Results in Nonlinear Analysis 3 (2020) No. 1, 24–34
Available online at www.resultsinnonlinearanalysis.com

Results in Nonlinear Analysis
ISSN 2636-7556

Peer Reviewed Scientific Journal

Modeling of Tumor-Immune Nonlinear Stochastic Dynamics with HSM

Nurgül Gökgöz[a,d], Hakan Öktem[b], Gerhard-Wilhelm Weber[c,d],

[a] *Department of Mathematics, Çankaya University, 06790 Etimesgut, Ankara, Turkey.*
[b] *19 Mayis University, Department of Aviation Electric and Electronics, Samsun, Turkey.*
[c] *Poznan University of Technology, Poland.*
[d] *Department of Scientific Computing, Middle East Technical University, Ankara, Turkey.*

Abstract

In this paper, we address the well-known Tumor-Immune Model of Kuznetsov *et al.*, converting it into a stochastic form, and for simulation purposes we employ Euler-Maruyama discretization process. Such a modeling, for being realistic in biology and medicine, requires the implication of memory components. We also explain how to calculate the state transition time and we elaborate on how to reduce the system dynamics after the state transition. In fact, we establish and evaluate Stochastic Kuznetsov *et al.* model, and we describe how to demonstrate the stability of the numerical method, addressing tumor growth in spleen of mice. This work ends with a conclusion and a prospective view at future research and application, with special focus on medicine and neuroscience of tumor analysis and treatment.

Keywords: Hybrid systems, Regime switching, Pattern memorization, Multistationarity, Regulatory dynamical systems, Medicine.
2010 MSC: ...

1. Introduction

Tumor growth causes of millions of deaths every years; therefore, it is a very active research area in many different disciplines of science and technology. If we consider the treatment of tumor growth, one of the main interactions to be investigated is tumor-immune dynamics. However, tumor-immune system dynamics exhibit a highly complex structure. Several scientific investigations have been undertaken from perspectives of different disciplines, trying to model those interactions. To mention some of them, one may refer to [1, 18] and the references given therein.

Email addresses: nurgul.gokgoz@gmail.com (Nurgül Gökgöz), hoktem@gmail.com (Hakan Öktem), gerhard.weber@put.poznan.pl (Gerhard-Wilhelm Weber)

Received January 14, 2020, Accepted: March 21, 2020, Online: March 27, 2020.

In recent years, *hybrid systems* became as a useful modeling approach to include regime switches and paradigm shifts into deterministic and, especially, stochastic dynamics of science, engineering, neuroscience and and medicine. Stochastic Hybrid Systems (SHS) which demonstrate a generalized class of those systems are dynamical systems with random continuous and discrete behaviors. Any natural phenomena that exhibits multiple modes can be modeled by SHS. Some of the examples can be found in air traffic management, manufacturing systems, biological networks, financial markets and operations research. The stochasticity in a hybrid system can result from the randomness in the continuous part or in the discrete part of it. Depending on where to allow randomness in a hybrid model, different types of stochastic hybrid models have been introduced to the literature. To name a few, there are piecewise deterministic Markov processes, switching diffusion processes, or stochastic hybrid systems that are controlled by a probability law which is determined by the previous hybrid state are the early contributions to the area. In [13], some of the stochastic hybrid models appearing in biological networks, have been classified and summarized. In order to investigate the different applications and various modeling versions and analysis of stochastic hybrid systems, one may see [5, 17], and the references therein. Moreover, for piecewise linear approaches used in regulatory systems, the paper [15] offers a good source. One of the most important properties of a regulatory system is that its ability to *memorize* parts of its history. In other words, a combination of the previous inputs into the system decides its stationary behavior and, in turn, the system's stationary state decides about the response to the system's future external input. This is the crucial mechanism for adoption and learning in these systems. In our work, we investigate one of the very well-known tumor-immune systems called as Kuznetsov et al. model, by including stochastic calculus and benefiting from a hybrid system's formalism. In order to achieve this goal, firstly, we give a definition of a hybrid system with memory. A Hybrid System with Memory (HSM) has been defined and applied in the works [7, 8, 16]. The procedure in [9] describes a Markovian procedure and simulates one system with two different discrete stochastic systems. The procedure defined in this work partitions the same system into subsystems and expects those subsystems act differently according to their memory sets and furthermore, it describes a non-Markovian procedure.

