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MODELLING THE CANCER GROWTH PROCESS BY STOCHASTIC DELAY DIFFERENTIAL EQUATIONS UNDER VERHULTS AND GOMPERTZ'S LAW

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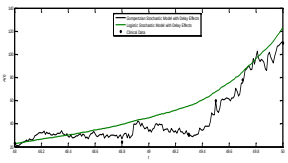
Graphical abstract



Abstract

In this paper, the uncontrolled environmental factors are perturbed into the intrinsic growth rate factor of deterministic equations of the growth process. The growth process under two different laws which are Verhults and Gompertz's law are considered, thus leading to stochastic delay differential equations (SDDEs) of logistic and Gompertzian, respectively. Gompertzian deterministic model has been proved to fit well the clinical data of cancerous growth, however the performance of stochastic model towards clinical data is yet to be confirmed. The prediction quality of logistic and Gompertzian SDDEs are evaluating by comparing the simulated results with the clinical data of cervical cancer growth. The parameter estimation of stochastic models is computed by using simulated maximum likelihood method. We adopt 4-stage stochastic Runge-Kutta to simulate the solution of stochastic models.

Keywords: Verhults law; Gompertz law; deterministic model; stochastic delay differential equations

Abstrak

Dalam kertas kerja ini, faktor-faktor persekitaran yang tidak terkawal diganggu ke atas faktor pertumbuhan kadar intrinsik untuk persamaan berketentuan bagi proses pertumbuhan. Proses pertumbuhan di bawah dua hukum yang berbeza iaitu Verhults dan Gompertz dipertimbangkan, seterusnya membawa kepada persamaan pembezaan stokastik dengan masa lengahan (SDDEs) logistik dan Gompertzian, masing-masing. Model Gompertzian berketentuan telah terbukti sesuai untuk data klinikal pertumbuhan kanser, bagaimanapun keberkesanan model stokastik terhadap data klinikal masih belum disahkan. Kualiti ramalan SDDEs logistik dan Gompertzian dinilai dengan membandingkan keputusan simulasi dengan data klinikal pertumbuhan kanser pangkal rahim. Anggaran parameter model stokastik dihitung dengan menggunakan kaedah simulasi kebolehjadian maksimum. stokastik Runge-Kutta peringkat 4 digunakan untuk mensimulasikan penyelesaian model stokastik.

Kata kunci: Hukum Verhults; hukum Gompertz; model berketentuan; persamaan pembezaan stokastik dengan masa lengahan

1.0 INTRODUCTION

According to the World Health Organization (WHO), cervical cancer is the second most common cancer afflicting women around the world, with an estimate 530,000 new cases in each year [1]. The National Cancer Society Malaysia (NCSM) reported that there were an average of 1500 is diagnosed with cervical cancer per year and most of the cases are in a stage four of the disease. The death rate due to cervical cancer is about 6% among women in Malaysia [2].

One of the factor to the increased of cancer death is the lack of understanding of the biological complexities of growth law of cancer cells. Recently, much attention has been directed towards growth law of cancer cells in order to improve both cancer screening and treatment. In fact, a mathematical model has been used as an effective tool in understanding the dynamic behavior of cancer progression and metastasis formation [3].

Many studies have been performed to determine which deterministic model is the best fitting the data for cancerous growth [4−8]. In deterministic model, there are two mathematical models of cancerous growth have been considered. Probably, for most deterministic model that can be found in the literature and shown to have a good agreement with the cancerous growth data is Gompertz model. It has been used in numerous studies involving animals [8−12] and human data [11, 13−15]. In addition, there is another form of deterministic model that often used in the description of cancerous growth, which is the logistic model [16−19].

In nature, the real biological system will always operate in a highly uncertain environment as a result of the noisy behavior of human body such as hormonal oscillations, blood pressure variations, respiration, variable neural control of muscle activity, enzymatic processes, energy requirements, cellular metabolism and sympathetic nerve activity that may lead in the presence of stochastic effects. The individual characterics like body mass index, genes, smoking and stress impact may also affect the cancerous growth behavior [20]. All these fluctuations can be regulated by factors that influence to control cancer cells proliferation and differentiation.

