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Estimation of uncertainty and variability in bacterial growth using Bayesian inference. Application to *Listeria monocytogenes*

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Abstract

The usefulness of risk assessment is limited by its ability or inability to model and evaluate risk uncertainty and variability separately. A key factor of variability and uncertainty in microbial risk assessment could be growth variability between strains and growth model parameter uncertainty. In this paper, we propose a Bayesian procedure for growth parameter estimation which makes it possible to separate these two components by means of hyperparameters. This model incorporates in a single step the logistic equation with delay as a primary growth model and the cardinal temperature equation as a secondary growth model. The estimation of *Listeria monocytogenes* growth parameters in milk using literature data is proposed as a detailed application. While this model should be applied on genuine data, it is highlighted that the proposed approach may be convenient for estimating the variability and uncertainty of growth parameters separately, using a complete predictive microbiology model.

Keywords: Predictive microbiology; Bayesian model; Uncertainty; Variability; Microbial risk assessment; *L. monocytogenes*

1. Introduction

Risk assessment is increasingly being used as a tool to evaluate food safety and public health hazards. This concept is now being recommended and applied for international trade purposes by international organisations such as the *Codex alimentarius*, the Food and Agriculture Organisation and the World Health Organisation (FAO-WHO, 1997; Codex Committee on Food Hygiene, 2000).

Quantitative risk assessment is generally based on a mathematical and statistical model of risk agent behaviour through a considered chain of processes (Marks et al., 1998). Risk assessment associated with a microbial hazard is somewhat complicated by the potential growth or decrease in the bacterial population according to the microenvironment, from food production to ingestion. Several mathematical models have been developed in the last few decades to describe and predict the growth of microorganism populations according to environmental factors (Ratkowsky et al., 1982; Rosso et al., 1995; van Gerwen and Zwietering, 1998). These models should then be included in microbial food safety risk assessment,

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either in a simplified form (Peeler and Bunning, 1994; Farber et al., 1996; Bemrah et al., 1998) or in their full form (Delignette-Muller and Rosso, 2000), as long as good estimates are available for all their parameters.

The precision of a quantitative risk assessment lies in its ability to reflect and evaluate the 'variability' and the 'uncertainty' of the risk estimate separately (Lammerding, 1997; Vose, 2000). In the field of risk analysis, 'uncertainty' is defined as the lack of perfect knowledge of a given variate value. It may generally be reduced by further experimental or sampling investigations. 'Variability' represents the true heterogeneity of a population irreducible by additional measurements (Anderson and Hattis, 1999). It corresponds to the well-known 'biological variability.' The separation of uncertainty and variability as sources of variation in model parameters has been shown to be an important issue in microbial risk assessment (Nauta, 2000).

One key source of microbial risk variability and uncertainty may be microbial growth variability and uncertainty (Delignette-Muller and Rosso, 2000). The bacterial population growth process is obviously variable: the growth curve observed for one strain may not be the same as that of another strain, even when all growth conditions are similar. So a main source of variability could be the strain effect (Begot et al., 1997; Nauta and Dufrenne, 1999). The characterisation of the growth process is also clearly uncertain: the most obvious source of uncertainty is related to microbial measurements that are definitely imperfect. In most published microbial risk assessments, although uncertainty and variability are both mentioned as sources of variation, they are treated alike (Nauta, 2000). Better growth model parameter estimation for risk assessment purposes should be able to separately evaluate the variability and uncertainty of the estimates. The aim of this study was to propose a way of meeting this challenge that is based on a Bayesian approach.

In a Bayesian framework, model parameters are random variates and not fixed as in other standard statistical approaches. Three steps can be distinguished: (i) a model is built, where each parameter is related to other parameters and variates until what we called 'terminal parameters' are reached; (ii) prior distributions over all terminal parameters are specified. They reflect the state of knowledge available before analysing the data set. Uninformative prior distributions are used when little is known about the parameters; (iii) posterior distributions over all parameters are computed using Bayes' theorem, combining prior distributions and observed data: less informative are prior distributions and more weight is given to the data in posterior density determination. Posterior distributions contain updated beliefs about model parameters; they can be used as the new state of knowledge for future studies. Details on Bayesian theory can be found for instance in Carlin and Louis (2000).

Variability and uncertainty concepts for a given parameter of interest will be modelled by means of hyperparameters. The variability of the parameter is considered to be determined by the conditional distribution of the parameter given the pivot values of the parameters defining its distribution. These latter parameters are denoted by the hyperparameters of the former parameter. As an example, if one assumes that parameter variability within a population can be modelled through a normal distribution, then the expected value and standard deviation of this distribution would be the hyperparameters. When the distributions of the hyperparameters are taken into account, then variability and uncertainty are modelled. In other words, uncertainty is modelled because the hyperparameters are random variates. Application to a case study is proposed below.

Listeria monocytogenes is a well-known foodborne pathogen that has been studied extensively since the first major recognised outbreak in the early 1980s (Schlech et al., 1983). The health and economic consequences of listeriosis support the development of risk analysis. The example detailed is the estimation of *L. monocytogenes* population growth in milk using literature data.

2. Materials and methods

2.1. Data

Growth curves have been selected from the literature according to the following criteria: (i) growth curves of *L. monocytogenes* were obtained in skimmed, partially skimmed or whole milk, without adding any substances, in a constant temperature environment; (ii) growth curves were estimated from viable counts; (iii) graphs or raw data were included in the original article. Twelve publications were selected including a total of

124 growth curves (Table 1). When necessary, graphs were scanned and individual points digitalised.

Two *L. monocytogenes* strains were considered different if (i) they were considered different in a given paper or (ii) they were studied in different papers. For example, a Scott A strain used in a paper was obviously considered different from a CA strain used in the same paper, but a Scott A strain was systematically considered different from another Scott A strain if the growth curves were taken from different papers. The *i* column of Table 1 shows the index value of the 22 studied strains found in this review.

2.2. Model

We assume that kinetics are identical in skimmed, partially skimmed or whole milk media (Donnelly and Briggs, 1986; Rosenow and Marth, 1987b; Marshall and Schmidt, 1988; Augustin and Carlier, 2000). We also assume that temperature T is the only varying environmental parameter influencing *L. monocytogenes* population growth in these papers.

2.2.1. Predictive microbiology model

The predictive microbiology model may be split into a 'primary' and a 'secondary' model. Primary models describe the kinetics of bacterial population growth. The primary model used was the logistic equation with delay, i.e. a transition between the lag phase and the exponential phase considered to be instantaneous (Kono, 1968; Baranyi et al., 1993; Rosso, 1995). It can be written as follows:

$$Y(t) = \mathrm{PM}_t + \varepsilon_{\mathrm{PM}} \tag{1}$$

where $Y(t)$ is the logarithm of the bacterial concentration at instant t, $\varepsilon_{\mathrm{PM}}$ the model error and

$$\mathrm{PM}_t = \begin{cases} y_0, & t \le \lambda(T) \\ y_{\max} - \log\{1 + [\exp(y_{\max} - y_0) - 1] \\ \quad \times \exp[-\mu_{\max}(T)(t - \lambda(T))]\}, & t > \lambda(T) \end{cases} \tag{2}$$

where y_0 is the logarithm of the initial bacterial concentration [unit: log(cfu ml^{-1})], $y_{\max}$ the logarithm of the maximal achievable concentration in the culture media [unit: log(cfu ml^{-1})], $\lambda(T)$ the lag time (unit: h) at temperature T and $\mu_{\max}(T)$ the maximum specific growth rate (unit: h^{-1}) at temperature T.

Secondary models describe the effect of growth environment on the set of primary model parameters. The change in $\mu_{\max}$ as a function of temperature T may be fitted using the secondary cardinal model of Rosso et al. (1993):

$$\mu_{\max}(T) = (\sqrt{\mathrm{SM1}_T} + \varepsilon_{\mathrm{SM1}})^2 \tag{3}$$

where $\varepsilon_{\mathrm{SM1}}$ is the model error and $\mathrm{SM1}_T$ is a function of T defined as:

$$\mathrm{SM1}_T = \begin{cases} 0, & T \notin [T_{\min}, T_{\max}] \\ \Big[\mu_{\mathrm{opt}}(T - T_{\max})(T - T_{\min})^2\Big] & \\ \quad \Big/\Big[(T_{\mathrm{opt}} - T_{\min})[(T_{\mathrm{opt}} - T_{\min}) & \\ \quad (T - T_{\mathrm{opt}}) - (T_{\mathrm{opt}} - T_{\max}) & \\ \quad (T_{\mathrm{opt}} + T_{\min} - 2T)]\Big], & T \in [T_{\min}, T_{\max}] \end{cases} \tag{4}$$

where μ_{opt} is the highest $\mu_{\max}(T)$ value achievable in the milk, $T_{\min}$ the temperature below which no growth occurs (unit: °C), $T_{\max}$ the temperature above which no growth occurs (unit: °C) and T_{opt} the optimal temperature (unit: °C), i.e. the temperature at which $\mu_{\max}(T)$ is the highest and equal to μ_{opt} if model error is neglected. The square root transformation for $\mu_{\max}$ is chosen for stabilising the variance (Zwietering et al., 1990; Schaffner, 1994).

