DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS
Supplement 2009

Website: www.aimSciences.org

pp. **719–728**

RANDOM COEFFICIENT DIFFERENTIAL EQUATION MODELS FOR MONOD KINETICS

Dan Stanescu

Department of Mathematics
University of Wyoming, Laramie, WY 82071, USA

Benito Chen-Charpentier

Department of Mathematics
University of Wyoming, Laramie, WY 82071, USA

Abstract. In modeling of populations and in many other applications parameters are either measured directly or determined by fitting parameters to a mathematical model. These parameters have variability depending on experimental error, the actual population used and many other factors. In this paper we consider that those parameters are random variables with given distributions. We write and solve random differential equations that model Monod growth kinetics. This type of kinetics is useful, for example, in modeling biofilm growth.

1. **Introduction.** A field of great interest in biology is the study of population growth, in particular of microorganisms such as bacteria. Field observations and laboratory experiments are expensive and very difficult to perform; in the field it is almost impossible to keep the external factors constant and uniform. In the laboratory there is much more control; however, the conditions may still vary in time and also be different from actual situations in the real environments of interest. Moreover, errors in measuring the population sizes occur frequently. Even when measurements are done with the utmost care, the measured values will differ between experiment batches; most times the variability is quite dramatic. This is due to the large sizes and/or variability of the populations, inaccuracies in the methods used to assess them, error (human or otherwise), as well as other unknown factors.

Mathematical models are necessary to be able to study different scenarios, to make predictions and, in general, to supplement the experimental results. These models involve parameters, such as the rate of growth, that are usually determined from the measurements of the population size by some sort of curve fitting. So the end result is that we have parameters that have some variation and therefore, models involving randomness. As previously mentioned, a new way to deal with the variation of the parameters is to consider them to be random variables with a specified, given distribution.

Many models for bacterial growth are given by differential equations. The coefficients of the equations can be deterministic or random. Differential equations with deterministic coefficients have been studied for a long time; their theory and

2000 *Mathematics Subject Classification.* Primary: 60H25, 65C20, 92D25.
Key words and phrases. Monod growth models, random coefficient differential equations.

methods of solution, both analytic and numeric, are well developed. However, in many situations, equations with random coefficients are better suited in describing the real behavior of quantities of interest than their counterpart with deterministic coefficients. Randomness in the coefficients may arise because of errors in the observed or measured data, variability in experiment conditions or uncertainties (variables that cannot be measured, missing data, etc) or lack of knowledge. Differential equations with random coefficients or incorporating stochastic effects have been increasingly used in the last few decades to deal with errors and uncertainty and represent a growing field of great scientific interest, see [11] and [9].

In this paper we'll use polynomial chaos to study the time evolution of a system governed by the Monod kinetic equations [8] under a variety of random inputs.

In this paper we consider Monod's model for bacterial growth. This model was first proposed by Monod [8] and is based on the assumption that the growth rate depends on the amount of available nutrients. The bacteria and nutrients are considered immobile and the parameters of the model are allowed to be random variables. Equations for the time evolution of their polynomial chaos expansion coefficients are obtained and solved numerically. From these coefficients, means, variances and even higher-order statistics can be obtained. The paper is structured as follows. In Section 2, the Monod mathematical model for bacterial growth with fixed parameters is briefly described. The polynomial chaos approach is presented in Section 3; a discussion of the types of chaos considered herein versus the different types of random inputs is undertaken in Section 4. Section 5 is devoted to numerical results. Finally, our conclusions in Section 6 end the paper.

2. **Monod Kinetic Models.**

Monod [8] proposed a model in which the growth rate depends on the amount of necessary nutrients. If the nutrients are present in abundance, the model resembles Malthusian growth [7]; as the amount of nutrients decreases, so does the growth rate. The model is more realistic and consequently more complicated. There are at least two coupled differential equations, one for the population of microorganisms and the other for the amount of nutrients.