Definition 1. *A Hybrid System with Memory H is a collection [7, 8]:*

$$H = (Q,\ X,\ U,\ T,\ Init,\ M,\ f,\ g,\ Inv,\ E,\ G,\ R),$$

consisting of

- *a set of discrete states $Q = \{q_1, \ldots, q_m\}$ which are the so-called locations,*
- *a space of continuous variables $X = \mathbf{R}^n$,*
- *a set of initial conditions $Init \subseteq Q \times X \times M$,*
- *a space of inputs $U = \mathbf{R}^z$ (control, disturbance or both),*
- *a space of independent variables $T \subseteq \mathbf{R}^k$, typically the time $T = [t_0, \infty)$,*
- *f and g are vector fields such that $f,\ g : Q \times X \times U \times M \longrightarrow X$, governing the continuous evolution,*
- *an invariant set (domain, subspace) for each $q \in Q$, $Inv : Q \longrightarrow P(X)$ where $P(\cdot)$ denotes the power set; each state's governing dynamics is valid within its invariant set,*
- *a set of edges (state transitions) $E \subset Q \times Q$,*
- *guard conditions for each edge $G :\ E \times M \longrightarrow P(X)$,*
- *a reset map for each edge $R :\ E \times X \times U \longrightarrow P(X)$,*
  - *for verifiability analysis, $R :\ E \times G \longrightarrow X$ can be considered,*
- *$M(t)$ consists of finite strings over M; it is a growing memory of past state transitions such that*

- $M(0) = (M_0) = (t_0, x_0, q_0)$,
- *if* $M(t;-) = M_0, M_1, \ldots, M_i$, *and* $x(t_j) \in g\{q(t),\, q \in Q\}$, *then* $M(t;+) = (M(t;-), M_{i+1})$,
- $M_{i+1} = (t_j,\, x(t_{j-}),\, q(t_{j-}))$.

With this definition, the prior evolution of the system is sampled at state transitions containing the time and the values of variables before and after the state transition. In this definition, $M(t)$ is a piecewise constant between the state transitions. The memory grows at each state transition. Thus, a HSM has a complexity that increases with time. By a *Stochastic Hybrid Systems with Memory (SHSM)*, we mean the space of continuous variables including stochastic dynamics through the vector field g given in the definition which stands for the diffusion and, therefore, stochastic differential equations.

2. The Stochastic Dynamics with Memory Model

As mentioned in the introduction, the model of Kuznetsov *et al.* is one of the most widely studied approaches towards tumor in the sense of tumor growth immune dynamics. Actually, it 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]:

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

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

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

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

One may find two different stochastic versions of Kuznetsov *et. al.*'s model in [9]. In this work, we use an another stochastic model which can be derived with a similar fashion used in [9] and an application of the procedure described in [2, 3]. Let us start with a stochastic model given by a system of two coupled stochastic differential equations (SDEs) which can be found in [8, 9]:

$$\begin{aligned} dX(t) = &\left[\sigma_1 + \frac{\rho_1 X(t)Y(t)}{\eta_1 + Y} - \mu_1 X(t)Y(t) - \delta_1 X(t)\right] dt \\ &\sqrt{\sigma} dW_1(t) + \sqrt{\frac{\rho X(t)Y(t)}{\eta + Y(t)}} dW_2(t) - \sqrt{\mu X(t)Y(t)} dW_3(t) - \sqrt{\delta X} dW_4(t), \\ dY(t) = &\left[\alpha Y(t)(1 - \beta Y(t)) - X(t)Y(t)\right] dt \\ &+ \sqrt{\alpha Y(t)(1 - \beta Y(t))} dW_5(t) - \sqrt{X(t)Y(t)} dW_6(t). \end{aligned} \tag{2.4}$$

where $dW_1, dW_2, dW_3, dW_4, dW_5$ and dW_6 are different Wiener processes [11, 14]. For the sake of convenience, we may regard the parameter τ of Equations (1)-(2) normalized to 1. For numerical solutions, we have applied

We use a comprehensive, slightly simplifying mathematical notation.