The change in λ according to the temperature is modelled using the relationship:

$$\ln(\lambda(T)\mu_{\max}(T)) = \ln(K) + \varepsilon_{\mathrm{SM2}}$$

which may be written as:

$$\lambda(T) = \frac{\exp(\ln(K) + \varepsilon_{\mathrm{SM2}})}{\mu_{\max}(T)} \tag{5}$$

Table 1
Growth database for *L. monocytogenes* in milk

Ref.	Fig.	Strain	i	T (°C)	Milk	N_n	t	$Y_n(t)$
El-Gazzar et al. (1991)	1a	V7	1	4	skimmed	7	0, 144, 240, 408, 480, 648, 720	3.98, 4.91, 6.11, 5.89, 5.76, 5.28, 6.46
	1c	CA	2	4	skimmed	7	0, 144, 240, 408, 480, 648, 720	3.8, 5.15, 6.4, 6.56, 7.33, 7.52, 6.69
	1b	V7	1	4	skimmed	6	0, 168, 264, 408, 504, 672	3.79, 3.28, 3.01, 3.91, 5.77, 6.91
	1c	CA	2	4	skimmed	6	0, 168, 264, 408, 504, 672	3.99, 3.13, 4.71, 5.07, 6.33, 7.25
	2a	V7	1	32	skimmed	6	0, 6, 12, 24, 30, 36	5.19, 5.92, 7.57, 8.42, 8.49, 8.55
	2c	CA	2	32	skimmed	6	0, 6, 12, 24, 30, 36	5.24, 6.38, 7.89, 8.37, 8.49, 8.56
	2b	V7	1	32	skimmed	6	0, 6, 12, 24, 30, 36	5.06, 6.02, 7.58, 8.42, 8.53, 8.53
	2d	CA	2	32	skimmed	6	0, 6, 12, 24, 30, 36	5.14, 6.33, 7.68, 8.34, 8.4, 8.34,
	3a	V7	1	40	skimmed	6	0, 6, 12, 24, 30, 36	5.32, 6.44, 7.76, 8.35, 8.46, 8.38
	3c	CA	2	40	skimmed	6	0, 6, 12, 24, 30, 36	5.12, 6.16, 7.27, 8.6, 8.2, 8.18
	3b	V7	1	40	skimmed	6	0, 6, 12, 24, 30, 36	5.2, 6.64, 7.83, 8.34, 8.43, 8.43
	3d	CA	2	40	skimmed	6	0, 6, 12, 24, 30, 36	5.14, 6.67, 7.76, 8.19, 8.22, 8.29
Pearson and Marth (1990)	1	V7	3	13	skimmed	9	0, 12, 36, 60, 84, 108, 132, 156, 180	2.98, 2.86, 4.36, 6.06, 7.04, 7.86, 8.2, 8.39, 8.39
	2	V7	3	13	skimmed	9	0, 12, 36, 60, 84, 108, 132, 156, 180	3, 2.93, 4.42, 6.02, 7.06, 7.87, 8.22, 8.41, 8.38
	6a	V7	3	30	skimmed	10	0, 3, 6, 9, 12, 15, 18, 24, 30, 36	2.98, 3.24, 4.3, 5.43, 6.26, 7.21, 7.52, 7.81, 7.9, 7.9
	6b	V7	3	30	skimmed	12	0, 3, 6, 9, 12, 15, 18, 24, 27, 30, 33, 36	2.95, 3.26, 4.16, 5.19, 6.14, 6.87, 7.42, 7.93, 7.95, 8.01, 8.18, 8.13
	6c	V7	3	30	skimmed	9	0, 3, 6, 9, 12, 15, 18, 21, 24	3.03, 3.34, 4.28, 5.48, 6.69, 7.34, 7.83, 7.92, 8.1
	6d	V7	3	30	skimmed	9	0, 3, 6, 9, 12, 15, 18, 20, 24	3.07, 3.33, 4.31, 5.34, 6.28, 6.97, 7.66, 7.91, 8.26
	7a	V7	3	30	skimmed	11	0, 3, 6, 9, 12, 18, 21, 24, 27, 30, 33	3.14, 3.42, 4.33, 5.5, 6.86, 7.61, 7.72, 7.75, 7.8, 7.69, 8.06
	7b	V7	3	30	skimmed	11	0, 3, 6, 9, 12, 18, 21, 24, 27, 30, 33	3.04, 3.23, 4.14, 5.15, 6.16, 7.37, 7.76, 7.95, 8.06, 8.22, 8.38
	7c	V7	3	30	skimmed	11	0, 3, 6, 9, 12, 18, 21, 24, 27, 30, 33	3.02, 3.42, 4.36, 5.52, 6.52, 7.68, 7.85, 7.87, 7.86, 7.89, 7.72
	7d	V7	3	30	skimmed	11	0, 3, 6, 9, 12, 18, 21, 24, 27, 30, 33	3.07, 3.21, 4.11, 5.12, 6.11, 7.55, 7.79, 7.91, 8.02, 8.05, 8.05
Rosenow and Marth (1987b)	1	CA	4	4	skimmed	10	0, 120, 240, 336, 432, 528, 696, 912, 1152, 1560	2.75, 2.78, 3.45, 4.28, 5.16, 6.22, 7.21, 7.63, 7.63, 7.49

Table 1 (*continued*)

Ref.	Fig.	Strain	i	T (°C)	Milk	N_n	t	$Y_n(t)$
Rosenow and Marth (1987b)	1	CA	4	4	whole	10	0, 120, 240, 336, 432, 528, 696, 912, 1152, 1560	2.75, 2.83, 3.47, 4.28, 5.32, 6.36, 7.46, 7.6, 7.57, 7.44
	2	V7	5	4	skimmed	10	0, 120, 240, 336, 432, 528, 624, 768, 1104, 1512	2.63, 2.98, 3.6, 4.34, 5.13, 5.95, 6.6, 7.16, 7.69, 7.79
	2	V7	5	4	whole	10	0, 120, 240, 336, 432, 528, 624, 768, 1104, 1512	2.63, 2.79, 3.08, 3.76, 4.63, 5.43, 6.03, 6.82, 7.5, 7.66
	9	CA	4	8	skimmed	10	0, 48, 96, 144, 192, 240, 288, 336, 408, 480	2.65, 2.63, 3.72, 4.84, 5.93, 6.89, 7.49, 7.67, 7.72, 7.75
	9	CA	4	8	whole	10	0, 48, 96, 144, 192, 240, 288, 336, 408, 480	2.65, 2.66, 3.57, 4.69, 5.64, 6.37, 7.38, 7.59, 7.75, 7.75
	10	V37CE	6	8	skimmed	10	0, 24, 48, 72, 120, 168, 216, 264, 336, 408	2.71, 2.76, 2.96, 3.45, 4.74, 5.52, 6.71, 7.2, 7.57, 7.82
	10	V37CE	6	8	whole	10	0, 24, 48, 72, 120, 168, 216, 264, 336, 408	2.71, 2.76, 2.94, 3.43, 4.47, 5.35, 6.56, 7.2, 7.71, 8.08
	11	Scott A	7	13	skimmed	8	0, 12, 24, 48, 72, 96, 120, 196	3.06, 3.2, 4.02, 5.46, 6.66, 7.57, 7.72, 8.06
	11	Scott A	7	13	whole	8	0, 12, 24, 48, 72, 96, 120, 196	2.96, 3.2, 4.02, 5.46, 6.66, 7.66, 7.81, 8.1
	12	CA	4	13	skimmed	9	0, 12, 24, 48, 72, 96, 120, 144, 196	2.77, 2.87, 3.26, 4.38, 5.56, 6.21, 6.9, 7.59, 7.9
	12	CA	4	13	whole	9	0, 12, 24, 48, 72, 96, 120, 144, 196	2.77, 2.87, 3.33, 4.38, 5.44, 6.21, 7.08, 7.67, 7.95
	14	V7	5	21	skimmed	9	0, 6, 12, 18, 24, 30, 38, 52, 78	2.85, 3.06, 4.13, 5.15, 6.1, 6.96, 7.76, 8.23, 8.34
	14	V7	5	21	whole	9	0, 6, 12, 18, 24, 30, 38, 52, 78	2.85, 3.06, 4.13, 5.15, 6.1, 6.96, 7.76, 8.41, 8.49
	16	V7	5	35	skimmed	10	0, 2, 4, 6, 8, 10, 12, 14, 24, 48	2.68, 2.77, 3.62, 4.53, 5.38, 6, 6.7, 7.18, 8.23, 8.44
	16	V7	5	35	whole	10	0, 2, 4, 6, 8, 10, 12, 14, 24, 48	2.68, 2.77, 3.62, 4.53, 5.38, 6.06, 6.7, 7.2, 8.23, 8.44
Marshall and Schmidt (1988)	1	Scott A	8	10	whole	6	0, 24, 48, 96, 144, 192	1.44, 1.61, 2.98, 4.4, 5.86, 7
	2	Scott A	8	10	skimmed	6	0, 24, 48, 96, 144, 192	1.48, 1.66, 2.97, 4.39, 6.02, 7.18
	3	Scott A	8	10	skimmed	6	0, 24, 48, 96, 144, 192	1.51, 1.67, 3.02, 4.41, 5.99, 7.08
Rosenow and Marth (1987a)	1	CA	9	13	skimmed	9	0, 12, 24, 48, 72, 96, 120, 144, 192	2.6, 2.67, 3.24, 4.94, 6.47, 7.9, 8.27, 8.31, 8.24
	2	V7	10	13	skimmed	9	0, 12, 24, 48, 72, 96, 120, 144, 192	2.86, 3.12, 4.03, 5.89, 7.32, 7.87, 8.1, 8.22, 8.24
	3	CA	9	13	skimmed	9	0, 12, 24, 48, 72, 96, 120, 144, 192	2.7, 2.7, 3.05, 4.75, 6.15, 7.43, 7.94, 8.02, 7.97
	4	V7	10	13	skimmed	9	0, 12, 24, 48, 72, 96, 120, 144, 192	2.82, 2.89, 3.59, 5.28, 6.75, 7.6, 7.91, 8.01, 7.96
Papageorgiou and Marth (1989)	1	Scott A	11	4	skimmed	17	0, 120, 240, 360, 480, 600, 720, 840, 960, 1080, 1200, 1320, 1440, 1560, 1680, 1800, 2160	2.91, 2.82, 3.22, 3.35, 3.71, 5.75, 6.26, 6.6, 7.06, 7.14, 7.36, 7.39, 7.33, 7.54, 7.48, 7.54, 7.48
	1	CA	12	4	skimmed	17	0, 120, 240, 360, 480, 600, 720, 840, 960, 1080, 1200, 1320, 1440, 1560, 1680, 1800, 2160	2.73, 2.79, 3.04, 4.19, 4.74, 5.35, 6.02, 6.66, 7.12, 7.18, 7.42, 7.58, 7.48, 7.54, 7.52, 7.58, 7.54

