Stationary Densities and Parameter Estimation for Delayed Stochastic Logistic Growth Laws with Application in Biomedical Studies

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Abstract –The study of nonlinear stochastic delayed process is significant for understanding nature of complex system in reductionistic viewpoints. This paper investigates the stochastic linear and logistic (Verhulst, Gompertz and Richards) models, and simulates the growth process of Ehrilch ascities tumor (EAT) in a mouse. In order to explain the oscillations of EAT growth we use a system of stochastic differential equations with time delay. We derive the exact and approximate stationary densities in the case of small time delays. For the estimation of parameters we propose the L^1 distance and maximum likelihood procedures. As an illustrative experience we use a real data set from repeated measurements on Ehrilch ascities tumor in a mouse. The results are implemented in the symbolic computational language MAPLE.

Key-Words: - Ehrilch ascities tumor, Stochastic differential equation, Density function, Fokker-Plank equation, Numerical solution.

1 Introduction

One of the most important nonlinear processes occurring in nature is the stochastic logistic growth process, which encompasses the Verhulst, Gompertz, Richards growth models. It is therefore important to understand how such processes can be simulated. We will be concerned with applications in growth modeling of Ehrilch ascities tumor (EAT) in a mouse. In applied sciences literature delay differential equations are widely used to model an oscillatory behavior of the processes of growth [3], [4], [6], [9], [12], [34], [37], [43]. In biological systems the retardation usually originates from maturing processes [24], [45]. The delay differential equations demonstrated more complicated dynamics than ordinary differential equations. The oscillations in the solutions of deterministic first order delay differential equations are usually generated by the delayed argument.

The excessive complexity of living organisms and the related issue of variability in biological systems present difficulty to mathematical modeling of growth. It is widely recognized that the biological systems operates in a highly uncertain environment [5], [11], [16], [27], [28], [29], [30], [33]. The randomness is usually caused by a limitation of our knowledge of analyzed growth process. However, most available time-delayed growth models are deterministic, which do not necessarily give a satisfactory deterministic prediction of mean trends. Many scientists in ecology, forest biometry, biomedicine, finance, physics agree that stochastic perturbations are a major determinant of the process of growth. In biological systems, there are many highly organized networks of physical, chemical and organic reactions and motions to sustain biological order within the system. These reactions and motions are essentially irreversible and they inevitably produce randomness. Fluctuations of the growth dynamics can be modeled in various ways. For example, it can be suggested to consider extensive (multiplicative, state-dependent) or intensive (additive, noise amplitude) random perturbations. As was shown [2], the additive and multiplicative noise perturbations of Ito type in a scalar delay deterministic equation may induce the oscillations in the previous deterministic non-oscillatory system. A periodic behavior of the stochastic model is amplified by the combination of noise and delay. The interaction of noise and delay supports oscillations. This phenomenon has been entitled as an autonomous stochastic resonance. It appears that in many ecological systems the growth process exhibit only small fluctuations around steady-state fixed points. This fact is a mathematical motivation to use the linear systems by delays and weak perturbation noises for the modeling of the growth processes in ecology, biology, biomedicine, finance and forestry. The linear evolution equations [2], [18] correspond to a linearization of the nonlinear evolution equations around the steady state amplitudes of the deterministic dynamics.

In this paper we study the dynamic behavior of nonlinear system, which include time structure. We firstly hypothesize a generalized stochastic logistic delay growth model by a nonlinear stochastic delay ordinary differential equation explaining this dynamic (inspired by a previous non-delayed stochastic logistic model [16], [31], [32], [33], [35]). The delayed model has a high complexity and requires much computer calculations. Our current computing power makes it relatively easy. We check the consequences of the model against EAT data. To our knowledge no studies have been performed on such biological data using such nonlinear methodologies. There are a number of advantages to the nonlinear stochastic models, including the ability to simulate first two moments and transition probability density, and to forecast the probability of treatment success or failure.

The present paper has three main goals. Firstly, we will determinate approximate and exact stationary distributions of stochastic linear model involving time delay, and linearize the nonlinear delay stochastic logistic differential equations around the steady state and study the stationary densities of the resulting equations. These distributions involve delay-dependent effective potential function. Secondly, we will adapt two approaches: the maximum likelihood procedure and the L^1 distance procedure for the estimating of the drift, diffusion parameters and the time delay size. During the past decades a variety of approaches for statistical inference in discretely observed diffusion processes have been developed [14], [28], [29], [31], [32], [40], [42]. Thirdly, we will analyze the growth of the EAT in a mouse under additive and multiplicative stochastic perturbations.

The paper is organized as follows. In Section 2 we fix the notation and definition of stationary distributions, and we describe the general methodology used for corresponding estimation methods. We apply this methodology to EAT data. Section 3 summarizes the present results and gives some conclusions and closing remarks.

2 Materials and Methods

In this section we determine the exact and approximate stationary distributions of some nonlinear time-delayed stochastic logistic growth models involving small delays. Our next objective is concerned with applications of stationary distributions to the modeling of EAT. In applied sciences stochastic growth models have pioneered the use of transition probability densities to describe movements among state levels [1], [12], [17], [23], [26], [35]. This methodology has been rarely adapted due to difficulties with estimating the transition probability density. The transition probability methodology has been based on the assumption that we deal with Markov processes. Unfortunately, in many cases, stochastic growth law with time-delayed feedback is described in terms of a stochastic delay differential equation. Hence, in many biological systems there is an effect of the long time memory on its current behavior and require a description in terms of non-Markov processes.

Let us consider a stochastic growth law described by an ordinary delay stochastic logistic differential equation with both the additive and multiplicative noises in the following form

$$dX(t) = f\left(X(t), X(t-\tau)\right)dt + \sigma\begin{cases} dW(t) \\ X(t)dW(t) \end{cases},$$

$$X(s) = \varphi(s), \quad s \in [t_0 - \tau; t_0],\ t \in [t_0; T], \tag{1}$$

when σ is a constant controlling the amplitude of noise, $W(t)$ is the standard Brownian motion (white noise), which is a random process whose increments are independent and normally distributed with zero mean and with variance equal to the length of the time interval over which the increment take place, $\varphi(s)$ is known function, $f(x(t), x(t-\tau)) = rG(x(t)) + \alpha x(t-\tau))$, $G(x(t)) = 1 - \frac{x(t)}{K}$ (Verhulst law), $G(x(t)) = \ln\frac{K}{x(t)}$ (Gompertz law), $G(x(t)) = 1 - \left(\frac{x(t)}{K}\right)^{\beta}$, $\beta \geq -1$ (Richards law), r the intrinsic growth rate, and K is the saturation level (also the ratio $\frac{r}{K}$ is known as the decay rate). Instead, both parameters r, K in our model are dependent on random variables that we can't include in our model without doing it too complex. The logistic type models have a rich history dating back to Verhulst (1838) [46] and are well-known in the applied sciences [16], [20], [21], [22], [25], [33], [35], [39], [44], [45], [47]. Above presented three logistic models are closely related. The Verhulst model is a two parameter symmetric model. The Richards and Gompertz models generalize Verhulst model and have asymmetric growth.

In general, stochastic process $X(t)$ can be characterized by means of transition probability density of the nonlinear Fokker-Planck partial differential equation (also known as the Chapman-Kolmogorov equation [10]). Next, we discuss a transition probability density of the stochastic process $X(t)$ described by (1). In the sequel $p(x,t)$ denote the probability density of the stochastic delay differential equation (1). It is shown [7], [8], that the delay Fokker-Planck equation of the stochastic process $X(t)$ with both the additive and multiplicative noise described by equation (1) takes the form

$$\frac{\partial}{\partial t}p(x,t) = -\frac{\partial}{\partial x}\int (f(x,x_\tau)p(x,t;x_\tau,t-\tau)dx_\tau + \frac{\sigma^2}{2}\begin{cases}\int \frac{\partial^2}{\partial x^2}p(x,t;x_\tau,t-\tau)dx_\tau \\ \int \frac{\partial^2}{\partial x^2}x^2 p(x,t;x_\tau,t-\tau)dx_\tau\end{cases}, \quad (2)$$

here $p(x,t;x_\tau,t-\tau)$ is the joint probability density of the stochastic process $X(t)$. The approximate stationary probability density for the stochastic delay differential equation (1) that involves the multiplicative noise has the following form

$$p_{st}^a(x) = \frac{N_c}{D_{eff}(x)}\exp\left(\int_0^x \frac{f_{eff}(x')}{D_{eff}(x')}dx'\right), \quad (3)$$

where N_c is a normalizing constant, the effective drift and diffusion coefficients $f_{eff}(x)$, $D_{eff}(x)$ are described by

$$f_{eff}(x) = \frac{1}{\sqrt{4\pi D^{(0)}(x)\tau}}\times \int_{-\infty}^{+\infty}(rxG(x)-\alpha x_\tau)\exp\left(-\frac{(x_\tau - x - f^{(0)}(x)\tau)^2}{4D^{(0)}(x)\tau}\right)dx_\tau, \quad (4)$$

