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A GOMPERTZIAN MODEL WITH RANDOM EFFECTS TO CERVICAL CANCER GROWTH

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Abstract. In this paper, a Gompertzian model with random effects is introduced to describe the cervical cancer growth. The parameters values of the mathematical model are estimated via maximum likehood estimation. We apply 4-stage Runge-Kutta (SRK4) for solving the stochastic model numerically. The efficiency of mathematical model is measured by comparing the simulated result and the clinical data of the cervical cancer growth. Low values of root mean-square error (RMSE) of Gompertzian model with random effect indicate good fits.

Keywords: Gompertzian model, maximum likehood estimation, 4-stage stochastic Runge-Kutta and cervical cancer
PACS: 87.10.Mn

INTRODUCTION

Cervical cancer is the third most common cancer among women behind breast cancer and colorectal cancer and the fourth leading cause of death among Malaysian [1]. The National Cancer Society Malaysia (NCSM) said that over 1500 women are diagnosed with cervical cancer each year. Cervical cancer accounts for 6% deaths among women in Malaysia [2]. Recently, effort has been paid to the investigation of tumor growth because a better understanding of the highly complex process is paramountly important to develop better prognoses for patients and more effective treatment plan. Taking the advantages of the methods of physics and engineering, most studies review of mechanistic mathematical models which consist of one or more differential equations [3]. Despite their simplicity, such models have been proved to be appropriate to predict the evolution of numerous tumor growth developments. Among the proposed models of those based upon the deterministic Gompertzian growth law appears to be particularly consistent with the evidence of tumor growth [4]. However, real biological systems will always exposed to random influences that are not completely understood or not feasible to model deterministically. To be realistic, models of tumor growth should include random effects or noise. These random fluctuations are the result of uncontrolled factors in human body such as hormonal oscillations, blood pressure variations, respiration, variable neural control of muscle activity, enzymatic processes, energy requirements, cellular metabolism, sympathetic nerve activity or individual characteristics like body mass index, genes, smoking, stress impacts, etc [5]. Therefore, a better model is needed to reflect the external randomness that affects the tumor growth behaviour. This research is carried out to model the growth of cervical cancer via Gompertzian stochastic model.

MATHEMATICAL MODELS

Mathematical expression of growth representation has been formulated in [6]. Beginning essentially as exponential growth, as time goes on, the process becomes damped and eventually stops. If $A(t)$ is the area (cm^2) of the tumor at time, t then it can be represented by the mathematical formula

$$dA(t) = (aA(t) - bA(t)\ln(A(t)))dt \tag{1}$$

where a is the intrinsic growth rate of the tumor which is a parameter related to the initial mitosis rate and b is the growth rate deceleration factor that related to the antiangiogenic process. Equation (1) is called a Gompertzian deterministic model introduced by [6] to describe and analyze the population dynamics in nature. This model was subsequently shown to fit well the tumor growth. However, real biological systems are subjected to environmental noise that are not completely understood or not feasible to model deterministically. Hence, Gompertzian deterministic

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model of tumor growth (1) should include random effects or noise that influence its growth. We assume that the variability of environmental conditions influences in the intrinsic growth rate, a. Hence, the uncontrolled factors is allowed into Equation (1) such that the intrinsic growth rate parameter

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

where $\sigma > 0$ is the diffusion coefficient and the process $W(t)$ for $t \geq 0$ is a white noise process having Gaussian distribution with mean zero and variance, Δt. The mathematical model tumor growth for cervical cancer can be defined by the stochastic differential equation of

$$dA(t) = (aA(t) - bA(t)\ln A(t))dt + \sigma A(t)dW(t) \tag{3}$$

Equation (3) is a Gompertzian stochastic model which has been used by [7] to describe in vivo tumor growth and its sensitivity treatment with antiangiogenic drugs. In this research, the Gompertzian stochastic model of Equation (3) will be used to describe the growth of the tumor for cervical cancer. Moreover, this research will verify the ability of Gompertzian stochastic model to simulate the clinical data.