From the previous research, it is well known that delay feedback also can play a crucial role in the modeling of cancerous growth. According to [21], the delay occurs during the time taken from cancerous cells undergo mitosis and the change in the proliferation rate to stimulate compensatory change in the apoptotic cell loss. It is also obvious that the dynamical behavior of cancer cell growth rate depends not only on its structure at the present time, but also on its structure at some previous time [21]. Therefore, mathematical model of biological system should include uncontrolled factors and time delay that stimulus the cancerous growth. This can be modeled by using stochastic delay differential equation (SDDE).

To date, it is believed in the deterministic case, the Gompertz and logistic models are frequent used for describing cancerous growth. However if the stochastic effect and time delay are taken into account it is the same case happen for SDDE. Therefore, by extending the deterministic model to a stochastic model with time delay, the model that adequately explained the cancerous growth need to be identified. Thus, it is the aimed of this research to compare the performance of stochastic Gompertz and logistic models with delay feedback in describing the behavior of cancerous growth.

This paper is organised as follows; Section 2 presents stochastic models with time delay for cervical cancer growth. In Section 3, numerical solution and parameter estimation of stochastic models with delay effects are performed. Then, the simulated results of the mathematical models and clinical data of cancerous growth are plotted and also the root mean-square error is measured in Section 4. Finally, Section 5 offers a brief discussion and some concluding remarks.

2.0 MATHEMATICAL MODELS

2.1 Gompertzian Model

The Gompertzian deterministic model was introduced by [22] and a thorough analysis of it can be found in [9]. The Gompertzian deterministic can be represented by mathematical formula

$$dA(t) = \left[a - b\ln A(t)\right]A(t)dt \tag{1}$$

where $A(t)$ denotes the area of the cancer cell at time t, a is the intrinsic growth rate of cancer cell which is a parameter of the initial mitosis rate and b describes the growth rate deceleration factor that relates to the antiangiogenesis process. Studies have shown that many mathematical models of cancerous growth are developed based on the assumption of the growth deceleration factors do not change [15, 23, 24] since the cancer cells usually have the ability to proliferate indefinitely [25]. Equation (1) should include stochastic effects or noise since the random fluctuations occur in cancerous growths which are not completely understood or not feasible to model deterministically. The stochastic differential equation is developed, by assuming that the intrinsic growth rate parameter varies according to

$$a \to a + \sigma\frac{dW}{dt} \tag{2}$$

where $\sigma > 0$ is a diffusion coefficient and the process of dW for $t \geq 0$ is a Gaussion white noise process with mean zero and variance, Δt. Hence, yield

$$dA(t) = \left[a - b\ln A(t)\right]A(t)dt + \sigma A(t)dW(t). \tag{3}$$

In such a case, time delay is considered for cancerous cell to up regulate rate of production of a particular growth factor, then growth factor modify rate of cell loss due to apoptosis [21]. Time delay, r is

introduced into the initial mitosis rate and antiangiogenesis process. Equation (3) is modified which evolves according to the stochastic Gompertzian model with delay effects

$$dA(t) = \left[aA(t-r) - bA(t-r)\ln A(t)\right]dt + \sigma A(t)dW(t). \quad (4)$$

2.2 Logistic Model

The deterministic logistic model has been proposed by [26]. It has the form

$$dA(t) = \left[a - bA(t)\right]A(t)dt \quad (5)$$

where $A(t)$ represents the area of the tumor at time t, a is the intrinsic growth rate of the tumor which is a parameter of initial mitosis rate and b describes the growth rate deceleration factor that relates to the antiangiogenic process. In the biological process, the mathematical model should include stochastic since there are many factors that cannot be controlled in human body. Hence, the intrinsic growth factor is allowed into equation (5) such that the initial mitosis rate parameter

$$a \to a + \sigma\frac{dW}{dt} \quad (6)$$

where $\sigma > 0$ is the diffusion coefficient and the process of dW for $t \geq 0$ is a Gaussion white noise process with mean zero and variance, Δt. Thus, logistic SDE is given by

