**PAPER • OPEN ACCESS**

# Modelling the cancer growth process by Stochastic Differential Equations with the effect of Chondroitin Sulfate (CS) as anticancer therapeutics

To cite this article: Mazma Syahidatul Ayuni Mazlan *et al* 2017 *J. Phys.: Conf. Ser.* **890** 012085

View the article online for updates and enhancements.

# Modelling the Cancer Growth Process by Stochastic Differential Equations with the Effect of Chondroitin Sulfate (CS) as Anticancer Therapeutics

**Mazma Syahidatul Ayuni Mazlan[1], Norhayati Rosli[1], Solachuddin Jauhari Arief Ichwan[2], Nina Suhaity Azmi[1]**

[1]Faculty of Industrial Sciences and Technology, Universiti Malaysia Pahang, 26300 Gambang, Kuantan, Pahang, Malaysia
[2]Kulliyyah of Dentistry, IIUM Kuantan Campus, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang, Malaysia

E-mail: `norhayati@ump.edu.my`

**Abstract.** A stochastic model is introduced to describe the growth of cancer affected by anti-cancer therapeutics of Chondroitin Sulfate (CS). The parameters values of the stochastic model are estimated via maximum likelihood function. The numerical method of Euler-Maruyama will be employed to solve the model numerically. The efficiency of the stochastic model is measured by comparing the simulated result with the experimental data.

## 1. Introduction
World Health Organization (WHO) reported that breast cancer is the most common women's malignancy with the majority of deaths occuring in the most part of the world [1]. In Malaysia, breast cancer was accounted for 32.1% of all cancers among women in 2007 [2, 3].

There are varieties of molecules with various pathway that contribute to the apoptosis mechanism in cancer cell. But, the final marker in apoptosis mechanism is caspase-3 [4]. Thus, the activation of caspase-3 pathway can be positioned as activitors of the death cascade of apoptosis [6]. Apoptosis plays an important roles in the cancer treatment and it is the most important mechanism for cancer therapy. Hence, a better understanding of apoptosis process opens a new class of targeted therapeutics in cancer treatment.

Generally, some of the treatment methods are surgery, chemotherpy, radiation therapy and targeted therapy. Targeted therapy is a much sharper method and has proven to be highly successful in cancer treatment, with fewer side effects [5, 7]. Nowadays, reseachers are investigating for potent, safe and effective anticancer drugs to overcome resistance and reduce side effects. Currently, the role of Chondroitin Sulfate (CS) as a potent in anticancer activities and also as anticancer are among the reserachers interest [8].

During years, some researchers have worked on mathematical modelling of the effect of targeted therapy on cancer treatment. However, to the best of our knowledge, no theoretical studies on proposing a stochastic model of targeted cancer therapies. In biological pocesses of cancer treatment, there are existing in nature that the cancer cell under treatment are exposing

to random influences due to the interplay of therapy and resistance [9]. This findings lead to the development of a mathematical model that subject to the random effects.