Here we consider a Monod-type microbial growth for microorganisms in test tubes, where there is essentially no convection or diffusion of either microbes or nutrients. Both microbes and nutrients are supposed to reside in a liquid phase, usually water. In the case when there is only one necessary nutrient (or equivalently only one nutrient limits the growth), Monod's model is given by:

$$\begin{aligned} \frac{d}{dt}(c_M) &= r_M(c_M, c_N) \quad \text{(microbes)}, \\ \frac{d}{dt}(c_N) &= r_N(c_M, c_N) \quad \text{(nutrients)}. \end{aligned} \tag{1}$$

Here c_i, $i = M, N$, represents the mass concentration of species i per unit volume of the liquid phase; r_i represents the total rate at which species i is produced via reactions and sources. The molecular species present are the microbes, labeled M, and the soluble nutrients, labeled N, Furthermore, we assume that the microbial death rate is proportional to the size of the population. The rate of microbial growth is given by the Monod kinetic reactions:

$$\mu(c_N) = \frac{\mu_{\mathrm{m}} c_N}{K_s + c_N}, \tag{2}$$

where μ_{m} is the maximum specific growth rate and K_s is that value of the concentration of nutrients c_N where the specific growth rate $\mu(c_N)$ has half its maximum value [1].

Invoking all simplifying assumptions to Equations (1) leads to the final form of the governing system of differential equations:

$$\begin{aligned} \frac{dc_M}{dt} &= \frac{\mu_{\mathrm{m}} c_N}{K_s + c_N} c_M - k_r c_M, \\ \frac{dc_N}{dt} &= -\frac{1}{Y} \frac{\mu_{\mathrm{m}} c_N}{K_s + c_N} c_M, \end{aligned} \tag{3}$$

where k_r is the first-order endogenous decay rate, and Y is the yield rate coefficient.

Equations (3) represent a coupled system of nonlinear ordinary differential equations with parameters $\mu_{\mathrm{m}}, K_s, k_r$ and Y; these equations need to be solved numerically even in the case of deterministic parameters. If the parameters are considered random variables the situation obviously becomes more complicated. While in principle all parameters as well as the initial conditions for c_M and c_N may be considered random, in order to make the model more tractable and also simplify the presentation we will consider a three-dimensional random parameter space. Since initial values of the concentrations of microbes and nutrients can usually be measured much more accurately than their values later on, we will consider these initial values to be deterministic. Another reason for considering these values deterministic is that, when performing the necessary curve fitting that establishes the mean values of the parameters based on measurements of the amounts of microbes and nutrients, the initial values are usually not part of the fitting process. Thus, the parameters that are considered random in the sequel are μ_{m}, Y and K_s. An additional simplification is achieved by the assumption that the ratio $\mu_y = -\mu_{\mathrm{m}}/Y$ is another random variable such that μ_y, μ_{m} and K_s are independent. While this assumption is not needed for the numerical solution, it will greatly improve the readability of the governing discrete equations. Furthermore, the endogenous decay rate is set to $k_r = 0$. The motivation for this simplification comes from the fact that the amount of nutrients in a test tube is usually consumed in a much shorter time than is necessary for the natural death of bacteria to contribute any significant changes in the population. The next section presents our approach to the numerical solution of the Monod model with the random coefficients thus identified using polynomial chaos.

3. Random Coefficients and Polynomial Chaos.

Given the stated assumptions, the Monod kinetic model that will be explored in the sequel can be written in the form

$$\begin{aligned} \frac{dc_M}{dt} &= \frac{\mu_{\mathrm{m}} c_N}{K_s + c_N} c_M, \\ \frac{dc_N}{dt} &= \frac{\mu_y c_N}{K_s + c_N} c_M, \end{aligned} \tag{4}$$

with the maximum specific growth rate, the half-growth concentration rate and μ_y random variables. Thus, these parameters are supposed to depend on the outcome ω of an experiment, $\mu_{\mathrm{m}} = \mu_{\mathrm{m}}(\omega)$, $\mu_y = \mu_y(\omega)$ and $K_s = K_s(\omega)$, where ω takes values in the set of all outcomes Ω. The latter is assumed to be properly equipped with a σ-algebra $\mathcal{F}$ and a probability measure P such that the triple $(\Omega, \mathcal{F}, P)$ forms a probability space [10]. The concentrations $c_M(t;\omega)$ and $c_N(t;\omega)$ then become stochastic processes. To develop a general methodology for the numerical solution of the evolution equations (4) as well as for estimating the various moments of

