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Performance of Linear and Stochastic Cell-growth Model of Ductal Carcinoma In Situ (DCIS)

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ABSTRACT

According to World Health Organization (WHO), in 2020 there were 2.3 million of women have been diagnosed with breast cancer and there are up to 685,000 deaths globally. 85% of breast cancer arises in the lining cells (epithelium) of the ducts known as ductal carcinoma in situ (DCIS). One of the contributing factors that increase cancer mortality is the lack of understanding of the biological complexities of cancer growth and its evolution. Mathematical-model approaches are widely used to quantitatively understand the behaviour of the cancer cells and the treatment resistance. In order to justify the treatment customization and convey the treatment inefficacy, the mathematical modelling is usually considered as a tool to support drug and treatment decision making. By now, several mathematical models via ordinary differential equations (ODEs) for the cancer cell growth process have been formulated in the literature. Unfortunately, due to the noise behaviour of cancerous cells, the developed linear model cannot represent the real behaviour of the cancer cells growth which led to the development of stochastic model of cancer cells growth. This study is devoted to comparing the performance of linear and stochastic cell growth model of DCIS. The linear model cell growth model of DCIS has been solved via Runge-Kutta method of order 4.0 while the stochastic cell growth model of DCIS has been solved via fifth-stage stochastic Runge-Kutta method (SRK5) of order 2.0. The numerical results obtained have been compared to the real cell growth data for DCIS patients and the best model representing the cell growth of DCIS has been concluded. This study has shown that stochastic Gompertzian model has a great representation of the real systems of breast cancer cell growth. This useful clinical knowledge provides a better understanding of cancer evolution to overcome the treatment resistance hence may help oncologists to design better treatment strategies and bring opportunities to treat cancer patients.

1. Introduction

The growth of abnormal cells uncontrollably leads to the formation of cancer cells that can start in almost any organ or tissue of the body. Even though there have been tremendous progress been

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made in conjunction to increase one's understanding of how the cancer cells growth and also increasing the way they respond to treatment, the financial cost and deaths of cancer cases continues to grow worldwide with estimated of 19.3 million new cancer cases and about 10 million cancer related deaths in 2020 which caused cancer to be nominated as the second leading cause of mortality throughout the world.

The condition where the abnormal cells are found inside a breast milk duct is known as ductal carcinoma in situ (DCIS). DCIS is represented as the first type of breast cancer since is unlikely to turn invasive as it remains confined within the milk duct and does not spread beyond. Thus, DCIS is considered as non-invasive breast cancer. DCIS requires an evaluation and discussion of treatment alternatives even if it is not an emergency. Surgery to remove all of the breast tissue or radiation therapy may be used as a kind of treatment. Another choice would be a clinical trial looking at active monitoring as an alternative to surgery.

One of the contributing factors that increase cancer mortality is the lack of knowledge of the biochemical complexity involved in the development of cancer and its evolution as mentioned in Yang *et al.*, [1]. The complicated and varied nature of cancer highlights the ongoing need to improve knowledge of how malignancies originate and how medical professionals should provide systematic treatments to maximize the therapeutic value for specific patients. Significant advancements in theoretical, clinical as well as experimental methods to comprehend the behavior of cancer cells, the mechanism, the progression of cancer, and therapeutic resistances have recently been made. According to Ma *et al.*, [2], within the last five years, attention has been given to intensively investigating the evolution of cancer cells through a model-based approach. Since the mathematical approach was proven to provide the quantitative characterization of cancer evolution, therefore, the use of mathematical modelling to enhance pharmacological and treatment decision making is widely regarded as a way to overcome treatment failure and rationalize therapy personalization. Mathematical-model approaches are widely used to quantitatively understand the behavior of the cancer cells and the treatment resistance. In previous research, it has been mentioned that the Hallmarks of Cancer provide a comprehensive conceptual framework for understanding numerous aspects of cancer biology and the causes of the disease's acknowledged variety. However, it can be quite challenging for a particular individual to comprehend how the hallmarks that happen affect their tumor's growth dynamics and responsiveness to treatment using only verbal thinking. In Bull and Byrne studies in [3], the authors illustrate how mathematical modeling might offer a complementary framework for addressing all difficulties and introduce a characteristic of mathematical oncology in order to characterize mathematical models to represent the dynamics of cancer cells. Six key mathematical characteristics have been identifying which are Single framework vs Hybrid framework, Homogeneous vs Heterogeneous, Spatially averaged vs Spatially resolved, Single scale vs Multi-scale, Deterministic vs Stochastic and Continuum vs Discrete [3]. Each characteristic represents a decision that will ascertain the degree of biological details to be weighed, the complexity to solve the model and all data that the model can provide. There are different mathematical modelling approaches with different complexities existed. This is due to each model representing a different combination of cancer characteristics in different ways which involve more biological complexity and more difficulties to analyze. Different mathematical models such as Ordinary differential equations, stochastic differential equations, partial differential equations, mixed systems of differential equations, cellular automata and off-lattice agent-based models combine cancer characteristics in different ways. It contributes to the different biological complexities involved [3].

