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Bayesian Inference of the Stochastic Gompertz Growth Model for Tumor Growth

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Abstract

A stochastic Gompertz diffusion model for tumor growth is a topic of active interest as cancer is a leading cause of death in Korea. The direct maximum likelihood estimation of stochastic differential equations would be possible based on the continuous path likelihood on condition that a continuous sample path of the process is recorded over the interval. This likelihood is useful in providing a basis for the so-called continuous record or infill likelihood function and infill asymptotic. In practice, we do not have fully continuous data except a few special cases. As a result, the exact ML method is not applicable. In this paper we proposed a method of parameter estimation of stochastic Gompertz differential equation via Markov chain Monte Carlo methods that is applicable for several data structures. We compared a Markov transition data structure with a data structure that have an initial point.

Keywords: Stochastic diffusion. Gompertz growth model, tumor growth, Bayesian, Markov data structure, sparse data structure.

1. Introduction

Mathematical modeling of tumor growth has developed into an important area of research since cancer is a prevalent disease in Korea. Biological, physical, and chemical behaviors of tumor growth can be explained using many differential equation models. The Gompertz growth model is a particularly popular model as it is simple and convenient to use. It has a large explanatory power representing real phenomena because all tumors follow a standard growth pattern of fast growth in the beginning and eventually reach a maximum size. Recently this model has been applied to tumor growth and many good examples of this application are available (Benzekry *et al.*, 2014; Bonate *et al.*, 2013). However, the Gompertz growth model often exhibits discrepancies between clinical data and theoretical predictions due to intense environmental fluctuations and varied diversities of patients. To consider such environmental fluctuations and diversities of patients, tumor growth models adopt the stochastic process (Lo, 2007; Nobile *et al.*, 1985). The case of the Gompertz growth model deserves a special mention because various expressions exists. Thus, there is no single deterministic model associated with the Gompertz growth model (Gutièrrez-Jáimez *et al.*, 2007).

If X_t is the volume of the tumor at time t, then the deterministic Gompertz growth model is defined by the differential equation

$$dX_t = me^{-\beta t}X_t dt, \tag{1.1}$$

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where m is the relative growth rate and β is the rate of decay of m. The variety of different tumor types is decided based on these parameters. Equation (1.1) has the solution in the form of a double exponential function

$$X_t = X_0 e^{\frac{m}{\beta}} \exp\left(-\frac{m}{\beta} e^{-\beta t}\right), \tag{1.2}$$

where X_0 is the initial volume and $X_0 e^{m/\beta}$ is the maximum volume of the tumor. There exists an inflection point corresponding to the maximum growth rate, for example, the quasistationary solution. Further, discrepancies often exist between clinical data and theoretical predictions, due to intense environmental fluctuations and varied diversities of patients (Lo, 2010). Stochastic differential equations often have properties that can be derived from the theory of ordinary differential equations.

If a continuous sample path of the process X_t were recorded over the interval $[0, T]$, direct maximum likelihood(ML) estimation of stochastic Gompertz differential equations would be possible based on the continuous path likelihood. This likelihood is very useful to provide a basis for the continuous record or infill likelihood function and infill asymptotics. The main justification for the use of the ML method lies in its desirable asymptotic properties, particularly its consistency and asymptotic efficiency under conditions of correct specification. Subsequently, various ML methods have been proposed. In practice, a continuous record is not available and ML estimators are infeasible (Phillips and Yu, 2009). The most common numerical methods include certain difficulties for ML estimator, such as the diversity for the Newton-Raphson method and its simulated annealing method and the inaccuracy for iterated method (Gutièrrez-Jáimez *et al.*, 2007). Generally, the likelihood functions of stochastic models may contain many integrals, which often makes a standard classical analysis difficult or even unfeasible. For example, the estimation methods of parameters (like Newton-Raphson method) require the most-widely used procedures to derive the maximum-likelihood estimate. In addition, there is a floating-point overflow problem in searching the parameter estimates of stochastic diffusion model due to the exponential component (Alili *et al.*, 2005; Linetsky, 2004; Lv and Pitchford, 2007). The advantage of the Bayesian approach using Markov chain Monte Carlo(MCMC) is that the researcher can replace the unobserved variables by simulated variables, relieving the burden of evaluating the likelihood function unconditional to the unobserved variables to allow a focus on the conditional likelihood function. In many cases, this makes Bayesian parameter estimation faster than classical maximum likelihood estimation (Paap, 2002).