NUMERICAL METHOD & PARAMETER ESTIMATION

Analytical solution of Gompertzian model with random effects is hard to be found, thus solving this model numerically is necessary. We apply a 4-stage Stochastic Runge-Kutta (SRK4) to approximate the numerical solution of Equation model (3). Details for implementing the numerical method known as:

4–stage Stochastic Runge–Kutta

In this section, we present 4–stage stochastic Runge–Kutta method for solving Gompertzian stochastic model of tumor growth. It was Werner [8] who introduced a so–called an s–stage explicit SRK for solving SDEs. The method was based on the increment of Wiener process, $J_1(t)$ which corresponds to the $\int_{t_n}^{t_{n+1}} dW(t)$. A simple generalization of SRK method introduced by [8] is

$$\begin{aligned} Y_i &= y_n + h\sum_{j=1}^{s} a_{ij} f(Y_j) + J_1 \sum_{j=1}^{s} b_{ij} g(Y_j), \quad i = 1,\ldots,s \\ y_{n+1} &= y_n + h\sum_{i=1}^{s} \alpha_i f(Y_i) + J_1 \sum_{i=1}^{s} \gamma_i g(Y_i) \end{aligned} \tag{4}$$

where $A = (a_{ij})_{s\times s}$ and $B = (b_{ij})_{s\times s}$ are matrices of real elements, $\alpha^T = (\alpha_1,\ldots,\alpha_s)$ and $\gamma^T = (\gamma_1,\ldots,\gamma_s)$ are row vectors in $\Re^s$. The stochastic component comes from J_1–integral. The method proposed by [8] cannot surpass the order of convergence greater than 1.0. Then, Burrage [9] refined the Equation (4) by introducing other stochastic elements apart from J_1. Arbitrary matrix $\mathbf{Z}$ and vector $\mathbf{z}^T$, were introduced whose elements are random variables. A general family of s–stage SRK is formulated by

$$\begin{aligned} Y_i &= y_n + \sum_{j=1}^{s} Z_{ij}^{(0)} f(Y_j) + \sum_{j=1}^{s} Z_{ij}^{(1)} g(Y_j), \quad i = 1,\ldots,s \\ y_{n+1} &= y_n + \sum_{i=1}^{s} z_i^{(0)} f(Y_i) + J_1 \sum_{i=1}^{s} z_i^{(1)} g(Y_i) \end{aligned}$$

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

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

$$
\begin{aligned}
z_i^{(0)} &= h\alpha_i, \quad i = 1,\ldots,s \\
z_i^{(1)} &= \sum_{l=1}^{q} \gamma_i^{(l)} \theta_l, \quad i = 1,\ldots,s
\end{aligned}
$$

An explicit SRK with strong order of 1.0 and 1.5 was developed by letting $q = 2$. For $q = 2$, then $\theta_1 = J_1$ and $\theta_2 = \frac{J_{10}}{h}$, where $J_{10} = \int_{t_n}^{t_{n+1}} \int_{t_n}^{t} dW(s)dt$. The random variable J_{10} is approximated by using the equation (5)

$$
\frac{J_{10}}{h} = \frac{\sqrt{h}}{2}\left(N_1 + \frac{N_2}{\sqrt{3}}\right) \tag{5}
$$

where N_1 and N_2 are standard normal distribution. An s–stage SRK therefore can be written as

$$
\begin{aligned}
Y_i &= y_n + h\sum_{j=1}^{s} a_{ij}^{(0)} f(Y_j) + \sum_{j=1}^{s} \left(b_{ij}^{(1)} J_1 + b_{ij}^{(2)} \frac{J_{10}}{h}\right) g(Y_j), \quad i = 1,\ldots,s \\
y_{n+1} &= y_n + h\sum_{i=1}^{s} \alpha_i^{(0)} f(Y_i) + \sum_{i=1}^{s} \left(\gamma_i^{(1)} J_1 + \gamma_i^{(2)} \frac{J_{10}}{h}\right) g(Y_i)
\end{aligned} \tag{6}
$$

Burrage & Burrage 4–stage SRK scheme with strong order of 1.5 is represented in tableu form

$\mathbf{A}$	$\frac{1}{2}$	0		
	0	$\frac{1}{2}$	0	
	0	0	1	0
α	$\frac{1}{6}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{6}$

$\mathbf{B^{(1)}}$	−0.72429163	0		
	0.4237534	−0.1994437	0	
	−1.5784755	0.84010034	1.7383751	0
$\gamma^{(1)}$	−0.78007	0.073637	1.4865	0.21992

$\mathbf{B^{(2)}}$	2.700200041	0		
	1.757261649	0	0	
	−2.918524118	0	0	
$\gamma^{(2)}$	1.69395	1.63610	−3.02400	−0.306049