By now, several mathematical models for the cancer cell growth process have been formulated in the literature. Classical mathematical models depicting the growth of tumors have influenced our understanding of cancer and have overall consequences for determining the optimal dosage and the timing of patients should be treated as studied by Ghaffari *et al.,* in [4]. However, Yin *et al.,* in [5] said it is evident that cancer evolution takes place in a highly uncertain environment as a result of the chaotic behaviour in the human body. To reflect the realistic behaviour of cancerous cell growth, a mathematical model that describes this process should take into account the stochastic effects. In 2021, a stochastic process that may affect the development of metastases in lung cancer has been included in research on the growth and metastatic spread. Kozlowska and Swierniak have mentioned in [6], this study has shown that a mathematical oncology approach could be used to determine which cancer therapy options could delay the emergence of metastases. Mathematical modelling of solid tumor growth starts when Gompertz created a mathematical model to describe his law of human mortality as proven in *Ma et al.*, [2]. There has been wide range of applications of the Gompertz model in predicting the growth of tumor cell. The deterministic Gompertz model can be written as

$$dS(t) = (\alpha S(t) - \beta S(t)\ln(S(t)))dt \tag{1}$$

where $S(t)$ represent the area in cm^2 of the tumor at time, t, α is a parameter related to the initial mitosis rate representing the intrinsic growth rate of the tumor and β which is the growth rate deceleration factor is related to the process known as antiangiogenic process. However, there are always differences between the curve predicted by the Gompertz model and the clinical data of tumour growth since there are inherent disturbances or oscillations in tumour growth. These inherent noises or fluctuations may be caused by hormonal changes, variations in blood pressure, breathing, variable neural control of muscle activity, enzymatic reactions, energy requirements, cellular metabolism, sympathetic nerve activity, or other differences in an individual's characteristics like body mass index, genes, smoking status, stress level, etc. [7]. Therefore, a better mathematical model to represent tumor growth was developed. The growth of cancer cells has been modelled via stochastic differential equations (SDEs) by incorporating random effects to the deterministic Gompertz model. Assuming that the variation of environmental conditions had influenced the rate of intrinsic growth, α, therefore the uncontrolled factors is allowed into (1) by writing the intrinsic growth parameter as

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

Note that $\sigma > 0$ is the diffusion coefficient and for $t \geq 0$, $W(t)$ is a stochastic process having Gaussian distribution with variance, Δt and mean zero. Hence, the stochastic differential equation for mathematical model of breast cancer tumor growth can be written as

$$dS(t) = (\alpha S(t) - \beta S(t) lnS(t))dt + \sigma S(t) dW(t) \tag{3}$$

The equation in (3) known as a stochastic Gompertzian model as in Mazlan and Rosli, [8] describing in vivo growth of tumor and its sensitivity treatment with the presence of antiangiogenic drugs. In this study, the stochastic Gompertzian model in (3) has been solved and compared to the deterministic Gompertz model, the forecasting model of breast cancer cell growth and the real data.

This study will reveal the performance of stochastic Gompertz model in describing the growth of breast cancer cells.