## 2. Mathematical Model

This section devotes to the development of stochastic model of the apoptotic mechanism induced by CS. It starts with the understanding of apoptosis pathway as shown in Figure 1.
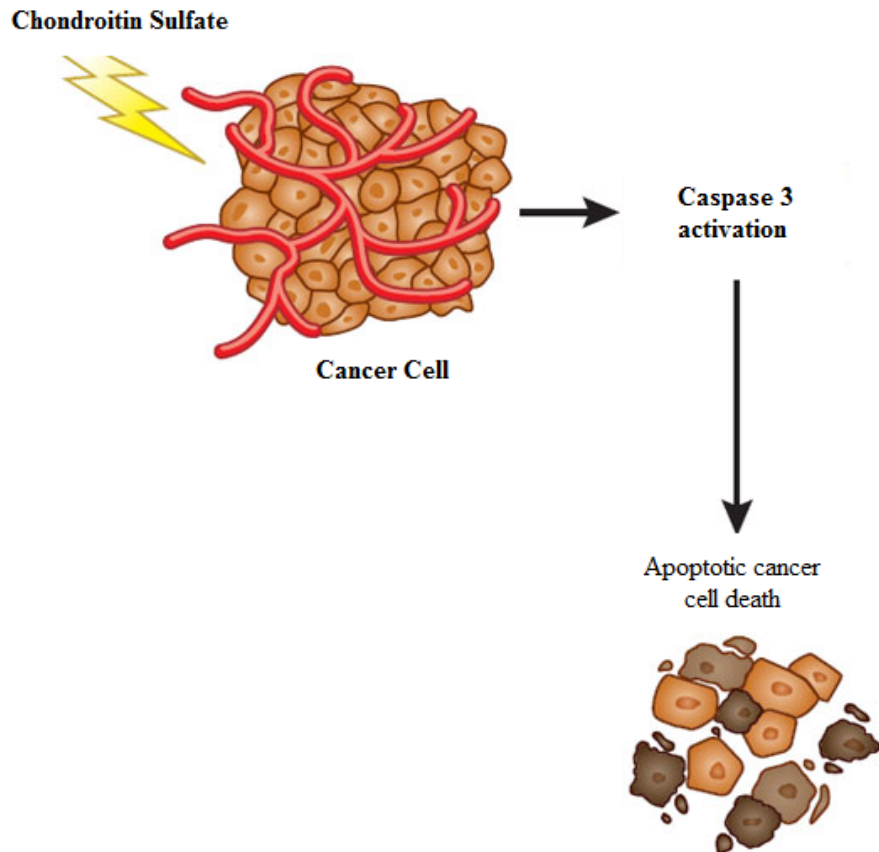


**Figure 1.** Apoptosis Pathway Induced by CS [10]

In Figure 1, CS binds to the cancer cells at a rate $k_1$. Subsequently the CS-cancer cells bound will induced the activation of Caspase-3. The activated Caspase-3 will promotes cell death or specifically known as apoptosis mechanism at a rate $k_2$. The mechanism of this pathway can be transformed into chemical reactions as

$$\lambda + X \xrightarrow[induce]{k_1} Y \xrightarrow[induce]{k_2} Apoptosis \qquad (1)$$
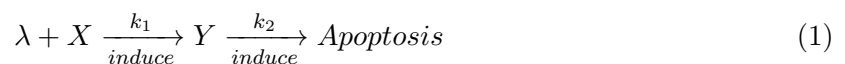
Reaction (1) can be transformed into ordinary differential equation (ODEs) as follows

$$dX = -k_1 \lambda X dt \qquad (2)$$

$$dY = (k_1 \lambda X - k_2 Y) dt \qquad (3)$$

ODEs (2) and (3) are transformed into SDEs by perturbing the parameters $k_1$ and $k_2$ in Equation (2) and (3), respectively such that

$$k_1 \rightarrow k_1 + \sigma \frac{dW}{dt} \tag{4}$$

$$k_2 \rightarrow k_2 + \sigma \frac{dW}{dt}. \tag{5}$$

These yields

$$dX = -k_1 \lambda X dt + \sigma_1 X dW(t) \tag{6}$$

$$dY = (k_1 \lambda X - k_2 Y)dt + \sigma_2 Y dW(t) \tag{7}$$

where $X$ is the cancer cell, $Y$ is the activation of caspase-3. Here, $\sigma > 0$ is the diffusion coefficient and the process $dW$ for $t \geq 0$ is a Gaussion white noise process with mean zero and variance, $\Delta t$.

