Results in Nonlinear Analysis 2 (2019) No. 1, 1–6
Available online at www.nonlinear-analysis.com

Results in Nonlinear Analysis
ISSN 2636-7556

Peer Reviewed Scientific Journal

Stochastic Dynamics of Tumor-Immune System: A Numerical Approach

Nurgül Gökgöz[a]

[a] *Department of Mathematics, Çankaya University, 06790 Etimesgut, Ankara, Turkey. Department of Scientific Computing, Middle East Technical University, Ankara-Turkey.*

Abstract

In this work, a very well known tumor-immune system model from the literature, Kuznetsov et al.'s model, is converted into two different Stochastic Differential Equation (SDE) models and an Itô formalism of the models are obtained. Furthermore, the models are made discrete by using Euler-Maruyama scheme, simulation results of the corresponding models are investigated and compared.

Keywords: Itô Calculus, Stochastic model, Markov chain, Euler-Maruyama method, Tumor-immune system.
2010 MSC: 65C30, 65C20, 65C40, 68U20, 92B99.

1. Introduction

Tumor is one of the leading causes of death around the world. Many researchers from various disciplines conduct experiments, construct mathematical models, explore gene expressions relationships in order to find a relationship of tumor growth with other mechanisms. A tumor cell usually encounters the immune system firstly. Therefore, investigating the relationship between tumor growth and immune system mechanism plays an important role especially when one wants to design a treatment that is compatible with the host. Since the problem is very complex, even in its simplest version, taking into account only tumor cells and immune cells makes sense. In recent years, deterministic and stochastic mathematical models of tumor-immune system, their analysis and their simulations have gained an important attention. Many researchers from different disciplines approached the problem from different perspectives in order to formulate the problem in a systematic way. To mention some of them, tumor-immune models [12, 15, 16], modeling of treatment on tumor-immune interactions [5, 11], using different approaches other than classical nonlinear system of

Email address: nurgul.gokgoz@gmail.com (Nurgül Gökgöz)

Received xx, 2019, Accepted xx, 2019, Online xx, 2019.

ordinary differential equations such as cellular automata-partial differential equations [14], game theoretic formulation [9] or kinetic theory approaches [6] exist in the literature. Among them, Kuznetsov et. al.'s model [12] is one of the most influential models that is studied the most. For further investigation of the models and other modeling approaches in the tumor-immune system literature, one may refer to [1, 8].

In this work, a very-well known model in tumor-immune system dynamics, Kuznetsov et al.'s model, is investigated. By using Allen's procedure [2, ch. 5], [4, ch. 9] and obtaining an Itô formalism at the end, two different system of SDEs of the model are obtained. Those models are made discrete and the simulation results are compared. The methodology described by Allen has been applied to an another tumor-immune model in [13] and also investigated in terms of viabiliy [7]. Here, we repeat the same procedure and obtain two SDE models. The organization of the paper can be summarized as follows; in Section 2, the deterministic model of Kuznetsov et al. is given. The procedure to obtain two different versions of system of SDEs are described and obtained. In Section 3, the discrete version of the two different SDE models are introduced and the corresponding simulation results are obtained. The paper finishes with a conclusion section, namely Section 4.

2. Stochastic Model

Kuznetsov et al.'s model is used to describe the kinetics of growth and is an approximate regression of the B-Lymphoma BCL_l in the spleen of mice [12]. The authors derived and compared their model with experimental data and statistical estimates of parameters identifying processes that cannot be measured in vivo [12]. The normalized version of the model has been represented as [12]:

$$\frac{dx}{d\tau} = \sigma + \frac{\rho xy}{\eta + y} - \mu xy - \delta x. \tag{2.1}$$

$$\frac{dy}{d\tau} = \alpha y(1 - \beta y) - xy. \tag{2.2}$$

In this system of equations, the parameter τ stands for the normalized time. In [12], the parameter values are given as follows:

$$\begin{aligned} &\sigma = 0.1181, \quad \rho = 1.131, \quad \eta = 20.19, \quad \mu = 0.00311, \\ &\delta = 0.3743, \quad \alpha = 1.636, \quad \beta = 2.0 \cdot 10^{-3}. \end{aligned} \tag{2.3}$$

By using the nonlinear system of equations (2.1) and (2.2), the authors have investigated the nonlinear dynamics in the sense of bifurcation. Since, their model is one of the most influential work among mathematical models of tumor-immune system, investigating the stochastic versions of this model becomes a necessity.