In this paper, we proposed the model employed by the MCMC, which have the characteristics with a noticeable convergence for parameter estimation, that consider the application of several data structures with a continuous data type as well as a sparse data type.

2. Stochastic Gompertz Model

Let us consider the usual form of the stochastic Gompertz differential equati ons, that is

$$dX_t = me^{-\beta t} X_t dt + \sigma X_t dW_t, \tag{2.1}$$

where W_t denotes the standard Wiener process.

Let $F(t, X_t) = \log(X_t)$. Then, Ito's lemma gives

$$\begin{aligned} d\left(\log\left(X_t\right)\right) &= \frac{1}{X_t} dX_t + \frac{\sigma^2 X_t^2}{2}\left(-\frac{1}{X_t^2}\right) dt \\ &= \frac{1}{X_t}\left(me^{-\beta t} X_t dt + \sigma X_t dW_t\right) - \frac{\sigma^2}{2} dt \\ &= \left(me^{-\beta t} - \frac{\sigma^2}{2}\right) dt + \sigma dW_t. \end{aligned}$$

Subsequently, $X_t|X_{t-1} \sim \mathrm{LN}((\frac{m}{\beta}e^{-\beta t}(e-1) - \sigma^2/2) + \log(X_{t-1}), \sigma^2)$ and $X_t|X_0 \sim \mathrm{LN}((\frac{m}{\beta}(1-e^{-\beta t}) - \sigma^2 t/2 + \log(X_0), \sigma^2 t)$, where LN denotes the log-normal distribution. In data structure case given an initial point, the probability density function of $Y_t = \log\left(X_t/X_0\right)$ is

$$h_{Y_t}\left(y_t\right) = \frac{1}{\sqrt{2\pi\sigma^2 t}} \exp\left(\frac{\left(y_t - \frac{m}{\beta}\left(1 - e^{-\beta t}\right) + \frac{\sigma^2 t}{2}\right)^2}{2\sigma^2 t}\right).$$

However, since $Y_t = \log\left(X_t/X_0\right)$, the probability density function of X_t given $X_0 = x_0$ is

$$f_{X_t}(x_t|x_0) = \frac{1}{x_t\sqrt{2\pi\sigma^2 t}} \exp\left(\frac{\left(\log\left(\frac{x_t}{x_0}\right) - \frac{m}{\beta}\left(1 - e^{-\beta t}\right) + \frac{\sigma^2 t}{2}\right)^2}{2\sigma^2 t}\right).$$

Therefore, after some algebra, that

$$E\left(X_t|X_0\right) = X_0 \exp\left(\frac{m}{\beta}\left(1 - e^{-\beta t}\right)\right), \tag{2.2}$$

and

$$\mathrm{Var}\left(X_t|X_0\right) = X_0^2\left(e^{\sigma^2 t} - 1\right)\exp\left(\frac{2m}{\beta}\left(1 - e^{-\beta t}\right)\right).$$

We derive the upper and lower bound of $(1-\alpha) * 100\%$ confidence interval of X_t at time t given X_0 as

$$X_{t\mathrm{U}} = X_0 \exp\left(\frac{m}{\beta}\left(1 - e^{-\beta t}\right) - \frac{\sigma^2 t}{2} + Z_{\frac{\alpha}{2}}\sigma^2 t\right), \tag{2.3}$$

$$X_{t\mathrm{L}} = X_0 \exp\left(\frac{m}{\beta}\left(1 - e^{-\beta t}\right) - \frac{\sigma^2 t}{2} - Z_{\frac{\alpha}{2}}\sigma^2 t\right). \tag{2.4}$$

In addition, we calculate a probability that X_t is greater than critical value c, *i.e.*

$$P\left(X_t > c|X_0\right) = 1 - \Phi\left(\frac{\log\left(\frac{c}{X_0}\right) - \frac{m}{\beta}\left(1 - e^{-\beta t}\right)}{\sigma^2 t}\right), \tag{2.5}$$

where Φ denotes the standard normal cumulative distribution function.

