding the full hierarchial model, the mixed model and the pooled model. Moreover, for the first two models, individual parameters are shown for curves

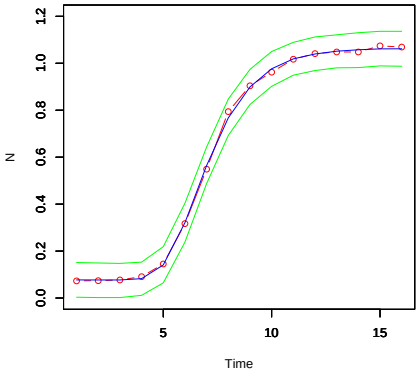
Figure 4: Fitting Growth Curves



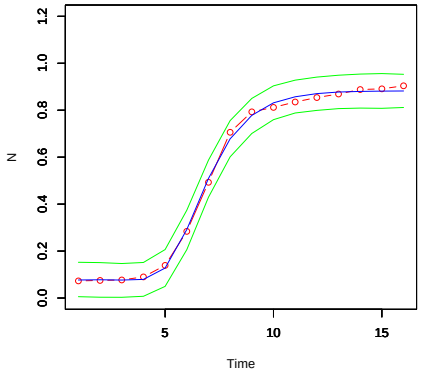
(a) Independent model



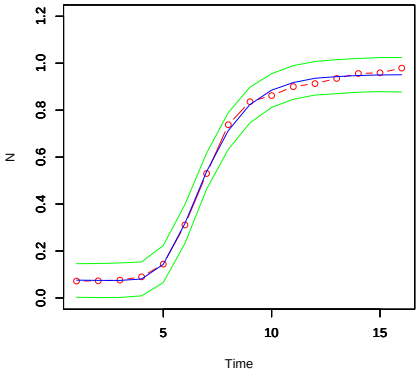
(b) Pooled model



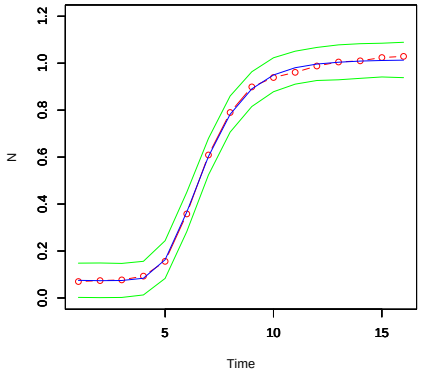
(c) Hierarchical model: curve 7



(d) Hierarchical Model: curve 12



(e) Hierarchical model: curve 17



(f) Hierarchical Model: curve 18

Table 1: Model comparison

Model	DIC3	PPLP	G	P
Hierarchical model	−1296	0.47	0.05	0.42
Mixed model	−1314	0.43	0.05	0.37
Separated model	−325	5.42	0.26	5.16
Pooled model	−1065	0.40	0.37	0.03

7, 12, 17 and 18 - the same curves represented graphically before. Comparison among the individual D_i parameter estimations shows a range of variation between 0.80 and 0.98 indicating that even keeping constant the environmental conditions, there are significant differences observed in the maximum absolute growth among the curves. Differences among the other individual parameters are also found. Comparing individual D_i and μ_i parameters between full hierarchical model and mixed model, estimations are very close. Regarding the population parameters, we observe that D and μ have the same estimated values in both models, 0.93 and 0.25 respectively. In contrast there is a difference in the lag estimate. In the hierarchial model the estimated value is equal to 4.26 while in the mixed model it is 4.03. In other words, for the parameters which are considered as random effects in both models the estimated values are equal, while for the lag parameters, considered as random in the full hierarchical model and fixed in the mixed model, the estimated values are different. The lag estimate in the mixed model is equal to the one in pooled model. Another important observation is that the standard errors of the estimations are smaller in the mixed model compared with the hierarchial model. Of course, the standard errors in the pooled model are the smallest as we explained before.

To asses the predictability of the models, now we will consider the case where the first 17 curves are fully observed and where only the first 6 values of the 18th curve are observed, so that we can try to predict the trajectory of the rest of the growth curve. Figure 5 shows the predictive curves for the hierarchial and pooled models respectively. The predictive curve for the hierarchical model is more accurate than the one for the pooled model. Moreover, when computing the mean squared error between the predictive curve and the real curve, the value for the former model is equal to 0.0020 while for the later is equal to 0.0042. In general, the more the growth process differs from the mean, the better the hierarchial model performs in comparison with the pooled model.