Applying Burrage & Burrage scheme to stochastic model (3), yields

$$
\begin{aligned}
Y_1 &= y(t_0) \\
Y_2 &= y(t_0) + \frac{1}{2}h(aY_1 + b\ln(Y_1)) + \left(-0.72429163J_1 + 2.7002000410\frac{J_{10}}{h}\right)\sigma Y_1 \\
Y_3 &= y(t_0) + \frac{1}{2}h\left(Y_1 + \frac{1}{2}(aY_1 + b\ln(Y_1))\right) + \left(-0.72429163J_1 + 2.7002000410\frac{J_{10}}{h}\right)\sigma Y_1 \\
&+ \left(0.4237534J_1 + 1.757261649\frac{J_{10}}{h}\right)\sigma Y_1 - 0.19944370\sigma Y_2 \\
Y_4 &= y(t_0) + h\frac{1}{2}\left(Y_1 + h\frac{1}{2}(aY_1 + b\ln(Y_1))\right) + \left(-0.72429163J_1 + 2.7002000410\frac{J_{10}}{h}\right)\sigma Y_1 \\
&+ \left(0.4237534J_1 + 1.757261649\frac{J_{10}}{h}\right)\sigma Y_1 - 0.19944370J_1\sigma Y_2 \\
&+ \left(-1.5784755J_1 - 2.918524118\frac{J_{10}}{h}\right)\sigma Y_1 + 0.84010034J_1\sigma Y_2 + 1.7383751J_1\sigma Y_3
\end{aligned}
$$

$$
\begin{aligned}
y(t) &= y(t_0)+h\Big(\frac{1}{6}(aY_1+b\ln(Y_1)+\frac{1}{3}(aY_2+b\ln(Y_2))+\frac{1}{3}(aY_3+b\ln(Y_3))+\frac{1}{6}(aY_4+b\ln(Y_4))\Big)\\
&+ \Big(\Big(-0.78007J_1+1.69395\frac{J_{10}}{h}\Big)\sigma Y_1+\Big(0.073637J_1+1.63610\frac{J_{10}}{h}\Big)\sigma Y_2+\Big(1.4865J_1-3.02400\frac{J_{10}}{h}\Big)\sigma Y_3\\
&+ \Big(0.21992J_1-0.306049\frac{J_{10}}{h}\Big)\sigma Y_4\Big) \qquad (7)
\end{aligned}
$$

The numerical scheme describes above was translated into Matlab program to obtain the approximate solution of tumor growth for cervical cancer at $t \in [48,50]$. Stochastic integrals of J_1 and $\frac{J_{10}}{h}$ can be generated by using Box-Muller method. We define a meshpoint with a uniform step size h on the interval $[t_0,T]$ and the numerical algorithm is presented below.

1. Define the fix step size, $h_n = t_{n+1}-t_n$ and integer number N such that $h=\frac{T}{N}$, for $t_n = n\cdot h$ and $n=0,\ldots,N$.
2. Do drift function, $f(A_n)=(aA_n-bA_n\ln(A_n))$ evaluation.
3. Do diffusion function, $g(A_n)=\sigma A_n$ evaluation.
4. Perform random number generator of stochastic integrals J_1 and $\frac{J_{10}}{h}$.
5. Perform an explicit 4-stage stochastic Runge-Kutta.

Maximum Likelihood Estimator

In this section, we apply a non–parametric simulated maximum likelihood approach to estimate the unknown parameters of stochastic model (3). While sample data for the tumor growth of cervical cancer are available, the parameters a, b and σ are unknown accurately and need to be estimated. The transition density of y_i starting from y_{i-1} and evolving to y_i is $p(t_i,y_i|t_{i-1},y_{i-1},\theta)$, where $\theta=a,b,\sigma$ are the parameters to be estimated. The maximum likelihood estimator for θ is obtained by maximizing the likelihood function of

$$L(\theta)=\prod_{i=1}^{n} p(t_i,y_i|t_{i-1},y_{i-1};\theta) \qquad (8)$$

In practice $L(\theta)$ will be approximated through Monte Carlo simulation according to the following algorithm proposed by [10]