In order to obtain a stochastic model, comprehending the birth and death ranges of each of tumor and immune variables is essential. The stochastic models obtained in this work, represents a Markovian behavior. Precisely, two Continuous Time Markov Chain (CTMC) models are presented by following Allen's procedure (see [2, ch. 5] or [4, ch. 9]). For consistency, the same notation will be used as in [2, ch. 5] or [4, ch. 9]. By choosing a representation for X, instead of x, and Y, instead of y, to be used in the stochastic model as random variables and by letting $Z = (X, Y)^T$ where T stands for the transpose of a matrix, a table that shows probabilities according to changes in the model can be constructed (see Table 1). The column "Change $(\Delta Z)_i$" represents the change in tumor and immune cell population. For example, $(1, 0)^T$ represents the increase in population X and no change in population Y and $(0, -1)^T$ represents the decrease in population Y and no change in population X. Since there is no migration between tumor cells and immune cells the other probabilities such as $(1, -1)^T$, etc. have been disregarded. The expectation vector and the corresponding approximate covariance matrix for the change in Z, ΔZ, with respect to a small period of time, Δt, can be represented respectively as follows,

$$E(\Delta Z)/\Delta t = \left(\sum_{i=1}^{4} p_i \Delta Z_i \right) / \Delta t = \gamma = \begin{pmatrix} \dfrac{\rho XY}{\eta + Y} - \mu XY - \delta X \\ \alpha Y(1 - \beta Y) - XY \end{pmatrix}, \tag{2.4}$$

i	Change, $(\Delta Z)_i$	Probability, p_i
1	$(1,0)^T$	$\left(\sigma + \frac{\rho XY}{\eta + Y}\right)\Delta t$
2	$(-1,0)^T$	$(\mu XY + \delta X)\,\Delta t$
3	$(0,1)^T$	$(\alpha Y)\,\Delta t$
4	$(0,-1)^T$	$\left(\alpha\beta Y^2 + XY\right)\Delta t$

Table 1: The probabilities according to the transition changes of Kuznetsov et al.'s tumor-immune system model.

$$E(\Delta Z(\Delta Z)^T)/\Delta t = \left(\sum_{i=1}^{4} p_i \Delta Z_i (\Delta Z_i)^T\right)/\Delta t \tag{2.5}$$
$$= \begin{pmatrix} \frac{\rho XY}{\eta + Y} - \mu XY - \delta X & 0 \\ 0 & \alpha Y(1-\beta Y) - XY \end{pmatrix}.$$

Depending on the transition probabilities given by Table 1, and assuming entries of the matrix in equation 2.5, Itô SDE model for Kuznetsov et. al.'s model has two different representations, such as

$$dZ(t) = \gamma(Z(t),t)dt + S(Z(t),t)dW(t), \tag{2.6}$$
$$dZ(t) = \gamma(Z(t),t)dt + B(Z(t),t)dW^*(t), \tag{2.7}$$

in compact form. In equations (2.6) and (2.7), the drift vector, namely, γ, is common, however, the matrices S and B represent diffusion matrices of size 2×2 and 2×4, respectively, and W and W^* stands for independent Wiener processes of (2.6) and (2.7), respectively. The drift terms are the same for those two equations (2.6) and (2.7), however diffusion matrices are different. In order to obtain two equivalent SDEs, the condition $S^2 = V = BB^T$ has to be satisfied [2, 3, 4]. By using the procedure of Allen (see [2, ch. 5] or [4, ch. 9]), the following two different system of Ito SDEs are obtained,