the well established and broadly accepted Euler-Maruyama method. The subsequent equations represent the discretized version of the model which can be found in [8, 9]:

$$\begin{aligned} X_{i+1} =& X_i + \left[\sigma + \frac{\rho X_i Y_i}{\eta + Y_i} - \mu X_i Y_i - \delta X_i\right]\Delta t \\ &+ \sqrt{\sigma}\Delta W_{1i}^* + \frac{\rho X_i Y_i}{\eta + Y_i}\,\Delta W_{2i}^* - \sqrt{\mu X_i Y_i}\Delta W_{3i}^* + \delta X_i\,\Delta W_{4i}^*, \\ Y_{i+1} =& Y_i + [\alpha Y_i(1-\beta Y_i) - X_i Y_i]\,\Delta t \\ &+ \sqrt{\alpha Y_i}\,\Delta W_{3i}^* - \sqrt{\alpha\beta Y_i^2 + X_i Y_i}\,\Delta W_{4i}^*. \end{aligned} \tag{2.5}$$

Since we have simulated the aforementioned system with Euler-Maruyama method, at this point, it is very important to question whether Euler-Maruyama method is stable for Equations (5)-(6). One may check stability of the numerical solution by considering a nonlinear test equation for SDEs, e.g., of the form

$$dZ_t = f(Z_t)dt + \sigma dW_t,$$

where f satisfies a one-sided dissipative Lipschitz condition. For further steps of stability testing, we refer to [10]. These transition probabilities, represented in Table 1, [9], give us the likelihoods of switching changes in

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 [9].

the states. When the dynamics arrives at hitting times τ, i.e., when intersecting and traversing characteristics submanifolds in state space, it comes to the hitting times. We propose that some of the transitions will not occur. According to the hitting time probabilities, we will have the following stochastic hybrid system. If $\tau^* = \tau_1$, then:

$$\begin{aligned} dX(t) =& \sigma_1 + \frac{\rho_1 X(t)Y(t)}{\eta_1 + Y} - \mu_1 X(t)Y(t) - \delta_1 X(t) + \sqrt{\sigma_1}dW_1(t) \\ &+ \sqrt{\frac{\rho_1 X(t)Y(t)}{\eta_1 + Y(t)}}dW_2(t) - \sqrt{\mu_1 X(t)Y(t)}dW_3(t) - \sqrt{\delta_1 X}dW_4(t), \\ dY(t) =& \alpha_1 Y(t)(1-\beta_1 Y(t)) - X(t)Y(t) + \sqrt{\alpha_1 Y(t)(1-\beta_1 Y(t))}dW_5(t). \\ &- \sqrt{X(t)Y(t)}dW_6(t). \end{aligned} \tag{2.6}$$

If $\tau^* = \tau_2$, then:

$$\begin{aligned} dX(t) =& \sigma_2 + \frac{\rho_2 X(t)Y(t)}{\eta_2 + Y} - \mu_2 X(t)Y(t) - \delta_2 X(t) + \sqrt{\sigma_2}dW_1(t) \\ &+ \sqrt{\frac{\rho_2 X(t)Y(t)}{\eta_2 + Y(t)}}dW_2(t) - \sqrt{\mu_2 X(t)Y(t)}dW_3(t) - \sqrt{\delta_2 X}dW_4(t), \\ dY(t) =& \alpha_2 Y(t)(1-\beta_2 Y(t)) - X(t)Y(t) + \sqrt{\alpha_2 Y(t)(1-\beta_2 Y(t))}dW_5(t) \\ &- \sqrt{X(t)Y(t)}dW_6(t), \end{aligned} \tag{2.7}$$

where $dW_1, dW_2, dW_3, dW_4, dW_5$ and dW_6 are different Wiener processes.

For making our results more realistic and to be adapted to real-world systems, we have searched the literature and we have employed the results obtained in the experiment of [6]. In that work, the authors use two groups of mice in order to decide on the effect of IL1-α. Their work states the role of tumor cell-associated IL1-α, in the induction of specific immune responses, eventually leading to tumor regression and the development of an immune memory, which prevents the mice from a fight with the violent tumor cells [6]. Concerning the data that illustrate different levels of tumor sizes according to different clones and so-called Stimulation Index, S.I., values can be seen from Figure 1, Figure 2 and Figure 3. Clone 2 has been injected with IL1-α, whereas Clone 5 has not been. As previously mentioned, according to different levels of IL1-α, different levels of tumor growth and effector cells have been observed. These effects can be seen from Figure 1, Figure 2 and Figure 3. Moreover, the precise values can be found in Table 2. In this table, S.I. refers the Stimulator Index which is the ratio for immune cells (the effector cell and stimulator cells) and the tumor size has been measured in millimeters (mm). By observing the data, one can see that Clone 2 and Clone 5 behave similarly until day 3. After Day 3, Stimulation Index is decreasing in Clone 5, and after Day 15, the tumor size is increasing in Clone 5. If we assume that this relationship of IL1-α on the immune system is not known previously, the one who observes the dynamics would question the differents behaviors of Clone 2 and Clone 5. Therefore, one may argue that there are functional relationships effecting the dynamics of the system and those functional relationships are captured in the memory set.