1. Divide the time interval $[t_{i-1},t_i]$ into N subintervals with a step size of $h=\frac{(t_{i-1}-t_i)}{N}$. The Gompertzian stochastic model is integrated on this discretization by using 4–stage stochastic Runge–Kutta method. This integration is repeated R times for $R=100$ to generate R approximations of the tumor growth A at t_i starting with y_{i-1} at t_{i-1}. The approximate values of tumor growth is denoted as $A_{t_i}^1\ldots A_{t_i}^R$, where $A_{t_i}^r$ is the integrated value of (3) in the r^{th}–simulation for $r=1,\ldots,R$.
2. A non–parametric kernel density then is constructed from the simulated values of $A_{t_i}^1\ldots A_{t_i}^R$ are used to construct a non–parametric kernel density estimate of the transition density (8)

$$p^R(t_i,y_i|t_{i-1},y_{i-1};\theta)=\frac{1}{Rh_i}\sum_{r=1}^{R}K\Big(\frac{y_i-A_{t_i}^r}{h_i}\Big) \qquad (9)$$

   where h_i is the kernel bandwith at time t_i and $K(\cdot)$ is a suitable symmetric, non–negative kernel function enclosing unit mass.
3. The previous procedure is repeated for each y_i and the $p^R(t_i,y_i|t_{i-1},y_{i-1};\theta)$ thus obtained used to construct $L^R(\theta)=\prod_{i=1}^{n}p^R(t_i,y_i|t_{i-1},y_{i-1};\theta)$.
4. $L^R(\theta)$ is maximized to obtain the approximated MLE θ^R of θ.

Hurn et al. [10] proposed a suitable choice of $K(\cdot)$ which is given by the normal kernel

$$K(u)=\frac{1}{\sqrt{(2\pi)}}\exp^{(\frac{-u^2}{2})} \qquad (10)$$

with bandwith given by

$$h_i=\frac{4}{3}^{\frac{1}{5}}s_iR^{\frac{-1}{5}}, \qquad i=1,\ldots,n \qquad (11)$$

RESULTS & DISCUSSION

This section presents the prediction quality of Gompertzian stochastic model to describe the growth of the tumor for cervical cancer.

Description of the Clinical Data

The cervical cancer data was taken from Hospital Sultanah Nur Zahirah (HSNZ) Kuala Terengganu. One patient, age 48 years old, has fulfilled the inclusion criteria was identified. The inclusion criteria were histopathologically and clinically diagnosed with cancer of cervix between 17^{th} March 2011 until 20^{th} March 2013, and without having any treatment related to cervical cancer in HSNZ. The variables of interest were time (in months) and the area of the cell growth for cervical cancer (in cm^2) were measured from the patient that has been diagnosed with cervical cancer up to the time she was referring to Total Abdominal Hysterectomy and Bilateral Salphingooopherectomy (TABHSO). Initial state is observed from the clinical data, $A(t_0) = 23cm^2$ where t_0 is an initial time that is the time in which the cell cancers was first detected.

Analysis of Gompertzian Stochastic Model

The likelihood function $L^R(\theta)$ for $R = 100$ are maximized to generate the estimated values of $\theta = \{a, b, \sigma\}$. The construction of $L^R(\theta)$ requires the generating of Wiener increments $\Delta W(t) = W(t_{i+1}) - W(t_i)$. For this purpose, these increments are generated via Box–Muller method and once created, those values are kept fixed for a given optimization procedure. The tumor growth of cervical cancer is simulated at equally spaced intervals of time $h_i = t_{i+1} - t_i = \frac{T}{N}$. Numerical method of 4–stage SRK is performed to simulate the trajectories in the interval time $[t_0, T]$ with initial condition, $A(t_0) = 23\text{cm}^2$. Numerical optimization algorithm was implemented using Matlab program and the estimated parameter values of $\theta = \{a, b, \sigma\}$ for $R = 100$ are listed in Table 1.

TABLE 1. Maximum Likelihood Estimates of Gompertzian Stochastic and Deterministic Model Parameters

Mathematical Model	a	b	σ
Gompertzian Stochastic Model	$9.288110e-001$	$-2.000000e+000$	$7.602268e-001$
Gompertzian Deterministic Model	$1.043000e+000$	$-0.074800e+000$	–

The following Figure 1 illustrates the plot of clinical data and the respective results of the empirical mean, 95 percent confidence interval, Q1–Q3 quartiles of the numerical solution over 100 trajectories. Figure 2 shows the result of the actual data, stochastic Gompterzian model and deterministic counterpart for tumor growth of cervical cancer. Based on Figure 2, it can be seen that the numerical results obtained via stochastic Gompertzian model are more consistent with the actual data, hence the tumor growth of cervical cancer is adequately describe by stochastic Gompterzian model. Moreover, the mathematical model with the incorporating of uncontrolled factors produce low values of MSE, hence indicate good fits.