## 3. Numerical Method and Parameter Estimation

The numerical solution of stochastic models are simulated via a Euler-Maruyama method with 0.5 order of convergence. This method can be represented by following formula

$$X_{n+1} = X_n + (-k_1 \lambda X_n)\Delta t + (\sigma_1 X_n)\Delta W_n \tag{8}$$

$$Y_{n+1} = Y_n + (k_1 \lambda X_n - k_2 Y_n)\Delta t + (\sigma_2 Y_n)\Delta W_n \tag{9}$$

where $\Delta t = t_{n+1} - t_n$ and $\Delta W_n = W(t_{n+1}) - W(t_n)$.

The increment of the Wiener process, $\Delta W_n$ is normal distributed with mean zero and variance, $\Delta t$.

### 3.1. Maximum Likelihood Estimator

A non–parametric simulated maximum likelihood approach is applied to estimate the unknown parameters of stochastic model. 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 $\theta$ is the parameters to be estimated. The maximum likelihood estimator for $\theta$ is obtained by maximizing the likelihood function of

$$L(\theta) = \prod_{i=1}^{N} p(t_i, y_i|t_{i-1}, y_{i-1}; \theta) \tag{10}$$

The Monte Carlo simulation is used to derive $L(\theta)$ which is proposed by [14]. The algorithm is presented below.

(i) 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 stochastic model is integrated on this discretization by using Euler-Maruyama method. This integration is repeated $R$ times for $R = 100$ to generate $R$ approximations of the cancer treated $X$ at $t_i$ starting with $y_{i-1}$ at $t_{i-1}$. The approximate values of cancer treated is denoted as $X_{t_i}^1 \ldots X_{t_i}^R$, where $X_{t_i}^r$ is the integrated value of stochastic model in the $r^{th}-$ simulation for $r = 1, \ldots, R$.

(ii) Then, a non–parametric kernel density is constructed from the simulated values of $X_{t_i}^1 \ldots X_{t_i}^R$ are used to construct a non–parametric kernel density estimate of the transition density (10)

$$p^R(t_i, y_i|t_{i-1}, y_{i-1}; \theta) = \frac{1}{Rh_i} \sum_{r=1}^{R} K\left(\frac{y_i - A_{t_i}^r}{h_i}\right) \tag{11}$$

where $h_i$ is the kernel bandwidth at time $t_i$ and $K(\cdot)$ is a suitable symmetric, non–negative kernel function enclosing unit mass.

(iii) 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 $L^R(\theta) = \prod_{i=1}^{N} p^R(t_i, y_i | t_{i-1}, y_{i-1}; \theta)$.

(iv) $L^R(\theta)$ is maximized to obtain the approximated MLE $\theta^R$ of $\theta$.

Hurn et al. [14] is proposed a suitable choice of $K(\cdot)$ which is given by the normal kernel

$$K(u) = \frac{1}{\sqrt{(2\pi)}} \exp^{(\frac{-u^2}{2})} \tag{12}$$

with bandwith given by

$$h_i = \frac{4^{\frac{1}{5}}}{3} s_i R^{\frac{-1}{5}}, \qquad i = 1, \ldots, N \tag{13}$$

## 4. Material and Methods

### 4.1. Cell Line
Human breast cancer (MCF7) was kindly provided by Dr. Solachuddin Jauhari Arief Ichwan From Kuliyyah of Dentistry, International Islamic University Malaysia (IIUM) Kuantan, Pahang. The cell was cultured in DMEM (Gibco, California, USA) medium and maintained in a humidified incubator with 5% $CO_2$ and 95% air at 37°C.

### 4.2. Preparation of CS Solution
Blue-spotted stingray were used for extraction of CS. For extraction process, the powder form of CS crudes were used for the experiment. CS crude products were courtesy from Dr Nina Suhaity from University Malaysia Pahang.