	Clone 2		Clone 5	
Days	S.I.	Tumor Size (mm)	S.I.	Tumor Size (mm)
0	1	3.05	1	3.125
3	1.988	3.7	2.129	3.75
7	2.344	4.35	1.443	4
10	2.822	6.35	0.914	5.5
15	3.011	7.345	0.914	8.5
20	3.411	6	0.886	15.125
40	3.266	3.7	0.943	29.125

Table 2: Stimulation Index, S.I., and Tumor size data of Clone 2 and Clone 5 [8].

In our tumor-immune problem, we should have two different regimes according to different hitting times and, therefore, two different memory values in the modified model of Kuznetsov et al. In that model, we will have a memory value as stated subsequently:

$$m_{=}(\tau, ((X_1 < 2.344 \wedge X_2 < 4) \vee (X_1 \geq 2.344 \wedge X_2 \geq 4)), q),$$

where $\tau \in \{\tau_1, \tau_2\}$. For instance, if $\tau^* = \tau_1$, $(X_1 < 2.344 \wedge X_2 < 4)$ and $q = q_1$, then we guess the system to behave like Clone 2. Moreover, the terms $\sqrt{\frac{\rho X(t)Y(t)}{\eta + Y(t)}}dW_2(t)$ and $\sqrt{\alpha Y(t)(1-\beta Y(t))}dW_5(t)$ in Equation(2.4) will drop out, and the equations will be:

$$\begin{aligned} dX(t) =& \sigma_1 - \mu_1 X(t)Y(t) - \delta_1 X(t) + \\ & \sqrt{\sigma_1}dW_1(t) - \sqrt{\mu_1 X(t)Y(t)}dW_3(t) - \sqrt{\delta_1 X}dW_4(t), \\ dY(t) =& - X(t)Y(t) - \sqrt{X(t)Y(t)}dW_6(t). \end{aligned} \tag{2.8}$$

In this case, the memory value is $M = (M(0), M(1))$. Moreover, if $\tau^* = \tau_2$, $(X_1 < 2.344 \wedge X_2 < 4)$ and $q = q_1$, we assess the system to behave like Clone 5. In this case, the terms $\sqrt{\mu X(t)Y(t)}dW_3(t)$, $\sqrt{\delta X}dW_4(t)$

