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ORIGINAL ARTICLE

Parameter estimation of the stochastic model for oral cancer in response to thymoquinone (tq) as anticancer therapeutics

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ABSTRACT – Oral Cancer is considered as one of the common problems of global public health and despite the progress in advanced research, the mortality rate has not been improved significantly in the last few decades. A natural product such as Thymoquinone, black seeds (TQ), is an active component of Nigella sativa or black cumin elicits cytotoxic effects on various oral cancer cell lines. A wide range of studies have been concluded that the TQ has two different anti-neoplastic actions that might trigger apoptosis, have the capacity to induce cell death in oral cancer cells. In the presence of TQ, oral cancer has been proved experimentally shows the decelerating trend of the growth. This article models the decelerating of the oral cancer growth by using a linear stochastic differential equation (SDEs). The Markov Chain Monte Carlo (MCMC) method used to estimate model parameters for 100, 500,1000 and 2000 simulations. The best set of kinetic parameters are identified. It can be seen that for 1000 simulations of the sample paths, the model fitted well the data, hence indicating a good fit. However, if the number of simulation is incerasing up to 2000, the parameter obtained shows instablity of the solution. This is due to the high numbers of noise generated, may influenced the stability of the solution.

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INTRODUCTION

In various fields, such as finance, physics, system biology, biochemical processes, and pharmacokinetics, stochastic differential equations (SDEs) have gained a lot of attention. SDEs introduce the uncertainty to a deterministic model described by ordinary differential equations (ODEs). SDEs can give a more flexible framework to account for the variation in states and parameters that define the underlying system than the deterministic counterpart. Experimental and computational research has made considerable progress in understanding cancer biology during the last few decades [1]. The biological system's tangible depiction has been used in the form of mathematical modeling of cancer either as continuous, discrete, or a (hybrid) mix of both, and has been thoroughly examined in the last decade [2-6].

The single equation model can be described to predict cancer cell dynamics through the available tumor size at a specific time and can estimate the model's parameters. The single equation model can only describe the cancerous cell growth pattern and distinguish the tumors in corresponds to their exponational growth [7]. TQ as a major constituent of black seed (*Nigella sativa*) has been well known for its anti-neoplastic anti-cancer properties in several different cancers including oral cancer [8]. However, there have been inadequate investigations on the toxicity of TQ in normal cells. A study reported that the water extract of *N. Sativa's* whole seeds has an inhibitory impact on oral cancer cells progression when applied at the concentration of 0.5% v/v in in-vitro conditions. The cytotoxic effect of TQ in particular oral cancer cell lines (HSC-3) but not in normal cells, according to the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium) test (human oral fibroblast cells). TQ seems to be a promising cancer chemotherapeutic candidate, according to [9].

Cancer patients in Muslim countries take Nigella sativa as a dietary supplement in addition to traditional chemotherapy [10-12]. Also, [13-15] have recently reported TQ's anticancer capabilities against human oral cancer cells. The mathematical approach in studying tumor growth is to explain the patterns of growth and predict the behaviour of the process. Mathematical models have been developed and used to describe the tumor growth pattern using data and help to estimate patient survival rate and offer a treatment of choice. From a promising application of a mathematical model [16, 17], by identifying the cells that play a role in cancer propagation, it was possible to determine parameters for stability analysis and anticipate tumour dynamics. These models help to describe the dynamics of interactions between the variables involve [18,19]. In modelling the process, the parameters added to the system need to be estimated. Monte Carlo Markov Chain (MCMC) method is one of the parameter estimation method that utilize the used of the generating the output variables based on the random input. It is used to simulate the repeated random sampling through the mathematical formulas in the model; where it determines how uncertainties in the input quantities to a functional relationship propagate through to the output can be accomplished using readily available data [18]. For Monte Carlo parameter estimation method, after an additive multinormal pseudo-random error has been added into the structural equation of the model or

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even into the model's coefficients, the variances are estimated from the sample variances of replicated simulation trials. The Monte Carlo non-parametric method is used because has advantage to give normalized values for mean and variance [20].

In the present study, we use linear SDE in section 2 to explain the declining trend of oral cancer cell HSC-3 in the presence of TQ. Data description is described in section 3. The parameters of the model are estimated by using the non-parametric MCMC method which is presented in section 4. MCMC method was run for 100,500,1000 and 2000 simulations.

