Deterministic and stochastic model for the effect of Chondroitin Sulfate (CS) in cancer cell

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ABSTRACT: Modern medical study show that the new therapeutic strategies known as targeted therapy can help in cancer prognoses. Chondroitin Sulfate (CS) an anti-cancer drug in targeted therapy has been proved able to reduce cell viability by promoting the activation of the Caspase3 (Casp3) in apoptosis pathway without causing toxicity. To better understand the effect of CS on the cancer cells, deterministic and stochastic model are proposed. The result shows the decreasing trend of the cancer cell in the presence of CS in both models.

Keywords: *Targeted therapy; Deterministic; Stochastic*

1. INTRODUCTION

Cancer treatment is a major public health problem worldwide. It causes the highest mortality rate in economically developed countries [1]. A natural way of removing the cancer cells from the body is through the apoptosis process [2]. Apoptosis is an active form of programmed cell death controlled by a network of genes and playing a key role in the pathogenesis of diseases including cancer [2]. Recent study had revealed the role of Chondroitin Sulfate (CS) which can promote the activation of Caspase3 (Casp3) hence activated the apoptotic activity [2]. The interaction between Casp3 and cancer can be assessed by using mathematical model. In fact, many factors influence the effect of cancer treatment, such as the severity of the disease, the strength of the immune system, patient's lifestyle and etc [1]. Model should include the effect of random (stochasticity). This paper proposes a system of deterministic and stochastic model for the accessing the interaction between Casp3 and cervical cancer cells (Hela). The model parameters are estimated using MCMC method. The influence on therapy outcome that describe the interactions between Casp3 and cancer cells was analyzed via simulations.

2. METHODOLOGY

At time *t*, let denote $C(t)$ the population of Casp3 activated by the presence of CS and $T(t)$ is the population of the cancer cells. The deterministic prey-predator model describing the interaction of two species is

$$\begin{aligned} \frac{dT}{dt} &= \alpha T - \beta TC \\ \frac{dC}{dt} &= s + \delta TC - \varepsilon C \end{aligned} \tag{1}$$

with the initial conditions $C(0) > 0, T(0) > 0$. In the first equation of system (1), the cancer cells is grow with the rate of α and the competition between Casp3 and cancer cells is reflected by the term $-\beta TC$. This interaction results in the death of the cancer cell. Then, Casp3 are activated due to the presence of anticancer drug CS with a constant source of *s*. The presence of cancer cell induced the production of the Casp3, which is reflected by the term δTC. Casp3 is removed from the system with the rate of ε. Considering the stochastic factors in Casp3-cancer cells interaction, the Wiener process, $W(t)$ is perturbed at the growth rate parameter of the cancer cells, α and the Casp3 death rate parameter, ε in system (2) such that

$$\begin{aligned} \alpha &\to \alpha + \sigma_1 \frac{dW_1(t)}{dt} \\ -\varepsilon &\to -\varepsilon + \sigma_2 \frac{dW_2(t)}{dt} \end{aligned} \tag{2}$$

where $\sigma_1 > 0, \sigma_2 > 0$ are the coefficients of diffusion function. The terms $W_1(t)$ and $W_2(t)$ represent the Wiener process which reflected the presence of the uncontrolled factors in the system. This yields a stochastic system

$$\begin{aligned} dT &= (\alpha T - \beta TC)dt + \sigma_1 T dW_1(t) \\ dC &= (s + \delta TC - \varepsilon C)dt + \sigma_2 C dW_2(t) \end{aligned} \tag{3}$$

3. RESULTS AND DISCUSSION

The experimental data of the MTT assay for Hela (cervical cancer) for $0 \le t \le 24$ hours is obtained from [3]. The kinetic parameters values are presented in Table 1. Source rate of CS is obtained experimentally, which is $s = 0.1 \mu\text{g/mL}$. The initial conditions are $C(0) = 0.1\ \mu\text{g/mL},\ T(0) = 0.2482\ \mu\text{g/mL}$. We simulate the results for system (1) and system (2) using Runge-Kutta and stochastic Runge-Kutta methods of order 4, respectively. For system (2), 100 simulations were performed and the average of the sample paths was plotted. Figures 1 and 2 depict the result of the system (1) and (2), respectively. It is obvious that the extinction of the cancer cells will increase with the increase of the activated Casp3 induced by CS. The kinetic parameter of the system (1) and (2) were obtained by using maximum likelihood method. The asymptotic 95% confidence

interval (CI) for the estimated parameter is approximated by $\left[\theta_p - 1.96 \cdot I_p^{-0.5}, \theta + 1.96 \cdot I_p^{-0.5}\right]$ where θ_p is the $p-$th element of the parameters and I_p is the $p-$th element on the diagonal of the Hessian matrix of $I(\theta)$.

