Fitting dynamic growth models of biological phenomena from sample observations through Gaussian diffusion processes

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Abstract

This paper addresses the building of stochastic models that adequately describe dynamic phenomena and, in particular, those that occur in the Biosciences. In this context, the empirical fitting of a Gaussian diffusion process from sample data of a dynamic growth phenomenon is considered. In order to do this, a methodology based on approximations to its mean and variance functions is presented. Finally, several applications based on simulated and real data have been carried out.

Key words: Dynamic systems, Stochastic modeling, Diffusion process, Gaussian diffusion process.

This paper is dedicated to the memory of Professor Luigi M. Ricciardi.

1 Introduction

One of the main goals of research in several fields of scientific knowledge is establishing models to explain the dynamic phenomena under study. Such models are often determined from theoretical considerations, by assuming hypotheses which allow for the development of manageable models suitable for applying them to real-life situations.

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Dealing with real phenomena usually involves random influences affecting the system under consideration, and several stochastic models have been devised to deal with this randomness. Of the variety of existing models, diffusion stochastic processes related to certain growth curves have been applied to a wide range of fields and particularly to the Biosciences. For example, in relation with the exponential curve, the lognormal diffusion process has been applied to the study of population growth (see Capocelli and Ricciardi, 1974a and Ricciardi, 1979); in relation with the logistic curve, Capocelli and Ricciardi (1974) introduced a logistic diffusion process that has beeen subsequently used in Biology. More recently, Román-Román and Torres-Ruiz (2012) have introduced a new diffusion process for modeling logistic-type behaviour patterns and applied it to the growth of a microorganic culture. On the matter of the Gompertz curve, Ricciardi et al. (1983) used a homogeneous Gompertz diffusion process to model population growth and neuronal activity, whereas Gutiérrez et al. (2007) introduced a Gompertz-type diffusion process and applied it to the growth of rabbits. Regarding the Bertalanffy curve, the diffusion process studied by Román-Román et al. (2010) was applied to studying the growth of fish.

Models need to be fitted to real observations of the phenomenon, and procedures must be put in place so that this fitting serves as a basis for further study. In addition, this approach usually allows to develop simulation procedures that are very useful in the first stages of new research initiatives.

In the applications mentioned before, the choice of a particular model was made taking into account that the trend of the diffusion process must fit the observed trend. This requires identifying the trend of the dynamic growth phenomenon with that of a known growth curve. Unfortunately, this is not possible in every case and, even when it is, there could be more than one applicable stochastic process. In fact, the development of these processes is based on the introduction of a noise term in the ordinary differential equation of the corresponding deterministic model. This results in a stochastic differential equation. Such process leads to an infinitesimal variance of the process proportional to the square of the variable under analysis (that is, of the type $\sigma^2 x^2$), which may not fit the available data.

In that case, despite the fact that such models are especially useful to make predictions from the estimated mean function of the process, results might not be good when other characteristics of interest are under analysis, such as the first-passage time (where the variability of sample paths may be of paramount importance).

For the previous reasons, it becomes necessary to build stochastic models using all observed information to determine, in the most approximate way, the form of the infinitesimal moments that define the diffusion.

The aim of the present paper is to build a Gaussian diffusion process from the observations in several instants of the dynamic phenomenon under study. Such process must adequately fit the sample mean and variance. Explicit knowledge of such model would enable solving problems related with fitting, forecasting and first-passage times, among others.

In Section 2 the stochastic model is considered, and its main relevant characteristics are described. The methodology for building the model based on approaches of its mean and variance functions is presented in Section 3. Finally, in Section 4 two applications are performed: to the growth of some microorganic cultures (based on simulated data), and to the growth of rabbits (based on real data).

2 The model

The dynamic model that we will consider is defined by the following stochastic differential equation

$$dX(t) = A(t)X(t)\,dt + B(t)\,dW(t), \tag{1}$$

where A and B are continuous functions defined on an interval $[t_0, T]$, with $B(t) > 0$, $t_0, T \in \mathbb{R}^+$, $W(t)$ the standard Wiener process, and initial condition $X(t_0) = x_0 \in \mathbb{R}^+$ (in the sense of $P[X(t_0) = x_0] = 1$) or $X(t_0) \sim N(\mu_0, \sigma_0^2)$.

The solution of (1)

$$X(t) = exp\left(\int_{t_0}^{t} A(s)\,ds\right)\left(X(t_0) + \int_{t_0}^{t} B(s)\,\exp\left(-\int_{t_0}^{s} A(u)\,du\right)\,dW(s)\right) \tag{2}$$

is a Gaussian diffusion process $\{X(t);\ t_0 \leq t \leq T\}$ characterized by infinitesimal moments

$$\begin{aligned} A_1(x,t) &= A(t)x \\ A_2(t) &= B^2(t). \end{aligned} \tag{3}$$

Note that the case of a degenerate initial distribution corresponds to the situation in which all the sample paths of the process start from the same value x_0.

2.1 Some interesting characteristics

In order to fit the model to the data we must focus on two key functions: the mean and the variance functions of the process. Moreover, obtaining the covariance function is necessary for the expression of the finite dimensional distributions of the process and, from these, of its transition probability density.