$$D_{eff}(x) = \frac{\sigma^2}{\sqrt{4\pi D^{(0)}(x)\tau}}\times \int_{-\infty}^{+\infty}x^2\exp\left(-\frac{(x_\tau - x - f^{(0)}(x)\tau)^2}{4D^{(0)}(x)\tau}\right)dx_\tau, \quad (5)$$

with $D^{(0)}(x) = \sigma^2 x^2/2$, $f^{(0)}(x) = rxG(x) - \alpha x$. For the stochastic delay differential equation (1) that involves the additive noise the approximate stationary probability density has the following form

$$p_{st}^a(x) = N_c\exp\left(\frac{2V_{eff}(x)}{\sigma^2}\right), \quad (6)$$

where the effective potential $V_{eff}(x)$ is described by

$$V_{eff}(x) = \frac{1}{\sigma\sqrt{2\pi\tau}}\times \int^x\left(\int_{-\infty}^{+\infty}(rxG(x)-\alpha x_\tau)\exp\left(-\frac{(x_\tau - x - f^{(0)}(x)\tau)^2}{2\sigma^2\tau}\right)dx_\tau\right)dx. \quad (7)$$

and the normalizing constant N_c is determined from the normalization condition

$$\int_{-\infty}^{+\infty}p_{st}^a(x)dx = 1.$$

2.1 Linear delay differential equation

In this section we consider the linear case of equation (1) with both additive and multiplicative noise

$$dX(t) = (K - aX(t) - bX(t-\tau))dt + \sigma\begin{cases}dW(t)\\ X(t)dW(t),\end{cases} \quad (8)$$

$X(s) = \varphi(s)$, $s\in[t_0-\tau;t_0]$, $t\in[t_0;T]$,

where parameters *a*, *b*, ($a+b>0$) correspond to friction coefficients, $\sigma>0$ corresponds to the fluctuation strength, *K*/(*a*+*b*) corresponds to the equilibrium fix point, τ the size of delay, the function $\varphi(s)$ describes the initial condition of the stochastic process on $[t_0-\tau;t_0]$. In this section for the stochastic linear delay differential equation (8) we pose two questions. First, how can be expressed approximate stationary probability density and exact stationary probability density. Second, how can the parameters *K*, *a*, *b*, τ, σ be estimated from experimental data.

2.1.1 Deterministic linear equation

The linear delay differential equation has the form

$$\frac{dx(t)}{dt} = K - ax(t) - bx(t-\tau), \quad (9)$$

$x(s) = \varphi(s)$, $s\in[t_0-\tau;t_0]$, $t\in[t_0;T]$,

when *K*, *a*, *b*, τ are nonnegative parameters, $a+b>0$. The solutions of equation (9) are oscillatory provided $b\tau > \frac{1}{e}$. The presence of a delay term in the scalar linear differential equation (9) induces the oscillation of all solutions if the delay τ is sufficiently long or large intensity *b*. Nonoscillatory solutions can still exist for small intensity or delay. Finally, the solutions of equation (9) undergo damped oscillations for $\frac{1}{e} < b\tau < \frac{\pi}{2}$, and diverging oscillations for $b\tau > \frac{\pi}{2}$.

Generally, the parameters *K*, *a*, *b*, τ have to be estimated from the data set $\{(t_i, x_i), i = 1,2,...,n\}$ on the dependent variable *x* and independent variable *t*. The problem of estimating parameters *K*, *a*, *b*, τ from historical data is one of choosing the estimates $\hat{K}$, $\hat{a}$, $\hat{b}$, $\hat{\tau}$, such that the predicted value $\hat{x}(t_i, K, a, b) \equiv \hat{x}(t_i) \equiv \hat{x}_i$ is close to observation x_i. We numerically integrate the linear delay ordinary differential equation (9) by means of a second-order scheme with constant step size Δt in the following form:

$$x_{i+1} = x_i + (K - ax_i - bx_{i-\theta})\Delta t + (K - ax_i - bx_{i-\theta})\frac{\Delta t^2}{2} + I_{\{i>\theta\}} b(bx_{i-2\theta} + ax_{i-\theta} - K)\frac{\Delta t^2}{2} \quad ,(10)$$

here $I_{\{\}}$ is the indicator function, $\Delta t = \frac{T - t_0}{N}$ is the step size, $\theta = \frac{\tau}{\Delta t}$, $i = -\theta, -\theta + 1, ..., 0, ..., N$. Next we estimate the parameters *K*, *a*, *b*, τ by least squares method, minimizing the sum of the squared deviation function:

$$S(K, a, b, \tau) = \left(x - \hat{x}\right)' \left(x - \hat{x}\right),$$

where $\hat{x}$ is the $n \times 1$ array of corresponding numerical integration of equation (9), x is the $n \times 1$ array of observed data.

2.1.2 Exact and approximate stationary probability densities

As suggested in [13], for small delays and diffusion function of the form $g(X(t))$, the drift term $K - aX(t) - bX(t-\tau)$ and the diffusion terms σ, $\sigma X(t)$ may be expanded using a Tailor expansion in the following form

$$K - X(t) - bX(t-\tau) = (1 + b\tau)(K - (a+b)X(t)) + O(\tau^2),$$

$$\sigma = (1 + b\tau)\sigma + O(\tau^2),$$

$$\sigma X(t) = (1 + b\tau)\sigma X(t) + O(\tau^2).$$

Hence, the stochastic delay linear differential equation (8) takes the approximate non-delay form

$$dX(t) = (1 + b\tau)(K - (a+b)X(t))dt + (1 + b\tau)\sigma dW(t) \quad (11a)$$

for the additive noise, and

$$dX(t) = (1 + b\tau)(K - (a+b)X(t))dt + (1 + b\tau)\sigma X(t) dW(t) \quad (11b)$$

for the multiplicative noise.

For the stochastic non-delay linear ($b = 0$, $\tau = 0$, $a > 0$) differential equation (8) exists an exact stationary density. The stationary solution for the additive noise takes the following form

$$p_{st}(x) = \frac{1}{\sigma}\sqrt{\frac{a}{\pi}} \exp\left(- \frac{a\left(x - \frac{K}{a}\right)^2}{\sigma^2} \right), \quad (12)$$

and for the multiplicative noise

$$p_{st}(x) = \frac{1}{\Gamma\left(\frac{2a}{\sigma^2} + 1\right)} \left(\frac{2K}{\sigma^2}\right)^{\frac{2a}{\sigma^2}+1} \times x^{-2\left(\frac{a}{\sigma^2}+1\right)} \exp\left(-2\frac{K}{\sigma^2 x}\right), \quad (13)$$

where $\Gamma(\cdot)$ is a gamma function.

We now investigate the exact stationary solution of the Fokker-Planck equation (2) for the stochastic delay linear differential equation (8) with the additive noise. In the additive case of equation (8), the delay Fokker-Planck equation (2) takes the form

$$\frac{\partial}{\partial x} p(x,t) = \frac{\partial}{\partial x}\left((ax - K)p(x,t) + b\int_{-\infty}^{+\infty} y p(x,t; y, t-\tau) dy \right) + \frac{\sigma^2}{2}\frac{\partial^2}{\partial x^2} p(x,t) \quad .(14)$$

Due to the Gaussian distribution of fluctuation force and the linear form of drift function, the exact stationary probability densities $p_{st}(x)$, $p_{st}(x,t; y, t-\tau)$ can been defined by

$$p_{st}(x) = \frac{1}{\sqrt{2\pi R(\tau)}} \exp\left(- \frac{\left(x - \frac{K}{a+b}\right)^2}{2R(\tau)} \right), \quad (15)$$

$$p_{st}(x,t;y,t-\tau)=\frac{c(\tau)\sqrt{1-d^2(\tau)}}{\pi}\times \exp\left(-c(\tau)\left(\left(x-\frac{K}{a+b}\right)^2+\left(y-\frac{K}{a+b}\right)^2- 2d(\tau)\left(x-\frac{K}{a+b}\right)\left(y-\frac{K}{a+b}\right)\right)\right), \quad (16)$$

where the parameters $c(\tau)$, $d(\tau)$ and variance $R(\tau)$ are unknown. Substituting (15) and (16) into (14) we have

$$c(\tau)=\frac{2b^2R(\tau)}{(2bR(\tau))^2-(\sigma^2-2aR(\tau))^2},$$

$$d(\tau)=\frac{\sigma^2-2aR(\tau)}{2bR(\tau)}.$$

For deriving the variance $R(\tau)$ of the process $X(t)$ was used the approach developed in [7]. The variance $R(\tau)$ takes the form

$$R(\tau)=\begin{cases}\frac{\sigma^2}{2}\left(\frac{1+b\varpi^{-1}\sin(\varpi\tau)}{a+b\cos(\varpi\tau)}\right), & b>a\ge 0\\ \frac{\sigma^2}{2}\left(\frac{1+b\varpi^{-1}\sinh(\varpi\tau)}{a+b\cosh(\varpi\tau)}\right), & a>b\ge 0,\\ \frac{\sigma^2}{2}(1+a\tau), & a=b>0\end{cases} \quad (17)$$

where $\varpi=\sqrt{|a^2-b^2|}$. For $b>a$ there exists τ^*, defined by equation $\tau^*=\frac{i}{\varpi}\arccos\left(-\frac{a}{b}\right)$, such that the stationary solution (15) exists only for $\tau\in[0;\tau^*)$. In particular, the statistical inference based on the exact solution (15), (17) is suited to stochastic linear delay equation (8) only for $\tau\in[0;\tau^*)$. Considering this we explore an approximate stationary probability density for the stochastic delay linear equation (8) with the additive noise.