### 4.3. Anti-Proliferation Assay
Cellular proliferation was determined by the ability of cells to convert soluble MTT (Sigma Aldrich, St. Louis, Missouri, USA) to an insoluble coloured formazan precipitate. Exponentially growing cells were plated onto 96-well plates following 24 hours at an initial density of $2 \times 10^4$/well, treated with defined concentrations of CS $(12.5, 25, 50$ and $100\mu g)$. Plates were centrifuged at 1000 rpm to collect floating cells using a microplate swing rotor centrifuge. Then carefully remove the media from the wells without disturbing the cell pellet. The cells were incubated in 30 $\mu$l MTT (Sigma-Aldrich, USA) at concentration of 5 $mg/ml$ in phosphate buffer saline (PBS) for 2 hrs. The intercellular formazan complex was dissolved in DMSO. The absorbance was measured at 570 $nm$ by a microplate reader.

## 5. Result and Discussion
In this section, the simulated results is presented to understand the effects of therapies on growth rate of cancer cell.

### 5.1. Analysis of Stochastic Model
For this purpose, the likelihood function $L^R(\theta)$ for $R = 100$ are maximized to generate the estimated values of $\theta = \{k_1, k_2, \sigma_1, \sigma_2\}$. The construction of $L^R(\theta)$ requires the generating of Wiener increments $\Delta W(t) = W(t_n) - W(t_{n-1})$. The increments are simulated by using Box–Muller method and those values are kept fixed for a given optimization procedure. The experimental data is generated at equally spaced intervals of time $h_n = t_n - t_{n-1} = \frac{T}{N}$. Numerical method is performed to simulate the trajectories in the interval time $[t_0, T]$ with initial condition of cell absorbance, $X(t_0) = 0.3123$. Numerical optimization algorithm was implemented using Matlab program and the estimated parameter values of $\theta = \{k_1, k_2, \sigma_1, \sigma_2\}$ for $R = 100$ are listed in Table 5.1.

**Table 1.** Maximum Likelihood Estimates of Stochastic Model Parameter

| Mathematical Model | $k_1$ | $k_2$ | $\sigma_1$ | $\sigma_2$ |
|---|---|---|---|---|
| Stochastic Model | -0.54 | 0.41 | 0.05 | 0.04 |

Figure 2 shows the simulated results of stochastic models (6) and(7) with experimental data. Based on Figure 2, the numerical result obtained via stochastic model is consistent with the experimental data.
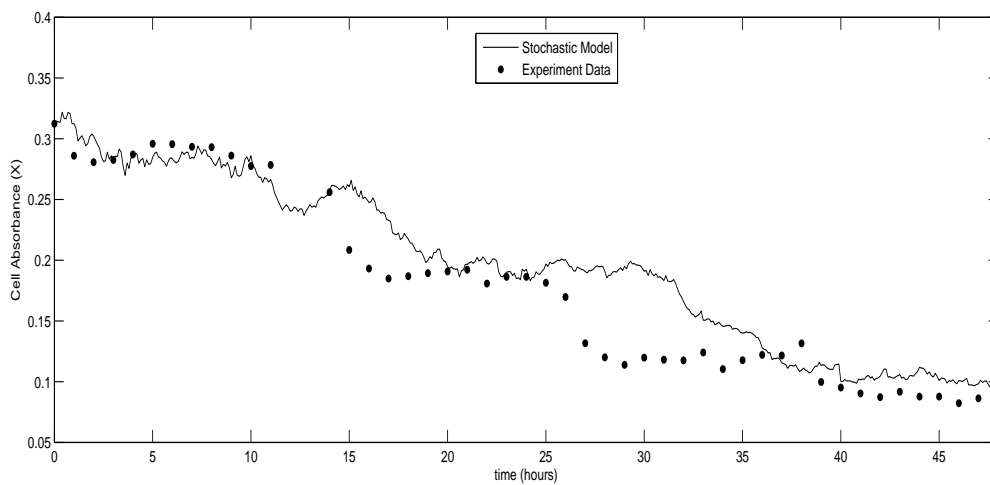