(continued on next page)

Table 1 (*continued*)

Ref.	Fig.	Strain	i	T (°C)	Milk	N_n	t	$Y_n(t)$
Papageorgiou and Marth (1989)	2	Scott A	11	22	skimmed	19	0, 6, 12, 24, 30, 36, 48, 54, 60, 72, 78, 84, 96, 108, 120, 144, 168, 192, 240	3.15, 3.15, 3.31, 4.23, 4.68, 4.98, 5.76, 6.24, 6.41, 7.02, 7.13, 7.19, 7.35, 7.47, 7.5, 7.53, 7.55, 7.5, 7.72
	2	CA	12	22	skimmed	19	0, 6, 12, 24, 30, 36, 48, 54, 60, 72, 78, 84, 96, 108, 120, 144, 168, 192, 240	2.97, 2.97, 3.09, 3.57, 3.92, 4.52, 5.4, 5.76, 6.58, 6.94, 7.22, 7.35, 7.53, 7.58, 7.64, 7.64, 7.69, 7.77, 7.92
Walker et al. (1990)	3	CRA433	13	8.7	–	10	0, 25, 47, 72, 144, 190, 219, 313, 481, 550	5.56, 5.48, 6.19, 7.56, 7.9, 7.96, 8.04, 8.06, 8.12, 8.07
	3	CRA433	13	1.5	–	13	0, 22, 143, 313, 397, 487, 534, 575, 644, 712, 812, 894, 984	5.27, 5.19, 5.21, 6.41, 6.94, 7.29, 7.46, 7.44, 7.54, 7.54, 7.58, 7.58, 7.65
Schaack and Marth (1988b)	1	V7	14	21	skimmed	6	0, 3, 6, 9, 12, 15	3.07, 3.02, 3.23, 3.88, 4.51, 5.0,
	2	V7	14	30	skimmed	6	0, 3, 6, 9, 12, 15	3, 3.08, 4.17, 5.2, 6.16, 7.12
	3	V7	14	21	skimmed	6	0, 3, 6, 9, 12, 15	3.07, 3.09, 3.4, 4.25, 4.63, 5.18
	4	V7	14	30	skimmed	6	0, 3, 6, 9, 12, 15	3.08, 3.26, 4.3, 5.35, 6.31, 7.17
	5	V7	14	21	skimmed	6	0, 3, 6, 9, 12, 15	3.03, 3.05, 3.17, 3.83, 4.51, 4.94
	6	V7	14	30	skimmed	6	0, 3, 6, 9, 12, 15	3.03, 3.08, 4.16, 5.27, 6.23, 7.01
	7	V7	14	21	skimmed	6	0, 3, 6, 9, 12, 15	3.07, 3.06, 3.4, 4.11, 4.68, 5.2
	8	V7	14	30	skimmed	6	0, 3, 6, 9, 12, 15	3.08, 3.19, 4.37, 5.56, 6.44, 7.14
	9	V7	14	21	skimmed	6	0, 3, 6, 9, 12, 15	3.12, 3.1, 3.36, 4.14, 4.72, 5.54
	10	V7	14	30	skimmed	6	0, 3, 6, 9, 12, 15	3.08, 3.3, 4.44, 5.59, 6.38, 7.16
	11	V7	14	21	skimmed	6	0, 3, 6, 9, 12, 15	2.99, 3.12, 3.36, 4.16, 4.53, 5.23
	12	V7	14	30	skimmed	6	0, 3, 6, 9, 12, 15	3.03, 3.41, 4.39, 5.6, 6.32, 6.86
	13	V7	14	21	skimmed	6	0, 3, 6, 9, 12, 15	3.12, 3.1, 3.59, 4.23, 4.91, 5.45
	14	V7	14	30	skimmed	6	0, 3, 6, 9, 12, 15	3.09, 3.37, 4.59, 5.56, 6.57, 7.4
Schaack and Marth (1988a)	1	V7	15	37	skimmed	6	0, 3, 6, 9, 12, 15	2.95, 3.41, 4.84, 5.93, 6.94, 7.36
	2	V7	15	42	skimmed	6	0, 3, 6, 9, 12, 15	2.94, 3.26, 4.31, 5.3, 6.03, 6.72
	3	V7	15	37	skimmed	6	0, 3, 6, 9, 12, 15	2.95, 3.45, 4.88, 6.07, 7.07, 7.5
	4	V7	15	42	skimmed	6	0, 3, 6, 9, 12, 15	3.23, 3.46, 4.02, 4.43, 5.41, 6.15
	5	V7	15	37	skimmed	6	0, 3, 6, 9, 12, 15	3.07, 3.5, 5.04, 6.11, 6.91, 7.41
	6	V7	15	42	skimmed	6	0, 3, 6, 9, 12, 15	3.1, 3.46, 4.53, 5.26, 6.1, 6.64

Table 1 (*continued*)