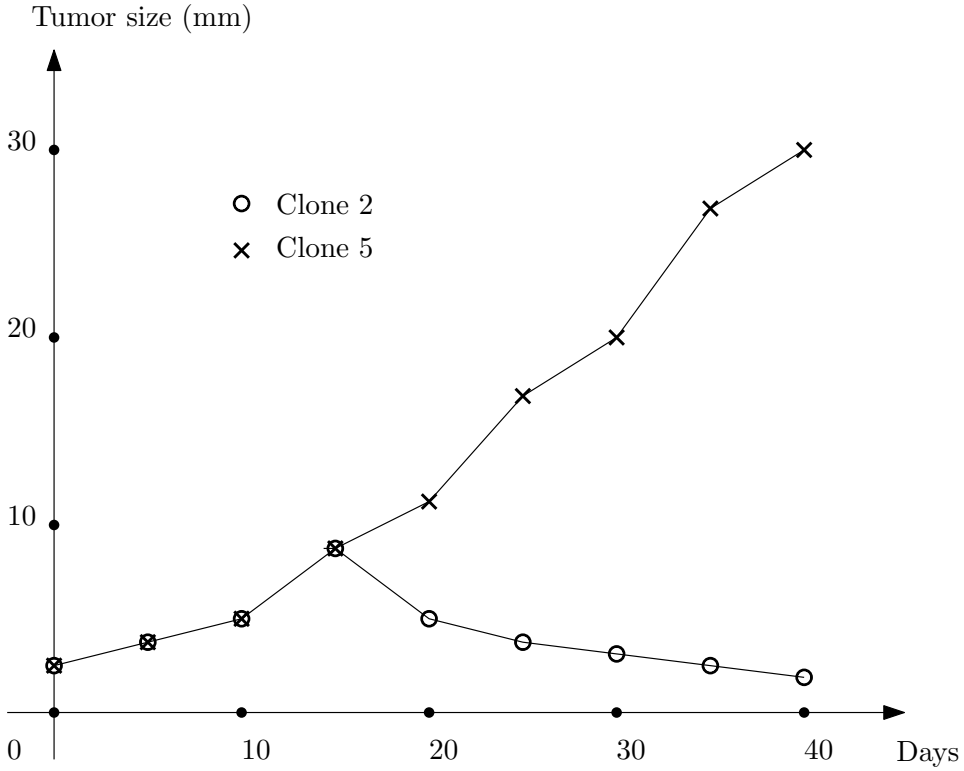

Figure 1: Tumor size of Clone 2 and Clone 5 according to days [6, 8].

and $\sqrt{X(t)Y(t)}dW_6(t)$ in Equation(2.4) will not be used and then, the equations will look as follows:

$$\begin{aligned} dX(t) =& \sigma_2 + \frac{\rho_2 X(t)Y(t)}{\eta_2 + Y} + \sqrt{\sigma_2}dW_1(t) + \sqrt{\frac{\rho_2 X(t)Y(t)}{\eta_2 + Y(t)}}dW_2(t), \\ dY(t) =& \alpha_2 Y(t)(1 - \beta_2 Y(t)) + \sqrt{\alpha_2 Y(t)(1 - \beta_2 Y(t))}dW_5(t); \end{aligned} \tag{2.9}$$

where the memory value is $M = M(0)$. The reason that we are not using some of the terms of Equation (2.4) is that those variables represents increase or decrease in X and Y. However, when we investigate the system, the immune variables of the system is not working in Clone 2 and tumor is not growing in Clone 5. Therefore, this means that those transitions are not valid for the model anymore and so those terms should be dropped. The reader may see a graphical representation of the states in Figure 4. You may read the graph as follows: start with q_1. If the memory set is equal to $M = (M(0), M(1))$ go to q_2 and from q_2, the system will turn back to q_1, if memory set is equal to $M = (M(0))$ go to q_3. Here, q_1 represents the healthy state of the host. Moreover, at the end of every state transition, the data given in Table 2, will be fitted to the corresponding equations of q_1, q_2 or q_3. More precisely, if the host is leaving q_1 and is entering q_2, then Equation (2.8) will be used and the parameter values of this system will be estimated according to the data set given in Table 2 and the same procedure will be applied to the Equation (2.9) in case of entering the state q_3. In order to determine the transition times and the probability whether the process reaches a state or not, we refer the reader to [3, Chapter 8]. The following steps summarize the procedure described in [3]. Moreover, we refer the interested reader to the work [21] in order to find parameter values in a piecewise linear model. If $Q(x,t)$ is the probability that the process does not reach states, we may say, A or B, within time $[0,t]$, then we can represent it as [3]:

$$Q(x,t) = \int_A^B p(y,x,t)dy,$$

where $p(y,x,t)$ stands for the density function of a transition from state x at time t to state y at time s,