$$dX(t) = \left[\sigma + \frac{\rho X(t)Y(t)}{\eta + Y(t)} - \mu X(t)Y(t) - \delta X(t)\right]dt \tag{2.8}$$
$$+ \sqrt{\sigma + \frac{\rho X(t)Y(t)}{\eta + Y(t)} - \mu X(t)Y(t) - \delta X(t)}\,dW_1(t)$$

$$dY(t) = [\alpha Y(t)(1-\beta Y(t)) - X(t)Y(t)]\,dt$$
$$+ \sqrt{\alpha Y(t)(1-\beta Y(t)) - X(t)Y(t)}\,dW_2(t),$$

and

$$dX(t) = \left[\sigma + \frac{\rho X(t)Y(t)}{\eta + Y(t)} - \mu X(t)Y(t) - \delta X(t)\right]dt \tag{2.9}$$
$$+ \sqrt{\sigma + \frac{\rho X(t)Y(t)}{\eta + Y(t)}}\,dW_1^*(t) - \sqrt{\mu X(t)Y(t) + \delta X}\,dW_2^*(t),$$
$$dY(t) = [\alpha Y(t)(1-\beta Y(t)) - X(t)Y(t)]\,dt$$
$$+ \sqrt{\alpha Y(t)}\,dW_3^*(t) - \sqrt{\alpha\beta Y(t)^2 + X(t)Y(t)}\,dW_4^*(t).$$

The equations (2.8) and (2.9) are explicit versions of (2.6) and (2.7), respectively. Obtaining other equivalent SDE models are also possible, however this is out of the scope of this paper and therefore they are omitted.

3. Euler-Maruyama Method and Simulation Results

In this section, a numerical approximation for the two system of SDEs obtained in Section 2 are represented. Depending on the simulation results, they have been compared with each other. If Euler-Maruyama method is applied to the equations (2.8) and (2.9) the following equations, (3.1) and (3.2), are obtained. By letting $(X(t_i), Y(t_i)) = (X_i, Y_i)$ where $t_i = 0, \Delta t, 2\Delta t, ..., T$ and $i = 0, 1, 2, ..., k-1$, we have,

$$\begin{aligned} X_{i+1} =& X_i + \left[\sigma + \frac{\rho X_i Y_i}{\eta + Y_i} - \mu X_i Y_i - \delta X_i\right] \Delta t \\ &+ \sqrt{\sigma + \frac{\rho X_i Y_i}{\eta + Y_i} - \mu X_i Y_i - \delta X_i}\, \Delta W_{1i} \end{aligned} \tag{3.1}$$

$$\begin{aligned} Y_{i+1} =& Y_i + [\alpha Y_i(1 - \beta Y_i) - X_i Y_i]\, \Delta t \\ &+ \sqrt{\alpha Y_i(1 - \beta Y_i) - X_i Y_i}\, \Delta W_{2i}, \end{aligned}$$

and

$$\begin{aligned} X_{i+1} =& X_i + \left[\sigma + \frac{\rho X_i Y_i}{\eta + Y_i} - \mu X_i Y_i - \delta X_i\right] \Delta t \\ &+ \sqrt{\sigma + \frac{\rho X_i Y_i}{\eta + Y_i}}\, \Delta W^*_{1i} - \sqrt{\mu X_i Y_i + \delta X_i}\, \Delta W^*_{2i}, \\ Y_{i+1} =& Y_i + [\alpha Y_i(1 - \beta Y_i) - X_i Y_i]\, \Delta t \\ &+ \sqrt{\alpha Y_i}\, \Delta W^*_{3i} - \sqrt{\alpha\beta Y_i^2 + X_i Y_i}\, \Delta W^*_{4i}. \end{aligned} \tag{3.2}$$