Ref.	Fig.	Strain	i	T (°C)	Milk	N_n	t	$Y_n(t)$
Schaack and Marth (1988a)	7	V7	15	37	skimmed	6	0, 3, 6, 9, 12, 15	2.73, 3.24, 4.87, 5.79, 6.75, 7.15
	8	V7	15	42	skimmed	6	0, 3, 6, 9, 12, 15	2.82, 3.24, 4.51, 5.41, 6.26, 6.71
	9	V7	15	37	skimmed	6	0, 3, 6, 9, 12, 15	2.92, 3.33, 4.85, 5.69, 6.66, 7.07
	10	V7	15	42	skimmed	6	0, 3, 6, 9, 12, 15	2.97, 3.41, 4.68, 5.64, 6.68, 7.08
	11	V7	15	37	skimmed	6	0, 3, 6, 9, 12, 15	3.06, 3.55, 4.93, 6.01, 6.88, 7.58
	12	V7	15	42	skimmed	6	0, 3, 6, 9, 12, 15	3.07, 3.54, 4.56, 5.4, 6.07, 6.68
	13	V7	15	37	skimmed	6	0, 3, 6, 9, 12, 15	3.08, 3.57, 4.9, 5.47, 6.99, 7.42
	14	V7	15	42	skimmed	6	0, 3, 6, 9, 12, 15	3.08, 3.6, 4.27, 5.57, 5.74, 6.51,
	15	V7	15	37	skimmed	6	0, 3, 6, 9, 12, 15	3.08, 3.89, 5.22, 6.51, 6.89, 7.15
	16	V7	15	42	skimmed	6	0, 3, 6, 9, 12, 15	3.12, 3.77, 4.56, 5.41, 6, 6.38
	17	V7	15	37	skimmed	6	0, 3, 6, 9, 12, 15	3.04, 3.64, 4.91, 6.1, 6.88, 7.43
	18	V7	15	42	skimmed	6	0, 3, 6, 9, 12, 15	2.99, 3.64, 4.56, 5.41, 6.2, 6.82,
Pearson and Marth (1990)	1	V7	16	30	skimmed	10	0, 3, 6, 9, 12, 16, 24, 28, 32, 40	3.12, 3.26, 3.57, 4.46, 5.33, 6.42, 7.9, 8.21, 8.41, 8.57
Brouillaud-Delattre et al. (1997)	1	Scott A	17	4	partially skimmed	31	0, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 456, 480, 504, 528, 552, 576, 624, 648, 672, 720, 792, 864, 984	3.18, 3.23, 3.15, 3.2, 3.2, 3.34, 3.51, 3.64, 3.99, 4.18, 4.4, 4.69, 4.85, 5.04, 5.26, 5.46, 5.7, 5.89, 6.15, 6.36, 6.49, 6.62, 6.88, 7, 7.34, 7.4, 7.38, 7.46, 7.56, 7.59, 7.52
	1	Scott A	17	4	partially skimmed	31	0, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 456, 480, 504, 528, 552, 576, 624, 648, 672, 720, 792, 864, 984	1.25, 1.17, 1.2, 1.31, 1.23, 1.37, 1.48, 1.67, 1.81, 2.04, 2.26, 2.4, 2.6, 2.74, 3, 3.18, 3.3, 3.43, 3.74, 3.87, 4.08, 4.2, 4.41, 4.57, 4.91, 5.04, 5.23, 5.58, 5.96, 6.41, 6.74
	1	Scott A	17	4	partially skimmed	25	0, 24, 48, 72, 96, 120, 144, 168, 216, 288, 336, 384, 456, 480, 504, 528, 552, 576, 624, 648, 672, 720, 792, 864, 984	0.08, 0.15, 0.15, 0.26, 0.3, 0.15, 0.38, 0.64, 1.16, 1.66, 2.04, 2.38, 2.93, 2.97, 3.23, 3.38, 3.63, 3.92, 4.34, 4.52, 4.82, 5.08, 5.69, 6.18, 6.63
	1	Scott A	17	4	partially skimmed	22	0, 24, 48, 72, 96, 120, 168, 216, 288, 336, 384, 456, 504, 552, 576, 624, 648, 672, 720, 792, 864, 984	−0.7, −0.4, −0.7, −0.7, −0.7, −0.7, −0.4, 0.2, 0.82, 1.27, 1.56, 2.09, 2.5, 3, 3.11, 3.78, 3.9, 4.15, 4.63, 5.18, 5.81, 5.87

(continued on next page)

Table 1 (*continued*)

Ref.	Fig.	Strain	i	T (°C)	Milk	N_n	t	$Y_n(t)$
Donnelly and Briggs (1986)	1a	F5069	18	37	whole	8	0, 2, 4, 6, 8, 10, 12, 24	0.59, 0.71, 1.07, 2.15, 2.73, 3.86, 4.71, 8.09
	1a	F5069	18	22	whole	5	0, 4, 8, 12, 24	0.95, 1.18, 1.84, 2.76, 4.97
	1a	F5069	18	10	whole	5	0, 24, 48, 72, 96	0.87, 3.98, 6.4, 7.58, 7.89
	1a	F5069	18	4	whole	5	0, 24, 48, 72, 96	0.65, 0.71, 1.02, 1.51, 2.1
	1b	F5069	18	37	skimmed	8	0, 2, 4, 6, 8, 10, 12, 24	1.07, 1.35, 2.17, 3.18, 3.98, 4.85, 5.3, 7.93
	1b	F5069	18	22	skimmed	5	0, 4, 8, 12, 24	1.13, 1.23, 2.24, 3.04, 5.49
	1b	F5069	18	10	skimmed	5	0, 24, 48, 72, 96	0.93, 1.42, 2.81, 4.76, 6.47
	1b	F5069	18	4	skimmed	5	0, 24, 48, 72, 96	0.93, 1.27, 1.53, 2.01, 2.52
	1c	F5069	18	37	partially skimmed	8	0, 2, 4, 6, 8, 10, 12, 24	0.71, 1.21, 1.63, 2.45, 3.13, 4.31, 5.16, 8.43
	1c	F5069	18	22	partially skimmed	5	0, 4, 8, 12, 24	1.51, 1.61, 2.27, 2.87, 5.04
	1c	F5069	18	10	partially skimmed	5	0, 24, 48, 72, 96	1.3, 1.79, 2.57, 3.56, 4.81
	1c	F5069	18	4	partially skimmed	4	0, 24, 72, 96	0.85, 1.37, 1.7, 1.87
	2a	F19113	19	37	whole	7	0, 2, 4, 6, 8, 10, 24	0.25, 0.67, 0.77, 0.85, 1.55, 2.06, 5.68
	2a	F19113	19	22	whole	3	0, 12, 24	1.07, 1.22, 3.49
	2a	F19113	19	10	whole	5	0, 24, 48, 72, 96	0.24, 1.28, 4.11, 5.87, 6.56
	2a	F19113	19	4	whole	5	0, 24, 48, 72, 96	0.14, 0.21, 0.26, 1.15, 2.06
	2b	F19113	19	37	skimmed	8	0, 2, 4, 6, 8, 10, 12, 24	0.45, 0.75, 1.26, 1.55, 2.22, 2.59, 2.78, 3.89
	2b	F19113	19	22	skimmed	4	0, 4, 12, 24	0.93, 0.96, 2.29, 3.07
	2b	F19113	19	10	skimmed	5	0, 24, 48, 72, 96	0.37, 0.75, 1.97, 2.62, 4.43
	2b	F19113	19	4	skimmed	5	0, 24, 48, 72, 96	0.51, 0.91, 1.1, 1.26, 1.5
	2c	F19113	19	37	partially skimmed	7	0, 4, 6, 8, 10, 12, 24	0.61, 0.67, 1.12, 1.26, 2.34, 3.28, 5.39
	2c	F19113	19	22	partially skimmed	4	0, 4, 12, 24	1.01, 1.26, 1.55, 3.02
	2c	F19113	19	10	partially skimmed	5	0, 24, 48, 72, 96	1.28, 1.36, 1.63, 2.32, 2.96
	2c	F19113	19	4	partially skimmed	5	0, 24, 48, 72, 96	1.26, 1.31, 1.5, 1.89, 2.48
	3	F199115	20	37	whole	8	0, 2, 4, 6, 8, 10, 12, 24	1, 1.11, 1.9, 2.68, 3.41, 3.98, 4.75, 7.5
	3	F199115	20	22	whole	5	0, 4, 8, 12, 24	1.19, 1.49, 1.95, 2.59, 4.29
	3	F199115	20	10	whole	5	0, 24, 48, 72, 96	0.61, 3.73, 6.07, 7.64, 8.08
	3	F199115	20	4	whole	5	0, 24, 48, 72, 96	0.85, 0.9, 1.11, 1.73, 1.95
	4a	F19111	21	37	whole	8	0, 2, 4, 6, 8, 10, 12, 24	0.76, 0.98, 1.43, 2.42, 2.95, 3.58, 4.33, 7.28
	4a	F19111	21	22	whole	5	0, 4, 8, 12, 24	1.21, 1.32, 1.82, 2.73, 4.75
	4a	F19111	21	10	whole	5	0, 24, 48, 72, 96	1.04, 2.01, 3.08, 3.66, 5.88
	4a	F19111	21	4	whole	5	0, 24, 48, 72, 96	0.89, 1.23, 1.41, 1.63, 2.03
	4b	F5027	22	37	whole	7	0, 4, 6, 8, 10, 12, 24	1.01, 1.48, 2.17, 3.36, 3.92, 4.55, 7.98
	4b	F5027	22	22	whole	5	0, 4, 8, 12, 24	1.23, 1.59, 2.17, 2.81, 4.94
	4b	F5027	22	10	whole	5	0, 24, 48, 72, 96	1.13, 1.91, 3.4, 4.58, 6.15
	4b	F5027	22	4	whole	5	0, 24, 48, 72, 96	1.08, 1.17, 1.47, 1.87, 2.23

where K is a variable depending on the strain and the physiological state of the inoculum and ε_{SM2} the model error. This relationship is based on the assumption that the lag time $\lambda(T)$ is proportional to the generation time $\log(2)/\mu_{max}(T)$ whatever the value of T (Zwietering et al., 1994; Rosso, 1995; Delignette-Muller, 1998) if model error is neglected. The logarithm transformation for K is used to stabilise the variance (Delignette-Muller, 1998).

2.2.2. Bayesian model

n ($n=1, \ldots, 124$) will denote the index of the growth curves of *L. monocytogenes* used. Each curve is obtained from N_n measurements of the growth of a bacterial strain i_n ($i=1,\ldots, 22$) at a constant temperature T_n. The data consist of a set of observations denoted by $Y_n(t)$ [unit: log(cfu ml^{-1})], the logarithm of the bacterial concentration at time t (unit: h) of strain i_n studied at temperature T_n (unit: °C) obtained from the growth curve n.