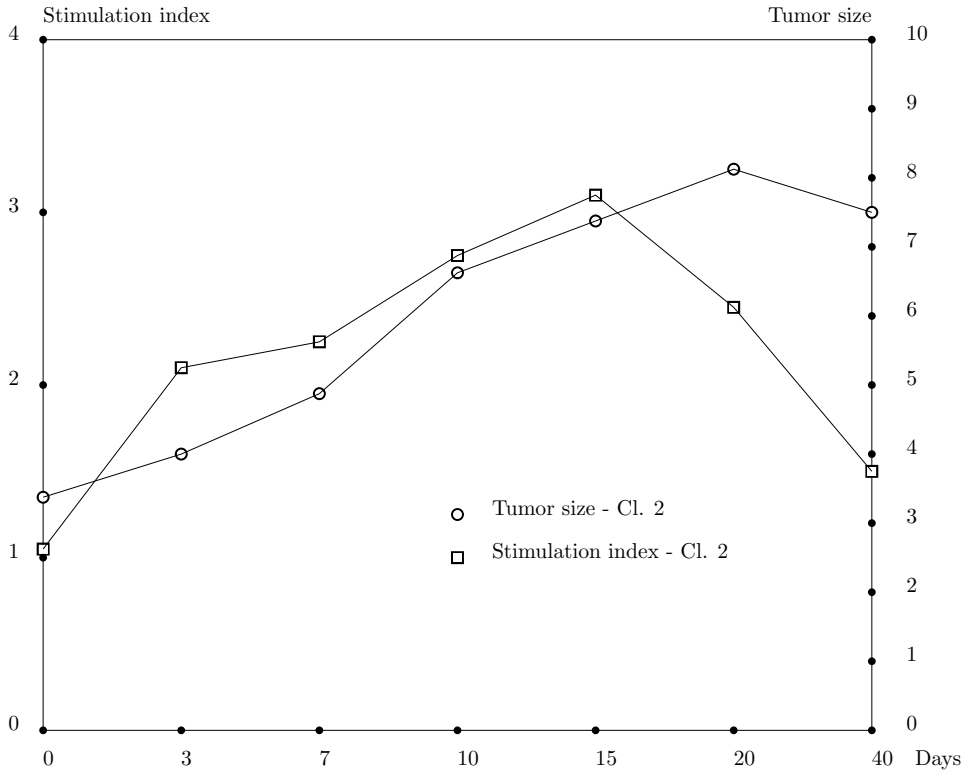

Figure 2: S.I. and tumor size of Clone 2 according to days [6, 8].

and $s < t$. Let $T(x)$ be the random variable representing the time for the stochastic process to reach states A or B, and $p_t(x,t)$ be the probability density function of it. Expected time of $T(x)$ can be found by [3, Chapter 8]:

$$E(T(x)) = \int_0^\infty Q(x,t)dt. \tag{2.10}$$

By using this procedure we can write the transition probability distribution function for the states, q_2, q_3, which will be the solution of the following backward Kolmogorov differential equations:

$$\begin{aligned} -\frac{\partial p(x,t)}{\partial t} &= \left(\sigma_1 + \frac{\rho_1 x(t)y(t)}{\eta_1 + Y} - \mu_1 x(t)y(t) - \delta_1 x(t)\right)\frac{\partial}{\partial x_i}p(x_i,t) + \\ &\left(\sqrt{\sigma_1} + \sqrt{\frac{\rho_1 x(t)y(t)}{\eta_1 + y(t)}} - \sqrt{\mu_1 x(t)y(t)} - \sqrt{\delta_1 X}\right)\frac{\partial^2}{\partial x_i x_j}p(x,t), \end{aligned} \tag{2.11}$$

$$\begin{aligned} -\frac{\partial p(x,t)}{\partial t} &= \left(\alpha_1 Y(t)(1-\beta_1 Y(t)) - X(t)Y(t)\right)\frac{\partial}{\partial x}p(x,t) + \\ &\left(\sqrt{\alpha_1 Y(t)(1-\beta_1 Y(t))}dW_5(t) - \sqrt{X(t)Y(t)}dW_6(t)\right)\frac{\partial^2}{\partial x_i x_j}p(x,t). \end{aligned} \tag{2.12}$$

3. Conclusion and Outlook

In this work, we refine the model of Kuznetsov et al. and we improve it by using stochastic calculus and memory formalism. We also discretize the model with Euler-Maruyama method and give the transition probabilities. Moreover, we give a precise description on how to find transition times, parameter values and also probabilities, if the process will make a transition from one state to another. Since we discretize the