2. Numerical Method

Solving the stochastic models will be challenging due to its complexity in representing random effects incorporated. In many cases analytic solutions are not available for these SDEs. Therefore, we are required to use numerical methods to approximate the solution. In ordinary differential equations (ODEs), Runge-Kutta (RK) method is a popular alternative to solve ODEs numerically. RK method is a free-derivative method since it does not require the use of the high order derivatives of functions where it can develop high-order accurate numerical methods using only the functions themselves. These characteristics of RK method somehow contribute to the convergency of the solution to the ODEs [9]. Since the accuracy in the solution of an initial value problem (IVP) can be guaranteed by solving the problem using variable step size [10], the Runge-Kutta Fehlberg (RKF45) method has been used to solve the Linear Gompertz model. It has a process to check whether the right step size h is being applied. Two distinct approximations for the solution are created and contrasted at each step. The approximation is approved if there is substantial agreement between the two responses. The step size is decreased if there is a discrepancy between the two responses to a given accuracy. The step size is increased if the solutions agree to more significant digits than necessary. Use of each of the following six values is necessary for each step:

$$
\begin{aligned}
k_1 &= hf(t_k, y_k) \\
k_2 &= hf\left(t_k + \frac{1}{4}h, y_k + \frac{1}{4}k_1\right) \\
k_3 &= hf\left(t_k + \frac{3}{8}h, y_k + \frac{3}{32}k_1 + \frac{9}{32}k_2\right) \\
k_4 &= hf\left(t_k + \frac{12}{13}h, y_k + \frac{1932}{2197}k_1 - \frac{7200}{2197}k_2 + \frac{7296}{2197}k_3\right) \\
k_5 &= hf\left(t_k + h, y_k + \frac{439}{216}k_1 - 8k_2 + \frac{3680}{513}k_3 - \frac{845}{4104}k_4\right) \\
k_6 &= hf\left(t_k + \frac{1}{2}h, y_k - \frac{8}{27}k_1 + 2k_2 - \frac{3544}{2565}k_3 + \frac{1859}{4104}k_4 - \frac{11}{40}k_5\right).
\end{aligned}
\tag{4}
$$

Then, an approximation to the solution of the IVP is made using Runge-Kutta method of order 4:

$$y_{n+1} = y_n + \frac{25}{216}k_1 + \frac{1408}{2565}k_3 + \frac{2197}{4101}k_4 - \frac{1}{5}k_5. \tag{5}$$

where the four function values k_1, k_3, k_4 and k_5 are used. A better value for the solution is determined using a Runge-Kutta method of order 5:

$$z_{n+1} = y_n + \frac{16}{135}k_1 + \frac{6656}{12825}k_3 + \frac{28561}{56430}k_4 - \frac{9}{50}k_5 + \frac{2}{55}k_6. \tag{6}$$

The optimal step size h can be determined by multiplying the scalar s times the current step size, h. The scalar s is

$$s = \left(\frac{tol\, h}{2\left| z_{k+1} - y_{k+1} \right|} \right)^{1/4} \approx 0.84 \left(\frac{tol\, h}{\left| z_{k+1} - y_{k+1} \right|} \right)^{1/4} \tag{7}$$

The great performances of RK method in solving ODEs attract researchers' attention to develop RK method in the field of SDEs. The development of stochastic Runge-Kutta (SRK) method for solving SDEs started when Rumelin in 1982 expanded the Runge-Kutta method in the area of SDEs by replacing the derivatives of the stochastic Taylor approximation in the Milstein scheme by differences [11]. In 2018, SRK method for SDEs with high order of convergence 2.0 has been developed by [12] known as fifth-stage SRK method (SRK5). The SRK5 scheme for solving SDEs can be written as

$$\begin{aligned} y_{n+1}(t) = {} & y_n(t_0) + h\sigma_1 f(Y_1) + h\sigma_2 f(Y_2) + h\sigma_3 f(Y_3) + h\sigma_4 f(Y_4) + h\sigma_5 f(Y_5) \\ & + (\delta_1^{(1)} J_1 + \delta_1^{(2)} \frac{J_{10}}{h}) g(Y_1) + (\delta_2^{(1)} J_1 + \delta_2^{(2)} \frac{J_{10}}{h}) g(Y_2) + (\delta_3^{(1)} J_1 + \delta_3^{(2)} \frac{J_{10}}{h}) g(Y_3) \\ & + (\delta_4^{(1)} J_1 + \delta_4^{(2)} \frac{J_{10}}{h}) g(Y_4) + (\delta_5^{(1)} J_1 + \delta_5^{(2)} \frac{J_{10}}{h}) g(Y_5) \end{aligned} \tag{8}$$