the solution, we follow a Generalized Polynomial Chaos (GPC) approach [4, 5, 13]. In this context, a random quantity $\chi(\omega)$ is projected on the space of polynomial chaoses

$$\chi(\omega) = \chi_0\Gamma_0 + \sum_{i_1=1}^{\infty}\chi_{i_1}\Gamma_1(\xi_{i_1}(\omega)) + \sum_{i_1=1}^{\infty}\sum_{i_2=1}^{i_1}\chi_{i_1 i_2}\Gamma_2(\xi_{i_1}(\omega),\xi_{i_2}(\omega)) + \dots \tag{5}$$

where the Γ_i are successive polynomial chaoses, of increasing degree, in their arguments [12, 6, 4]. This expansion has been shown to converge, for the particular case of Hermite expansion, for second-order random processes [2]. Other orthogonal polynomials and their relationship with various distributions of random variables are discussed in the paper by Xiu and Karniadakis [13].

The polynomial chaoses can be arranged in a sequence $\Phi_i(\boldsymbol{\xi}(\omega))$, such that the expansion of the random variables and stochastic processes appearing in equation (4) takes the form, i.e.:

$$c_M(t;\omega) = \sum_{i=0}^{\infty} c_{Mi}(t)\Phi_i(\boldsymbol{\xi}(\omega)); \quad K_s(\omega) = \sum_{j=0}^{\infty} K_{sj}\Phi_j(\boldsymbol{\xi}(\omega)), \tag{6}$$

where Φ_i are properly chosen polynomial basis functions of the random variable vector $\boldsymbol{\xi}$. The number of variables in $\boldsymbol{\xi}$ represents the dimension of the chaos. We will perform two types of expansions, in terms of Jacobi polynomials and Hermite polynomials (the usual Wiener chaos expansion [12]). They will be applied to the two different types of probability distribution functions that can occur for the parameters, with or without compact support, respectively. In the first case $\boldsymbol{\xi}(\omega)$ is a vector of random variables with beta distribution (the uniformly distributed random variable being a special case corresponding to Legendre polynomials as special case of the Jacobi polynomials); in the second case it is a vector of standard Gaussian random variables. A Galerkin projection using the orthogonality of the basis functions $\langle\Phi_i,\Phi_j\rangle = \delta_{ij}\langle\Phi_i,\Phi_i\rangle$, together with truncation of the polynomial chaos series to a finite number of terms will then lead to a system of ordinary differential equations governing the time evolution of the chaos coefficients of the solutions c_{Mi}, c_{Ni} of the system of differential equations (4).

A proper description of the random parameters in terms of the independent chaos variables in $\boldsymbol{\xi}$ must take into account the correlation between these parameters. Since we assume the three parameters to be independent random variables, each of them will be expanded as a functional of only one separate variable in $\boldsymbol{\xi}$; their random space is one-dimensional. More precisely, writing our expansions for these parameters only up to order one for readability, we will have

$$\begin{aligned} \mu_{\mathrm{m}} &= \bar{\mu}_{\mathrm{m}} + \mu_{\mathrm{m}1}\Gamma_1(\xi_1) + \mu_{\mathrm{m}2}\Gamma_1(\xi_2) + \mu_{\mathrm{m}3}\Gamma_1(\xi_3) \\ \mu_y &= \bar{\mu}_y + \mu_{y1}\Gamma_1(\xi_1) + \mu_{y2}\Gamma_1(\xi_2) + \mu_{y3}\Gamma_1(\xi_3) \\ K_s &= \bar{K}_s + K_{s1}\Gamma_1(\xi_1) + K_{s2}\Gamma_1(\xi_2) + K_{s3}\Gamma_1(\xi_3), \end{aligned} \tag{7}$$