The mean function of the process (2), $m(t) = E[X(t)]$, verifies the ordinary differential equation

$$\frac{dm(t)}{dt} - A(t)m(t) = 0, \tag{4}$$

with initial condition $m(t_0) = E[X(t_0)]$ and, therefore, has the following expression

$$m(t) = E[X(t_0)]\, e^{\int_{t_0}^{t} A(s)\, ds}. \tag{5}$$

The variance function, $\sigma^2(t) = Var[X(t)]$, verifies the ordinary differential equation

$$\frac{d\sigma^2(t)}{dt} - 2A(t)\sigma^2(t) = B^2(t), \tag{6}$$

with initial condition $\sigma^2(t_0) = Var[X(t_0)]$ and, therefore, has the following expression

$$\sigma^2(t) = e^{2\int_{t_0}^{t} A(s)\, ds} \left(Var[X(t_0)] + \int_{t_0}^{t} B^2(s)\, \mathrm{e}^{-2\int_{t_0}^{s} A(u)\, du}\, ds \right). \tag{7}$$

For any values of $s, t \in [t_0, T]$, the covariance function is given by

$$C(s,t) = e^{\int_{t_0}^{s} A(u)\, du + \int_{t_0}^{t} A(u)\, du} \left(Var[X(t_0)] + \int_{t_0}^{s\wedge t} B^2(u)\, \mathrm{e}^{-2\int_{t_0}^{u} A(r)\, dr}\, du \right), \tag{8}$$

where $s \wedge t = min(s,t)$.

Moreover, since the process is Gaussian, given n time instants, $t_1, t_2, \ldots, t_n$, the vector $(X(t_1), X(t_2), \ldots, X(t_n))'$ has a normal multivariate distribution

$$N_n\left[\begin{pmatrix} m(t_1) \\ \vdots \\ m(t_n) \end{pmatrix}, \begin{pmatrix} C(t_1,t_1) & \ldots & C(t_1,t_n) \\ \vdots & \ddots & \vdots \\ C(t_n,t_1) & \ldots & C(t_n,t_n) \end{pmatrix}\right].$$

Finally, from the unidimensional and bidimensional marginal distributions, the transition density function can be obtained

$$f(x,t|y,\tau) = \left(2\pi\, e^{2\int_{t_0}^{t} A(\theta)\,d\theta} \int_{\tau}^{t} e^{-2\int_{t_0}^{u} A(\theta)\,d\theta} B^2(u)\,du\right)^{-\frac{1}{2}} \times$$
$$exp\left(-\frac{\left(x - ye^{\int_{\tau}^{t} A(\theta)\,d\theta}\right)^2}{2e^{2\int_{t_0}^{t} A(\theta)\,d\theta} \int_{\tau}^{t} e^{-2\int_{t_0}^{u} A(\theta)\,d\theta} B^2(u)\,du}\right), \quad \tau < t.$$

3 Methodology and fitting

3.1 The problem

Let us suppose that we have data representing the evolution of a dynamic phenomenon, that is, the evolution in time of a characteristic of interest (it could be the weight of an animal, the volume of a tumor, the number of tumor cells, etc) for a sample of individuals in a population. Concretely, let $x_{ij},\ i = 1,\ldots,d,\ j = 1,\ldots,n$, be the observed values of the characteristic under study in time instants $t_1,\ldots,t_n$, for d specific individuals.

Our problem is how to build a Gaussian diffusion process to explain a phenomenon under study from the information provided by the data sample without resorting to a predetermined model or making overly restrictive assumptions about the model.

Since a diffusion process is completely characterized by its infinitesimal moments and initial distribution, we will focus on the description of the obtention of functions A and B in (3). Obviously, the initial distribution is determined by the initial data of the sample paths available.

3.2 Aproximation of the function A

From (4) the function A can be expressed in terms of the mean function as

$$A(t) = \frac{m'(t)}{m(t)}, \tag{9}$$

and therefore it is required that function m is differentiable.

In order to calculate function A we must find a differentiable approximation to the mean function of the process. In order to find such approximation several choices are available:

- Selecting, if it exists, a known growth curve or, more generally, a ρ-parametric function

  $$m_\rho : [t_0, T] \longrightarrow \mathbb{R},$$

  that adequately describes the growth pattern of the phenomenon under study. Some examples are: the exponential curve for rapid boundless growth, and the logistic, Gompertz or Bertalanffy curves for growth patterns that are sigmoidal, bounded and with an inflection point.
  Parameter ρ (which can be uni- or multidimensional) of the selected function can be estimated, for instance, through least squares regression from the available sample paths, resulting in an approximation $m_{\widehat{\rho}}(t)$.
- From the mean sample path

  $$m_j = \frac{\sum_{i=1}^{d} x_{ij}}{d}, j = 1, \ldots, n, \tag{10}$$

  finding and approximation, $m_*(t)$, of function $m(t)$ through interpolation.

From the resulting approximation, the approximation to function $A(t)$ can be found through

$$A_*(t) = \frac{m'_{\widehat{\rho}}(t)}{m_{\widehat{\rho}}(t)}, \tag{11}$$

in the first case or

$$A_*(t) = \frac{m'_*(t)}{m_*(t)},$$

in the second case.

3.3 Approximation of the function B

Once we have an approximation of the function A (and included in (6)), in order to find the function B we must calculate a differentiable approximation to the variance function of the process. To this end, it seems logical that we should use the information provided by the sample variance [1] throughout the observed time instants, i.e.,

$$v_j = \frac{\sum_{i=1}^{d}(x_{ij} - m_j)^2}{d}, j = 1, \ldots, n. \tag{12}$$

However, unlike the smooth behavior often showed by the mean of sample paths, sample variance may exhibit a high degree of fluctuation, thus conditioning the choice for the approximation procedure of $\sigma^2(t)$. In fact, choosing to approximate $\sigma^2_*(t)$ for function $\sigma^2(t)$ through interpolation techniques from values (12) may lead to inadequate results if the sample variability is high. This is because the interpolation procedure must yield a differentiable function, which may clash with finding an optimal approximation due to the nature of the data.