$$dA(t) = \left[a - bA(t)\right]A(t)dt + \sigma A(t)dW(t). \quad (7)$$

The stochastic model of cancer growth only depends on the structure at the present time. The dynamical behavior of cancerous growth not only relies on the structure of its growth at some present time but also depend on the structure at some previous time [21]. By introducing time delay, r in connection with initial mitosis rate and antiangiogenesis process, equation (7) has the form

$$dA(t) = \left[aA(t-r) - bA(t-r)A(t)\right]dt + \sigma A(t)dW(t). \quad (8)$$

Equation (8) is known as stochastic logistic model with delay effects. In this work, the performance of models (4) and (8) in describing the growth of cervical cancer are investigated. Moreover, the clinical data are used to determine the model that provides the best fit for cancerous growth.

3.0 NUMERICAL METHOD

The analytical solution of stochastic models with delay effects (4) and (8) are difficult to be solved, thus numerical method is used to approximate the strong solution of SDDEs. In this paper, we adopt a 4-stage stochastic Runge-Kutta (SRK4) to simulate solution of Gompertzian (4) and logistic (8) stochastic model with time delay. SRK is known as derivative-free method. According to [27], the formulation of SRK method for SDDE is

$$\begin{aligned} Y_i^{(n)}(t) &= Y(t_0) + \sum_{j=1}^{s} Z_{ij}^{(0)} f\left(Y_j^{(n)}(t), Y_j^{(n-m)}(t)\right) \\ &\quad + \sum_{j=1}^{s} Z_{ij}^{(1)} g\left(Y_j^{(n)}(t)\right) \\ y(t) &= y(t_0) + \sum_{j=1}^{s} z_i^{(0)} f\left(Y_i^{(n)}(t), Y_i^{(n-m)}(t)\right) \\ &\quad + \sum_{j=1}^{s} z_i^{(1)} g\left(Y_i^{(n)}(t)\right) \end{aligned} \quad (9)$$

where, $Z_{ij}^{(0)}$, $Z_{ij}^{(1)}$, $z_i^{(0)}$ and $z_i^{(1)}$ are written as

$$\begin{aligned} Z_{ij}^{(0)} &= \Delta a_{ij}, & i,j &= 1,\ldots,s. \\ Z_{ij}^{(1)} &= \sum_{l=1}^{q} b_{ij}^{(l)}\theta_l, & i,j &= 1,\ldots,s. \\ z_i^{(0)} &= \Delta\alpha_i, & i,j &= 1,\ldots,s. \\ z_i^{(0)} &= \sum_{l=1}^{q} \gamma_i^{(l)}\theta_l, & i,j &= 1,\ldots,s. \end{aligned} \quad (10)$$

For $q = 2$, then $\theta_1 = J_1$ and $\theta_2 = \frac{J_{10}}{h}$, where $J_1 = \int_{t_n}^{t_{n+1}} dW(s)ds$ and $J_{10} = \int_{t_n}^{t_{n+1}}\int_{t_n}^{t} dW(s)ds$. The random variables J_1 and J_{10} is approximated by using

$$J_1 = \sqrt{h}G_1, \qquad \frac{J_{10}}{h} = \frac{\sqrt{h}}{2}\left(N_1 + \frac{N_2}{\sqrt{3}}\right)$$

where N_1 and N_2 are standard normal distribution. Thus, $s-$stage SRK is represented as

$$\begin{aligned} Y_i^{(n)}(t) &= Y(t_0) + \Delta\sum_{j=1}^{s} a_{ij}^{(0)} f\left(Y_j^{(n)}(t), Y_j^{(n-m)}(t)\right) \\ &\quad + \sum_{j=1}^{s}\left(b_{ij}^{(1)}J_1 + b_{ij}^{(2)}\frac{J_{10}}{h}\right) g\left(Y_j^{(n)}(t)\right) \\ y(t) &= y(t_0) + \Delta\sum_{j=1}^{s} \alpha_i^{(0)} f\left(Y_i^{(n)}(t), Y_i^{(n-m)}(t)\right) \\ &\quad \sum_{j=1}^{s}\left(\gamma_i^{(1)}J_1 + \gamma_i^{(2)}\frac{J_{10}}{h}\right) g\left(Y_i^{(n)}(t)\right) \end{aligned} \quad (11)$$