where $\mu_{\mathrm{m}2} = \mu_{\mathrm{m}3} = 0$, $\mu_{y1} = \mu_{y3} = 0$ and $K_{s1} = K_{s2} = 0$ such that the three random parameters are uncorrelated. On the other hand, the expansions for the output stochastic processes c_M and c_N become three-dimensional chaos expansions. For c_M, for example, the expansion will take the form

$$c_M(t;\omega) = \bar{c}_M(t) + c_{M1}(t)\Gamma_1(\xi_1) + c_{M2}(t)\Gamma_1(\xi_2) + c_{M3}(t)\Gamma_1(\xi_3). \tag{8}$$

For all random quantities, the first coefficient in the expansion represents the mean and will be denoted either by subscript zero or by an overbar, i.e. $\bar{c}_M(t) = c_{M0}(t)$.

We are now ready to develop the discrete equations used in the numerical study. The first equation in (4) is first written in the form:

$$(K_s + c_N)\,\frac{dc_M}{dt} = \mu_{\mathrm{m}} c_N c_M.$$

Introducing the polynomial chaos expansions leads to

$$\left(\sum_{k=0}^{P} K_{sk}\Phi_k + \sum_{j=0}^{P} c_{Nj}\Phi_j\right)\sum_{i=0}^{P}\frac{dc_{Mi}}{dt}\Phi_i = \sum_{l=0}^{P}\sum_{j=0}^{P}\sum_{i=0}^{P} c_{Mi}c_{Nj}\mu_{\mathrm{ml}}\Phi_i\Phi_j\Phi_l, \tag{9}$$

where an appropriate ordering of the basis functions Φ_i is used and their dependence on the random variables $\boldsymbol{\xi}$ results from the ordering and is not indicated explicitly. A Galerkin projection on the respective Hilbert space of random variables is obtained by demanding that the residual be orthogonal on the subspace spanned by the basis functions. In particular, taking the inner product of the above equation with basis function Φ_L results in

$$\sum_{i=0}^{P}\sum_{j=0}^{P}(K_{sj} + c_{Nj})\,\langle\Phi_i\Phi_j, \Phi_L\rangle\frac{dc_{Mi}}{dt} = \sum_{i=0}^{P}\sum_{j=0}^{P}\sum_{l=0}^{P} c_{Mi}c_{Nj}\mu_{\mathrm{ml}}\langle\Phi_i\Phi_j\Phi_l, \Phi_L\rangle. \tag{10}$$

This is seen to be a matrix equation for the vector of unknown variables

$$\vec{c}_M = \begin{bmatrix} c_{M0} \\ c_{M1} \\ \cdot \\ \cdot \\ \cdot \\ c_{MP} \end{bmatrix} \tag{11}$$

of the form $Ad(\vec{c}_M)/dt = \vec{b}_M$, where the matrix A and the vector $\vec{b}_M$ are themselves time-dependent. The entry on line L, column i of the matrix A is given by

$$A[L,i] = \sum_{j=0}^{P}(K_{sj} + c_{Nj})\,\langle\Phi_i\Phi_j, \Phi_L\rangle$$

A similar equation $Ad(\vec{c}_N)/dt = \vec{b}_N$, with the same matrix A, is obviously obtained for the c_N part of the solution, with μ_y on the right hand side in place of μ_{m}. Initially these two equations are coupled and thus should be solved together as a system of the form

$$\begin{bmatrix} A & 0 \\ 0 & A \end{bmatrix}\frac{d}{dt}\begin{bmatrix} \vec{c}_M \\ \vec{c}_N \end{bmatrix} = \begin{bmatrix} \vec{b}_M \\ \vec{b}_N \end{bmatrix}. \tag{12}$$

However, upon the use of an explicit Runge-Kutta method and linearization of the coefficient matrix and the right-hand side values (using known values of the coefficients from the previous stage), the system decouples and the matrix can be easily inverted to obtain updated coefficient values.