where

$$Y_1 = Y_0^{(n)}$$

$$Y_2 = Y_0^{(n)} + ha_{21} f(Y_1^{(n)}) + \left(b_{21}^{(1)} J_1 + b_{21}^{(2)} \frac{J_{10}}{\Delta} \right) g(Y_2^{(n)})$$

$$\begin{aligned} Y_3 = {} & Y_0^{(n)} + ha_{31} f(Y_1^{(n)}) + ha_{32} f(Y_2^{(n)}) \\ & + \left(b_{31}^{(1)} J_1 + b_{31}^{(2)} \frac{J_{10}}{h} \right) g(Y_1^{(n)}) + \left(b_{32}^{(1)} J_1 + b_{32}^{(2)} \frac{J_{10}}{h} \right) g(Y_2^{(n)}) \end{aligned}$$

$$\begin{aligned} Y_4 = {} & Y_0^{(n)} + ha_{41} f(Y_1^{(n)}) + ha_{42} f(Y_2^{(n)}) + ha_{43} f(Y_3^{(n)}) \\ & + \left(b_{41}^{(1)} J_1 + b_{41}^{(2)} \frac{J_{10}}{h} \right) g(Y_1^{(n)}) + \left(b_{42}^{(1)} J_1 + b_{42}^{(2)} \frac{J_{10}}{h} \right) g(Y_2^{(n)}) \\ & + \left(b_{43}^{(1)} J_1 + b_{43}^{(2)} \frac{J_{10}}{h} \right) g(Y_3^{(n)}) \end{aligned}$$

$$\begin{aligned} Y_5 = {} & Y_0^{(n)} + ha_{51} f(Y_1^{(n)}) + ha_{52} f(Y_2^{(n)}) + ha_{53} f(Y_3^{(n)}) + ha_{54} f(Y_4^{(n)}) \\ & + \left(b_{51}^{(1)} J_1 + b_{51}^{(2)} \frac{J_{10}}{h} \right) g(Y_1^{(n)}) + \left(b_{52}^{(1)} J_1 + b_{52}^{(2)} \frac{J_{10}}{h} \right) g(Y_2^{(n)}) \\ & + \left(b_{53}^{(1)} J_1 + b_{53}^{(2)} \frac{J_{10}}{h} \right) g(Y_3^{(n)}) + \left(b_{54}^{(1)} J_1 + b_{54}^{(2)} \frac{J_{10}}{h} \right) g(Y_4^{(n)}) \end{aligned}$$

and J_1 and J_{10} represent the stochastic integrals. In Butcher's tableau form, the numerical scheme of SRK5 method can be written below.

$$\mathbf{A}=\begin{matrix}\frac{12}{637} & & & & \\ \frac{1}{264} & \frac{19}{790} & & & \\ \frac{53}{559} & \frac{-313}{438} & \frac{-103}{702} & & \\ \frac{-365}{259} & \frac{564}{289} & \frac{-271}{236} & \frac{-109}{581} & \end{matrix}$$

$$\sigma=\begin{matrix}\frac{277}{197} & \frac{505}{999} & \frac{-463}{908} & \frac{4603}{671} & \frac{-4219}{581}\end{matrix}$$

$$\mathbf{B}^{(1)}=\begin{matrix}\frac{643}{937} & & & & \\ \frac{45}{59} & \frac{-59}{741} & & & \\ \frac{43}{448} & \frac{453}{968} & \frac{278}{737} & & \\ \frac{15}{202} & \frac{-377}{833} & \frac{149}{400} & \frac{3}{962} & \end{matrix}$$

$$\delta^{(1)}=\begin{matrix}\frac{413}{264} & \frac{1678}{817} & \frac{-543}{406} & \frac{-423}{661} & \frac{-257}{401}\end{matrix}$$

$$\mathbf{B}^{(2)}=\begin{matrix}\frac{-13}{486} & & & & \\ \frac{16}{977} & \frac{-40}{749} & & & \\ \frac{1}{12} & \frac{-49}{818} & \frac{42}{871} & & \\ \frac{-41}{681} & \frac{-1}{27} & \frac{7}{236} & \frac{-1}{612} & \end{matrix}$$

$$\delta^{(2)}=\begin{matrix}\frac{-489}{379} & \frac{259}{745} & \frac{-231}{692} & \frac{170}{277} & \frac{55}{83}\end{matrix}$$