The variables ΔW_{1i} and ΔW_{2i} in (3.1) and the variables ΔW^*_{1i}, ΔW^*_{2i}, ΔW^*_{3i} and ΔW^*_{4i} in (3.2) are written instead of $\sqrt{t}\vartheta$ where for each of those ΔW variables there will be a different ϑ and they represent random variables that are sampled from a normal distribution with zero mean and unit variance. Moreover, the parameters σ, ρ, η, μ, δ, α and β are constant values as in (2.3). The initial values $x(0) = 5$ and $y(0) = 50$ are used as proposed in [12] and the simulations are obtained using MATLAB. As it can be seen from Figure 1 and Figure 2, even though the randomness differs, the two SDE models are consistent with each other. The values of $y(t)$, colored with blue in the figures, takes approximate values at the end of 100 days and moreover, the values of $x(t)$, colored with red, drops to 0 within $0 - 5$ days in both of those models.

4. Conclusion

In this work, two different system of SDEs for Kuznetsov et al.'s model are obtained. They have been made discrete and simulated. The two SDE models are compared with each other and also they are compared with the deterministic version of the model. The simulation results show that even though the random behavior is different in the two stochastic models, they show alike behaviors. The models obtained have not been investigated in the sense of viability [7] and therefore it can be concluded that the obtained SDE models may show complete different behaviors from the deterministic version, in the sense of stability. As a future work, the stability of the proposed system of SDEs will be investigated and moreover, the viability of them will be investigated. Even though the two different SDE models do not make a big difference for the model of Kuznetsov et. al this may not be the case for other biological models. Therefore, there is a need to explore more general rules e.g. upper and lower bound for the errors, the domain of the parameter values, the stability properties depending on those observations. Moreover, as mentioned, other equivalent SDE models can be obtained by the same procedure. Thus, all possible equivalent SDE models will be classified and their most general forms will be investigated in terms of stability and viability.

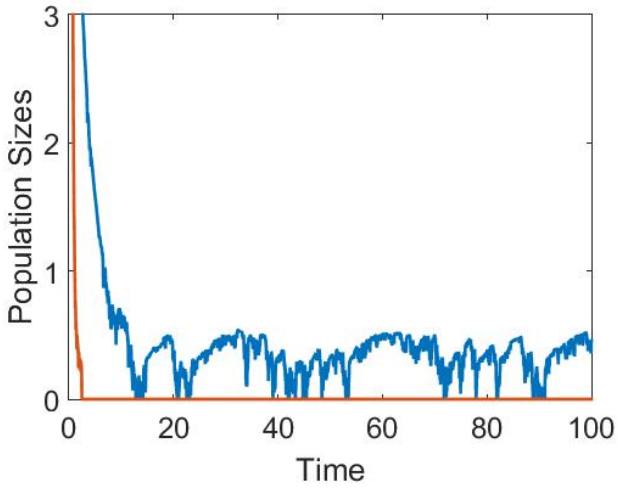

Figure 1: the simulations of model given by (2.8) and (3.1). The blue line corresponds to $x(t)$ and the red line corresponds to $y(t)$ and the initial values are taken as $x(0) = 5$ and $y(0) = 50$.