When X_t is observed continuously, a log-likelihood function for the continuous record $(X_t)_{t=0}^T$ may be obtained directly from the Radon Nikodym(RN) derivative of the relevant probability measures.

The RN derivative produces the relevant probability density and can be regarded as measurement change among the absolutely continuous probability measures, the calculation being facilitated by the Girsanov theorem. With the availability of a continuous record, it follows that the exact log-likelihood can be constructed via the Girsanov theorem (Karatzas, 1991)

$$l(m,\beta,\sigma) = \int_0^T \frac{\left(me^{-\beta t} - \frac{\sigma^2}{2}\right)}{\sigma^2} d\log(X_t) - \frac{1}{2}\int_0^T \frac{\left(me^{-\beta t} - \frac{\sigma^2}{2}\right)^2}{\sigma^2} dt.$$

However, if a continuous record of $(X_t)_{t=0}^T$ is not available, then ML estimators of the exact log-likelihood are infeasible (Phillips and Yu, 2009).

3. Inference Using MCMC

In practice, we do not have fully continuous data except a few special cases. As a result, the exact ML method is not applicable. Therefore, we propose a method of parameter estimation of stochastic Gompertz differential equation via Bayesian inference that is applicable for several data structures. The advantage of this Bayesian inference is the ability to apply not only a Markov transition data structure $X_t|X_{t-1}$ as well as a data structure given an initial point $X_t|X_0$ such as fish otolith data.

Let us consider a discrete sampling of the process, based on d sample paths, for times t_{ij}, $(i = 1,\ldots,d;\ j = 1,\ldots,n_i)$. That is, we observe the variables $X_{t_{ij}}$, the values of which, $\{x_{ij}\}_{i=1,\ldots,d;j=1,\ldots,n_i}$, make up the sample of the inferential study. We assume gamma prior distributions for $\tau = 1/\sigma^2 \sim \Gamma(v_1, v_2)$, $m \sim \Gamma(\alpha_1,\beta_1)$, and $\beta \sim \Gamma(\alpha_2,\beta_2)$ and exponential prior distributions $Exp(1)$ for hyperparameters $v_1, v_2, \alpha_1, \alpha_2, \beta_1$, and β_2. We obtain the following full conditional distributions for MCMC when $f(\gamma|\cdot)$ is expressed as the full conditional distribution of γ given the data and other parameters, for Markov transition data structure case, $X_t|X_{t-1}$,

$$f_\tau(\tau|\cdot) \propto \tau^{\frac{dn}{2}+v_1-1} \exp\left(-\sum_{i=1}^{d}\sum_{j=1}^{n_i} \frac{\tau\left(\log\left(\frac{X_{ij}}{X_{ij-1}}\right) - \frac{m}{\beta}\left(e^{-\beta t_{ij}}(e-1)\right) + \frac{t_{ij}}{2\tau}\right)^2}{2t_{ij}} - v_2\tau\right), \tag{3.1}$$

$$f_m(m|\cdot) \propto m^{\alpha_1-1} \exp\left(-\sum_{i=1}^{d}\sum_{j=1}^{n_i} \frac{\tau\left(\log\left(\frac{X_{ij}}{X_{ij-1}}\right) - \frac{m}{\beta}\left(e^{-\beta t_{ij}}(e-1)\right) + \frac{t_{ij}}{2\tau}\right)^2}{2t_{ij}} - \beta_1 m\right), \tag{3.2}$$

$$f_\beta(\beta|\cdot) \propto \beta^{\alpha_2-1} \exp\left(-\sum_{i=1}^{d}\sum_{j=1}^{n_i} \frac{\tau\left(\log\left(\frac{X_{ij}}{X_{ij-1}}\right) - \frac{m}{\beta}\left(e^{-\beta t_{ij}}(e-1)\right) + \frac{t_{ij}}{2\tau}\right)^2}{2t_{ij}} - \beta_2\beta\right), \tag{3.3}$$