For the limiting case ($\tau\to 0$) the exact stationary probability density (15) coincides with the non-delayed stationary probability density (12).

Now, let us study the approximate stationary density of the stochastic linear delay process with the additive noise described by equation (8). In the linear delay case (8) we have that $f(x,x_\tau)=K-ax-bx_\tau$, $f^{(0)}(x)=K-(a+b)x$. Hence, equations (6)-(7) give the following forms

$$V_{eff}=(1-b\tau)Kx-(1-b\tau)(a+b)\frac{x^2}{2}$$

$$p_{st}^a(x)=\frac{1}{\sigma}\sqrt{\frac{(a+b)}{\pi(1+b\tau)}}\exp\left(-\frac{(a+b)}{(1+b\tau)\sigma^2}\left(x-\frac{K}{a+b}\right)^2\right). \quad (18)$$

On the other hand, replacing K by $(1+b\tau)K$, a by $(1+b\tau)(a+b)$, and σ^2 by $(1+b\tau)^2\sigma^2$ in equation (12), we get the same approximate stationary probability density (18) of the stochastic process $X(t)$ described by (8) with the additive noise.

Now we are dealing with the approximate stationary probability density of the stochastic linear delay differential equation (8) with the multiplicative noise. Using the before-mentioned notations, we have that $f(x,x_\tau)=K-ax-bx_\tau$, $f^{(0)}(x)=K-(a+b)x$, $D^{(0)}(x)=\frac{\sigma^2x^2}{2}$ and equations (3)-(5) take the following form

$$f_{eff}(x)=(1-b\tau)(Kx-(a+b)x),$$

$$D_{eff}(x)=\sigma^2x^2,$$

$$p_{st}^a(x)=\left(\frac{(1+b\tau)K}{\sigma^2}\right)^{\frac{(1+b\tau)(a+b)}{\sigma^2}}/\Gamma\left(\frac{(1+b\tau)(a+b)}{\sigma^2}\right)\times x^{-\left(\frac{(1+b\tau)(a+b)}{\sigma^2}+1\right)}\exp\left(-\frac{(1+b\tau)K}{\sigma^2x}\right). \quad (19)$$

2.1.3 Stochastic linear model estimation

There are many approaches to estimating the parameters. Very popular approaches for the estimating of parameters are the maximum likelihood procedure and the L^1 distance procedure. The estimation approaches that we follow are the L^1 distance procedure and the maximum likelihood procedure [31], [32]. The parameters *K*, *a*, *b*, τ, σ may be divided into two groups: the drift parameters *K*, *a*, *b*, τ and the diffusion parameter σ. A natural approach would be to first estimate by least squares estimate method the parameters of the deterministic ordinary delay linear differential equation (9), which represents the drift part of the stochastic ordinary delay linear differential equation (8).

Now we discuss the minimizing of the L^1 distance between the observed density (histogram) $p_e(x,t)$ and the fitted density (exact stationary or approximate stationary probability densities) $p(x;K,a,b,\tau,\sigma)$, $p(x;K,a,b,\tau,\sigma)\equiv p_{st}(x)$ or $p(x;K,a,b,\tau,\sigma)\equiv p_{st}^a(x)$ defined by equations

(12), (13), (15), (18), (19)). The function $p_e(x,t)$ depends on the observed data, and the function $p(x;K,a,b,\tau,\sigma)$ depends on the used stochastic growth law. The L^1 distance is defined by

$$d(K,a,b,\tau,\sigma)=\frac{1}{m}\sum_{i=1}^{m}\int_{0}^{+\infty}\left|p_e(x,t^j)-p(x;K,a,b,\tau,\sigma)\right|dx, \quad (20)$$

where m is the number of division of time. In order to simulate numerically the integral defined by the right-hand side of equation (20), we define an observed density as

$$p_e(x^i,t^j)=\frac{1}{\Delta\cdot n}\sum_{k=1}^{n}1_{\left\{x^i-\Delta/2\le x_k<x^i+\Delta/2\right\}},$$

where $1_{\left\{x^i-\Delta/2\le x_k<x^i+\Delta/2\right\}}$ is one if the observation x_k is in $\left[x^i-\Delta/2; x^i-\Delta/2\right[$ and zero otherwise, $x^i=\Delta\cdot i$, n is the number of observations, Δ is the step size. Hence, the numerical approximation of equation (20) takes the form

$$d_1(K,a,b,\tau,\sigma)\approx\frac{1}{m}\sum_{j=1}^{m}\sum_{i=1}^{\infty}\left|p_e(x^i,t^j)-p(x^i;K,a,b,\tau,\sigma)\right|\Delta.$$

Next we consider the maximum likelihood procedure for estimating the parameters of the stochastic ordinary delay linear differential equation (8). The basic idea of the method is that an original stochastic differential equation (9) with the multiplicative noise is first converted into a stochastic differential equation with a constant diffusion part by transformation $Y(t)=\ln(X(t))$. In non delay case ($b=0,\tau=0$), the maximum likelihood function for the observed data $\left\{(t_i,x_i),\quad i=1,2,...,n\right\}$ takes the form:

$$L(r,K,\beta,\sigma)=-\frac{1}{2}\sum_{i=2}^{n}\left[\frac{\left(x(t_i)-E_{i-1}\right)^2}{V_{i-1}}+\ln(2\pi V_{i-1})\right],$$

$$E_{i-1}=x(t_{i-1})+\left(x(t_{i-1})-\frac{K}{a}\right)\left(\exp\left(-a\Delta t_{i-1}\right)-1\right),$$

$$V_{i-1}=\frac{\sigma^2\left(1-\exp\left(-2a\Delta t_{i-1}\right)\right)}{2a},$$

for the additive noise, and

$$L(r,K,\beta,\sigma)=-\frac{1}{2}\sum_{i=2}^{n}\left[\frac{\left(\phi(x(t_i))-E_{i-1}\right)^2}{V_{i-1}}+\ln(2\pi V_{i-1})\right]+\sum_{i=0}^{n}\ln\left(\frac{d\phi(x(t_i))}{dx}p_i(x_i)\right),$$

$$E_{i-1}=\ln x(t_{i-1})+\left(\frac{\left(2a+\sigma^2\right)x(t_{i-1})}{2K}-1\right)\times\left(\exp\left(-\frac{K\Delta t_{i-1}}{x(t_{i-1})}\right)-1\right)+\frac{\sigma^2x(t_{i-1})}{2K}\times\left(\exp\left(-\frac{K\Delta t_{i-1}}{x(t_{i-1})}\right)-1+\frac{K}{x(t_{i-1})}\Delta t_{i-1}\right),$$

$$V_{i-1}=\frac{\sigma^2x(t_{i-1})}{2K}\left(1-\exp\left(-\frac{2K\Delta t_{i-1}}{x(t_{i-1})}\right)\right),$$

$$\phi(x(t_i))=\ln(x(t_i))$$

for the multiplicative noise.

In the time-delay case $b\neq 0,\tau\neq 0$

$$E_{i-1}=x(t_{i-1})+\left(x(t_{i-1})-\frac{K}{a+b}\right)\times\left(\exp\left(-\left(1+b\tau\right)\left(a+b\right)\Delta t_{i-1}\right)-1\right),$$

$$V_{i-1}=\frac{\left(1+b\tau\right)\sigma^2\left(1-\exp\left(-2\left(1+b\tau\right)\left(a+b\right)\Delta t_{i-1}\right)\right)}{2\left(a+b\right)}$$

for the additive noise, and

$$E_{i-1}=\phi(x(t_{i-1}))+\left(\frac{\left(2(a+b)+(1+b\tau)\sigma^2\right)x(t_{i-1})}{2K(1+b\tau)}-\frac{1}{(1+b\tau)}\right)\times\left(e^{-\frac{(1+b\tau)K\Delta t_{i-1}}{x(t_{i-1})}}-1\right)+\frac{\sigma^2x(t_{i-1})}{2K}\times\left(e^{-\frac{(1+b\tau)K\Delta t_{i-1}}{x(t_{i-1})}}-1+\frac{(1+b\tau)K}{x(t_{i-1})}\Delta t_{i-1}\right),$$

$$V_{i-1}=\frac{\sigma^2x(t_{i-1})}{2K\left(1+b\tau\right)}\left(1-e^{-\frac{2(1+b\tau)K\Delta t_{i-1}}{x(t_{i-1})}}\right),$$

$$\phi(x(t_i))=\frac{1}{1+b\tau}\ln(x(t_i)),$$

for the multiplicative noise.