It was [27] who proposed a SRK4 scheme for SDDEs with strong order 1.5. The numerical scheme of SRK4 is presented in the following tableu form

$$\begin{array}{c|ccc} & \frac{1}{2} & & \\ A & 0 & \frac{1}{2} & \\ & 0 & 0 & 1 \\ \hline \alpha & \frac{1}{6} & \frac{1}{3} & \frac{1}{3} \quad \frac{1}{6} \end{array}$$

$$\begin{array}{c|ccc} & -\frac{11}{18} & & \\ B^{(1)} & \frac{23}{66} & -\frac{47}{198} & \\ & 0 & \frac{1}{2} & \frac{1}{2} \\ \hline \gamma^{(1)} & -1 & 0 & \frac{22}{16} \quad \frac{5}{16} \end{array}$$

$$\begin{array}{c|ccc} & \frac{358}{18865} & & \\ B^{(2)} & -\frac{358}{18865} & -\frac{362097}{18865} & \\ & -\frac{362097}{18865} & -\frac{28998}{18865} & \frac{78219}{3773} \\ \hline \gamma^{(2)} & 2 & 0 & -\frac{81}{40} \quad \frac{1}{40} \end{array}$$

The numerical scheme describes above was translated into C program and the strong solution of SDDE (4) and (8) for cancerous growth is simulated. Numerical algorithm is listed below.

1. Define the fixed step-size, $\Delta = \frac{T}{N}, t_n = (n-1)\Delta$, for $n = 1,...,N$.
2. Define an integer number N_r such that the delay can be expressed in terms of the step size $r = N_r\Delta$.
3. Define the step, such as the step is step $= \frac{T}{r}$.
4. Evaluate initial function phi([step][n-1]) at the initial interval $t \in [-r, 0]$.
5. Print the solution phi([step][n-1]) for $t \in [-r, 0]$.
6. Evaluate drift function, f .
7. If $step = 1$, the drift function isf(y[step][n-1],phi[step][n-1]) else the drift function is computed as f(y[step][n-1],y[step][(n-1)-N_r]).
8. Evaluate diffusion function, g(y[step][n-1])
9. Generate a random number generator, *randn* .
10. Perform an explicit SRK4 of order 1.5.

4.0 PARAMETER ESTIMATION

Natural approach of parameter estimation methods for SDDEs was developed for SDDEs with additive noise and no delay in diffusion. Parameter estimation of SDDEs with multiplicative noise and small delay was developed by [28]. In cervical cancerous growth, time delay is considerably small [29], hence we adopt a method proposed by [28] to estimate the parameter of SDDE (4) and (8). The drift and diffusion functions in (4) and (8) are expanded using Taylor series around $A(t)$ and only terms up to first order in dt are kept. SDDE (4) and (8) can be reduced to the SDE

$$dA = f_a(A)dt + \sigma g_a(A)dW(t) \tag{12}$$

where

$$f_a(A_0) \equiv f(A_0, A_0)\left(1 - r\frac{\partial}{\partial A_r} f(A_0, A_0)\right)$$

and (13)

$$g_a(A_0) \equiv g(A_0)\left(1 - r\frac{\partial}{\partial A_r} f(A_0, A_0)\right)$$

for $\frac{\partial}{\partial A_r} f(A_0, A_0) \equiv \frac{\partial}{\partial A_r} f(A_0, A_r)\Big|_{A_r = A_0}$. By substituting (13) to drift and diffusion functions in (12) yields

for Gompertzian model

$$dA = (aA_0 - bA_0 \ln A_0)(1 + r(a-b)A_0)dt + \sigma A_0(1 + r(a-b)A_0)dW(t) \tag{14}$$

and for logistic model we have

$$dA = (aA_0 - bA^2{}_0)(1 + r(a-b)A_0)dt + \sigma A_0(1 + r(a-b)A_0)dW(t) \tag{15}$$

The non-parametric simulated maximum likelihood approach is used to estimate the unknown parameters for stochastic models (14) and (15).