for data structure case given an initial point, $X_t|X_0$,

$$f_\tau(\tau|\cdot) \propto \tau^{\frac{dn}{2}+v_1-1} \exp\left(-\sum_{i=1}^{d}\sum_{j=1}^{n_i} \frac{\tau\left(\log\left(\frac{X_{ij}}{X_{i0}}\right) - \frac{m}{\beta}\left(1-e^{-\beta t_{ij}}\right) + \frac{t_{ij}}{2\tau}\right)^2}{2t_{ij}} - v_2\tau\right), \tag{3.4}$$

$$f_m(m|\cdot) \propto m^{\alpha_1-1} \exp\left(-\sum_{i=1}^{d}\sum_{j=1}^{n_i} \frac{\tau\left(\log\left(\frac{X_{ij}}{X_{i0}}\right) - \frac{m}{\beta}\left(1-e^{-\beta t_{ij}}\right) + \frac{t_{ij}}{2\tau}\right)^2}{2t_{ij}} - \beta_1 m\right), \tag{3.5}$$

Table 1: Results of Markov transition data structure and data structure given initial point

parameters	Markov structure			Initial structure		
	mean	sd	median	mean	sd	median
m	1.2100	0.0438	1.1960	1.2010	0.0479	1.1910
b	0.1697	0.1687	0.1687	0.1734	0.1927	0.1734
σ^2	0.0281	0.0205	0.0214	0.0305	0.0284	0.0274

$$f_\beta(\beta|\cdot) \propto \beta^{\alpha_2-1} \exp\left(-\sum_{i=1}^{d}\sum_{j=1}^{n_i} \frac{\tau\left(\log\left(\frac{X_{ij}}{X_{i0}}\right) - \frac{m}{\beta}\left(1-e^{-\beta t_{ij}}\right) + \frac{t_{ij}}{2\tau}\right)^2}{2t_{ij}} - \beta_2\beta\right), \tag{3.6}$$

for both cases,

$$f_{v_1}(v_1|\cdot) \propto \frac{v_2^{v_1}\tau^{v_1-1}e^{-v_1}}{\Gamma(v_1)}, \tag{3.7}$$

$$f_{\alpha_1}(\alpha_1|\cdot) \propto \frac{\beta_1^{\alpha_1}m^{\alpha_1-1}e^{-\alpha_1}}{\Gamma(\alpha_1)}, \tag{3.8}$$

$$f_{\alpha_2}(\alpha_2|\cdot) \propto \frac{\beta_2^{\alpha_2}m^{\alpha_2-1}e^{-\alpha_2}}{\Gamma(\alpha_2)}, \tag{3.9}$$

$$f_{v_2}(v_2|\cdot) = Gamma(v_1+1, \tau+1),$$
$$f_{\beta_1}(\beta_1|\cdot) = Gamma(\alpha_1+1, m+1),$$
$$f_{\beta_2}(\beta_2|\cdot) = Gamma(\alpha_2+1, \beta+1).$$

Equation (3.1)–(3.9) are nonstandard distributions. However, these distributions can be sampled using the following Metropolis-Hastings algorithm step:

1. Sample $\hat{\tau} \sim \Gamma(\tau^{(i)}, 1)$.
2. Set $\tau^{(i+1)} = \hat{\tau}$ with probability $\min\left(1, f_\tau(\hat{\tau}|\cdot)/f_\tau\left(\tau^{(i)}|\cdot\right)\right)$.

   Otherwise, set $\tau^{(i+1)} = \tau(i)$.

Then, we apply the Metropolis-Hastings algorithms in the same manner for m, β, v_1, α_1, and α_2 within the Gibbs sampling algorithm.