2.1.4 Analysis of the EAT growth data

Let us discuss a numerical example to illustrate theory established in the previous sections 2.1.2, 2.1.3. In 1995, Schuster et al. [41] studied the development of Ehrilch ascities tumor (EAT) in a mouse by creating a microtumor model based on the Verhulst law with time delay. The mathematical reasons for the usage of time delay authors based by the oscillatory behavior of delay differential equations. The drift term of our presented stochastic model (1) differs from the classical deterministic form of the delay Verhulst equation [6], [15], [43], Schuster's model [41], generalized West-Delsanto's model [16], fuzzy dynamic's model [25], and 3-dimensional optimal control problem (see, [21], [22], and references therein).

Now we formally follow the ideas presented for the linear delay stochastic model in sections 2.1.2, 2.1.3, since it corresponds to the linearized form of all logistic models (1).

Compatibility is a central aspect to the responsible application of models to the applied sciences. In this paper the analysis of models' precision is based on the data used to fit them. We will examine three statistics: coefficient of determination for nonlinear regression (R^2), relative error (RE%), and Acaike's Information Index (AII) as follows:

$$R^2 = \left(r_{x_i \overline{X}_i}\right)^2,$$

$$RE\% = \frac{1}{(n-p)\overline{x}}\sum_{i=1}^{n}\left(x_i - \overline{X}_i\right),$$

$$AIC = n\ln\hat{\sigma}^2 + 2(p+1) - \min\left(n, \ln\hat{\sigma}^2 + 2(p+1)\right),$$

where $r_{x_i \overline{X}_i}$ the correlation coefficient between the measured x_i and the estimated $\overline{X}_i$ n is the total number of observations, $\overline{x}$ is the average value of the observed data, p the number of model parameters, $\hat{\sigma}^2$ the estimation of the mean squared error of the model defined by

$$\hat{\sigma}^2 = \frac{1}{n}\sum_{i=1}^{n}\left(y_i - \hat{y}_i\right)^2 .$$

In this paper we additionally check the acceptability of our stochastic models by calculating the Shapiro-Francia statistic [38], W', and plotting the normal percentile plot of residuals.

The stochastic differential equation (8) has been numerically integrated by means of a second order Euler weak scheme with step size $\Delta t = 1/3$ day. We initially simulate $s = 6000$ trajectories defined by

$$\begin{aligned}\hat{X}_{i+1,j} &= \hat{X}_{i,j} + \left(\hat{K} - \hat{a}\hat{X}_{i,j} - \hat{b}\hat{X}_{i-\theta,j}\right)\Delta t + \hat{\sigma}\Delta W_{i,j} + \\ &\left(\hat{K} - \hat{a}\hat{X}_{i,j} - \hat{b}\hat{X}_{i-\theta,j}\right)\frac{\Delta t^2}{2} - \hat{a}\hat{\sigma}\frac{\Delta t}{2}\Delta W_{i,j} + \\ &I_{\{i>\theta\}}\hat{b}\left(\hat{b}\hat{X}_{i-2\theta,j} + \hat{a}\hat{X}_{i-\theta,j} - \hat{K}\right)\frac{\Delta t^2}{2} - \hat{b}\hat{\sigma}\frac{\Delta t}{2}\Delta W_{i-\theta,j}\end{aligned} \tag{21}$$

for the additive noise, and

$$\begin{aligned}\hat{X}_{i+1,j} &= \hat{X}_{i,j} + \left(\hat{K} - \hat{a}\hat{X}_{i,j} - \hat{b}\hat{X}_{i-\theta,j}\right)\Delta t + \\ &\hat{\sigma}\Delta W_{i,j} + \frac{1}{2}\left(\hat{\sigma}\right)^2\left(\Delta W_{i,j} - \Delta t\right) + \\ &\left(\hat{K} - \hat{a}\hat{X}_{i,j} - \hat{b}\hat{X}_{i-\theta,j}\right)\frac{\Delta t^2}{2} - \\ &\hat{\sigma}\left(\hat{a}\hat{X}_{i,j} - \left(\hat{K} - \hat{a}\hat{X}_{i,j} - \hat{b}\hat{X}_{i-\theta,j}\right)\right)\frac{\Delta t}{2}\Delta W_{i,j} + \\ &I_{\{i>\theta\}}\left(\begin{aligned}&\hat{b}\left(\hat{b}\hat{X}_{i-2\theta,j} + \hat{a}\hat{X}_{i-\theta,j} - \hat{K}\right)\frac{\Delta t^2}{2} - \\ &\hat{\sigma}\left(\hat{b}\hat{X}_{i-\theta,j} + \left(\hat{b}\hat{X}_{i-2\theta,j} + \hat{a}\hat{X}_{i-\theta,j} - \hat{K}\right)\right)\frac{\Delta t}{2}\Delta W_{i-\theta,j}\end{aligned}\right)\end{aligned} \tag{22}$$

for the multiplicative noise (here $I_{\{\cdot\}}$ is the indicator function, $N = \frac{T - t_0}{\Delta t}$ is the number of steps, $\theta = \frac{\hat{\tau}}{\Delta t}$, $i = -\theta, -\theta+1, \ldots, 0, \ldots, N$, $W_{0,j} = 0$, $W_{i,j} = W_{i-1,j} + dW$. $i = 1,2,\ldots,N$), dW is an independent random variable of the form $\sqrt{\Delta t}N(0;1)$, $\Delta W_{i,j} = W_{i,j} - W_{i-1,j}$, $i = 1,2,\ldots,N$, $\Delta W_{i-\theta,j} = W_{i,j} - W_{i-\theta,j}$, $i = \theta, \theta+1\ldots, N$, for $i = -\theta, -\theta+1, \ldots, 0$ the initial values $\hat{X}_{i,j}$ are defined by $\hat{X}_{i,j} = \frac{\hat{K}}{\hat{a}+\hat{b}} + \left(x_0 + \frac{\hat{K}}{\hat{a}+\hat{b}}\right)\exp\left(\left(\hat{a}+\hat{b}\right)\Delta t_i\right)$, x_0 is constant). The mean prediction value $\overline{X}_i$ is calculated by

$$\overline{X}_i = \frac{1}{s}\sum \hat{X}_{i,j} \quad i = 1,2,\ldots,N .$$

The estimation method that we follow is first estimate by least squares estimate method the parameters of the deterministic linear model (9), which represents the drift term of the stochastic linear model (8), and then use the maximum likelihood procedure to estimate the parameter σ, which represents the amplitude of diffusion. Practically we could estimate simultaneously all parameters appearing in equation (8) by the maximum likelihood procedure. Unfortunately, the precise of such estimate suffers from the adjusted transformation $Y(t) = \ln(X(t))$ of the original process $X(t)$, and the linearization of the drift term of transformed process $Y(t)$.

The parameter estimates for both additive and multiplicative models and their corresponding goodness of fit statistics are shown in Table 1. The additive and multiplicative models provide very similar results, as indicated by the graphs that represent the mean predicted curves on the trajectory of the observed EAT in a mouse over time (Figure 1), and the goodness of fit statistics (Table 1). The additive and multiplicative models explain 93% and 93.4% of the total variance. An analysis of the results in Table 1 based on the above mentioned three goodness of fit statistics indicate that the stochastic delay linear growth model with multiplicative noise fits better than with additive noise. The goodness of fit statistics R^2, *RE%, AIC* (Table 1) show us that the delay linear model fits better than the non delay linear model.

Because the quality of fit, measured by statistics R^2, *RE%, AIC*, does not necessarily reflect the quality of future prediction, we examine the residuals. A basic graphical approach for checking normality of residuals is the normal percentile plot. The normal percentile plot compares the *ith* ordered value of residual, r_i, with the *i/(n+1)th* value of the standard normal distribution, $z_i = \phi^{-1}(i/(n+1))$ (rankits). The normal percentile plots are reported in Figure 2. Both almost straight lines formed by the normal percentile plots in Figure 2 indicate that each of models gives the correct residuals. The values of the Shapiro-Francia statistics for the time delay stochastic linear model with the additive noise, 0.9826, and multiplicative noise, 0.9842, are above the 5% critical point $W'(0.05;13) = 0.9310$. So, these values are consistent with the assumption that the residuals have a normal distribution.

It is evident that the growth of a tumor may be affected by the environment such as chemotherapy and radiotherapy. The treatments not only kill the tumors, but also activate them.

The amplitude of multiplicative noise reflects environment's random changes. The additive noise gives a diffusion factor in the tumor growth process. The stationary mean and variance are presented in Table 2, and shown in Figure 3. In delay case we used the approximate stationary densities (18), (19), since the exact stationary density (17) does not exist for the parameter estimates presented in Table 1. The increase in mean means that the tumor grows up, otherwise extincs. The increase in variance means that the tumor falls down, otherwise grows up. As we can see in Figure 1, the variance has tendency to grow for both linear delayed models. In Figure 3 we can see the differences between the stationary distributions of both additive and multiplicative models. Although the additive and multiplicative curves are quatitatively different (by shape), they are quantitavely similar (by first moment).

Table 1. Parameter estimates and goodness of fit statistics.