4. **Random input representation.** In most situations a subset of the random input coefficients of the model must satisfy constraints inherent to the model itself. For example, in the case of the Monod model (4) that we are using, the parameter K_s should be necessarily positive; thus assuming a normal distribution for K_s is not appropriate. It could be argued that μ_{m} should also be positive for growth to occur; however, this parameter may be allowed to have a normal distribution with a

positive mean. In this case the implicit assumption is that the growth conditions are varying to such an extent that population decrease, instead of growth, sometimes occurs, possibly because of other factors not accounted for in the model. The amount of nutrients is expected to decrease continuously, therefore the parameter μ_y should be negative.

If all the input parameters are random variables with the same type of distribution, the polynomial chaos basis is easy to choose. For example, if all the three parameters in the model were assumed to have normal distributions, a Hermite chaos expansion would be a natural choice. On the other hand, if all the three parameters were assumed to have uniform distributions, a Legendre chaos expansion would be preferred. Let us note, however, that even in this case the output distribution is not necessarily best described by these choices of basis functions. Even more importantly, the three parameters will likely have different distributions. Consider for example the perfectly valid case where K_s is assumed to have an uniform distribution, $-\mu_y$ a Gamma distribution, while μ_{m} has a normal distribution, and suppose one chooses to use the Hermite chaos expansion. Then obviously a first step in the solution process is to represent K_s and $-\mu_y$ using a Hermite chaos expansion. Here we describe our methodology for doing so, which is based on mappings from other distributions to the normal. Specifically, if ξ is a standard normal random variable then

$$u(\xi) = a + (b-a)\frac{1+\operatorname{erf}(\xi/\sqrt{2})}{2}$$

has a uniform $U(a,b)$ distribution, and

$$\gamma(\xi) = ab\left(\xi\sqrt{\frac{1}{9a}} + 1 - \frac{1}{9a}\right)^3$$

has a Gamma(a,b) distribution. The Hermite coefficients of a random variable η for which a mapping from the standard normal is known can be readily computed by performing the inner product with Gaussian measure,

$$\eta_i = \frac{1}{\langle \Phi_i^2 \rangle} \langle\, \eta(\xi), \Phi_i(\xi)\, \rangle. \tag{13}$$

For the case of Legendre chaos expansions, the variables ξ are uniformly distributed random variables. The above method in this case can be applied easily if the cumulative distribution function of the variable $\eta(\xi)$ can be inverted (i.e. one uses the inverse transform method [10]) to map the random variable η on the probability space of uniformly distributed random variables. Given the cumulative distribution function $F_\eta(x)$ and ξ uniformly distributed in $(0,1)$, the random variable $F_\eta^{-1}(\xi)$ has the same distribution as η. The inner products of η with the basis functions can then be computed as:

$$\eta_i = \frac{1}{\langle \Phi_i^2 \rangle}\langle \eta, \Phi_i \rangle = \frac{1}{\langle \Phi_i^2 \rangle}\int_0^1 F_\eta^{-1}(\xi)\Phi_i(\xi)d\xi. \tag{14}$$

5. **Numerical Experiments.** Cunningham *et al.* [3] did experiments for biofilm growth and determined a set values for the kinetic parameters. In their paper no endogenous decay rate is used; the Monod kinetics coefficients are taken as $\mu_{\max} = 0.05\mathrm{s}^{-1}$, $K_s = 0.32\mathrm{mg/ml}$, and $Y = 0.16$. The bacterial species used is *Pseudomonas aeruginosa*. Initial values of the concentrations are $c_M(t=0) =$

0.043μg/ml and $c_N(t=0) = 0.4\mu$g/ml. To model the same system with our approach we take μ_y to have a mean value of $-\mu_{\max}/Y = -0.3125\text{s}^{-1}$ and investigate the effect of randomness in the coefficients by considering a set of two cases:

- **Case 1.** All three parameters have uniform distributions: $K_s \sim U(0.28, 0.36)$, $\mu_{\max} \sim U(0.04, 0.06)$, $\mu_y \sim U(-0.325, -0.3)$. Legendre chaos expansion used.
- **Case 2.** $K_s \sim \text{Gamma}(3.2, 0.1)$, leading to the same mean as in the above cases but a larger variance of $\text{Var}[K_s] = 0.032$. The other two parameters have Gaussian distributions with the same means and variances as in case 1. Hermite chaos expansion used.