For the previous reasons, we recommend selecting a known θ-parametric function

$$s_\theta : [t_0, T] \longrightarrow \mathbb{R}^+,$$

differentiable in $[t_0, T]$, and whose functional form is suggested by the data. As in the case of the mean function, the parameters of the selected function must be estimated in order to find an approximation $s_{\widehat{\theta}}(t)$.

Given that the approximation of the function B will be obtained from

$$B_*(t) = \sqrt{s'_{\widehat{\theta}}(t) - 2A_*(t)s_{\widehat{\theta}}(t)}, \tag{13}$$

the selected function must also verify that

$$s'_{\widehat{\theta}}(t) > 2A_*(t)s_{\widehat{\theta}}(t). \tag{14}$$

This condition may restrict the application of the proposed methodology to the type of data available. In fact, the condition described above may restrict the choice of the type of function s_θ (for example, in the case of a process with

[1] Note that, for this case more than one sample path is required, whereas calculating m_j in (10) would only require one.

positive trend, this function must be increasing) or the range of variation of the parameters involved. In the applications of Section 4 we will address this problem for cases in which the condition is not met in some subinterval of the time interval. We propose a modification for the obtention of B_* from the function s_θ (after fitting it to the data based only on the shape suggested for the sample variability of each case).

Finally, if we are to consider preset parametric functions for the mean and the variance function, or only for the variance function, we must address the maximum likelihood estimation of the parameters of the resulting process. In order to do this, the likelihood function

$$\mathbb{L}(\rho,\theta)=\prod_{i=1}^{d}\prod_{j=2}^{n} f(x_{ij},t_{ij}|x_{ij-1},t_{ij-1})$$

must be found. After some algebra, we have

$$\begin{aligned}\mathbb{L}(\rho,\theta)=&\prod_{i=1}^{d}\prod_{j=2}^{n}\left(2\pi\left(s_{\widehat{\theta}}(t_{ij})-\frac{m_{\widehat{\rho}}(t_{ij})}{m_{\widehat{\rho}}(t_{ij-1})}s_{\widehat{\theta}}(t_{ij-1})\right)\right)^{-\frac{1}{2}}\\ &\times exp\left(-\frac{\left(x_{ij}-x_{ij-1}\frac{m_{\widehat{\rho}}(t_{ij})}{m_{\widehat{\rho}}(t_{ij-1})}\right)^2}{2\left(s_{\widehat{\theta}}(t_{ij})-\frac{m_{\widehat{\rho}}(t_{ij})}{m_{\widehat{\rho}}(t_{ij-1})}s_{\widehat{\theta}}(t_{ij-1})\right)}\right).\end{aligned}$$

Note that this procedure is not advisable, as it adds, to the restrictive hypothesis of preset functions for its mean and variance, that its application can become overly difficult due to the number of parameters involved and the complexity of the equation system to be solved.

4 Applications

In this section two applications are performed: one to the growth of some microorganic cultures (based on simulated data), and another to the growth of rabbits (based on real data). In the first application, the validity of the model is proven, and in the second one we show the improvement provided by fitting the process through our model.

4.1 Application 1: Growth of microorganic cultures

The data considered for this application are originated in a simulation of the logistic process proposed by Román-Román et al. (2012) for the study of the growth of microorganic cultures (measured in density, or number of individuals per millilitre) by considering that the intrinsic growth rate is 0.25 per day and the equilibrium density is 1000 individuals per mililitre. We consider a total of 50 containers (that is, 50 sample paths), in which cultures are placed at the beginning of the study ($t_0 = 0$) with a density of five individuals per mililitre (i.e. a degenerate distribution on $x_0 = 5$ for $t_0 = 0$).

The graphics on Figure 1 show the simulated sample paths and their observed mean and variance for a choice of $\sigma = 0.01$

The observed mean suggests that we must consider a logistic function as the best candidate to approximate the mean function of the process. Therefore, we propose

$$m_{k,b,c}(t) = \frac{k}{1 + b\, e^{-ct}}$$

and the least square estimation of its parameters from the simulated sample paths leads to

$$\widehat{k} = 981.5475, \quad \widehat{b} = 195.3095, \quad \widehat{c} = 0.2506.$$

Figure 2 shows the observed mean together with the mean function of the Gaussian process.

Using (11), we find

$$\widehat{A}(t) = \frac{\widehat{b}\widehat{c}}{e^{\widehat{c}t} + \widehat{b}}.$$

For the approximation of $\sigma^2(t)$, $s_{\widehat{\theta}}(t)$, we have considered the type-exponential function

$$s_\theta(t) = exp\left(\sum_{i=1}^{3} \theta_i t^i\right) - exp\left(\sum_{i=1}^{3} \theta_i t_0^i\right)$$