Noise	Parameters					Statistics		
	K	a	b	τ	σ	R^2	*RE%*	AIC
Additive	164380061	0.1090			152915007	0.7432	38.09	499.35
Multiplicative	164380061	0.1090			0.2413	0.7450	37.60	499.01
Additive	106215545	0.0000	0.2627	8.8619	196690406	0.9304	19.8	482.37
Multiplicative	106215545	0.0000	0.2627	8.8619	0.1640	0.9394	18.5	481.75

Table 2. Stationary mean and variance.

Noise	Non-delay process		Delay process	
	Mean	Variance	Mean	Variance
Additive	$0.16077\ 10^{10}$	$0.55192\ 10^{17}$	$0.43424\ 10^{9}$	$0.15519\ 10^{18}$
Multiplicative	$0.15079\ 10^{10}$	$0.82866\ 10^{18}$	$0.41998\ 10^{9}$	$0.43349\ 10^{16}$

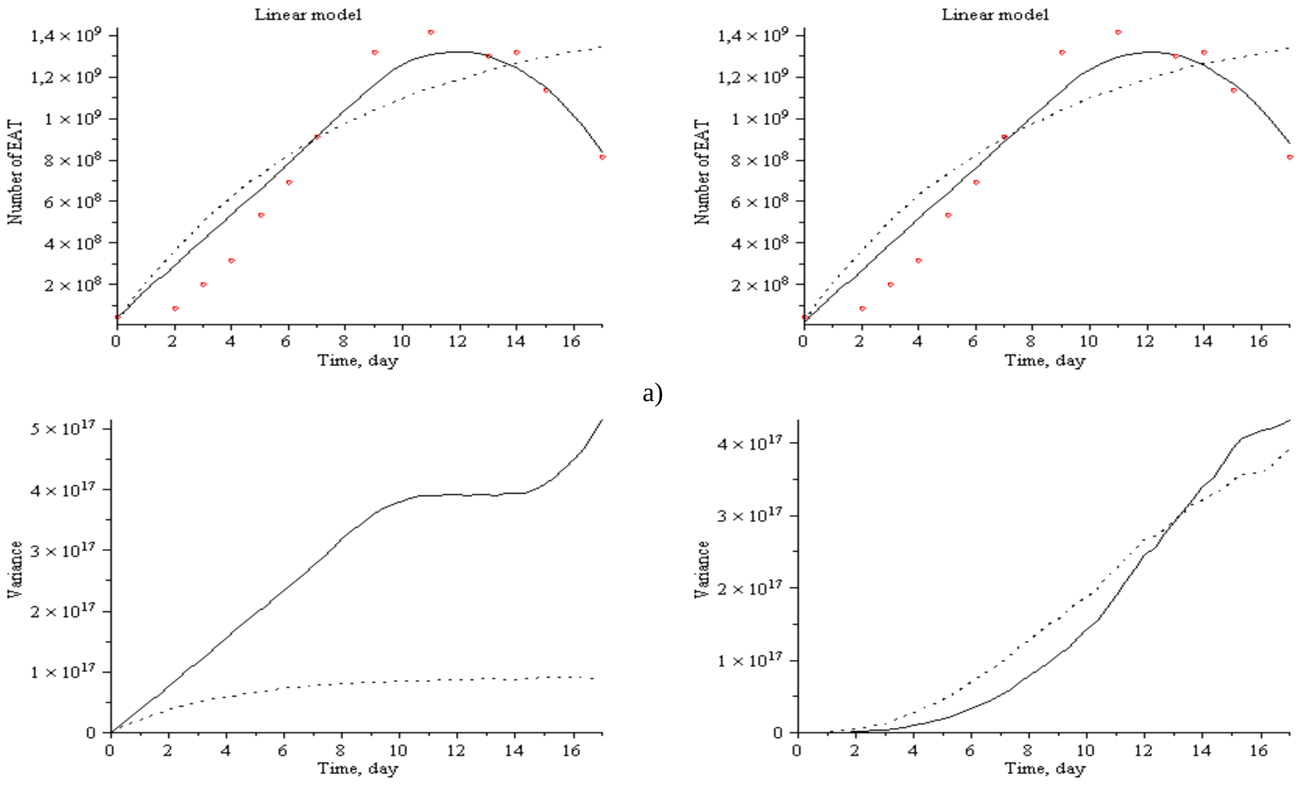


Fig. 1. Curves on the stochastic linear trajectory of mean (a), and variance (b) of the observed EAT in mouse over time (solid line –delayed, dot line – non-delayed): additive noise (left), multiplicative noise (right).

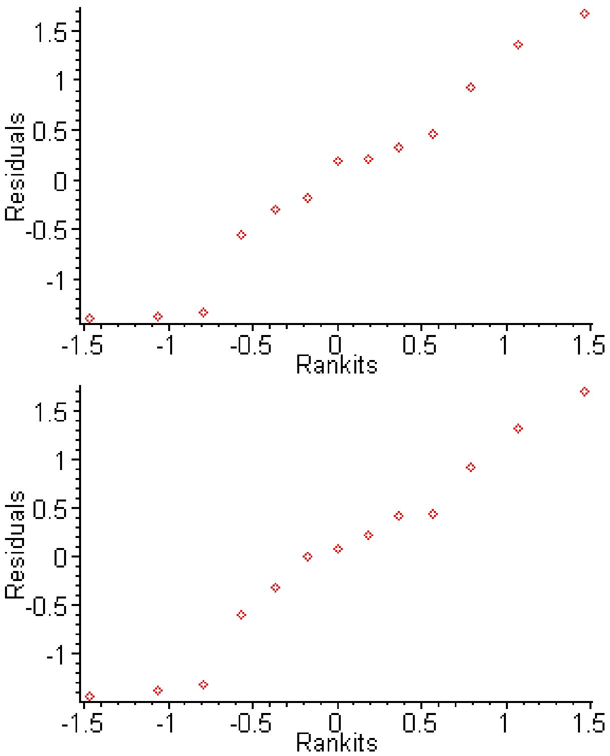


Fig. 2. Normal percentile plots: additive noise (top), multiplicative noise (bottom).

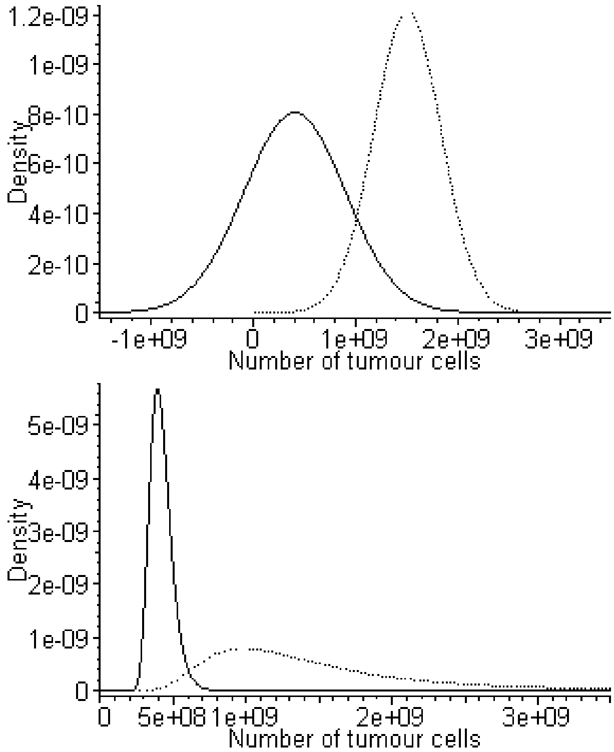


Fig. 3. Stationary probability densities (solid line – delayed, dot line – non-delayed): additive noise (top), multiplicative noise (bottom).

For the delayed stochastic linear growth model (8) we are not able to determinate the exact transition probability density of the process $X(t)$. So we simulate an approximate transition probability density of the process $X(t)$ using a Monte Carlo simulation method and the 2.0 order weak Euler scheme (21)-(22). However, discretization introduces a bias in the simulation of density, which tends to 0 as Δ tends to 0. The simulated probability densities (number of simulations $s = 6000$, $\Delta t = 1/3$) are shown in Figure 4.

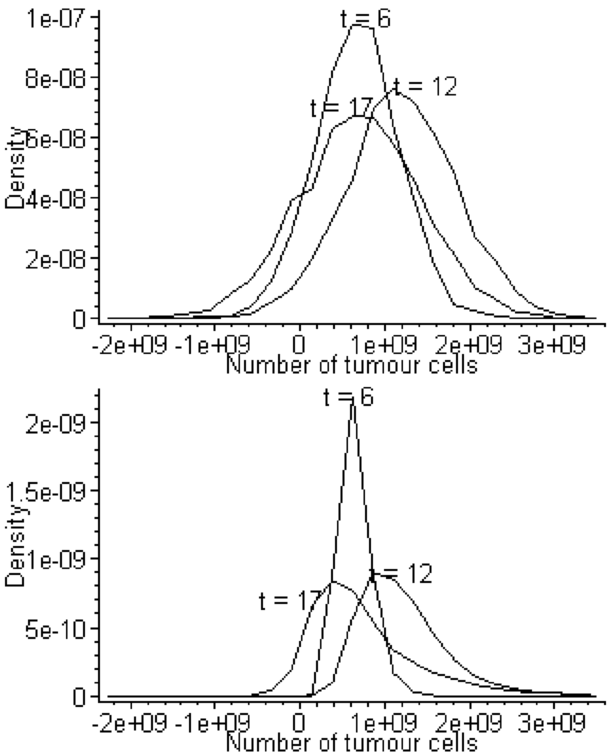


Fig. 4. Simulated transition probability densities for linear model: additive noise (top), multiplicative noise (bottom).