In the two cases the chaos dimension is three; the polynomial chaos order has also been set to three. Figure 1 shows the results obtained by Legendre chaos for the case of uniform distributions. In this and the next figure, we also plot the standard deviation interval, i.e. plot the curves $c_M - \sqrt{\text{Var}[c_M]}$ and similarly for c_N. The value of the variance can be computed from the coefficients in the expansion. For c_M, for example, the variance is

$$\text{Var}[c_M(t)] = \sum_{i=1}^{P} c_{Mi}^2(t) * \text{Var}[\Phi_i]. \tag{15}$$

The introduction of the Gamma distribution and the larger variance causes the results for Case 2, Figure 2, to be considerably different from the first case. We want to mention that, although the time integration was performed for a relatively long time, no stability problems have been noticed. We plan to investigate the impact of using different chaos orders (i.e. the convergence of the expansion) in future work.

6. **Conclusions.** There are many models for microbial growth. The Monod model is a simple one that incorporates the amount of available nutrients into the growth rate, thus limiting the amount of growth. It is more realistic than exponential or logistic growth model but also more complicated. Real data is hard to obtain and has large variability. The scattering of data is due to changes in populations, experimental conditions and to errors and other uncertainties. Incorporating randomness in the population model is a natural alternative to deterministic models to account for the variability. In this paper, we have modified Monod's model to take into account the randomness in the coefficients. The system of two random coefficient differential equations in time was solved approximately by using the method of polynomial chaos. Several different hypotheses on the distribution functions of the random coefficients were used to show the power of the method and the differences in the results for different assumptions in the probability distribution functions of the random coefficients.