**Figure 2.** Simulation Results of Stochastic Model with the Experimental Data of Cancerous Growth with Treatment

Figure 3 is illustrates the result of Equation (7) over 100 trajectories. To confirm whether apoptotic in these cells were mediated by caspase-3, the upregulated transcript levels of these caspase in MCF-7 were simulated. It is shown that CS effects on caspase-3 activation are at the trancriptional level.
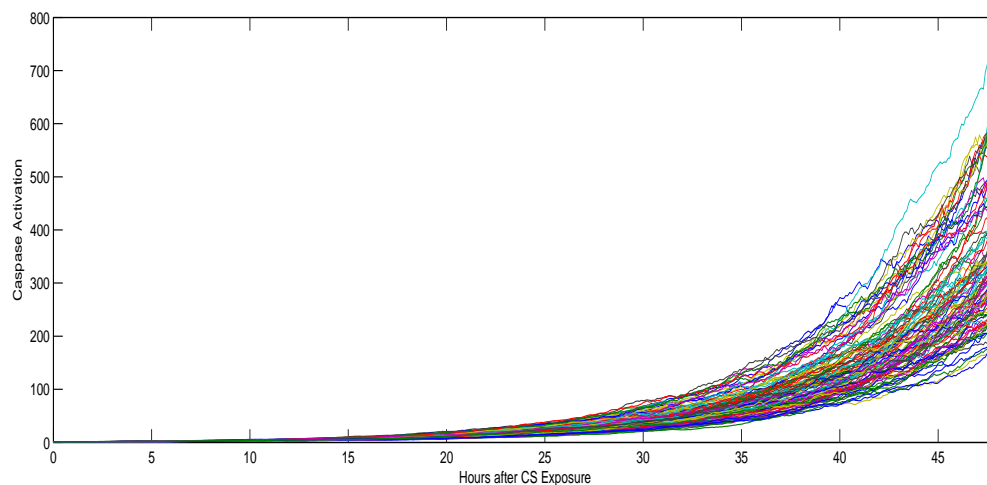
**Figure 3.** Caspase-3 activity assay

## 6. Conclusion

It is clear that for reducing cancerous growth, drug targeted therapy should be started as soon as the cancer cell is detected and should be scheduled frequently. This finding provides useful knowledge on the understanding of the interaction of CS with the cancer cell.

## References

[1] Stewart B and Wild C 2014 *World cancer report 2014* (Geneva, Switzerland: WHO Press)
[2] Zainal Ariffin O and Nor Saleha IT 2011 *Malaysia cancer statistics data and figure 2007* (Kuala Lumpur: National Cancer Registry)
[3] Kuan GL, Papapreponis P and Hin YM 2015 *Malaysian Journal of Public Health Medicine* **15** 62-8
[4] Ichwan SJ, Al-Ani IM, Bilal HG, Suriyah WH, Taher M and Ikeda MA 2014 *Chin J Physiol* **57** 249-255
[5] Abbott LH and Michor F 2006 *British Journal of Cancer* **95** 1136–1141
[6] Biosciences BD 2010 *Caspase-3 activation: An indicator of apoptosis in image-based assays*
[7] Ivana B, Benjamin A and Martin AN 2012 *Trends in Molecular Medicine* **18** 311–316
[8] Asimakopoulou AP, Theocharis AD, Tzanakakis GN and Karamanos NK 2008 *In Vivo* **22** 385-389
[9] Baar M, Coquille L, Mayer H, Hlzel M, Rogava M, Tting T and Bovier A 2016 *Scientific Reports* **6**
[10] Connell PP and Weichselbaum RR 2011 *Nature Medicine* **17** 7
[11] Ghobrial IM, Witzig TE and Adjei AA 2005 *CA Cancer J Clin* **55** 178-194
[12] Rüemelin W 1982 *SIAM Journal of Numerical Analysis* **19** 604613
[13] Burrage PM 1999 Runge-Kutta methods for stochastic differential equations Ph.D thesis (The University of Queensland Brisbane)
[14] Hurn AS and Lindsay KA and Martin VL 2003 *Journal of Time Series Analysis* **24** 45–63