2.2 Logistic delay stochastic equation

Next we consider the delay stochastic differential equation (1). When $\sigma = 0$, we have the deterministic delay differential equation

$$\frac{dx(t)}{dt} = rx(t)G(x(t)) + \alpha x(t-\tau), \tag{23}$$

$$x(s) = \varphi(s), \quad s \in [t_0 - \tau; t_0],\, t \in [t_0; T].$$

A steady state solution x_* of equation (23) is defined by $rx_* G(x_*) + \alpha x_* = 0$. The non-zero solution $x_* \equiv x(t) \neq 0$ is not a solution of the perturbed equation (1). Hence, we linearize equation (1) around the non-zero steady state. This linearization yields the stochastic linear differential equations

$$dX(t) = \begin{pmatrix} \dfrac{K(r+\alpha)^2}{r} - \\ (r+2\alpha)X(t) + \alpha X(t-\tau) \end{pmatrix} dt + \sigma \begin{cases} dW(t) \\ X(t)dW(t) \end{cases} \tag{24}$$

Verhulst model,

$$dX(t) = \begin{pmatrix} rK\exp\left(\dfrac{\alpha}{r}\right) - \\ (r+\alpha)X(t) + \alpha X(t-\tau) \end{pmatrix} dt + \sigma \begin{cases} dW(t) \\ X(t)dW(t) \end{cases} \tag{25}$$

Gompertz model,

$$dX(t) = \begin{pmatrix} K\beta(r+\alpha)(r+\alpha)^{\frac{1}{\beta}} - \\ (\beta(r+\alpha)+\alpha)X(t) + \alpha X(t-\tau) \end{pmatrix} dt + \sigma \begin{cases} dW(t) \\ X(t)dW(t) \end{cases} \tag{26}$$

Richards model.

The parameters of the deterministic model (23), which represents the drift term of the stochastic model (1) we estimate by least squares estimate method, using the order 2.0 scheme of equation (23), and then use the maximum likelihood procedure to estimate the parameter σ, using the linearized forms (24)-(26) of logistic growth models. The parameter estimates for all logistic models and their corresponding goodness of fit statistics are shown in Table 3. The order 2.0 weak Euler scheme of stochastic differential equation (23) takes the following form

$$\begin{aligned} \hat{X}_{i+1,j} &= \hat{X}_{i,j} + \left(\hat{r}G(\hat{X}_{i,j}) + \hat{\alpha}\hat{X}_{i-\theta,j}\right)\Delta t + \hat{\sigma}\Delta W_{i,j} + \\ &\left(\hat{r}G(\hat{X}_{i,j}) + \hat{\alpha}\hat{X}_{i-\theta,j} + \frac{1}{2}\left(\hat{\sigma}\right)^2 G''(\hat{X}_{i,j})\right)\frac{\Delta t^2}{2} + \\ &\hat{\sigma}G'(\hat{X}_{i,j})\frac{\Delta t}{2}\Delta W_{i,j} + \\ &I_{\{i>\theta\}}\left\{\hat{\alpha}\left(\hat{r}G(\hat{X}_{i-\theta,j}) + \hat{\alpha}\hat{X}_{i-2\theta,j}\right)\frac{\Delta t^2}{2} + \hat{\sigma}\hat{\alpha}\frac{\Delta t}{2}\Delta W_{i-\theta,j}\right\} \end{aligned} \tag{27}$$

for the additive noise, and

$$\hat{X}_{i+1,j}=\hat{X}_{i,j}+\left(\hat{r}G(\hat{X}_{i,j})+\hat{\alpha}\hat{X}_{i-\theta,j}\right)\Delta t+\hat{\sigma}\Delta W_{i,j}$$
$$+\frac{1}{2}\left(\hat{\sigma}\right)^2\hat{X}_{i,j}\left(\left(\Delta W_{i,j}\right)^2-\Delta t\right)+$$
$$\left(\hat{r}G(\hat{X}_{i,j})+\hat{\alpha}\hat{X}_{i-\theta,j}+\frac{1}{2}\left(\hat{\sigma}\hat{X}_{i,j}\right)^2G''(\hat{X}_{i,j})\right)\frac{\Delta t^2}{2}+ \qquad (28)$$
$$\left(\hat{\sigma}\hat{X}_{i,j}G'(\hat{X}_{i,j})+\hat{\sigma}\left(\hat{r}G(\hat{X}_{i,j})+\hat{\alpha}\hat{X}_{i-\theta,j}\right)\right)\frac{\Delta t}{2}\Delta W_{i,j}+$$
$$I_{\{i>\theta\}}\left\{\begin{array}{l}\hat{\alpha}\left(\hat{r}G(\hat{X}_{i-\theta,j})+\hat{\alpha}\hat{X}_{i-2\theta,j}\right)\frac{\Delta t^2}{2}+\\ \hat{\sigma}\hat{X}_{i-\theta,j}\,\hat{\alpha}\frac{\Delta t}{2}\Delta W_{i-\theta,j}\end{array}\right\}$$

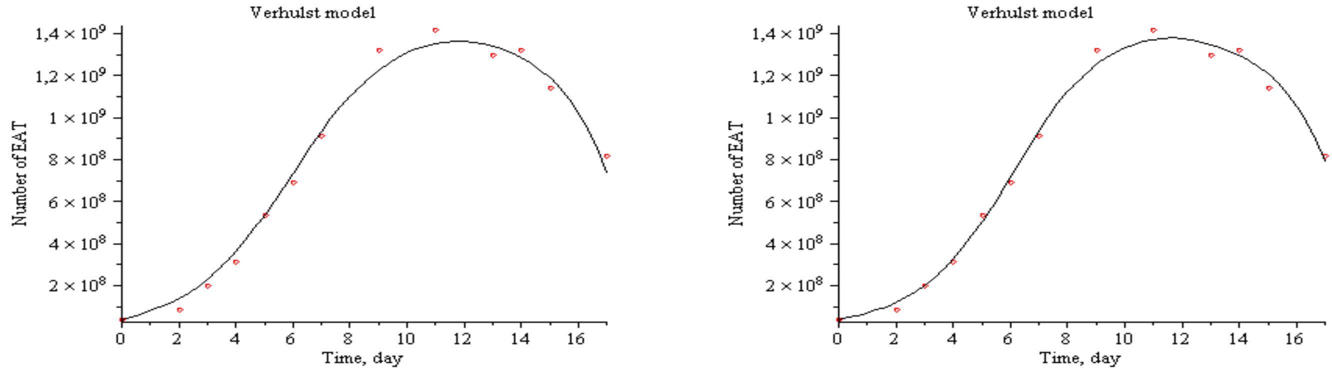
for the multiplicative noise.

The values of the Shapiro-Francia statistics for all time delay and non-delay stochastic models with the additive and multiplicative noises are above the 5% critical point $W'(0.05;13)=0.9310$. It is evident that these values are consistent with the assumption that the residuals have a normal distribution.

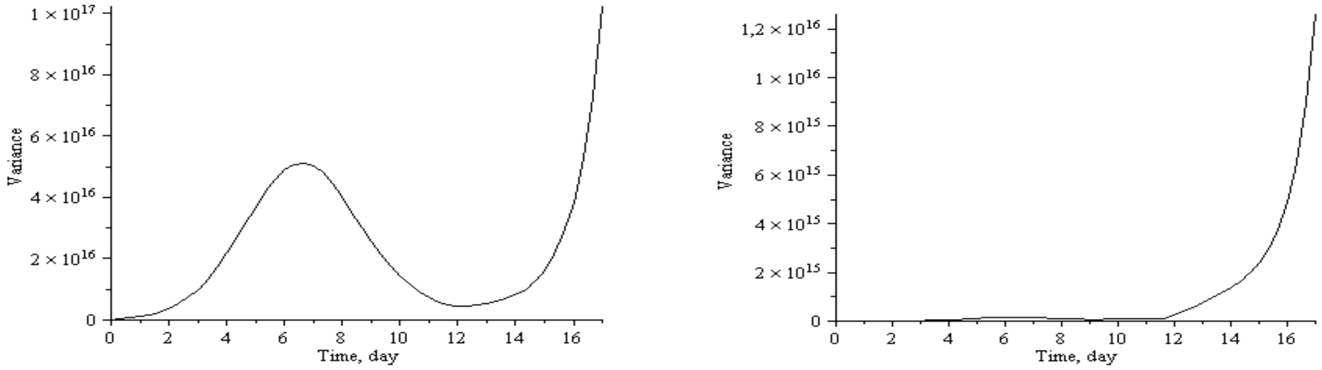
The predicted mean, variance and normal percentile plot curves of the Verhulst, Gompertz, Richards models are shown in Figure 5. The summaries of the R^2, *RE%*, *AIC* goodness of fit statistics are presented in Table 3. Hence, all delayed logistic models of EAT growth have very high goodness of fit statistics. The normal percentile plots in Figure 5 show that all models of EAT growth fit the observed data set very well at 5% confidence level. As we can see from Table 3, all stochastic delayed logistic models perform the observed data set well and produce consistently better goodness of fit statistics then stochastic delay linear model. For the goodness of fit statistics presented in this paper, the Richards law shows superior quality. The Richards type simulated transition probability density functions of the tumor growth process $X(t)$ are shown in Figure 6. As we see in Figures 5, 6 the spreading of the transition probability density function for the additive noise is higher than in the multiplicative case. The stochastic logistic equations of tumor growth provide an adequate description of EAT dynamics. Note that the mean of EAT's trajectory not monotonically evolves toward the steady-state value for the all used stochastic logistic growth models, and the path by which the variance of EAT's trajectory evolves to the steady-state value not always increasing too for the Verhulst, Gompertz and Richards models.