5.0 RESULT AND DISCUSSION

This section presents the simulated results of the Gompertzian and logistic stochastic model with delay effects to the cervical cancer growth. To validate the effectiveness of (4) and (8) in describing the cancerous growth, the simulated results are compared with the clinical data.

The clinical data was collected from Hospital Sultanah Nur Zahirah (HSNZ) Kuala Terengganu. A 48

year-old woman diagnosed with cervical cancer and without having any treatment from HSNZ was identified. The approval letter was obtained from research committee of Jabatan Kesihatan Negeri Terengganu [reference number: JKNT.TR:600-12Jld 4(25)]. The measured variables were time (in months) and area of cervical cancer cell (in cm^2). Initial condition is $A(t_0) = 23cm^2$, the area of cervical cancer at time that it was first detected. The estimated kinetic parameter values of a, b, σ and r are listed in Table 1.

Table 1 The estimated parameters for a, b, σ and r.

Mathematical model	a	b	σ	r
Gompertzian stochastic model with delay effects	$8.921190e-001$	$-2.886771e-001$	$4.502213e-001$	1
Logistic stochastic model with delay effects	$4.022810e-002$	$-3.111000e-002$	$3.381226e-002$	1

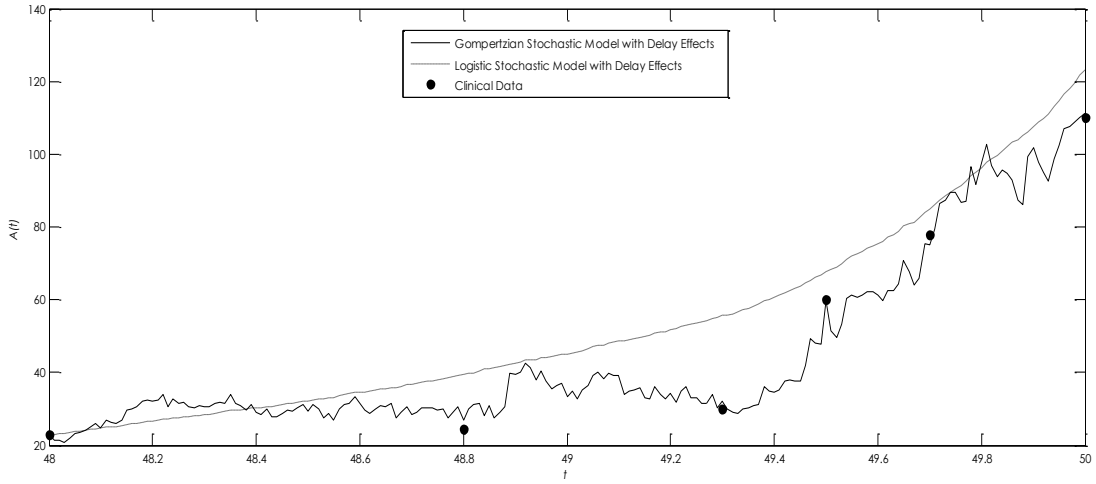


Figure 1 Simulation results of clinical data, Gompertzian and logistic stochastic model with delay effects

Figure 1 shows the results of the clinical data, Gompertzian and logistic stochastic model with delay effects counterpart for cervical cancer growth. Based on Figure 1, it can be seen that the numerical results obtained via Gompertzian stochastic model with delay effects is more consistent with the actual data compared to logistic stochastic model with delay effects, hence the cervical cancer growth is adequately describe by Gompterzian stochastic model with delay effects. From Table 2, Gompertzian model with the incorporating of uncontrolled factors and delay effects produce low values of MSE, hence indicate good fits.

6.0 CONCLUSION

The numerical solution of Gompertzian stochastic model with delay effects for cervical cancer growth shows the experimental data with more adequacy as indicated by low values of MSE. This study found that the cervical cancer growth can be better presented and understood via Gompertzian stochastic model with delay effects compared to logistic stochastic model with delay effects.

Table 2 MSE of Gompertzian and logistic stochastic model with delay effects

Mathematical model	**MSE**
Gompertzian stochastic model with delay effects	0.0627
Logistic stochastic model with delay effects	1.5724

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