The model uses the following parameters:

- the logarithm of the maximal achievable concentration in the culture broth y_{max}, which is assumed to be constant for a given culture medium (one parameter);
- the logarithm of the initial bacterial concentration, which is assumed to be defined at the growth curve level (124 parameters). It will be denoted $y_{n,0}$. The order of magnitude of $y_{n,0}$ is defined by the experimenter;
- the optimal growth rate, which is assumed to be strain and medium dependent (Rosso, 1995) (22×1 parameters) and will be denoted $\mu_{opt,i}$;
- the cardinal values, which are assumed to be strain dependent (22 parameters per cardinal value) and will be denoted $T_{min,i}$, $T_{opt,i}$ and $T_{max,i}$ for the

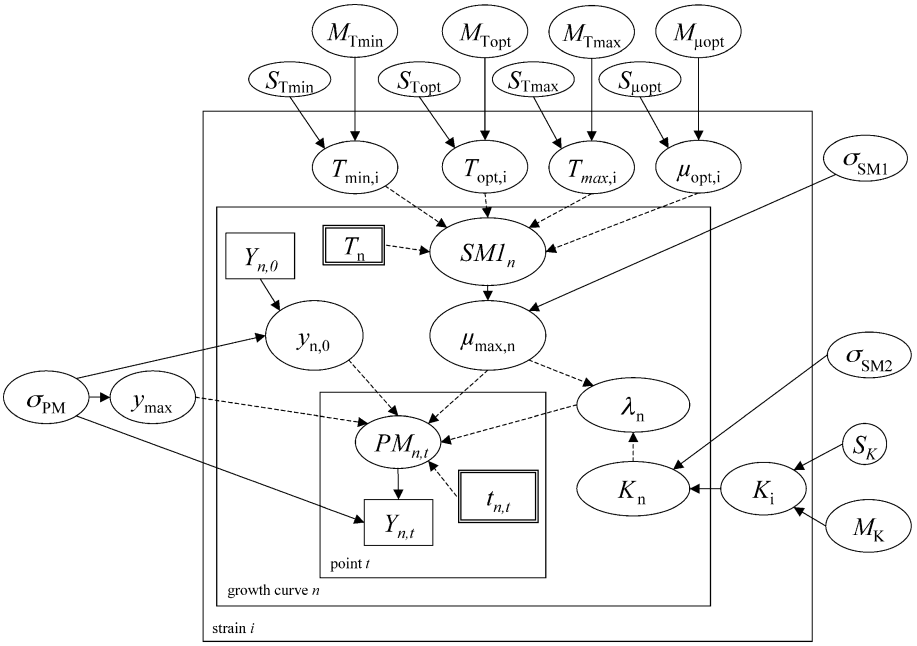

Fig. 1. Directed acyclic graph of the model. All model quantities are presented as nodes. Data ($Y_{n,t}$ and $Y_{n,0}$) are denoted by rectangles; covariates ($t_{n,t}$ and T_n) are denoted by double-rectangles and parameters are denoted by ellipses. Arrows run between nodes from their direct influence ('parents') to the 'descendants,' indicating the conditional independence assumptions of the model: given its parent nodes, each node is independent of all other nodes in the graph except its 'descendants.' Solid arrows indicate stochastic dependences while dashed arrows indicate logical functions. Stochastic and logical links are fully described in Table 2.

minimal, optimal and maximal growth temperatures of strain i, respectively;
- the K value in Eq. (5), which is assumed to be strain and physiological stage dependent. Assuming an identical physiological stage for a 'strain' as defined previously, K is assumed to be strain dependent only (22 parameters) and will be denoted K_i;
- the standard deviation of the error of the primary model (Eq. (1)) denoted σ_{PM} (one parameter);
- the standard deviation of the error of the secondary model for μ_{max} (Eq. (3)) denoted σ_{SM1} (one parameter);
- the standard deviation of the error of the secondary model for λ (Eq. (5)) denoted σ_{SM2} (one parameter).

Moreover, the strain parameters $\mu_{opt,i}$, $T_{min,i}$, $T_{opt,i}$, $T_{max,i}$ and K_i will be assumed to follow parent distributions specified by hyperparameters. $M_{\mu_{opt}}$, $M_{T_{min}}$, $M_{T_{opt}}$, $M_{T_{max}}$ and M_K will denote the expected values of the corresponding distributions, $S_{\mu_{opt}}$, $S_{T_{min}}$, $S_{T_{opt}}$, $S_{T_{max}}$ and S_K the standard deviations of the corresponding distributions. As an example, $\mu_{opt,i}$ is linked to $M_{\mu_{opt}}$ and $S_{\mu_{opt}}$ in this Bayesian model according to $N(M_{\mu_{opt}}, S_{\mu_{opt}})$, $N(a, b)$ being a normal distribution with expected value a and standard deviation b.

The directed acyclic graph (Whitaker, 1990) of this model may be represented as in Fig. 1. By closely observing this figure, it is possible to notice all the conditional independences used in the model easily. As an example, given $M_{T_{opt}}$ and $S_{T_{opt}}$, $T_{opt,i}$ is independent of all the other nodes, except $SM1_n$. Distributions and links between parameters, covariates and variates are expressed in Table 2. Note that parameters $\mu_{opt,i}$ and K_i are constrained to be positive.

2.3. Prior distributions

We chose fairly uninformative prior distributions. Expected values for the prior distribution of $M_{\mu_{opt}}$, $M_{T_{min}}$, $M_{T_{opt}}$, $M_{T_{max}}$ and M_K were the estimates obtained by Augustin and Carlier (2000) from a literature review of all published growth curves of *L. monocytogenes* using standard nonlinear regression. A prior standard deviation of 4 was chosen for $M_{T_{min}}$, a prior standard deviation of $\sqrt{10}$ was chosen for $M_{T_{opt}}$, $M_{T_{max}}$ and M_K and a prior standard deviation of 1 was chosen for $M_{\mu_{opt}}$. These standard deviations allow the prior distributions to vary within a wide range of values. For example, the 95% credible interval, defined as the interval between the 2.5th and the 97.5th percentiles of a given distribution, is $[-10.54\ °C, 5.14\ °C]$ for $M_{T_{min}}$. Other prior credible intervals are given in Table 3. Note that in Bayesian theory, for posterior and prior distributions, we deal with 'credible intervals' which is different from the frequentist (i.e. non-Bayesian) concept of 'confidence intervals' (Press, 1998).

Table 2
Description of the links indicated in Fig. 1

Node	Type	Definition
$Y_{n,t}$	stochastic	$N(PM_{n,t}, \sigma_{PM})$
$PM_{n,t}$	logical	Eq. (2)[a]
y_{max}	stochastic	$N(8.5, \sigma_{PM})$
$y_{n,0}$	stochastic	$N(Y_{n,0}, \sigma_{PM})$
$\mu_{max,n}$	stochastic	$(\mu_{max,n})^{1/2} \sim N(\sqrt{SM1_n}, \sigma_{SM1})$
$SM1_n$	logical	Eq. (4)[b]
λ_n	logical	$K_n/\mu_{max,n}$
K_n	stochastic	$\log(K_n) \sim N(\log(K_i), \sigma_{SM2})$
$\mu_{opt,i}$	stochastic	$NT(M_{\mu_{opt}}, S_{\mu_{opt}})I(0, \infty)$[c]
$T_{min,i}$	stochastic	$N(M_{T_{min}}, S_{T_{min}})$
$T_{opt,i}$	stochastic	$N(M_{T_{opt}}, S_{T_{opt}})$
$T_{max,i}$	stochastic	$N(M_{T_{max}}, S_{T_{max}})$
K_i	stochastic	$N(M_K, S_K)I(0, \infty)$[c]

[a] The node is linked according to the primary model (Eq. (2)).
[b] The node is linked according to the secondary model (Eq. (4)).
[c] $X \sim N(a, b)I(0, \infty)$ denote a quantity X from a normal distribution with expected value a and standard deviation b, where $[0; \infty]$ represents interval censoring (see Spiegelhalter et al., 1996, p.16, for details).

The prior distributions of the standard deviation of the model errors, i.e. σ_{PM}, σ_{SM1} and σ_{SM2}, were chosen according to Spiegelhalter et al. (1996). For precision parameters (the reciprocal of the square of the standard deviation, i.e. σ_{PM}^{-2}, σ_{SM1}^{-2} and σ_{SM2}^{-2}), the authors recommend a $G(10^{-3}, 10^3)$ prior distribution, where $G(a, b)$ is the gamma distribution of shape parameter a and scale parameter b (as parameterised in R software, © The R Core Team, 2001). This very particular distribution reasonably favours high values for the standard deviation (Spiegelhalter et al., 1996).