TABLE 2. MSE of Gompertzian Stochastic and Deterministic Models

Mathematical Model	MSE
Gompertzian Stochastic Model	0.6020
Gompertzian Deterministic Model	10.0579

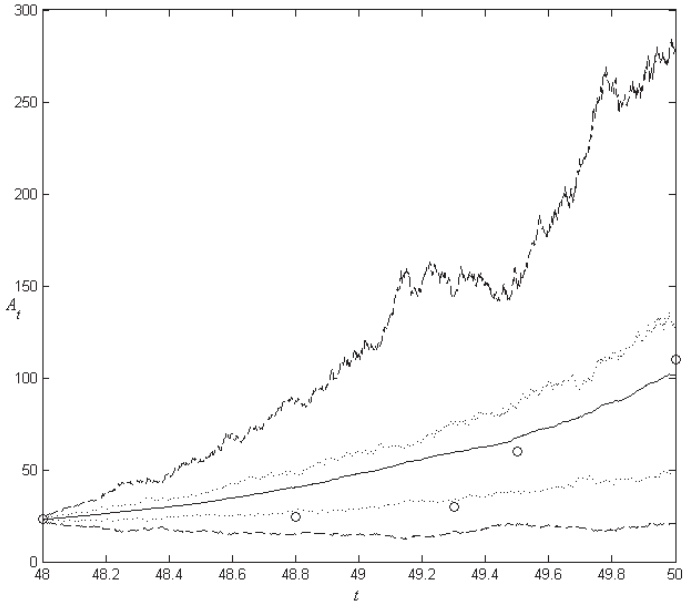

FIGURE 1. Empirical mean, 95 percent CI, Q1-Q3 quartiles of the numerical solution over 100 trajectories and data observations

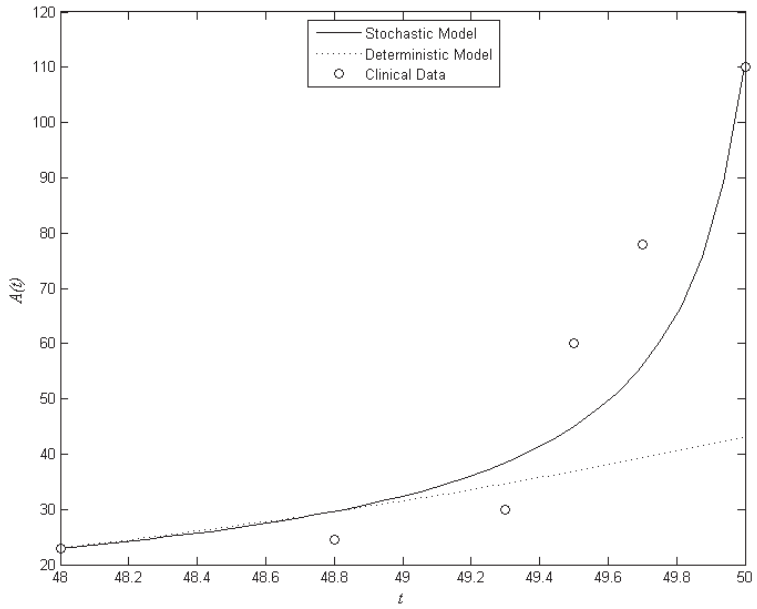

FIGURE 2. Simulation Results of Stochastic Gompertzian, Deterministic Gompertzian Models and the Actual Data of Cervical Cancer Growth

CONCLUSION

The numerical solution of stochastic Gompertzian model for cervical cancer describes the experimental data with more adequacy as indicated by low values of MSE compare to the deterministic Gompertzian model. In real biological

system, the cancerous growth is subjected to random effects since there are many uncontrolled environmental factors that influenced the system. This study found that the stochastic model describes real behavior of cancer growth adequately compare to the deterministic counterpart. Hence, it is worthwhile to note that the cancerous growth for cervical cancer can be better presented and understood via stochastic Gompertzian model. This finding provides useful knowledge on the understanding of the uncontrolled factors that affect the cervical cancer cell. However, apart from that, in reality the patients do not aware when the cancer cell begin to grow. Further work can be done to solve the latter problem by the inclusion of time delay into stochastic model, the research that will be considered.

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