and the least square estimation of its parameters from the simulated sample

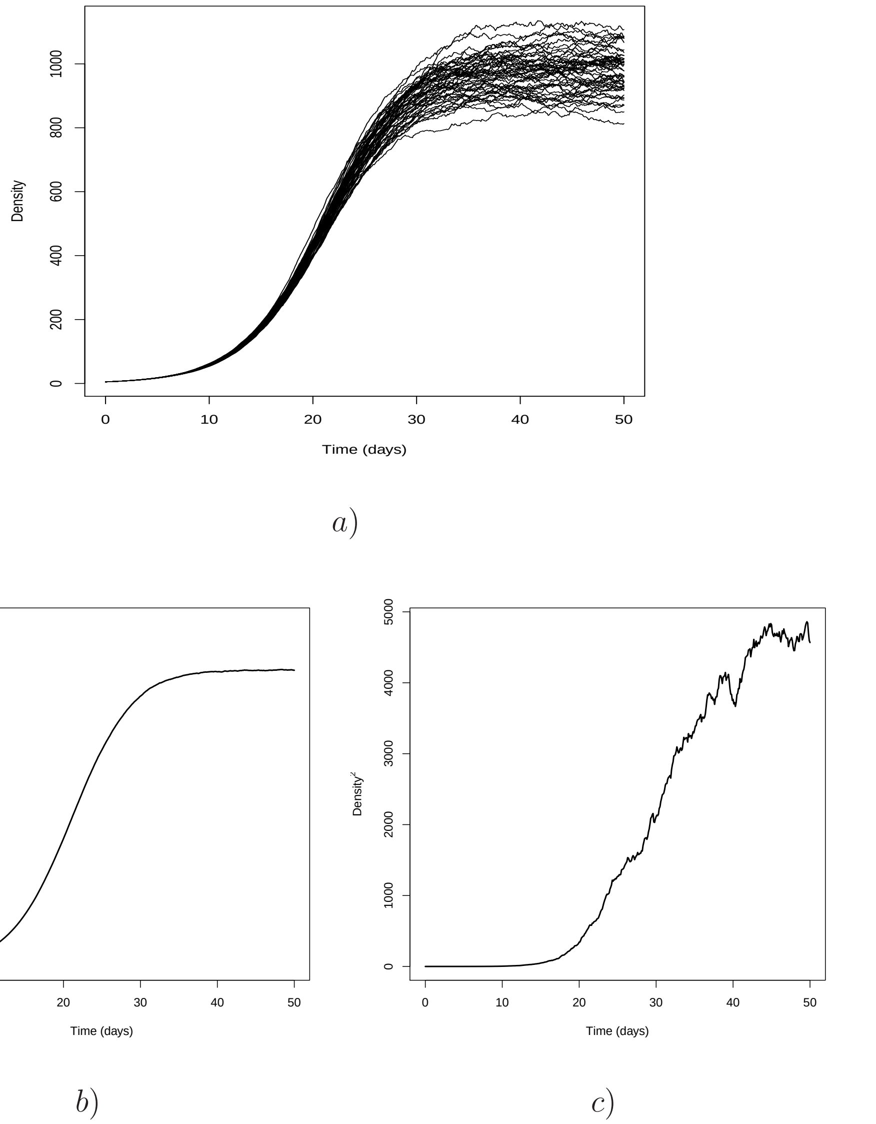

Figure 1. For the logistic process in application 1: Simulated sample paths (a), observed mean function (b) and observed variance function (c).

paths leads to

$$\widehat{\theta_1} = 0.4477, \quad \widehat{\theta_2} = -0.0076, \quad \widehat{\theta_3} = 3.9924 \times 10^{-5}.$$

At this point, we must check that the condition (14) is verified. Figure 3 shows the function $s_{\widehat{\theta}}(t) - 2A_*(t)s_{\widehat{\theta}}(t)$ in the interval $[t_0, T]$.

As it can be observed, condition (14) is not verified in some parts of the interval, and therefore function B_* can not be directly found from (13). A

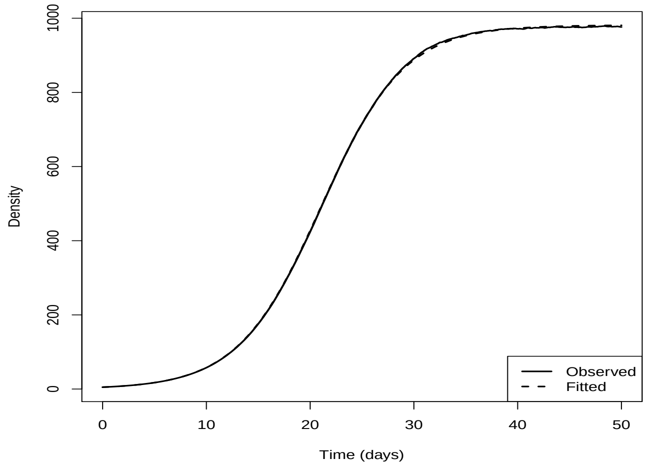

Figure 2. Observed and fitted mean functions for application 1.

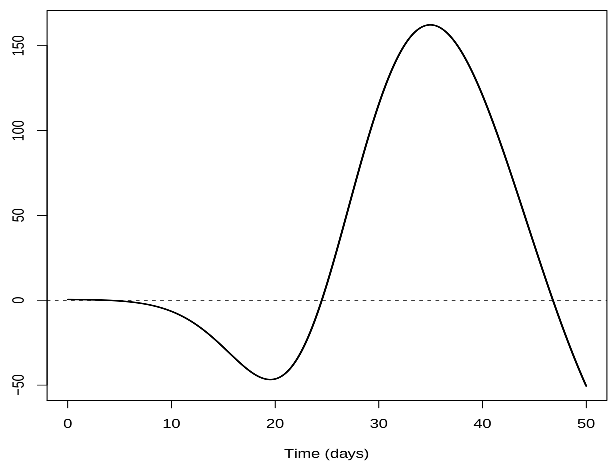

Figure 3. $s'_{\widehat{\theta}}(t) - 2A_*(t)s_{\widehat{\theta}}(t)$ in the interval $[t_0, T]$ for the application 1.