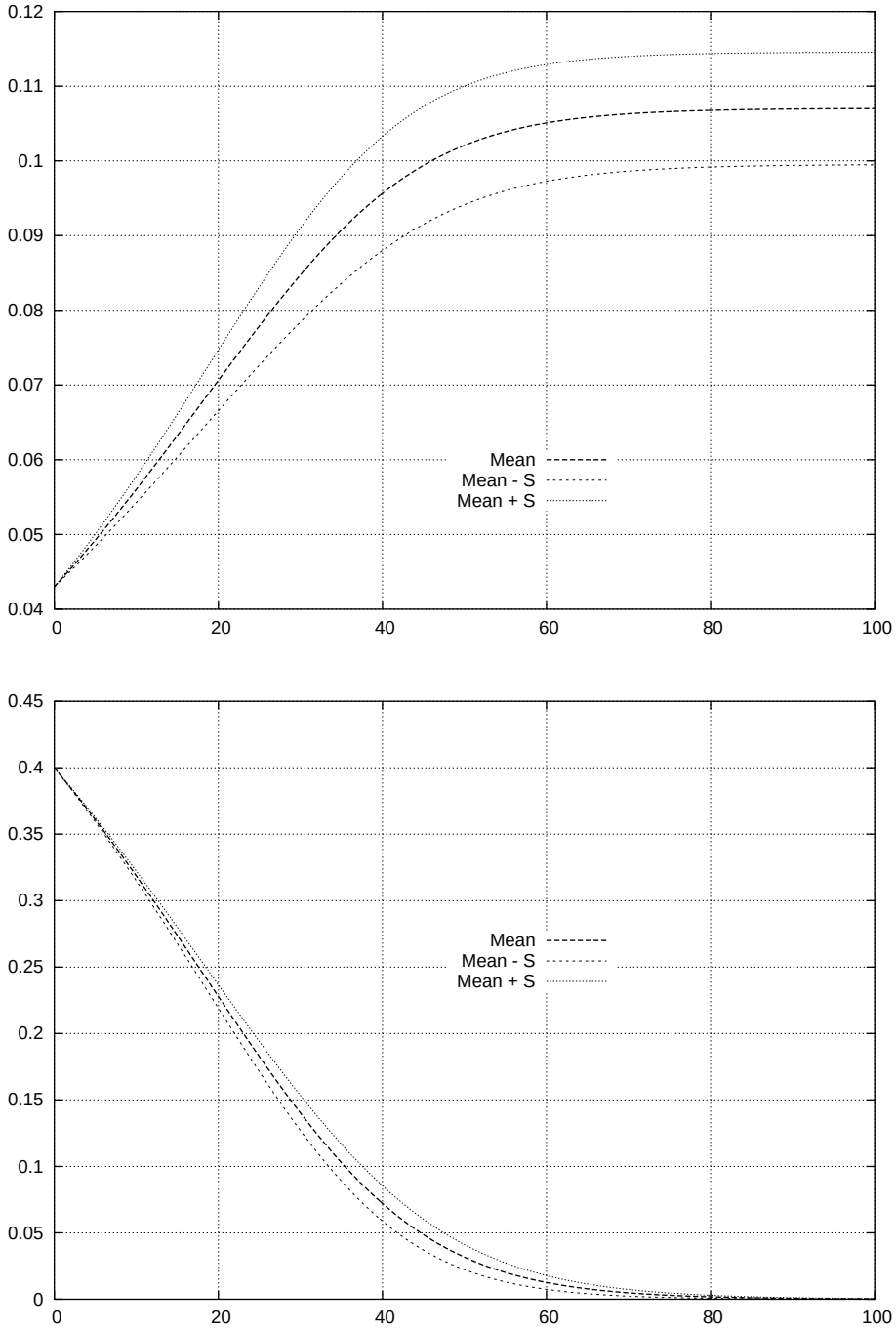

FIGURE 1. Results for the mean concentrations and their variance for Case 1. Top figure: c_M. Bottom figure: c_N.