On the other hand, Box-Jenkins Model is one of the mathematical models designed to forecast data ranges based on inputs from a specified time series. In order to provide accurate forecasts, the Box-Jenkins Model is able to perform analyses on a wide variety of time series data. The approach enables the model to identify trends by employing moving averages, seasonal differencing, and autoregression in order to provide forecasts, which is why Autoregressive Integrated Moving Average (ARIMA) models are a variant of Box-Jenkins model. It is not uncommon for people to use the phrases ARIMA and Box-Jenkins interchangeably. This method is the most common method used in price prediction research. The SRK5 method presented above has been used to solve stochastic Gompertzian model for breast cancer cell growth in (3). The approximate solution to this model will then be compared to the deterministic Gompertzian model in (1), forecasting model of cancer cell's growth and the clinical data of breast cancer patients.

3. Result & Discussion

The linear Gompertzian model has been solved via RKF45 while stochastic Gompertzian model for breast cancer has been solved by using SRK5 method in (8) for 2 breast cancer patients, labelled as Patient 1 and Patient 2. This Gompertzian stochastic model has been solved and compared to the linear Gompertzian model, Time Series Forecasting model and also real data and the result have been presented as in Figures 1 and 2. Figures 1 and 2 evince that the Gompertzian stochastic model predicts the expansion of breast cancer cells in a manner that is commensurate with the actual data of the area of cancer cells for Patients 1 and 2. This is because the stochastic Gompertzian model can accurately depict the system of cancer cell proliferation even when random factors are present.

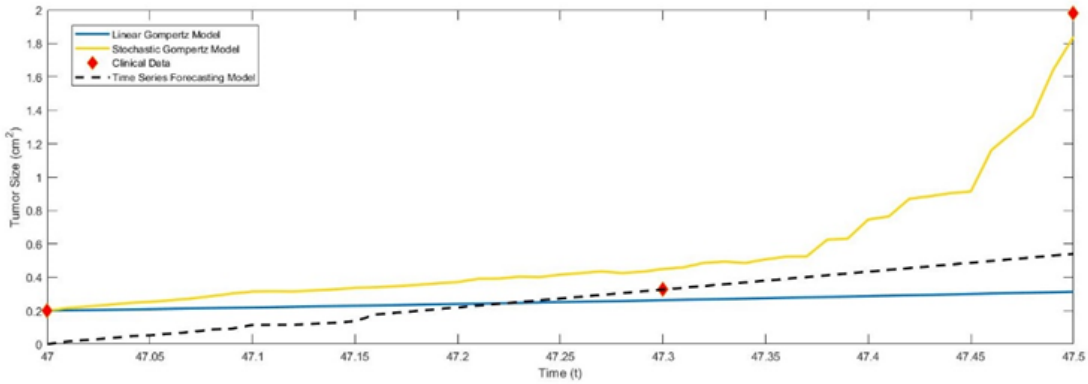

Fig. 1. The comparison of the solutions via Linear Gompertzian model, Stochastic Gompertzian model, Time series Forecasting model and the clinical data of breast cancer cells for Patient 1