Table 1 Kinetic parameter values and 95% CI

Model	Kinetic Parameter	Parameter Values (95% CI)
System (1)	α	0.03 [0.01, 0.05]
	β	0.25 [0.20, 0.30]
	δ	0.75 [0.01, 1.00]
	ε	0.08 [0.10, 0.50]
System (2)	α	0.01 [0.01, 0.10]
	β	0.20 [0.20, 1.00]
	δ	0.50 [0.10, 0.50]
	ε	0.01 [0.01, 1.00]
	σ_1	0.05 [0.01, 0.05]
	σ_2	0.05 [0.01, 0.10]

The interaction of the Casp3 and cancer cell induced apoptosis process (the process of shrink the cancer cell size). For time interval 0 to 24 hours, the simulated result of the Hela cell line is decreasing that agreeing with the experimental data, while the activated Casp3 is increasing. Then the predicted result for 60 to 200 hours for Figure 1 shows the cancer cell and Casp3 reach steady state solution, indicate number of these two types of cells remains unchanged.

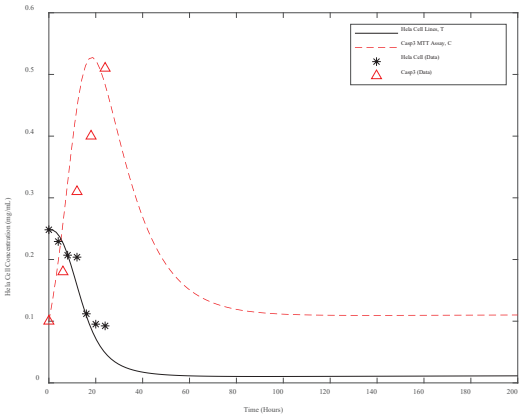

Figure 1 Simulated result of ODE (1).

In Figure 2, as the amount of the Casp3 is considerably significant (due to the environmental factor that may boost the patient's immune system) for time interval 40 to 120 hours, the simulated result of the Hela cell lines drops sharply. This indicates the present of Casp3 promoting apoptotic activity, hence may help in reducing the size of the cancer cells.

Table 2 shows the RMSE value of system (1) and (2) for the time interval 0 to 24 hours. It can be seen that RMSE for the system (2) is smaller than the system (1), hence indicate good fit of the model and reveal the perturbation of the system with the environmental noise is considerably helpful to reflect the behaviour of the noisy system.

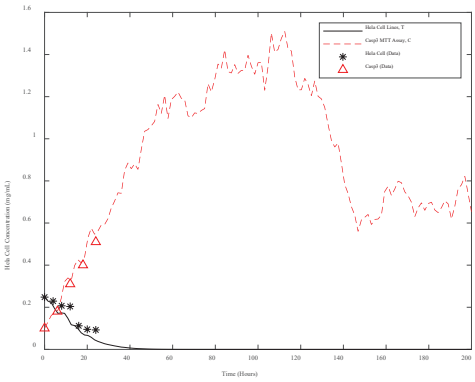

Figure 2 Simulated result of SDE (2).

Table 2 RMSE values

Model	Variable	RMSE
System (1)	Cancer (T)	0.080968
	Casp3 (C)	0.209865
System (2)	Cancer (T)	0.037128
	Casp3 (C)	0.208963

4. CONCLUSION

This paper proposed deterministic and stochastic models of the system interaction between Hela cell lines and anticancer therapeutics of CS. CS activated Casp3 and promoting the apoptotic activity that able to shrink the size of the cancer and the system reach steady state solution (remain unchanged) after some period time of *t*. Overall both models are helpful in understanding the behaviours of the cancer cells in the presence of anticancer therapeutics.

ACKNOWLEDGEMENT

The authors would like to thank the Ministry of Higher Education for providing financial support under Fundamental research grant No. FRGS/1/2019/STG06/UMP/02/2 (University reference RDU1901139) and Universiti Malaysia Pahang for additional financial support under Postgraduate Research grant PGRS1903202.

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