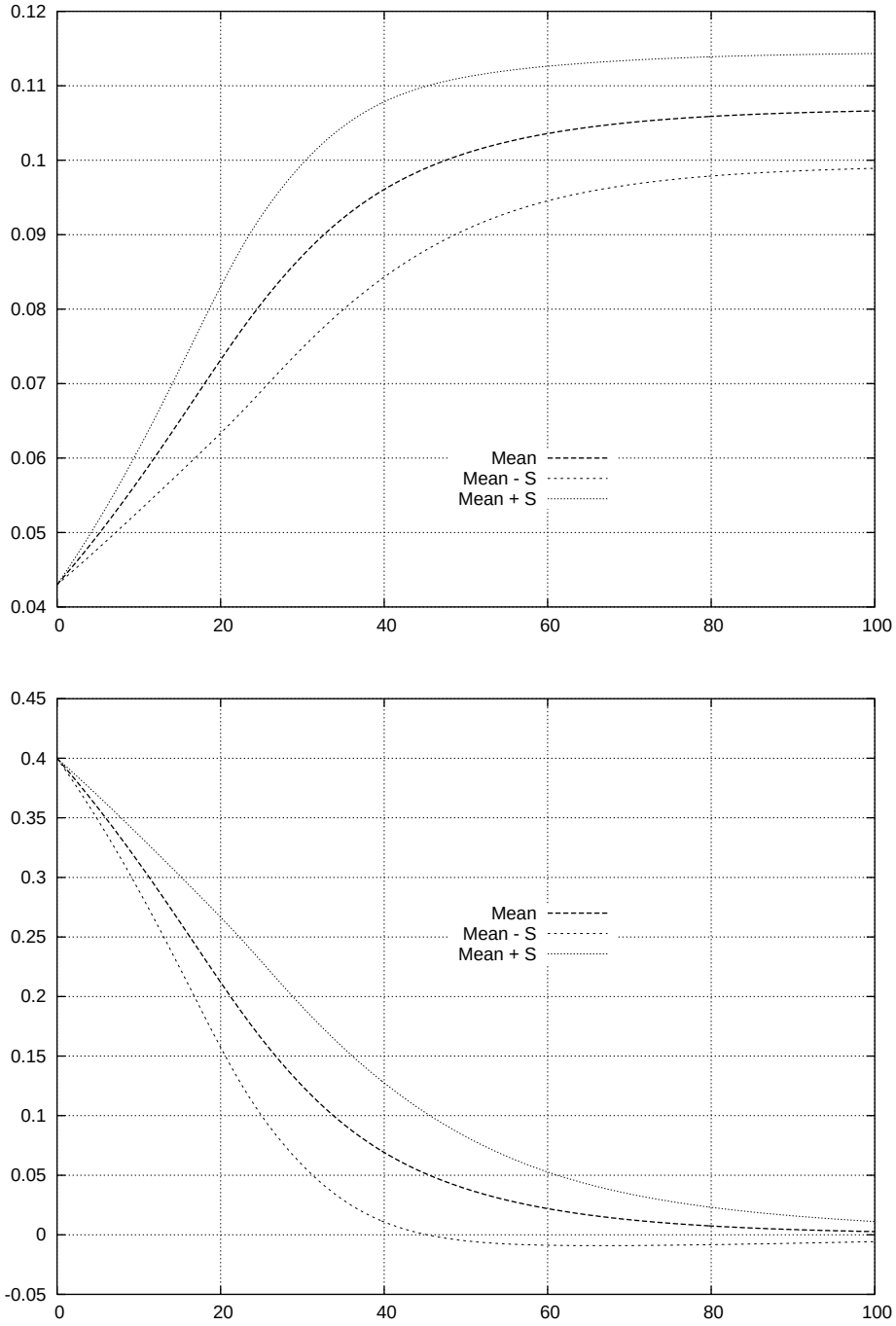

FIGURE 2. Results for the mean concentrations and their variance for Case 3. Top figure: c_M. Bottom figure: c_N.

REFERENCES

[1] J. E. Bailey and D.F. Ollis "Biochemical Engineering Fundamentals," McGraw-Hill, New York, NY, 1986.
[2] R. Cameron, and W. Martin, *The orthogonal development of nonlinear functionals in series of Fourier-Hermite functionals*, Ann. Math., **48** (1947), 385–392.
[3] A. B. Cunningham, W.G. Characklis, F. Abedeen and D. Crawford, *Influence of the biofilm accumulation on porous media hydrodynamics*. Environ. Sci. Technol. **25** (1991), 1305–1311.
[4] R. Ghanem and P. D. Spanos, "Stochastic Finite Elements: A Spectral Approach," Dover Publications, Mineola, NJ, 1991.
[5] R. W. Walters and L. Huyse, "Uncertainty Quantification for Fluid Mechanics with Applications," ICASE Report No. 2002-1, NASA Langley Research Center, Hampton Va 2002.
[6] G. Kallianpur, "Stochastic Filtering Theory," Springer, Berlin, 1980.
[7] T. R. Malthus, "An Essay on the Principal of Population", Oxford World's Classics Paperbacks, Oxford University Press, Oxford, 1999.
[8] J. Monod, *The growth of bacterial cultures*, Annu. Rev. Microbiol. **3** (1949), 371-394.
[9] B. Oksendal, "Stochastic Differential Equations", Sixth Edition, Springer-Verlag, Heidelberg, 2003.
[10] S. Ross, "A First Course in Probability," Prentice Hall, New Jersey, 2002.
[11] T. Soong, "Probabilistic Modeling and Analysis in Science and Engineering," Wiley, New York, 1992.
[12] N. Wiener, *The homogeneous chaos*, Am. J. Math., **60** (1938), 897–936.
[13] D. Xiu, and G. E. Karniadakis, *The Wiener-Askey polynomial chaos for stochastic differential equations*, SIAM J. Sci. Comput. **24** (2002), 619–664.

Received June 2008; revised February 2009.

E-mail address: stanescu@uwyo.edu
E-mail address: bchen@uwyo.edu