MATHEMATICAL MODEL AND PARAMETER ESTIMATION

Linear stochastic differential equation is defined by

$$dX_t = -a(X_t)dt + \sigma dW_t, \quad X(0) = X_0 \tag{1}$$

where X_t is the cancer cell and σ is the diffusion coefficient. X_0 is the initial number of cancer cells at the initial time $t_0 = 0$. Also $a > 0$ is the cancer growth rate parameter and constant. W_t is the m-dimensional Wiener .The parameter estimation for SDE requires estimating the parameters $a > 0$ and $\sigma > 0$. The unknown parameters of the stochastic model are estimated using a non-parametric maximum likelihood approach. Starting and developing the transition density of y_i from y_{i-1} and evolving to y_i is $\mathrm{p}(t_i, y_i \mid t_{i-1}, y_{i-1}, \boldsymbol{\theta})$, where $\boldsymbol{\theta}$ is the parameter to be estimated. The MLE (maximum likelihood estimator) of the $\boldsymbol{\theta}$ is attained by expanding the likelihood function to its maximum value of

$$L(\boldsymbol{\theta}) = \prod_{i=1}^{N} \mathrm{p}(t_i, y_i \mid t_{i-1}, y_{i-1}; \boldsymbol{\theta}) \tag{2}$$

To derive $L(\boldsymbol{\theta})$ which is proposed by [14], the Monte Carlo simulation is used. Monte Carlo algorithms are efficient numerical tool mostly used to solve the SDE problems.
The algorithm of MC method is as follows:

(i) The time interval is divided as $[t_{i-1}, t_i]$ into N subintervals have step size of $h = \dfrac{(t_{i-1}, t_i)}{N}$. The Milstein method is used to simulate the stochastic model. The integration is performed for $R = 100$ times, hence R approximations of the treated cancer, X_{t_i} starting with y_{i-1} at t_{i-1} is obtained. $X_{t_i}^1, ..., X_{t_i}^R$ are the approximate values of the treated cancer, where $X_{t_i}^r$ is the integrated value of the stochastic model in the rth -simulation for $, r = 1, ..., R$.

(ii) From the simulated values of $X_{t_i}^1, ..., X_{t_i}^R$, a non-parametric kernel density is used to estimate of the transition density in (3) such that

$$p^R(t_i, y_i \mid t_{i-1}, y_{i-1}; \theta) = \frac{1}{R_{h_i}} \sum_{r=1}^{R} K\left(\frac{y_i - A_{t_i}^r}{h_i}\right) \tag{3}$$

where h_i is the kernel bandwidth at the time t_i and $K(.)$ is a right symmetric, non-negative kernel function.

(iii) The previous strategy is revised for every y_i and the $p^R(t_i, y_i \mid t_{i-1}, y_{i-1}; \theta)$, hence will generate $L^R(\boldsymbol{\theta}) = \prod_{i=1}^{N} \mathrm{p}(t_i, y_i \mid t_{i-1}, y_{i-1}; \boldsymbol{\theta})$

(iv) To find the approximated MLE θ^R of θ, $L^R(\theta)$ is maximized. Hurn et al. [21] recommended the best option of $K(.)$ provided because the normal kernel

$$K(u) = \frac{1}{\sqrt{(2\pi)}} \exp^{\left(\frac{-u^2}{2}\right)} \tag{4}$$

with the bandwidth is

$$h_i = \frac{4^{\frac{1}{5}}}{3} s_i R^{\frac{-1}{5}}, \quad i = 1, ..., n.$$

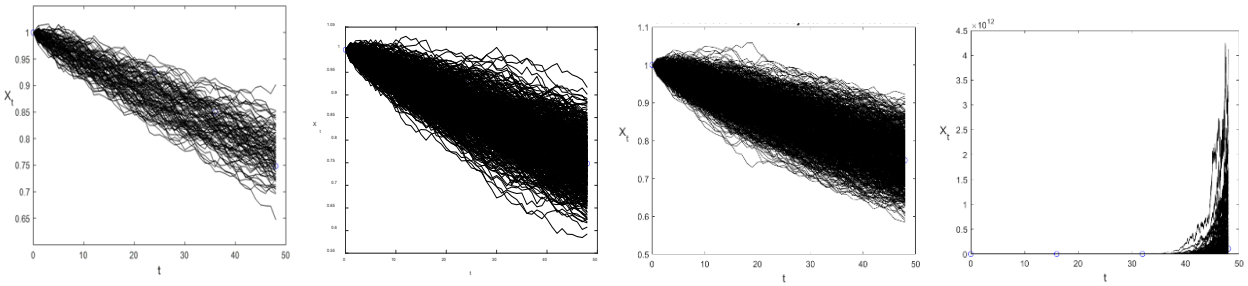
The aforementioned algorithm was proposed by [20, 22]. It was translated into SDE Toolbox and this article utilized the MCMC method of SDE Toolbox. Data description is presented in next section.