Table 3. Parameter estimates and goodness of fit statistics for logistic growth models

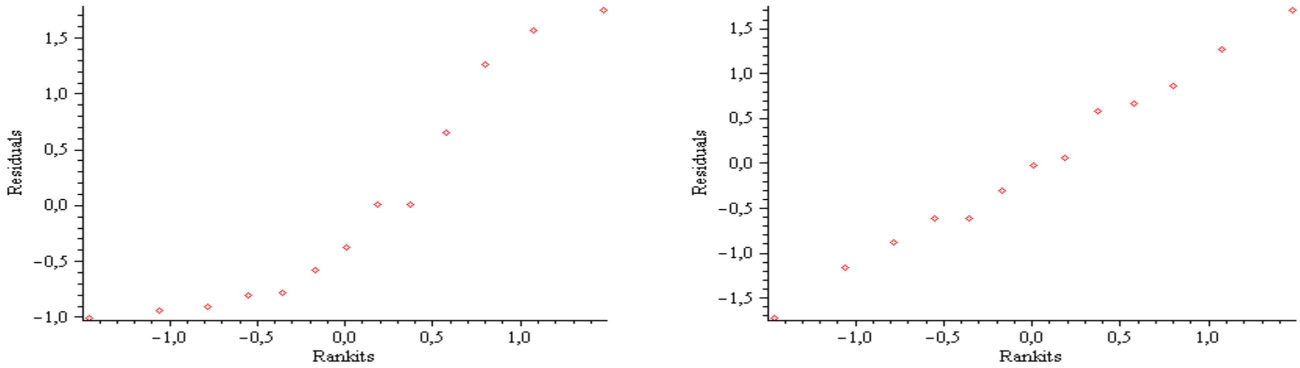
Model	Noise	Parameters						Statistics			
		r	K	β	α	τ	σ	R^2	*RE%*	AIC	*W'*
Verhulst	Additive	0.567	1241932694.				85532511..	0.824	31.58	494.5	0.931
	Multiplicative	0.567	1241932694.				0.1969	0.894	24.25	487.9	0.947
	Additive	0.543	1422721716		-826	11.823	36050467	0.990	7.65	457.7	0.940
	Multiplicative	0.543	1422721716		-.826	11.823	0.093	0.994	5.80	450.4	0.996
Gompertz	Additive	0.317	1272123477.				31801499.	0.851	29.01	492.2	0.962
	Multiplicative	0.317	1272123477.				0.278	0.854	28.68	492.0	0.979
	Additive	0.220	1776053855		-.364	9.7382	17172051	0.982	10.19	465.1	0.968
	Multiplicative	0.220	1776053855		-.364	9.7382	0.140	0.982	10.10	464.8	0.975
Richards	Additive	0.500	1217468088.	2.629			78365123..	0.863	28.06	490.5	0.968
	Multiplicative	0.500	1217468088	2.629			0.215	0.872	27.52	489.8	0.975
	Additive	0.5307	1421767563	1.073	-.848	11.679	23019341	0.991	7.09	455.7	0.987
	Multiplicative	0.5307	1421767563	1.073	-.848	11.679	0.048	0.995	5.62	449.6	0.990



(a)


Variance
Time, day
Variance
Time, day

(b)


Residuals
Rankits
Residuals
Rankits

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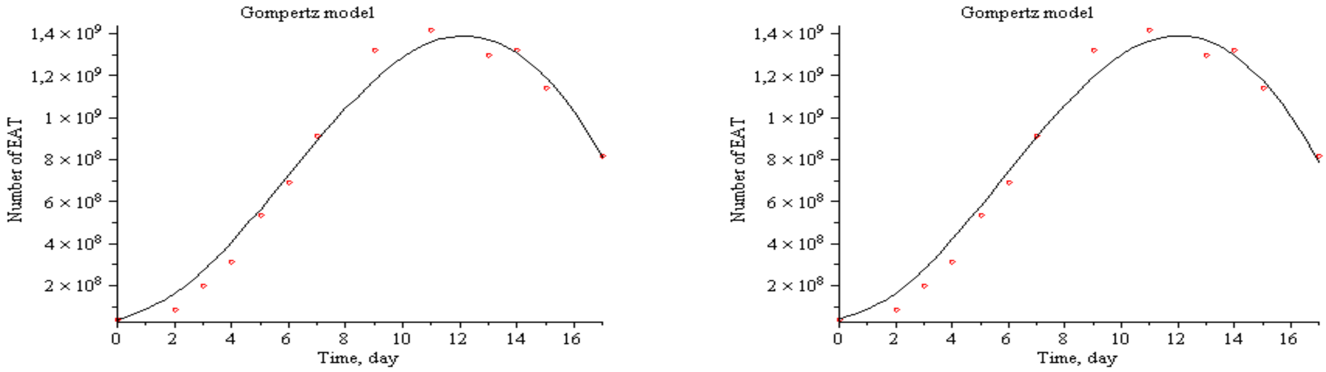
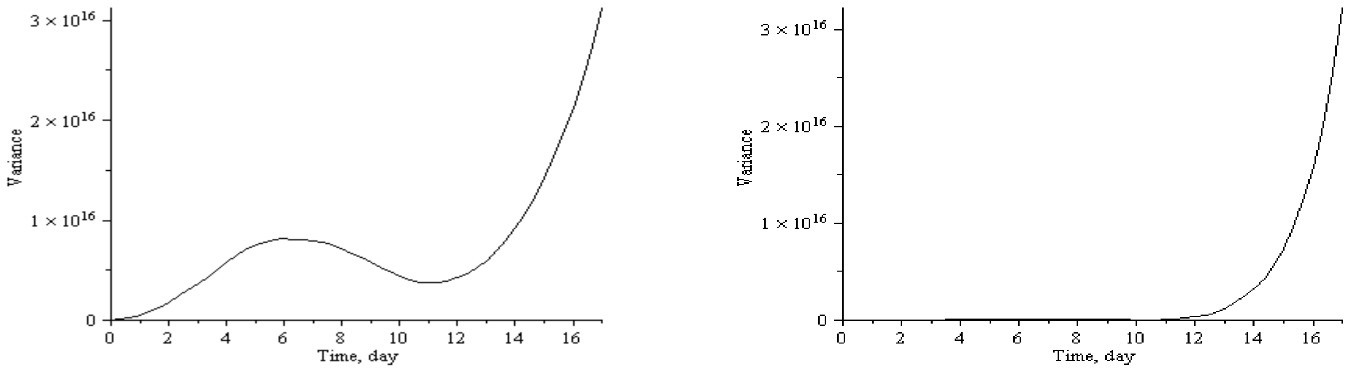
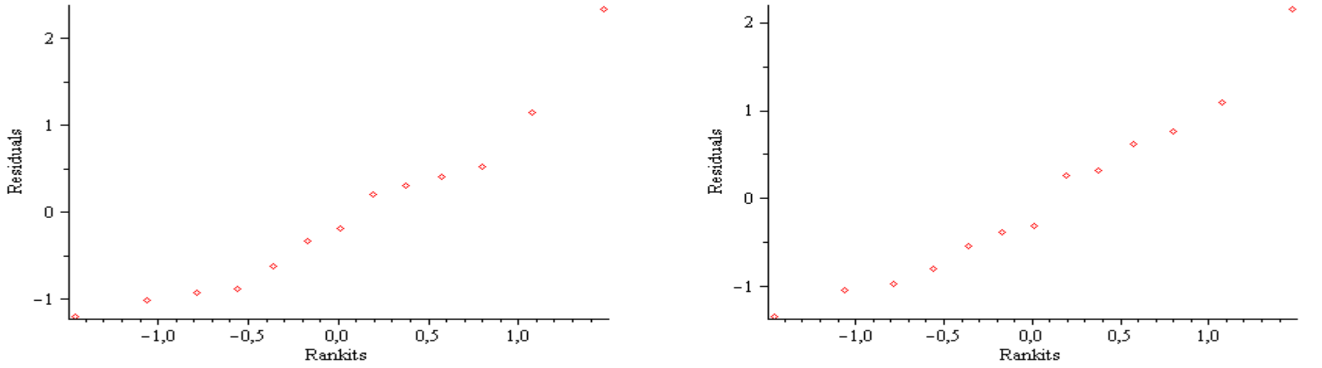