preliminary suggestyion to deal with this is to consider

$$B^2_{**}(t) = |s'_{\widehat{\theta}}(t) - 2A_*(t)s_{\widehat{\theta}}(t)|. \tag{15}$$

This would, however, cause an increase in the variance of the Gaussian process, since the variance function can be expressed, from (7), as

$$\sigma^2(t) = m^2(t)\left(\frac{Var[X(t_0)]}{(E[X(t_0)])^2} + \int_{t_0}^{t} \frac{B^2(s)}{m^2(s)}\, ds\right),$$

and

$$\int_{t_0}^{t} \frac{B_{**}^2(s)}{m_*^2(s)}\, ds \geq \int_{t_0}^{t} \frac{B_*^2(s)}{m_*^2(s)}\, ds.$$

Such increase can be quantified as

$$\frac{\displaystyle\int_{t_0}^{T} \frac{|s'_{\widehat{\theta}}(u) - 2A_*(u)s_{\widehat{\theta}}(u)|}{m_*^2(u)}\, du}{\displaystyle\int_{t_0}^{T} \frac{s'_{\widehat{\theta}}(u) - 2A_*(u)s_{\widehat{\theta}}(u)}{m_*^2(u)}\, du}$$

so that a constant may be defined to compensate for the increase:

$$\Delta = \sqrt{\left(\int_{t_0}^{T} \frac{s'_{\widehat{\theta}}(u) - 2A_*(u)s_{\widehat{\theta}}(u)}{m_*^2(u)}\, du\right)\left(\int_{t_0}^{T} \frac{|s'_{\widehat{\theta}}(u) - 2A_*(u)s_{\widehat{\theta}}(u)|}{m_*^2(u)}\, du\right)^{-1}}$$

thus approximating the function B of the Gaussian process through $\Delta|s'_{\widehat{\theta}}(t) - 2A_*(t)s_{\widehat{\theta}}(t)|^{\frac{1}{2}}$. In this case, the value found for Δ is $\sqrt{0.0998}$. Finally, Figure 4 shows the variance function obtained for the Gaussian process, together with the observed variance.

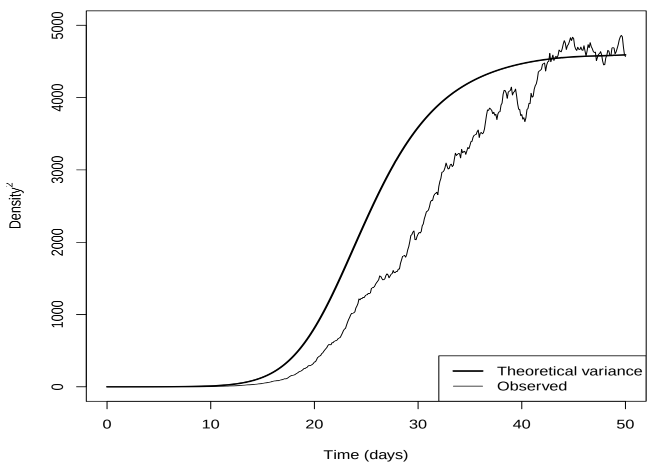

Figure 4. Observed and fitted variance functions for application 1.

In order to check the suitability of the Gaussian process obtained we have simulated sample paths for this process (see Figure 5). It can be observed that they exhibit a similar behavior pattern to that of the simulated paths of the original logistic process (see Figure 1 a)). This leads to conclude that the process generates a very approximate model of the growth pattern exhibited by the original phenomenon.

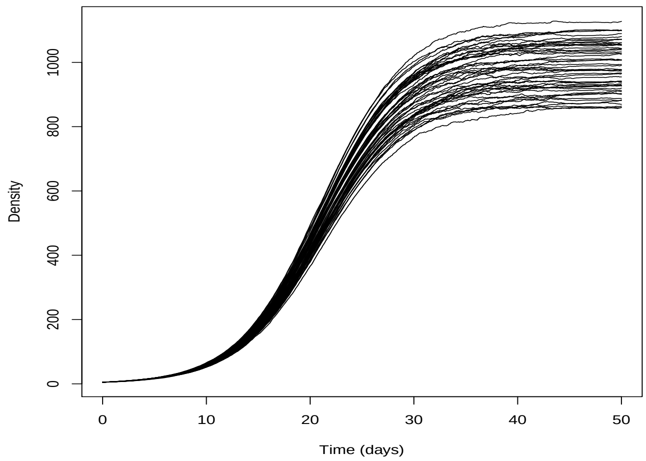

Figure 5. Simulated sample paths of the fitted process in application 1.

4.2 Application 2: Growth of rabbits

The following example is based on research developed by A. Blasco et al. (2003) on some aspects related to the growth of rabbits. In Gutiérrez et al. (2007), a Gompertz-type process was fitted to data according to the observed sigmoidal behavior of paths and to their bounds being dependent on the initial values. Figure 6 displays the evolution of weight (in grams) of 29 rabbits through 30 weeks, as well as their observed mean and variance.