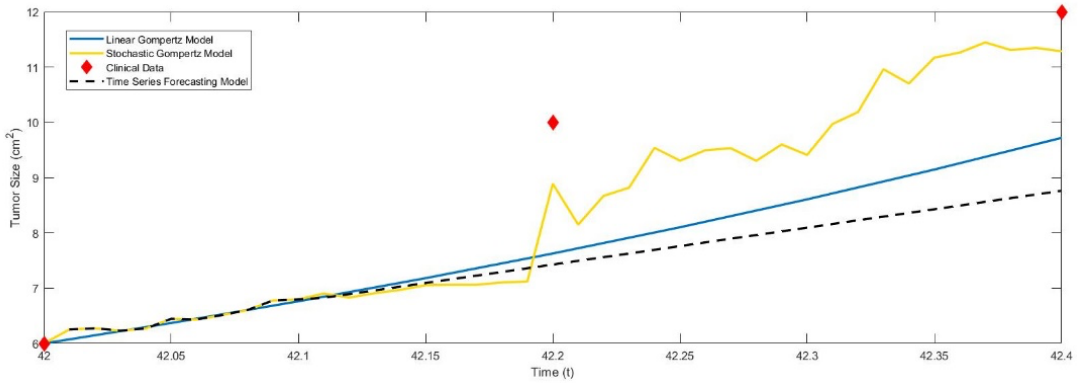

Fig. 2. The comparison of the solutions via Linear Gompertzian model, Stochastic Gompertzian model, Time series Forecasting model and the clinical data of breast cancer cells for Patient 2

The comparison of root mean-square error (RMSE) and global error across all models to actual breast cancer patient data can support this agreement. The following formula can be used to determine the RMSE.

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - x_i)^2}{n}} \tag{9}$$

where xi is the experimental data, y_i is the approximated solution and n is number of observations. Meanwhile, Global error can be written as

$$Err = \frac{1}{m}\sum_{i=1}^{m} | y_{t_{Ni}} - x_{t_{Ni}} | \tag{10}$$

t_N : endpoint of the simulations.

$y_{t_{Ni}}$: numerical solution of SDE at endpoint $t = t_N$.

$x_{t_{Ni}}$: exact solution of SDE at endpoint $t = t_N$.

i : number of trajectories used in each numerical simulations where for this research, $m = 100$.

The analysis of the RMSE and Global error can be summarized in the following Table 1 and Table 2 respectively.

Table 1
Mean-square error (MSE) of Linear Gompertzian model, Stochastic Gompertzian model and Time Series forecasting

Mathematical Model	Patient 1	Patient 2
Linear Gompertzian Model	0.92513	3.60947
Stochastic Gompertzian Model	0.01129	0.58147
Time Series Forecasting Model	0.70400	5.69999

Table 2
Global error of Linear Gompertzian model, Stochastic Gompertzian model and Time Series forecasting model

Mathematical Model	Patient 1	Patient 2
Linear Gompertzian Model	0.0167	0.0228
Stochastic Gompertzian Model	00014	0.0071
Time Series Forecasting Model	0.0144	0.0324

Low values of MSE and global error, as shown in Tables 1 and 2, which suggest good fits, are produced when the solution is obtained using the stochastic Gompertzian model, which incorporates random components and is therefore more consistent with the actual data. This result showed that the stochastic Gompertzian model more accurately predicts the tumor progression of breast cancer than the linear Gompertzian model and the time series forecasting model.

4. Conclusions

The stochastic Gompertzian model for breast cancer results is better able to describe the presented data than the deterministic Gompertzian model, as seen by the low values of MSE and global error. The growth of the cancer cell is susceptible to random influences in the real system because there are numerous uncontrollable external factors impacting it. Many studies on the development of cancers have utilised the Gompertzian deterministic model. However, there are always differences between the curve predicted by Gompertzian deterministic and the clinical data of tumor growth because there are inherent disturbances or oscillations in tumor growth. Consequently, a more accurate mathematical model to depict the tumor growth model was created. This study showed that the stochastic Gompertzian model more faithfully represents the real behaviour of cancer growth than its deterministic counterpart. It is important to remember that the stochastic Gompertzian model will give a better picture of the malignant progression for breast cancer since it takes into account the random events that could disrupt the real system. This finding advances our knowledge of the uncontrolled factors that affect breast cancer cells. Additionally, it is better characterising the development of cancer, which has the potential to be very helpful in the future personalization and optimisation of anticancer treatments. It is strongly advised that medical professionals take into account this mathematical model-based strategy, which can assist in providing a better treatment and also aid cancer patients overcome a treatment resistance. This study has demonstrated the stochastic Gompertzian model's excellent potential for creating a digital

replica of the real systems. As a result, oncologists will be able to model and forecast the behaviour of cancer cells in the future and direct them in making decisions. The ability to tailor care makes it possible to treat cancer as a chronic illness.

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