Gompertz model
Number of EAT
Time, day
Gompertz model
Number of EAT
Time, day

(a)


Variance
Time, day
Variance
Time, day

(b)



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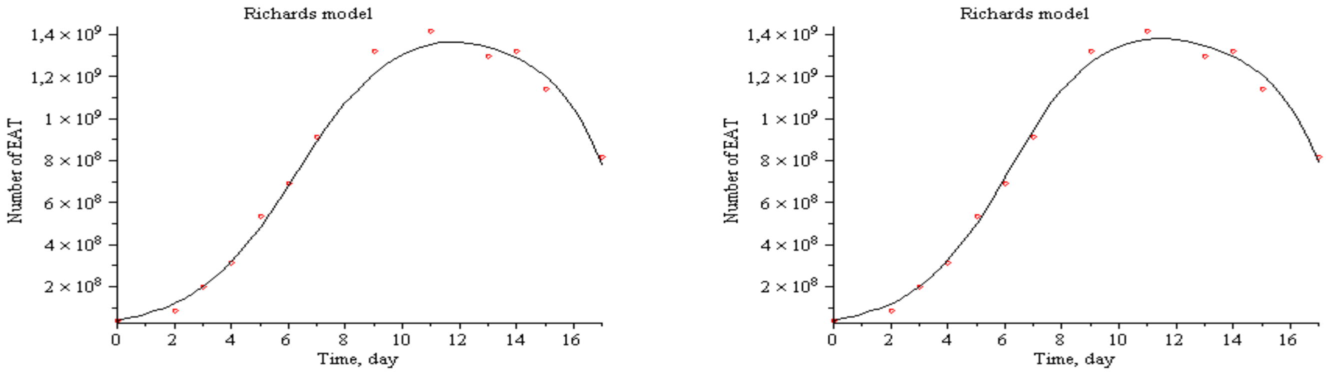
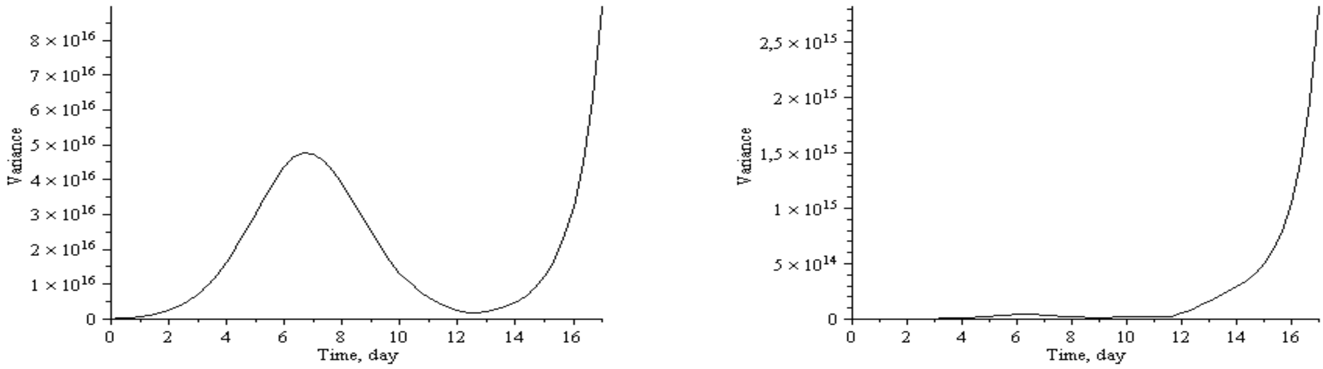


(a)



(b)

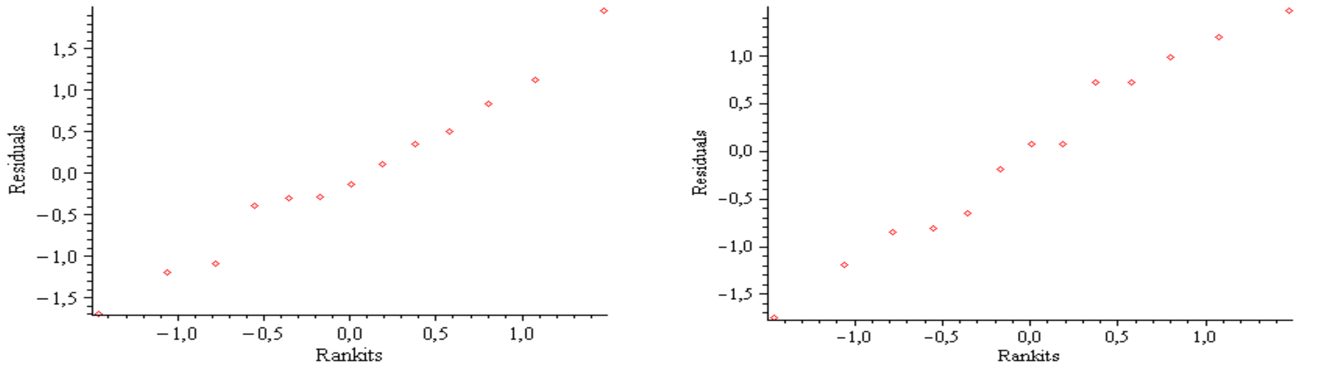


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Fig. 5. Curves on the Verhulst, Gompertz, Richards mean trajectory (a), variance (b), normal percentile plot (c): additive noise (left), multiplicative noise (right).

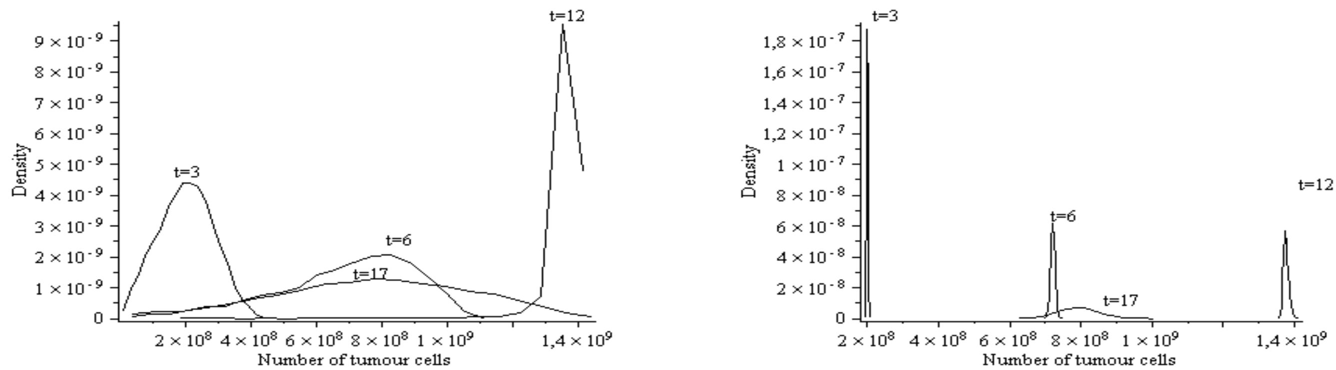

Fig. 6. Simulated transition probability densities for Richards model: additive noise (left), multiplicative noise (right).

3 Conclusions

The stochastic logistic single-species population model that we have considered is one of the several possible stochastic versions of the corresponding deterministic logistic population growth in a random fluctuating environment characterized by white noise. Obviously no model can perfect describe every growth pattern phenomenon that researches encountered in their practice and the same is true for our used stochastic time delay models. From an examination of Figures 1, 5 and Tables 1, 3, it is obvious that the all used logistic stochastic models fit better the linear stochastic model and their variances are much less too. Numerical simulations suggest that the variance of all used models with the multiplicative noise grows up and it means that the tumor falls down. Hence, stochastic models may provide new insight (not possible in a deterministic model) into the evolution and treatment of tumor. In these data, stochastic logistic type growth models with multiplicative noise are more effective in predicting the tumor growth then with the additive noise.

In the final note, we wish to point out that the method implemented here for obtaining the population dynamics, based on postulated growth model as a function of the time, could be modified incorporating more growth laws. The dynamics of population growth can be expanded using more predictor variables of single-species population.

The research presented here can be extended in several directions. First type of possible extension is to understand better the main features of the growth processes of the biological, ecological, physical, economical systems, in order to choose the most adequate mathematical model. Second type of extension is to apply the delayed stochastic logistic growth laws to theoretical examination of the growth processes in biology, ecology, biomedicine, physics, economics.

Finally, it is interesting to consider an alternative information theoretic approach of modeling and assessing of dynamics of single-species population. The information theoretical measures play a crucial theoretical role in physics of macroscopic equilibrium systems. The Shannon's entropy and Fisher's information represent promising tools to illustrate the behavior of multidimensional systems in biology, ecology, biomedicine. A stable steady state in biology is important for an understanding of biosystems as dynamical complex processes. A departure from steady state indicates a negative unhealthy situation of biosystem. The importance of stable steady state, as a criteria for biological well-being, emphasize many researches.

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