The sample paths begin at different initial values and therefore a non-degenerate initial distribution must be considered. The observed sigmoidal behavior suggests that a Gompertz-like function would be adequate to model the trend. Nevertheless, the variance observed does not show a growing trend, a condition that precludes the use of the methodology described in the present paper (given that a mean positive function is considered). This condition appears momentarily around week 15, when three of the rabbits display an anomalous behavior. For the purposes of this application, the information provided by these three rabbits has not been included. Figure 7 shows the evolution of weight (in grams) of the 26 selected rabbits through 30 weeks, along with their observed mean and variance

In this case, the initial distribution estimated is $N(178.24, 17.237)$. For the

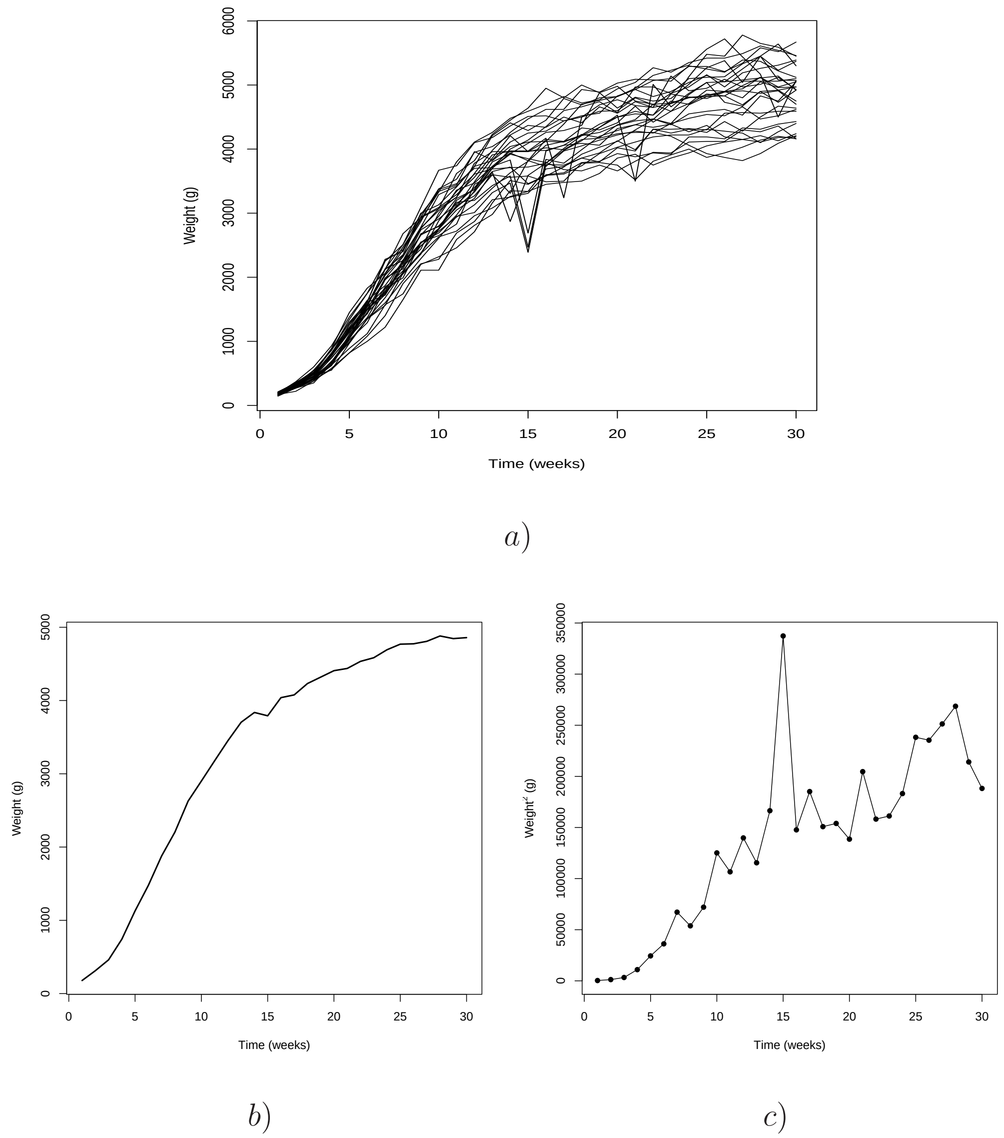

Figure 6. Weights of 29 rabbits along the first 30 weeks (a), observed mean (b) and observed variance (c).

approximation of the mean function we propose a Gompertz-type function

$$m_{k,r,b}(t) = k\, e^{-\frac{r}{b} e^{-bt}}, \tag{16}$$

and the least square estimation of parameters from the simulated paths leads to

$$\widehat{k} = 4824.569, \quad \widehat{r} = 0.8255, \quad \widehat{b} = 0.2047.$$

