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Modeling of Tumor-Immune Nonlinear Stochastic Dynamics with HSM

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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 [**? ?**] and the references given therein.

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

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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 [**?**], 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 [**?** **?**], and the references therein. Moreover, for piecewise linear approaches used in regulatory systems, the paper [**?**] 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 [**?** **?** **?**]. The procedure in [**?**] 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 [**?** **?**]:*

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

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* [1]

[1] We use a comprehensive, slightly simplifying mathematical notation.

- $M(0) = (M_0) = (t_0, x_0, q_0)$,
- *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 [**?**]. The authors derived and compared their model with experimental data and statistical estimates of parameters identifying processes that cannot be measured in vivo [**?**]. The normalized version of the model has been represented as [**?**]:

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

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

In this system of equations, τ stands for the normalized time. In the paper [**?**], 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 [**?**]. In this work, we use an another stochastic model which can be derived with a similar fashion used in [**?**] and an application of the procedure described in [**?** **?**]. Let us start with a stochastic model given by a system of two coupled stochastic differential equations (SDEs) which can be found in [**?** **?**]:

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

where dW_1, dW_2, dW_3, dW_4, dW_5 and dW_6 are different Wiener processes [**?** **?**]. For the sake of convenience, we may regard the parameter τ of Equations (1)-(2) normalized to 1. For numerical solutions, we have applied the well established and broadly accepted Euler-Maruyama method. The subsequent equations represent the

discretized version of the model which can be found in [? ?]:

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

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 [?]. These transition probabilities, represented in Table 1, [?], give us the likelihoods of switching

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 [?].

changes in 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 [**?**]. 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 [**?**]. 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 **??**, Figure **??** and Figure **??**. 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 **??**, Figure **??** and Figure **??**. Moreover, the precise values can be found in Table **??**. 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 [**?**].

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(**??**) 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 $\sqrt{\mu X(t)Y(t)} dW_3(t)$, $\sqrt{\delta X} dW_4(t)$