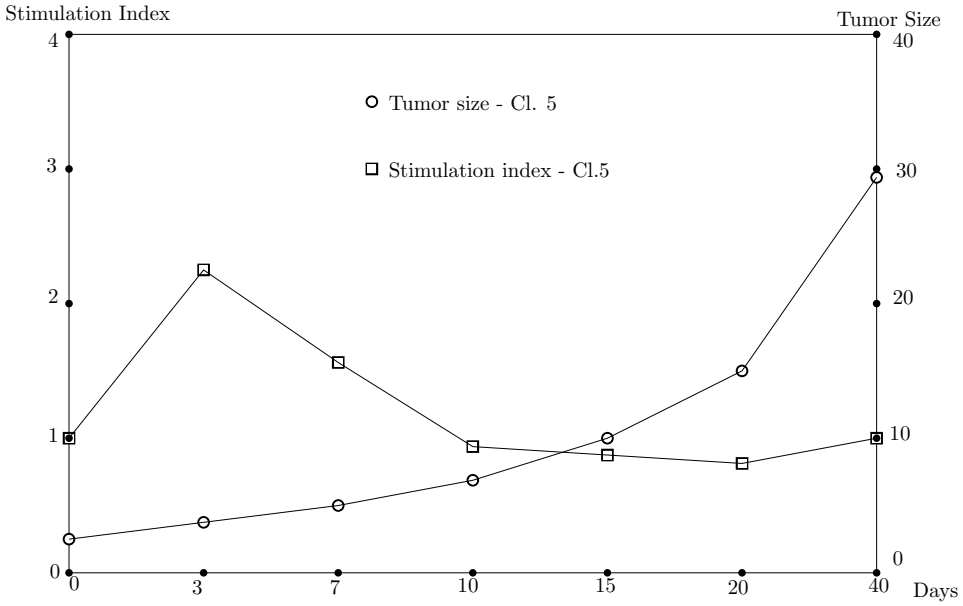

Figure 3: S.I. and tumor size of Clone 5 according to days [6, 8].

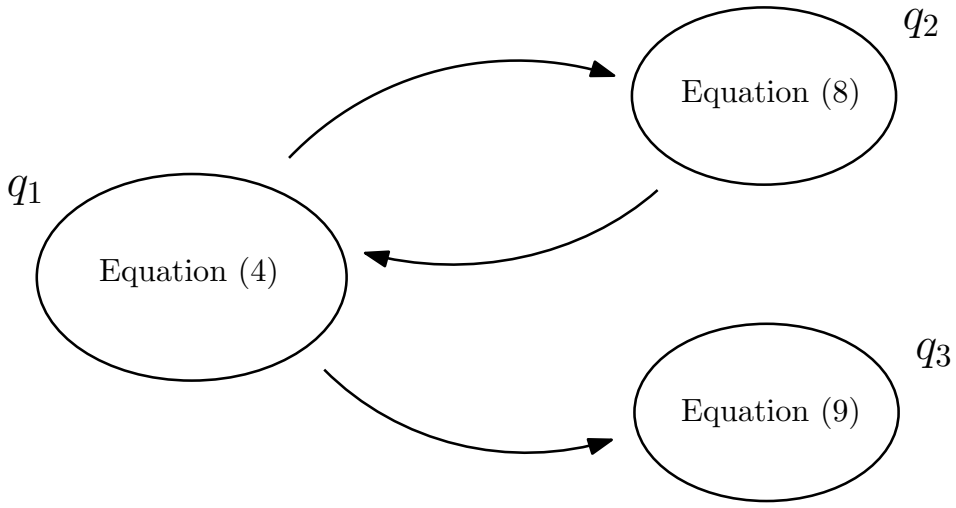

Figure 4: Basic representation of the states for Stochastic Kuznetsov et al. model.

model, we describe how to check the stability of the numerical method. Furthermore, in order to make our model realistic, we use medical data from the literature. As a future development of the model, we plan to include jumps into our dynamics, representing instantaneous changes such as, e.g., mutations, switches through the outer environment, and to establish a stochastic optimal control subject to our stochastic dynamics, e.g., for an optimal chemotherapy on tumor diseases and on further kinds of cancer. In such a stochastic optimal control, also delay could be included as a further form of memory [19, 20] and moreover dynamic programming technique could also be applied to obtain Hamilton-Jacobi-Bellman equation [4, 22]. Finally, as an alternative form of implying memory, we mention so-called Fractional Brownian Motions; for a reference on their parametric assessment, we refer the reader to the paper [23].

Acknowledgment

This work has been supported by The Scientific and Technological Research Council of Turkey (TUBITAK) project 104T133. This work is a part of the corresponding author's PhD. thesis [8].