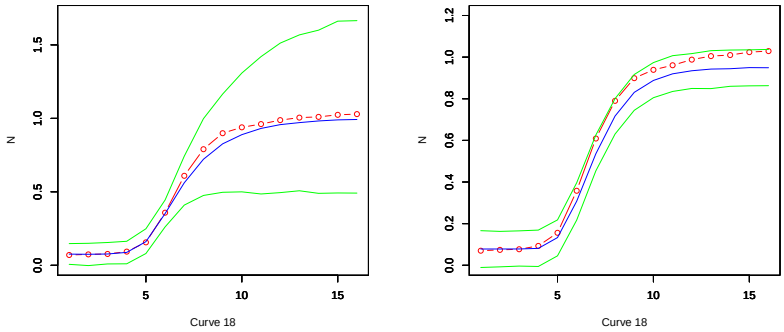
Finally, we will consider the case of prediction for a new curve, $\widetilde{J}$ which has not been observed. The procedure is as follows. First, having observed the previous 17 curves, we will predict the cell density of the new curve at $t = 0$. Then, given the true value of the bacteria density at that time, we predict the following value and so on. Figure 6 shows the predictive curves for a new

Table 2: Parameter estimations

Model	Curve	D	λ	μ
HM	7	0.98 (0.023)	4.00 (0.184)	0.25 (0.020)
	12	0.80 (0.022)	4.03 (0.222)	0.22 (0.023)
	17	0.88 (0.023)	3.91 (0.204)	0.23 (0.020)
	18	0.94 (0.022)	3.82 (0.188)	0.25 (0.020)
	Population	**0.93** (0.083)	**4.26** (0.367)	**0.25** (0.024)
MM	7	0.98 (0.020)		0.24 (0.0169)
	12	0.80 (0.019)		0.22 (0.012)
	17	0.87 (0.019)		0.23 (0.013)
	18	0.92 (0.019)		0.26 (0.013)
	Population	**0.93** (0.081)	**4.03** (0.015)	**0.25** (0.023)
PM	Population	**0.87** (0.007)	**4.03** (0.066)	**0.23** (0.007)

experiment for the hierarchical model and the pooled model, respectively.

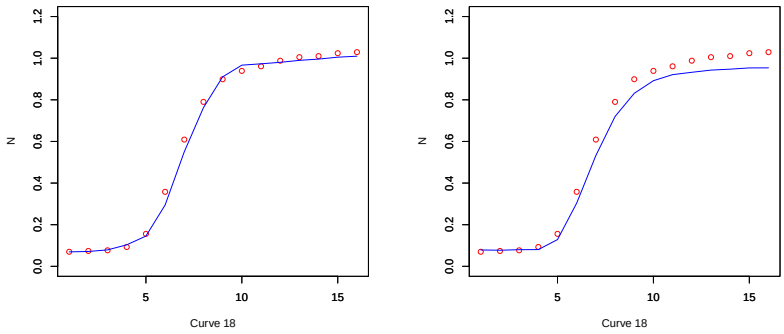
Figure 5: Predictive Future Observations



(a) Hierarchical model (b) Pooled model

Once again, the hierarchial model outperforms the pooled model with the predicted curve being very close to the true curve. The mean square error of the predictions are equal to 0.0006 and 0.0040, for the hierarchical and the pooled model respectively, being significantly lower for the hierarchical model.

Figure 6: Predictive Future Experiment



(a) Hierarchical model (b) Pooled model

5 Conclusions

We have illustrated that hierarchical models can be used to model bacterial growth functions when several replications of the same experiment under equal environmental conditions such as temperature, acidity level and salt concentration are available. Sub-models, keeping fixed some of the growth parameters, are also suitable. Hierarchical models are a good compromise between goodness of fit and simplicity of the model as we clarify in the application. A number of extensions to this work are possible.

Firstly, in this work we have extended the modified Gompertz equation to the case of a hierarchical models, but the approach is equally applicable to other bacteria growth models. Furthermore, it can also be applied to the cases where we assume no parametric growth model and instead use a nonparametric approach. Finally, in the present study we have considered experiments under fixed environmental conditions. A natural extension of this work is to also consider modeling what happens given changes in these conditions.

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