$S_{\mu_{opt}}$, $S_{T_{min}}$, $S_{T_{opt}}$, $S_{T_{max}}$ and S_K are the standard deviations of random effects in this hierarchical model. When the likelihood function is flat, which

Table 3
Prior distributions used for hyperparameters and parameter y_{max}

Parameter	Distribution	$P_{0.025}$[a]	Median	$P_{0.975}$[b]
$M_{T_{min}}$	$N(-2.7, 4)$	−10.5	−2.70	5.14
$M_{T_{opt}}$	$N(37.0, 3.16)$	29.2	37.0	44.9
$M_{T_{max}}$	$N(45.5, 3.16)$	37.7	45.5	53.3
$M_{\mu_{opt}}$	$N(0.70, 1)$	−1.26	0.70	2.66
M_K	$N(3.09, 3.16)$	−4.75	3.09	10.9
σ_{PM}	$\sigma_{PM}^{-2} \sim G(0.001, 1000)$	13,270	1.4×10^{149}	∞
σ_{SM1}	$\sigma_{SM1}^{-2} \sim G(0.001, 1000)$	13,270	1.4×10^{149}	∞
σ_{SM2}	$\sigma_{SM2}^{-2} \sim G(0.001, 1000)$	13,270	1.4×10^{149}	∞
$S_{T_{min}}$	$S_{T_{min}}^{-2} \sim G(1.68, 2.82)$	0.266	0.510	1.53
$S_{T_{opt}}$	$S_{T_{opt}}^{-2} \sim G(1.68, 2.82)$	0.266	0.510	1.53
$S_{T_{max}}$	$S_{T_{max}}^{-2} \sim G(1.68, 2.82)$	0.266	0.510	1.53
$S_{\mu_{opt}}$	$S_{\mu_{opt}}^{-2} \sim G(3.26, 14.6)$	0.0948	0.153	0.306
S_K	$S_K^{-2} \sim G(3.26, 1.31)$	0.316	0.510	1.02
y_{max}	$N(8.50, \sigma_{PM})$	6.54[c]	8.50	10.5[c]

[a] 2.5th percentile.
[b] 97.5th percentile.
[c] This value is dependent on σ_{PM}; its expected value is presented using $\sigma_{PM} = 1$.

is the case in such predictive microbiology models, some external judgement of plausible values for these dispersion parameters is unavoidable (Spiegelhalter et al., 1996). The purpose is then to use expert knowledge to specify a reasonable prior distribution for these parameters. We adapted a method proposed by Smith et al. (1995) (see Appendix A). Prior distributions finally used are provided Table 3.

2.4. Bayesian inference

The direct calculation of full conditional posterior distributions is most often impossible, especially for models including many parameters. Markov-Chain Monte-Carlo (MCMC) techniques are powerful in such cases: instead of calculating the exact posterior density, these computer-intensive techniques generate chains of simulated values for parameters, with the sampling algorithm converging to the posterior distributions of interest. Gibbs sampling (Gelfand and Smith, 1990), derivative-free adaptative rejection sampling (Gilks, 1992), slice sampling or the Metropolis–Hasting algorithm may be used, alone or combined, for such purposes (Gilks et al., 1996). More details on MCMC techniques can be found in Gilks et al. (1996).

Here, Bayesian inferences were performed using WinBUGS software (© MRC Biostatistics Unit,

Table 4
Descriptive statistics of empirical posterior distributions of hyperparameters and parameter y_{max} and corresponding adjusted distributions

Parameter	Mean	S.D.	$P_{0.025}$[a]	Median	$P_{0.975}$[b]	Adjusted distribution[c]
$M_{T_{min}}$	−2.47	0.69	−3.87	−2.45	−1.19	$N(-2.47, 0.690)$
$M_{T_{opt}}$	37.3	0.56	36.3	37.3	38.5	$LND(2.19, 0.0621, 28.3)$
$M_{T_{max}}$	45.0	0.95	43.3	44.9	47.1	$LND(2.08, 0.117, 36.9)$
$M_{\mu_{opt}}$	0.69	0.05	0.59	0.69	0.79	$GD(601, 0.00199, -0.508)$
M_K	1.36	0.14	1.09	1.36	1.64	$LND(0.981, 0.0534, -1.32)$
σ_{PM}	0.23	0.01	0.22	0.23	0.24	$LN(-1.46, 0.0254)$
σ_{SM1}	0.04	0.00	0.03	0.04	0.05	$G(88.4, 0.000463)$
σ_{SM2}	0.44	0.07	0.32	0.44	0.58	$G(41.2, 0.0107)$
$S_{T_{min}}$	1.26	0.61	0.35	1.21	2.59	$W(2.21, 1.43)$
$S_{T_{opt}}$	0.56	0.25	0.27	0.50	1.21	$LND(-1.02, 0.538, 0.140)$
$S_{T_{max}}$	0.59	0.32	0.26	0.50	1.46	$LND(-1.05, 0.645, 0.164)$
$S_{\mu_{opt}}$	0.18	0.03	0.13	0.18	0.25	$LND(-1.73, 0.160, -9.06 \times 10^{-4})$
S_K	0.40	0.08	0.27	0.39	0.57	$LND(-1.32, 0.269, 0.112)$
y_{max}	7.92	0.02	7.89	7.92	7.96	$BD(8.89, 9.47, 7.84, 8.01)$

[a] 2.5th percentile.
[b] 97.5th percentile.
[c] $N(a, b)$, normal distribution with expected value a and standard deviation b; $X \sim LND(a, b, c)$ if $\ln(X-c) \sim N(a, b)$[1], $X \sim GD(a, b, c)$ if $(X-c) \sim G(a, b)$ where $G(a, b)$ is the gamma distribution with shape parameter a and scale parameter b; $W(a, b)$, Weibull distribution with shape parameter a and scape parameter b; $X \sim BD(a, b, c, d)$ if $(X-c)/(d-c) \sim B(a, b)$ where $B(a, b)$ is the beta distribution with shape parameters a and b. Parameterisation of distributions are those of R software (© The R Core Team, 2001).

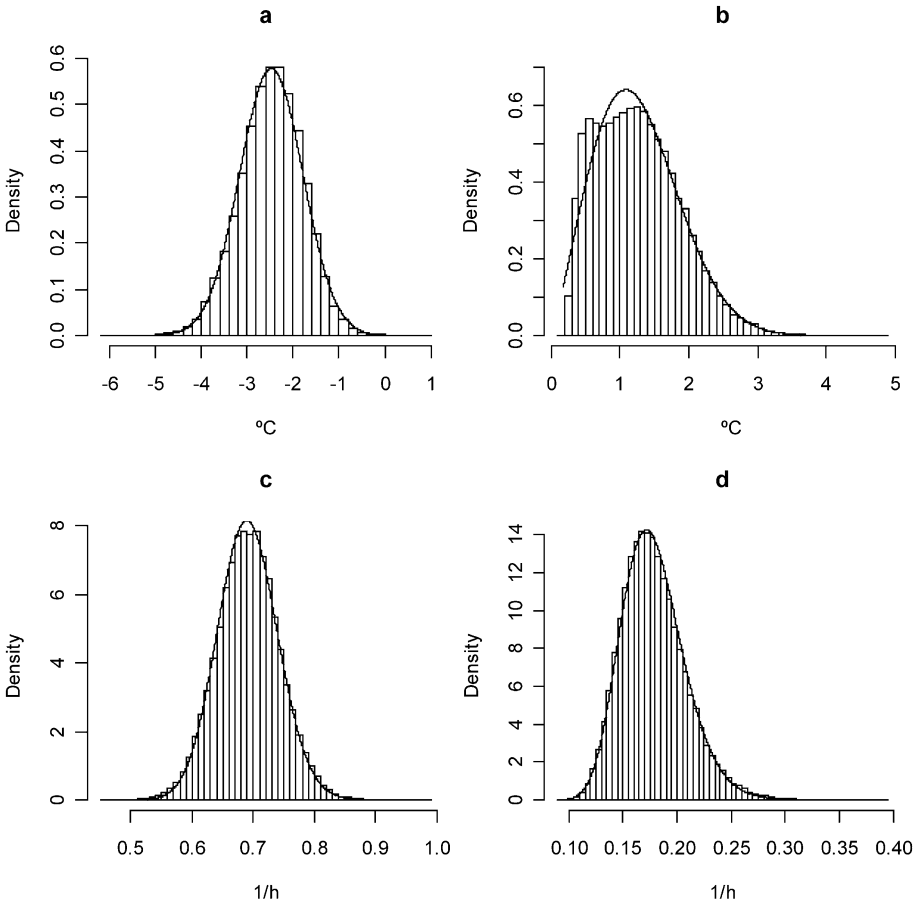

Fig. 2. Empirical posterior densities of parameters $M_{T_{min}}$ (a), $S_{T_{min}}$ (b), $M_{\mu_{opt}}$ (c), $S_{\mu_{opt}}$ (d) and corresponding adjusted distributions.