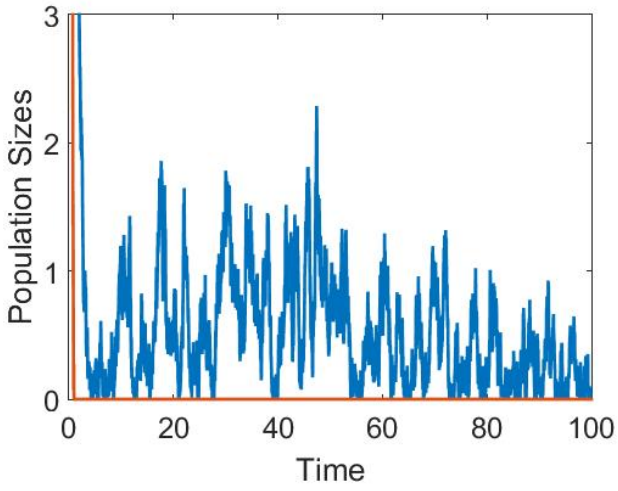

Figure 2: The simulations of model given by (2.9) and (3.2). The blue line corresponds to $x(t)$ and the red line corresponds to $y(t)$ and the initial values are taken as $x(0) = 5$ and $y(0) = 50$.

Acknowlegement

This work is partially constructed from the author's PhD. thesis [10]. This work has been partially supported by The Scientific and Technological Research Council of Turkey (TÜBİTAK) project number 104T133.

Competing Interests

The author declares no competing interests.

References

[1] J.A. Adam, N. Bellomo, A Survey of Models for Tumor-Immune System Dynamics, Birkhäuser, Boston, MA, 1996.
[2] E. Allen, Modeling with Ito Stochastic Differential Equations,Springer, 2007.
[3] E.J. Allen, L.J.S. Allen, A. Arciniega, P. Greenwood, Construction of equivalent stochastic differential equation models. *Stoch. Anal. Appl.*, 26, pages: 274-297, 2008.
[4] L.J.S. Allen, An Introduction to Stochastic Processes with Applications to Biology, CRC Press, 2011.
[5] J.C. Arciero, T.L. Jackson, D. Kirschner, A Mathematical Model of Tumor-Immune Evasion and siRNA Treatment, *Discrete and Continuous Dynamical Systems- Series B*, Volume 4, Number 1, Pages:39-58, 2004.
[6] N. Bellomo, M. Delitala, From the mathematical kinetic, and stochastic game theory to modelling mutations, onset, progression and immune competition of cancer cells, *Physics of Life Reviews*, Volume 5, Issue 4, Pages 183-206, December 2008.
[7] J. Cresson, S. Sonner, A note on a derivation method for SDE models: Application in biology and viability criteria, *Stochastic Analysis and Applications*, Vol. 36, No. 2, pages 224-239, 2018.
[8] A. Eladdadi, P. Kim, D. Mallet, Mathematical Models of Tumor-Immune System Dynamics, Springer, 2014.
[9] R.A. Gatenby, T.L. Vincent, Application of quantitative models from population biology and evolutionary game theory to tumor therapeutic strategies, *Mol Cancer Ther.*, 2(9):919-27, 2003.
[10] N. Gökgöz, Modeling Stochastic Hybrid Systems with Memory with An Application to Immune Response of Cancer Dynamics, METU PhD. Thesis, 2014.
[11] D. Kirschner, J.C. Panetta. Modeling immunotherapy of the tumor-immune interaction. *J Math Biol.*, 37(3):235-52, 1998.
[12] V.A. Kuznetsov, I.A. Makalkin, M.A. Taylor, A.S. Perelson, Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcations analysis. *Bull Math Biol.*, 56(2):295-321, 1994.
[13] X. Liu, Q. Li, J. Pan. A deterministic and stochastic model for the system dynamics of tumorâĂŞimmune responses to chemotherapy. *Physica A: Statistical Mechanics and its Applications*, Volume 500, Pages 162-176, 2018.
[14] D.G. Mallet, L.G. De Pillis, A cellular automata model of tumorâĂŞimmune system interactions, *Journal of Theoretical Biology*, Volume 239, Issue 3, Pages 334-350, 2006.
[15] L.G. de Pillis, A.E. Radunskaya, C.L. Wiseman, A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth, *Cancer Res.*, 65(17):7950-8, 2005.
[16] M. Robertson-Tessi, A. El-Kareh, A. Goriely. A mathematical model of tumor-immune interactions. *J Theor Biol.*, 294:56-73, 2012.