Figure 8 shows the observed mean together with the mean function of the

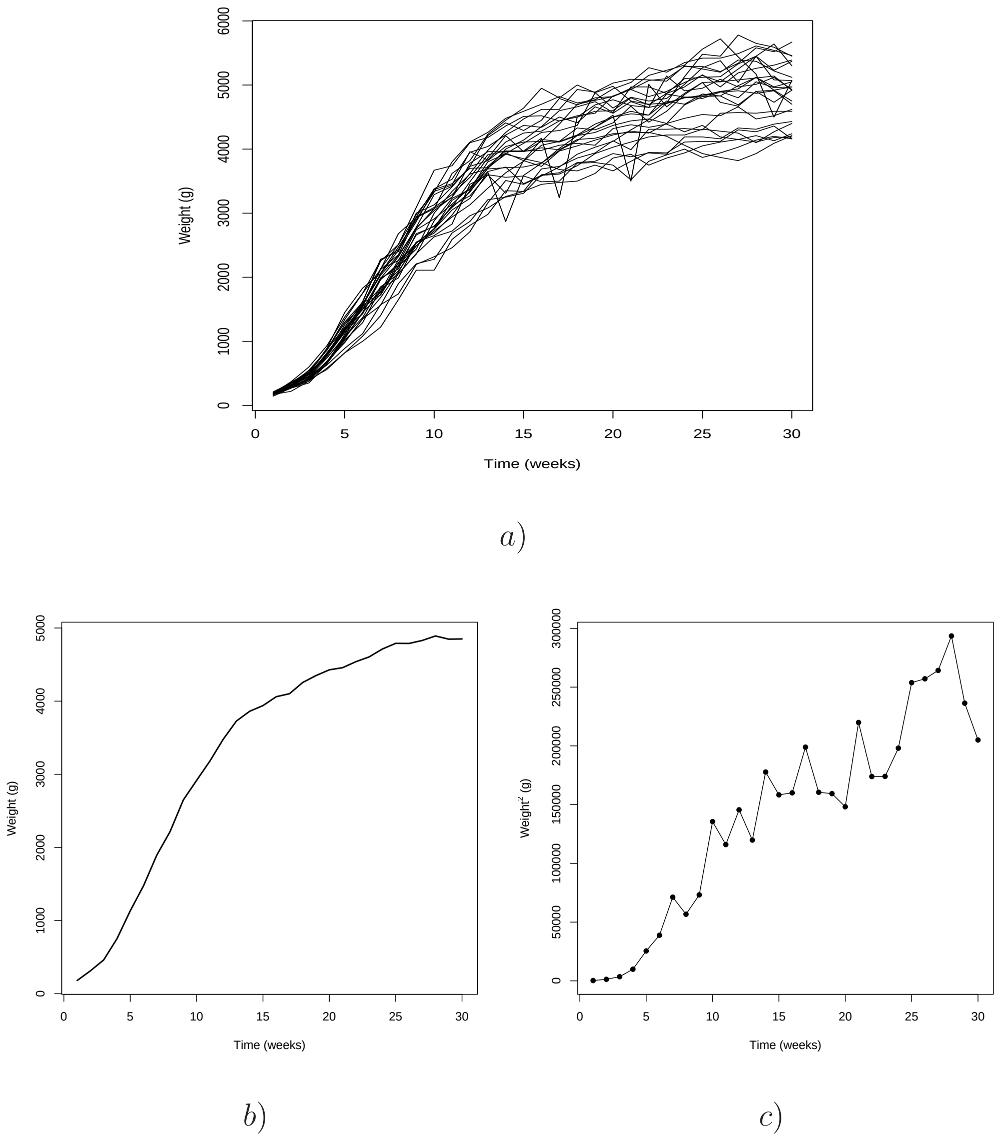

Figure 7. Weights of the 26 selected rabbits along the first 30 weeks (a), observed mean (b) and observed variance (c).

Gaussian process.

From the estimation of the mean function A by through $m_{\widehat{k},\widehat{r},\widehat{b}}$ an approximation to the function results as

$$A_*(t) = \widehat{r}e^{-\widehat{b}t}$$

In order to approximate the variance function we propose the parametric function

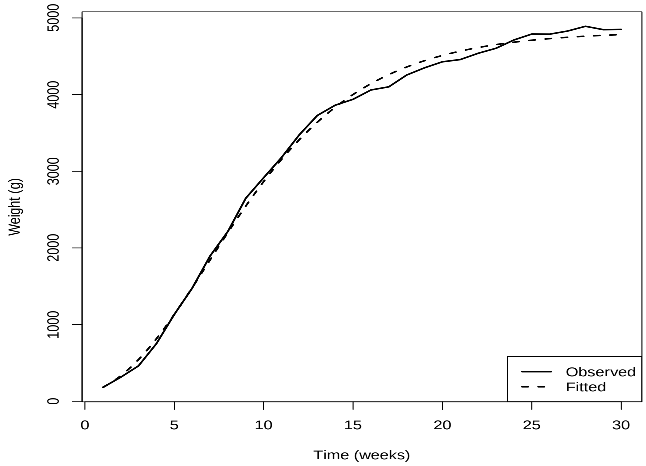

Figure 8. Observed and fitted mean functions for application 2.

$$s_\theta(t) = exp(\theta_1 t + \theta_2 t^2 + \theta_3 t^3)$$

and the least square estimation of parameters from the simulated paths leads to

$$\widehat{\theta_1} = 1.7135, \quad \widehat{\theta_2} = -0.0788, \quad \widehat{\theta_3} = 0.0012.$$

Again, as can be appreciated in Figure 9, condition (14) is not verified for a part of the time interval in this case. For this reason, the strategy used in application 1 has been employed, resulting in a value of $\Delta = \sqrt{0.73}$. Figure 10 shows the obtained variance function of the Gaussian process together with the observed variance.

In order to compare the Gaussian process built in this application to the one proposed by Gutiérrez et al (2007), a new estimation of the latter has been made taking into account only the information provided by the 26 selected rabbits. The estimated Gompertz-type process has infinitesimal

$$A_1(x,t) = 0.7486e^{-0.1823t}x$$
$$A_2(x,t) = (0.062)^2 x^2$$

and initial distribution $\Lambda(5.1911, 0.0937)$.

Figures 11 and 12 show the simulated paths for both processes. These clearly display how the model suggested in the present paper exhibits a more similar

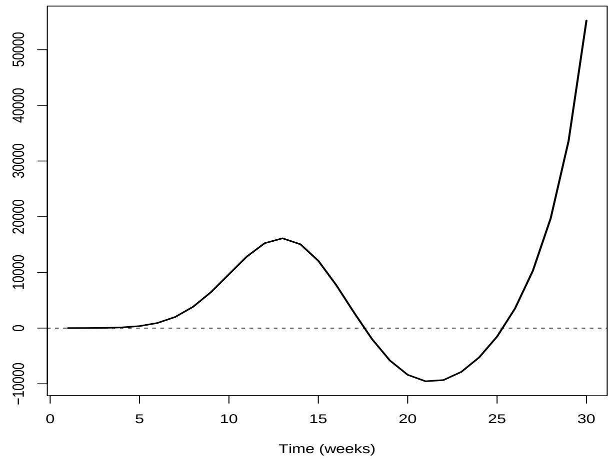

Figure 9. $s'_{\widehat{\theta}}(t) - 2A_*(t)s_{\widehat{\theta}}(t)$ in the interval $[t_0, T]$ for the application 2.