4. Application

The presented data were based on studies developed by Schuster and Schuster (1995) for some aspects related to the number of the Ehrlich ascites tumor(EAT). We used the transplantation 14d data. We applied the Bayesian models using Gibbs sampling with Metropolis-Hastings (as shown in the previous section) to estimate parameter properties of the EAT cell number. Table 1 summarized the statistics of the estimated parameters using conditional distribution which were Markov transition data structure and data structure given initial point. Figure 1 showed that the samples of the data structure of initial point were wider than those of Markov transition data structure. The standard deviation of the data structure of initial point was greater than Markov transition data structure; however, we could get parameter estimators with a data structure given initial point. This was the advantage of this Bayesian inference. Figure 2 contains trace plots and density estimation plots of m, b, and σ^2, the relative growth rate, the rate of decay, and the volatility of growth equation respectively with the data

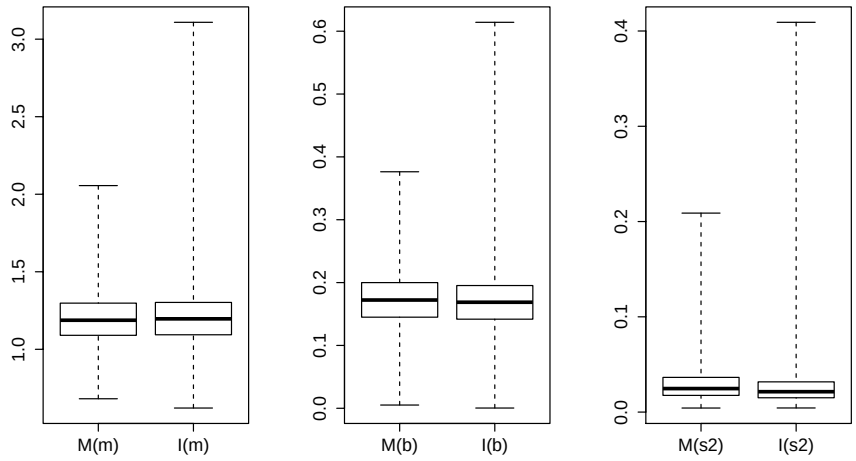

Figure 1: *Boxplots of parameters with Markov transition data structure and data structure given initial point*

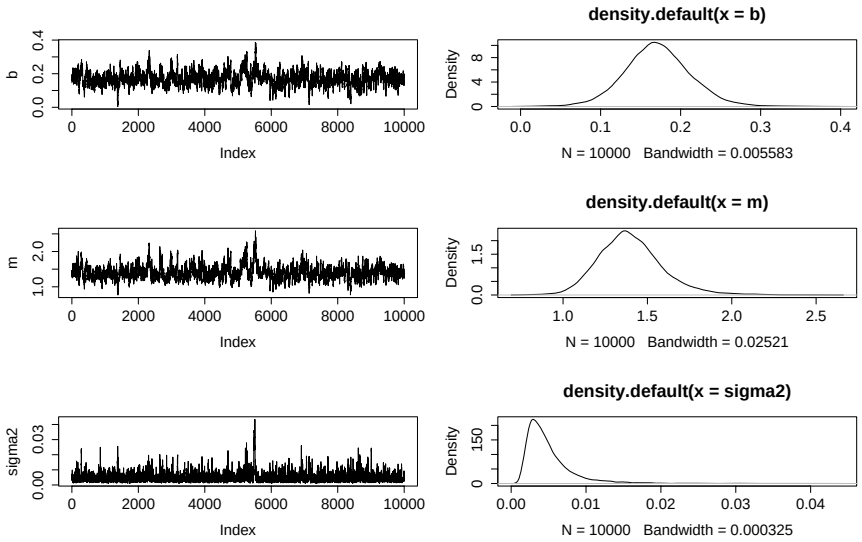

Figure 2: *Sample paths and posterior densities of parameters with Gibbs sampling*

structure of initial point. The model converges quickly and becomes stable; subsequently, the initial values are forgotten after approximately 100 iterations. The estimates of parameters are obtained after 10,000 iterations of the algorithm and a burn-in period of 5,000 iterations. The estimates of the relative growth rate and the rate of decay of m are equal to $m = 1.1910$ and $\beta = 0.1734$, which is the median of posterior samples. The values of $X_t|X_0$ were log-normally distributed with the expected value and variance given as follows:

$$E\left(X_t|X_0\right) = X_0 \exp\left(\frac{1.1910}{0.1734}\left(1 - e^{-0.1734t}\right)\right),$$