Competing Interests

The authors declare that they have 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.J. Allen, L.J.S. Allen and A. Arciniega, P. Greenwood, Construction of equivalent stochastic differential equation models, Stoch. Anal. Appl., 26, pages: 274-297, 2008.
[3] L.J.S. Allen, An introduction to stochastic processes with applications to biology, Second edition. CRC Press, Boca Raton, FL, 2011.
[4] N. Azevedo, D. Pinheiro and G.-W. Weber, Dynamic programming for a Markov-switching jump-diffusion, Journal of Computational and Applied Mathematics, 267, pages 1-19, 2014.
[5] C.G. Cassandras and John Lygeros, Stochastic Hybrid Systems, CRC Press, FL, 2006.
[6] T. Dvorkin, X. Song, S. Argov, R. M. White, M. Zoller, S. Segal, C. A. Dinarello, E. Voronov and R. N. Apte, Immune phenomena involved in the in vivo regression of fibrosarcoma cells expressing cell-associated IL-1alpha, J Leukoc Biol., 80(1):96-106, 2006.
[7] N. Gökgöz, Development of Tools For Modeling Hybrid Systems With Memory, Msc. Thesis, Scientific Computing, Institute of Applied Mathematics, Middle East Technical University, Ankara, Turkey, 2008.
[8] N. Gökgöz, Modeling Stochastic Hybrid Systems With Memory With an Application to Immune Response of Cancer Dynamics, PhD Thesis, Scientific Computing, Institute of Applied Mathematics, Middle East Technical University, Ankara, Turkey, 2014.
[9] N. Gökgöz, Stochastic Dynamics of tumor-immune system: a numerical approach, Results in Nonlinear Analysis, pages 1-6, 2019.
[10] D.J. Higham and P.E. Kloeden, Numerical methods for nonlinear stochastic differential equations with jumps,Numerische Mathematik, Vol 101, No. 1, pp. 101-119, 2005.
[11] I. Karatzas and S.E. Shreve, Brownian Motion and Stochastic Calculus, Springer, 1991.
[12] V.A. Kuznetsov, I. A. Makalkin, M.A. Taylor and A.S. Perelson, Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcations analysis, Bull Math Biol., 56(2):295-321, 1994.
[13] X. Li, O. Omotere, L. Qian and E.R. Dougherty, Review of stochastic hybrid systems with applications in biological systems modeling and analysis, EURASIP Journal on Bioinformatics and Systems Biology, 2017. DOI 10.1186/s13637-017-0061-5
[14] B. Øksendal, Stochastic Differential Equations: An Introduction with Applications, Springer-Verlag Berlin Heidelberg, 2003.
[15] H. Öktem. A survey on piecewise-linear models of regulatory dynamical systems, Nonlinear Analysis, 63, 336-349,2005.
[16] H. Öktem, A. Hayfavi, N. Calışkan and N. Gökgöz, An Introduction of Hybrid Systems with Memory, International Workshop on Hybrid Systems Modeling, Simulation and Optimization, Koç University, Istanbul, May 14-16 2008.
[17] G. Pola, M.L. Bujorianu, J. Lygeros and M.D. Di Benedetto, Stochastic Hybrid Models: An Overview, IFAC Proceedings Vol. 36, (pp. 45âĂŞ50), 2003.
[18] L. Preziosi, Cancer Modelling and Simulation, CRC Press, 2003.
[19] E. Savku, N. Azevedo and G.-W. Weber, Optimal Control of Stochastic Hybrid Models in the Framework of Regime Switches, Modeling, Dynamics, Optimization and Bioeconomics II, DGS III, Porto, Portugal, February 2014, and Bioeconomy VII, Berkeley, USA, March 2014 - Selected Contributions, pages 371-387, 2014.

[20] E. Savku and G.W. Weber, A Stochastic Maximum Principle for a Markov Regime-Switching Jump-Diffusion Model with Delay and an Application to Finance, J Optim Theory Appl, pages 696-721, 2017.

[21] A.M. Selçuk and H. Öktem, An improved method for inference of piecewise linear systems by detecting jumps using derivative estimation, Nonlinear Analysis: Hybrid Systems, 3:3 (277-287), 2009.

[22] B.Z. Temoçin and G.W. Weber, Optimal control of stochastic hybrid system with jumps: A numerical approximation, Journal of Computational and Applied Mathematics (JCAM) 259 (2014) 443-451, in special issue at the occasion of ICACM - International Conference on Applied and Computational Mathematics Ankara, Turkey, October 3-6, 2012.

[23] F. Yerlikaya-Özkurt, C. Vardar-Acar, Y. Yolcu-Okur and G.-W. Weber, Estimation of Hurst parameter of fractional Brownian motion using CMARS method, Journal of Computational and Applied Mathematics (JCAM) 259 (2014) 843-850, in special issue at the occasion of ICACM - International Conference on Applied and Computational Mathematics Ankara, Turkey, October 3-6, 2012.