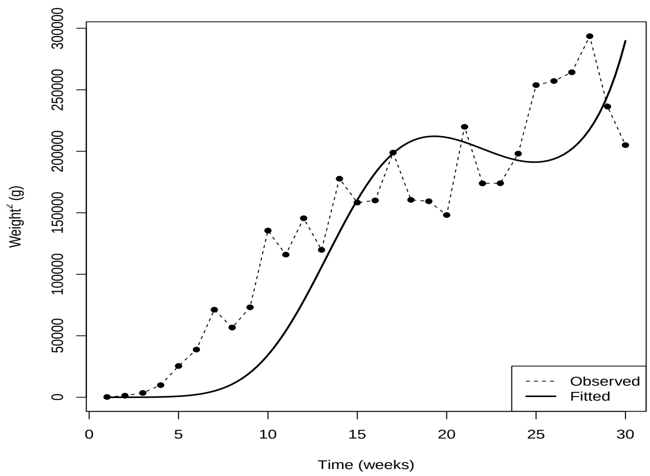

Figure 10. Observed and fitted variance functions for application 2.

behavior to the growth observed in rabbits that the Gompertz-type process proposed in Gutiérrez et al. (2007).

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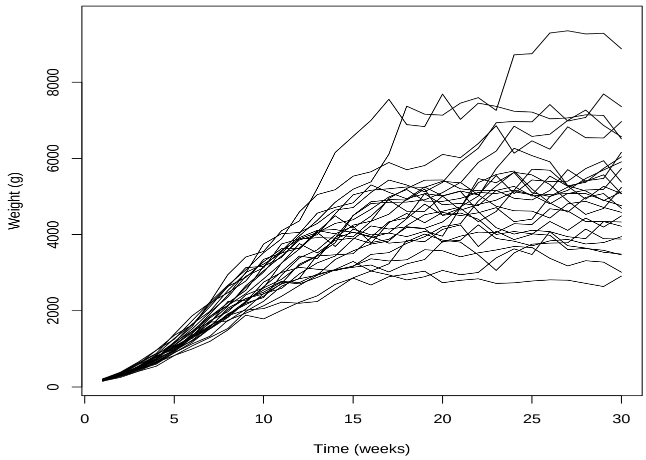

Figure 11. Simulated sample paths of the Gompertz-type fitted process in application 2.

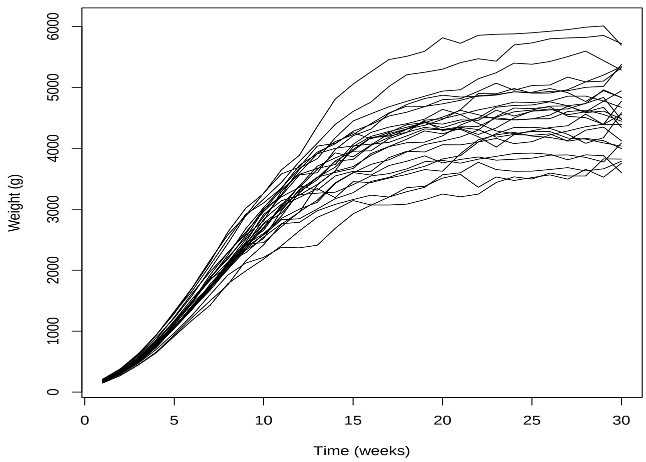

Figure 12. Simulated sample paths of the fitted process in application 2.

References

[1] Albano, G., Giorno, V., Román-Román, P., Torres-Ruiz, F., 2011. Inferring the effect of therapy on tumors showing stochastic Gompertzian growth. Journal of Theoretical Biology 276, 67–77.

[2] Blasco, A., Piles, M., Varona, L., 2003. A Bayesian analysis of the effect of selection for growth rate on growth curves in rabbits, Genetics selection evolution 35, 21-41.

[3] Capocelli, R. M., Ricciardi, L.M., 1974. A diffusion model for population growth in random environment, Theoretical Population Biology 5, 28-41.

[4] Capocelli, R.M., Ricciardi, L. M., 1974. Growth with regulation in random environment, Kybernetik 15, 147-157.

[5] Gutiérrez, R., Román, P., Romero, D., Serrano, J.J., Torres, F., 2007. A new gompertz-type diffusion process with application to random growth. Math. Biosc. 208, 147–165.

[6] Ricciardi, L.M., 1979. On a conjecture concerning population growth in random environment, Biological Cybernetics 32, 95-99.

[7] Ricciardi, L. M., Sacerdote, L., Sato, S., 1983. Diffusion approximation and first-passage-time problem for a model neuron II. Outline of a computation Method, Math. Biosc. 64, 29-44.

[8] Román-Román, P., Romero, D., Torres-Ruiz, F., 2010. A diffusion process to model generalized von Bertalanffy growth patterns: Fitting to real data. J. Theor. Biol. 263, 59–69.

[9] Román-Román, P., Torres-Ruiz, F., 2012. Modelling logistic growth by a new diffusion process: Application to biological systems. BioSystems. 110, 9-21.