Spiegelhalter et al., 2000).[1] After an adaptation phase (also called 'burn-in phase', Gilks et al., 1996), of 5×10^4 iterations, the convergence of the MCMC algorithm was checked by visually analysing three independent MCMC chains using three different initial values for parameters S and σ. Gelman and Rubin convergence statistics, as modified by Brooks and Gelman (1998), were also calculated and examined. Inferences were made on the pool of 2×10^4 iterations following the burn-in phase for the three chains, i.e. 6×10^4 iterations.

[1] The WinBUGS code written for this study is available on request from the first author.

2.5. Parameterisation of the empirical posterior distributions

The posterior distributions obtained from MCMC techniques are not parametric. In order to provide practical parametric distributions for risk assessment purposes, standard parametric distributions were fitted to empirical posterior distributions for hyperparameters $M_{\mu_{opt}}$, $M_{T_{min}}$, $M_{T_{opt}}$, $M_{T_{max}}$, M_K, $S_{\mu_{opt}}$, $S_{T_{min}}$, $S_{T_{opt}}$, $S_{T_{max}}$ and S_K and parameter y_{max} using maximum likelihood estimates. The distribution that minimised the Anderson and Darling statistic (1952) was finally chosen (for a more detailed discussion on goodness-of-fit statistics in distribution fitting, see, e.g. Vose, 2000). Further details on

standard parametric distributions tested can be found in Pouillot et al. (2001).

3. Results

Descriptive statistics of empirical posterior distributions are summarised in Table 4. Note that the convergence of MCMC chains appeared to be very slow since about 4×10^4 iterations were needed. Posterior distributions for M_K, $M_{T_{min}}$, $M_{T_{opt}}$, $M_{T_{max}}$, $M_{\mu_{opt}}$ and y_{max} are reasonably symmetric, while those for σ_{PM}, σ_{SM1}, σ_{SM2}, S_K, $S_{T_{min}}$, $S_{T_{opt}}$, $S_{T_{max}}$ and $S_{\mu_{opt}}$ are slightly skewed to the right. Fig. 2 shows the empirical posterior densities for four example parameters: $M_{T_{min}}$, $S_{T_{min}}$, $M_{\mu_{opt}}$ and $S_{\mu_{opt}}$.

Posterior means of T_{min}, T_{opt} and T_{max} (-2.5, 37.3 and 45.0 °C, respectively) are relatively close to their prior expected values (-2.7, 37.0 and 45.5 °C, respectively), while their posterior standard deviation values (0.69, 0.56 and 0.95 °C) are far lower than their prior standard deviation values (4.0, 3.2 and 3.2 °C). Note that prior standard deviations were chosen so as to be high enough to give relatively uninformative priors.

The posterior mean of μ_{opt} (0.69 h^{-1}) is close to its prior expected value (0.70 h^{-1}), but inferences have reduced the standard deviation of this estimate from 1 h^{-1} (uninformative prior) to an estimated value of 0.05 h^{-1} (posterior). The K posterior mean (1.36) is far lower than its prior expected value (3.09); the posterior 95% credible interval for this parameter does not contain the prior expected value. This could reflect incorrect specification of the prior distribution for this parameter.

Variability is quantified by precision parameters $S_{T_{min}}$, $S_{T_{opt}}$, $S_{T_{max}}$, $S_{\mu_{opt}}$ and S_K. The mean of the posterior distribution of $S_{T_{min}}$ (1.26 °C) remains high compared to those of $S_{T_{opt}}$ (0.56 °C) and $S_{T_{max}}$ (0.59 °C), suggesting that the variability of T_{min} is relatively high. Standard deviation of $\mu_{opt,i}$ around $M_{\mu_{opt}}$ was estimated to be 0.18 h^{-1}; standard deviation of K_i around M_K was estimated to be 0.40. Note that the estimated variability around the mean values was comparable to those expected by the expert, except for the median variability around T_{min} for which the estimate is greater (model estimate: 1.21 vs. expert estimate: 0.51), and the median variability around K for which the estimate is smaller (model estimate: 0.39 vs. expert estimate: 0.51).

Rank correlation coefficients between paired parameters are lower than 0.2, except for the pair $M_{T_{min}} - M_{T_{opt}}$ (-0.39) and the pair $M_{T_{min}} - M_{T_{max}}$ (0.36), suggesting a relatively weak dependence between model parameters.

Table 4 provides the parametric distributions fitted to the empirical distributions. All fitted distributions were very close to the empirical distributions, except for $S_{T_{min}}$, for which the posterior distribution was slightly bimodal (see Fig. 2b).

4. Discussion

On the basis of this example, it was highlighted that bacterial growth parameters may be estimated using a complete predictive microbiology model by means of a Bayesian approach. We used data from the literature. In most cases, data were reproduced only by means of diagrams. This approach certainly adds measurement errors, which should be estimated in a specific study. Moreover, data were collected from published growth curves obtained in various laboratories. Using our definition of the 'bacterial strain,' the laboratory, physiological and strain effects are confounded in this study. Due to the data collection (partial information on the exact physiological state of the strain, on the exact nature of the isolate used, on the counting method, . . .), we are able to measure specifically neither interlaboratory variability nor physiological state effects. Part of the uncertainty concerning model parameters and/or the model errors might be due to these superimposed error. Data for estimating strain variability should be obtained by observing a large number of strains, representative of the overall variability in the criteria under study for the genus or species considered, using an optimal experimental design which makes it possible to reduce and estimate any growth variability other than the strain effect. In the absence of such experimental data, and despite the fact that only a few different *L. monocytogenes* strains have been studied in the literature, this kind of meta-analysis is a right way to obtain a better representation of *L. monocytogenes* variability.

The example illustrated in this study uses predictive models from the literature without any a priori

specific knowledge on their ability to fit observed data. The validation of the models used are discussed elsewhere (Rosso et al., 1993, 1995; Augustin and Carlier, 2000). Moreover, the paradigm of the relationship $\lambda(T) \times \mu_{max}(T) = K$, constant for a given strain, has been largely revisited (Buchanan and Klawitter, 1991; Membré et al., 1999; Augustin and Carlier, 2000) and a more complete model should be included for $\lambda(T)$ (McKellar et al., 1997; Bréand et al., 1999; Augustin et al., 2000). Indeed, any other adequate model could be implemented in such a Bayesian procedure. Nevertheless, using the secondary cardinal model of Rosso et al. (1993), the biological interpretation of all model parameters made it possible to specify prior distribution from expert knowledge easily, which is of great interest in such a Bayesian procedure.

Our experience using this model showed that its fairly flat likelihood function does not allow the use of totally uninformative distribution for precision parameters, S, as previously described (Spiegelhalter et al., 1996). Information was thus injected into the model by specifying prior information from expert knowledge on between-strain variability. Other prior distributions were fairly uninformative since prior credible intervals covered a very wide range of values. While no systematic sensitivity analysis was implemented to evaluate the influence of these prior distributions, various assays have been implemented using various prior distributions (results not shown): while convergence was obtained in more or less iterations, all led to similar estimates suggesting the model was relatively robust.

In almost all referenced papers aimed at fitting predictive microbiology models to observed data, a two-stage evaluation is performed: (i) the first stage is to fit a primary growth model to observed experimental data, which derives estimated parameters (generally μ_{max}, λ, y_0 and y_{max}); (ii) the second stage is to independently fit a secondary growth model to these estimated parameters (generally μ_{max} and λ) as a function of controlling factors (temperature, pH, water activity, etc.). These two steps are usually not linked (e.g. Wijtzes et al., 1993; Rosso et al., 1995; George et al., 1996). The consequence is that first stage estimate uncertainty is generally not taken into account: as examples, a lack of fit of the primary model to a given set of data is not considered and parameters estimated from a lot of observed values are generally given the same weight in the second step as parameters estimated from few observed points. This strategy is obviously an approximation and could lead to poor estimates. In this paper, we demonstrate the feasibility of fitting a secondary growth model to observed data in a single step. A few frequentist 'one-step procedures' have been developed in recent years. Bréand et al. (1999) showed an improvement in parameter estimator precision in a single model describing the relationship between regrowth lag time and mild temperature increase for *L. monocytogenes*. Bernaerts et al. (2000) illustrate this kind of direct approach in a dynamic temperature profile for *Escherichia coli K12*. In our approach, this overall fitting can be performed relatively easily since Bayesian models are flexible.

In our example, the agreement between the results and conventional two-stage frequentist models can be checked directly from the deviation between the means of the prior and posterior distributions, since prior distribution means were chosen according to standard two-stage nonlinear regression model results (Augustin and Carlier, 2000) and prior standard deviations were high. Taken as a whole, the results are highly concordant with those obtained by standard nonlinear regression models, except for parameter K whose Bayesian estimate is far lower than previous estimates. A comparable procedure using the same data should be provided to confirm this piece of evidence. The high interstrains variability for parameter T_{min} and parameter K (Augustin and Carlier, 2000) is confirmed. This might be due to the influence of the physiological state of the cell, keeping in mind that strain and physiological state are confounded factors in our study.