DATA DESCRIPTION

The oral cancer cell lines have been planted for 24 hrs using 96-well plates till they reached the density level of 70-80% confluency per well. Later, samples were further incubated for 24 hrs of the time period. The 20 µL MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide at concentration of 5 mg/mL (Sigma Aldrich, US) was added to each sample at a concentrations level of 5mg/mL Further, for 4 hrs the mixture was kept at 37°C in humidified conditions and the experimental value was used as averages standard error mean (SEM) of triplicates and expressed as a percentage of the control values.

RESULTS AND DISCUSSION

This section contains the numerical simulations of MCMC methods for 100, 500,1000 and 2000 trajectories. The value of $X_0 = 1$, $a = 0.5$ and step size is $h = 0.001$. The solution of SDE (1) is simulated using Euler's method. Figure 1 (a), (b), (c) and (d) shows the true solution (dark solid lines) for 100, 500,1000 and 2000(cannot observe) trajectories.



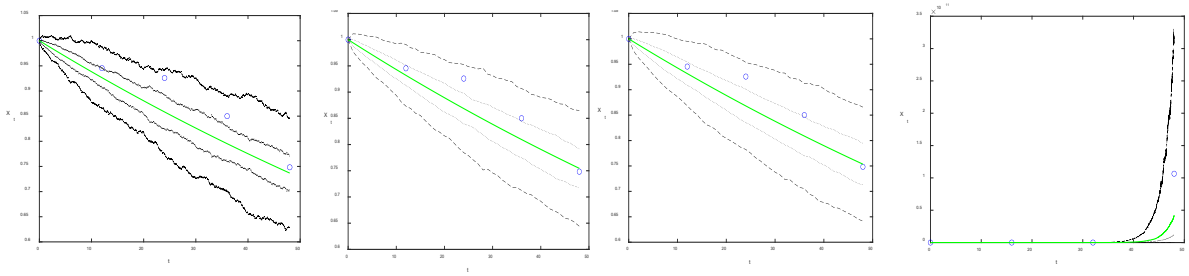
(a) (b) (c) (d)

Figure 1. Simulation results of SDE (1) for (a) 100, (b) 500 and (c) 1000 and (d) 2000 simulations.

The mean and 95 percentiles of the solution of 100, 500,1000 and 2000 simulation of SDE (1) are computed and the 95% confidence interval of the solution mean are depicted in Figure 2 (a), (b), (c) and (d). The green line represents the average solution of simulations, and the blue dot is the experimental data. The black line depicts the 95 percentiles of the solution.

Table 1. Estimated parameters and 95% confidence interval.

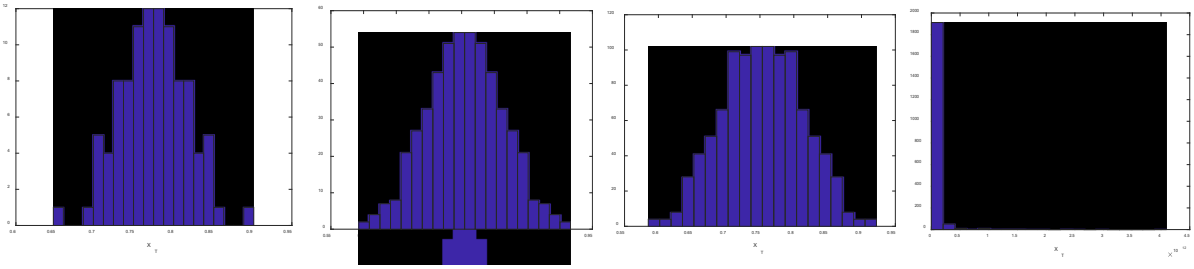
Trajectories	Parameter	Estimated Values	Confidence Interval
100	a	5.307620e-03	[0.0032573, 0.0073579]
	σ	8.335209e-03	[0.0038440, 0.0128260]
500	a	5.850240e-03	[0.0027801, 0.0089204]
	σ	9.106071e-03	[0.0020542, 0.0161580]
1000	a	5.877555e-03	[0.0033452, 0.0084099]
	σ	9.672986e-03	[0.0044814, 0.0148650]
2000	a	5.894822e-01	[0.5865400, 0.5924200]
	σ	3.025830e-01	[0.2950000, 0.3101700]



(a) (b) (c) (d)

Figure 2. Mean and 95 percentile of (a) 100, (b) 500, (c) 1000 and (d) 2000 simulated result.

The estimated parameter of SDE (1) and their corresponding 95% confidence interval is presented in Table 1. The distribution of the solution of SDE (1) is shown in Figure 3 (a), (b), (c) and (d).