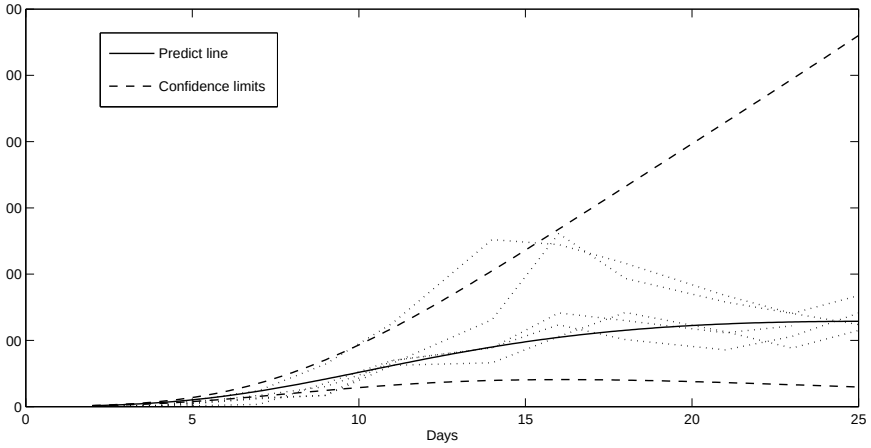

Figure 3: *Predict line and confidence limits of EAT cell number*

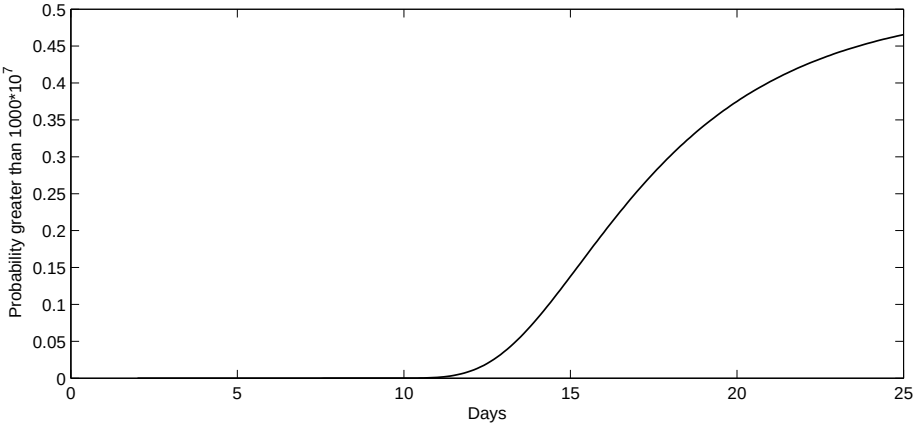

Figure 4: *Probabilities greater than* $1000 * 10^7$ *of EAT cell number*

and

$$\mathrm{Var}\,(X_t|X_0) = X_0^2\left(e^{0.0169t} - 1\right)\exp\left(\frac{2 * 1.1910}{0.1734}\left(1 - e^{-0.1734t}\right)\right).$$

Tumor sizes distribution usually reveals that the variance of the response variable increases with time. In Figure 3, the estimation of the predict line, which is the expected value equation (2.2), and a confidence interval of 95% , whose bounds are equation (2.3) and equation (2.4), is presented. The upper bound of the confidence interval increase considerably as time increases. Figure 4 indicates that the probabilities equation (2.5) exceed a certain threshold, which we set as $1000 * 10^7$. It sharply increases after a period of time(15 days). These probabilities are an advantage of the stochastic model without the ordinary Gompertz model.

5. Conclusion

In this paper, we proposed the parameter estimation method of the stochastic Gompertz growth equation using Bayesian techniques. The new algorithms are based on the idea that it is possible to apply the missing or sparse data structures in which we cannot get the exact ML estimator. In close study of the following, we are going to develop and apply the stochastic differential equations to the relations between cell size and death rates. The relations between cell size and death rates are identified will then be able to predict the probabilities of death rates as time increases.

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