In our model, the secondary model parameters are defined at the strain level. No within-strain variability is considered for parameters $\mu_{opt,i}$, $T_{min,i}$, $T_{opt,i}$, $T_{max,i}$ and K_i. Modelled distributions for these parameters reflects uncertainty. In a different approach explicitly modelling within strain variability, a specific study design including appropriate within strain repetitions should be used. The method developed in this paper was designed to separately evaluate growth interstrains variability and uncertainty: the pivot (here we took the expected value) of the posterior distribution of dispersion parameters (estimated by the mean of the posterior distribution of $S_{\mu_{opt}}$, $S_{T_{min}}$, $S_{T_{opt}}$, $S_{T_{max}}$ and

S_K) may be interpreted as being the expected value of the variability in each parameter around the respective modelled hyperparameters M. The posterior density for hyperparameters $M_{\mu_{opt}}$, $M_{T_{min}}$, $M_{T_{opt}}$, $M_{T_{max}}$ and M_K can be interpreted as being the uncertainty concerning the expected growth parameters for all strains. The overall posterior distribution of dispersion parameters may be interpreted as being the uncertainty concerning the variability in each parameter around the modelled hyperparameters. Note that, as for nearly all modelling, the uncertainty is nevertheless evaluated conditionally on the assumed model. The 'model uncertainty' (Vose, 2000) is not dealt in this study.

Assuming model parameter independences, marginal posterior distributions or proposed adjusted marginal distributions can be incorporated in microbial risk assessment models. The modelling of variability amongst strains would be direct. For example, for risk assessment purposes, a $N(\widehat{M}_{T_{min}}, \widehat{S}_{T_{min}})$, i.e. a $N(-2.47,\ 1.26)$, could be used to simulate T_{min} variability, assuming that pivots for T_{min} distribution may be estimated from the mean of their posterior distributions. In order to model parameter variability and uncertainty, a two-step simulation procedure should be used iteratively: in the first step, an $M^*_{T_{min}}$ value and an $S^*_{T_{min}}$ value could be randomly selected from their respective empirical or fitted posterior distributions; in a second step, a $T_{min,\ i}$ value could be simulated using $T_{min,\ i} \sim N(M_{T_{min}},\ S^*_{T_{min}})$. This separation of variability and uncertainty can be used straightforwardly in a 'Monte-Carlo' second-order modelling (Nauta and Dufrenne, 1999; Vose, 2000) (Fig. 3).

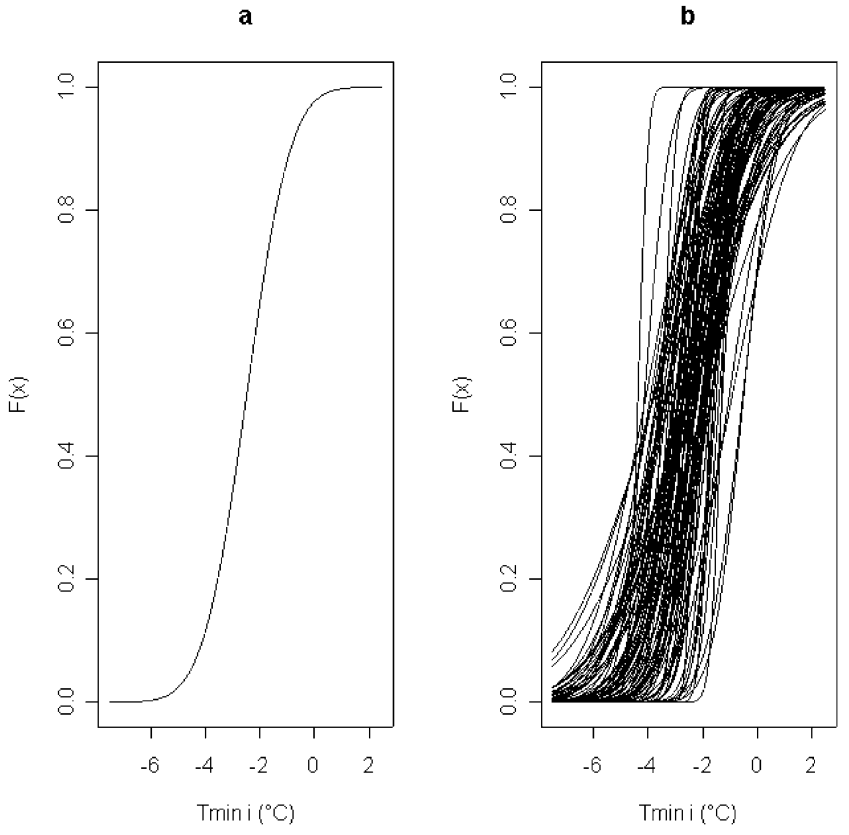

Fig. 3. (a) Modelling of $T_{min,i}$ parameter variability amongst strains expressed by the cumulative density function of $N(-2.47,\ 1.26)$. (b) Modelling of $T_{min,i}$ parameter variability and uncertainty using a second-order simulation: 100 $M^*_{T_{min}}$ values are randomly selected from a $N(-2.47,\ 0.690)$ distribution and 100 $S^*_{T_{min}}$ values are randomly selected from a $W(2.21,\ 1.43)$ distribution. The 100 respective cumulative density function $T_{min,i} \sim N(M^*_{T_{min}}, S^*_{T_{min}})$ are presented.

To our best knowledge, the use of Bayesian statistics for parameter estimation is original in the context of predictive microbiology model. The use of such a method has other advantages, particularly when the estimated parameters ought to be estimated for risk assessment purposes. Firstly, the concept of parameter variability and uncertainty seems natural in the Bayesian approach to parameters as random variables. Secondly, the Bayesian concept makes it possible to use various sources of information available to quantify the state of knowledge: expert information or previous data may be used to define prior distributions, which are then updated with new evidence or new data. This forms an elegant way of combining various sources of information or incorporating new data in a risk assessment study. As an example, the posterior distributions we obtained could be used as prior distributions for a future study. Thirdly, Bayesian statistics make it possible to make inferences on hyperparameters relatively easily, while this would be more difficult in conventional frequentist statistics. Lastly, valid computer programmes for Bayesian inferences have now been implemented and validated.

The Bayesian approach is a valuable tool for evaluating growth parameters using predictive microbiology models for risk assessment purposes. Complementary studies, on a validated set of data, should be implemented in order to confirm the benefits of using such procedures.

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Appendix A. Specification of the prior distribution of standard deviation parameters from external judgement (adapted from Smith et al., 1995)

Let us assume that

$$X \sim N(\mu,\ \sigma), \tag{A.1}$$

where X is a model parameter and μ is the expected value. σ is the standard deviation parameter for which we wish to establish the prior density: it represents the natural variability in X amongst the observations. Smith et al. (1995) recommend the use of a Gamma distribution to model the precision parameter, defined as the reciprocal of the square of the standard deviation. We assume then that the distribution of σ^{-2} is in the following form:

$$\sigma^{-2} \sim G(a,\ b). \tag{A.2}$$

The purpose is to specify a and b from expert knowledge on variability in X. The expert is asked to supply the following two centred intervals: (i) $[\mu - l_1; \mu + l_1]$, his estimation of the "most probable" plausible order of magnitude of X amongst the observations; (ii) $[\mu - l_2;\ \mu + l_2]$, his estimation of the "extreme" order of magnitude of X, meaning that he would be rather surprised to find greater variability in X between observations.

We interpret these estimations as being a prior belief that 95% of subjects have X values within a range of $[\mu - l_1; \mu + l_1]$ when σ_1 is a plausible value of σ, and that 95% of subjects have X values within a range of $[\mu - l_2; \mu + l_2]$ when σ_2 is an extreme value of σ.

According to relationship (A.1), we have $\sigma_1 = l_1/1.96$ and $\sigma_2 = l_2/1.96$, since 1.96 is the 97.5th percentile of the standard normal distribution. We then interpret σ_1, the plausible value of σ, as the 50th percentile of the distribution of σ and σ_2, the extreme value of σ, as the 2.5th percentile of the distribution of σ. Using these two estimates, we specify the parameters a and b using numerical inversion.

Application: French Food Safety Agency (AFSSA) experts on predictive microbiology gave half-ranges $[l_1, l_2]$ of [1, 3] for T_{min}, T_{opt} and T_{max}, producing the estimates $\sigma_1 = 0.51$ and $\sigma_2 = 1.53$. The proposed half-range for μ_{opt} was [0.3, 0.6] ($\sigma_1 = 0.15$ and $\sigma_2 = 0.31$), the one for K was [1, 2] ($\sigma_1 = 0.51$ and $\sigma_2 = 1.02$). This leads to the prior distributions specified in Table 3.

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