(a) (b) (c) (d)

Figure 3. Distribution of the X_t (a)100, (b) 500 (c) 1000 and (d) 2000 simulated result.

In Figures 1 and 2 (a) ,(b), (c) and (d) it can be seen that the solution of SDE (1) shows the declining trend of the HSC-3 cancer line in the presence of TQ. The model is adequately explaining this process as depicted by the average of 100, 500, 1000 and 2000 simulated solutions and the data are in the 95 percentile of the solution. Figure 3 (a), (b), (c) and (d) shows the distribution of the solution is approximated Gaussian distribution with the mean parameter for 100,500, 1000 and 2000 is approximately 0.77,0.76,0.75 and 0.04 respectively. The Gaussian distribution plot for 1000 simulations is close to the normal curve, indicating that the distribution of the solution approximate Gaussian distribution as the number of sample paths increase. Monte-Carlo statistics of the SDE (1) for 100,500,1000 and 2000 simulated results are computed and the values are depicted in Table 2. Before making conclusions from the created model, every fitted model should be tested and checked on its performance. This is essentially a check to see if the fitted model's projected values are close to the observed data. This is referred to as "fitness of fit" [23]. The increasing number of simulations like 2000 generate more sample paths that will give the possibility of the behaviour of cancer cell proliferation under different types of environmental noise. However, when the number of simulations is too large in SDEs, the noise generated by the Wiener process may contribute to the instability of the solution. The Monte-Carlo statistics were obtained at the endpoint of time 48 hours. It can be summarized, the mean and median of 1000 simulated solutions of SDE (1) at time 48 hours approximately 7.5 (same values), hence indicating that the solution is approximated Gaussian distribution with the standard deviation from mean is 0.0592. The measures of symmetry as depicted by the process skewness is in the range of -0.5 to 0.5, hence indicate the data solutions of HSC-3 are fairly symmetrical (a bell-shaped curve). The process kurtosis is less than 3, hence lack outliers in the data set. The process moment of a random process, X for order 2 till 7 has been computed and depicted in Table 2.

Table 2. Monte-Carlo statistics of SDE (1) for 100, 500, 1000 and 2000 trajectories at end point of time 48 hours.

Statistics	Estimated Value(100)	(500)	(1000)	(2000)
Mean	7.6460e-01	7.5454e-01	7.5355e-01	4.1330e+10
Variance	3.3688e-03	3.2528e-03	3.5285e-03	3.9831e+22
Median	7.6460e-01	7.5454e-01	7.5355e-01	1.8824+09
95 percent confidence interval	[6.5038e-01, 8.78837e01]	[6.4407e-01, 8.6501e-01]	[6.4144e-01 ,6.6566e-01]	[1.9518e+07, 3.1258e+11]
The process first and third quartiles	[7.2338e01, 8.0583e01]	[7.1741e-01, 7.9164e-01]	[7.1293e-01, 7.9416e-01]	[2.9837e+08, 1.2275e+10]
Process skewness	9.7533e-15	7.0129e-18	2.0925e-14	1.0991e+01
Process kurtosis	2.3401e+00	2.7649e+00	2.6177e+00	1.5968e+02
Process moment of order 2	3.3351e-03	3.2463e-03	3.5250e-03	3.9811e+22
Process moment of order 3	1.9071e-18	1.3010e-21	4.3859e-18	8.7379e+34
Process moment of order 4	2.6558e-05	2.9255e-05	3.2591e-05	2.5334e+47
Process moment of order 5	6.8474e-20	-1.3891e-21	6.8800e-20	8.3317e+59
Process moment of order 6	2.9754e-07	3.9364e-07	4.5208e-07	2.9511e+72
Process moment of order 7	1.7417e-21	-6.6597e23	1.36954e-21	1.0945e+85

CONCLUSION

The study considers the model fitting using non-parametric estimation method with one of the most common MCMC methods in use. In vitro experimentation, TQ at the concentration level of 0.008mg/mL is the optimal dose for the treatment of HSC-3 cancer cell lines growth. The graphical visualization of dose-effect has shown that the simulated result using SDE (1) is consistent with obtained experimental data of HSC-3 interaction with TQ as reflected the declining trends of cell line growth. The Monte-Carlo statistics simulations show that the results follow the trajectories of the experimental data (decreasing trend) for 100, 500 and 1000 simulations. However, as the number of simulation is 2000 the solution is instable. The instability of the solution might happen due to the noise generated by the Wiener process for 2000 simulation is high. In this research the focus is only for one equation model. However, to capture the behaviour of the dynamical system for the interaction of oral cancer and TQ, the model need to be extended to a system of SDEs that is can be considered for future research.

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