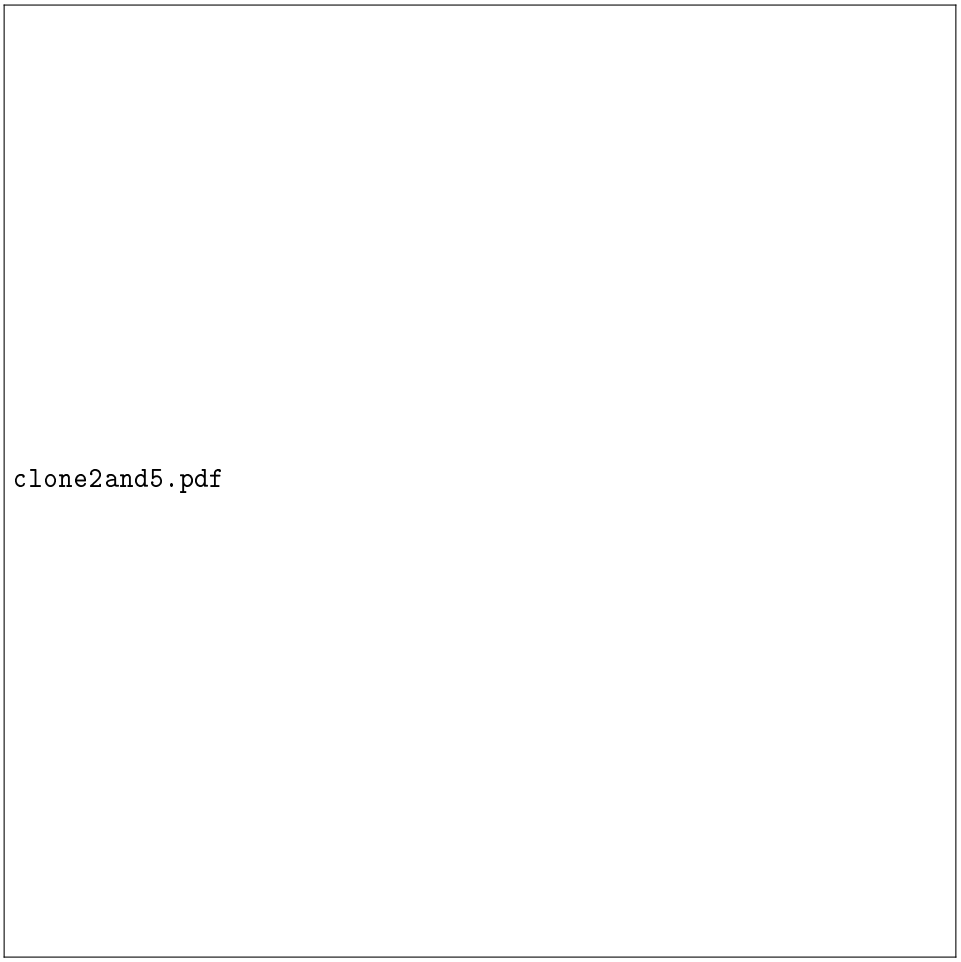

Figure 1: Tumor size of Clone 2 and Clone 5 according to days [? ?].

and $\sqrt{X(t)Y(t)}dW_6(t)$ in Equation(??) 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 Equatin (??) 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 ??. 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 ??, 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 (??) will be used and the parameter values of this system will be estimated according to the data set given in Table ?? and the same procedure will be applied to the Equation (??) 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 [? , Chapter 8]. The following steps summarize the procedure described in [?]. Moreover, we refer the interested reader to the work [?] in order to find parameter values in a piecewise

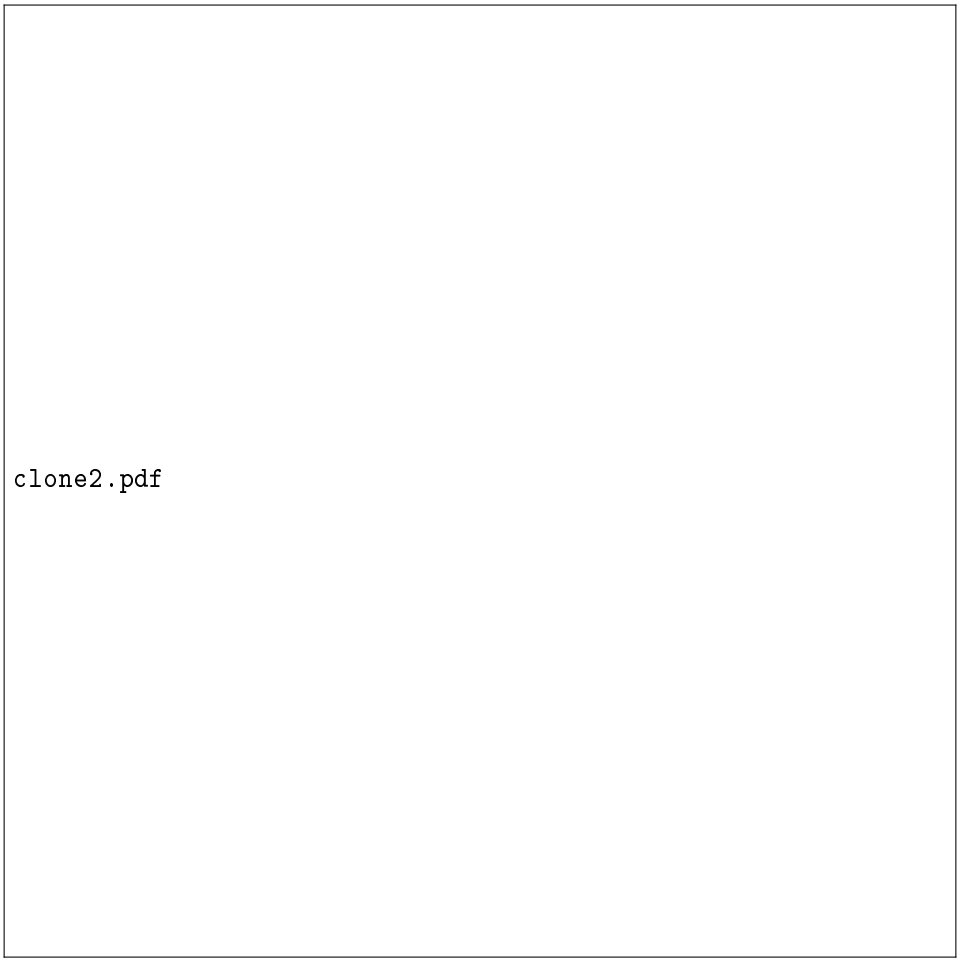

Figure 2: S.I. and tumor size of Clone 2 according to days [? ?].

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 [?]:

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

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, 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 [? , 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:

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

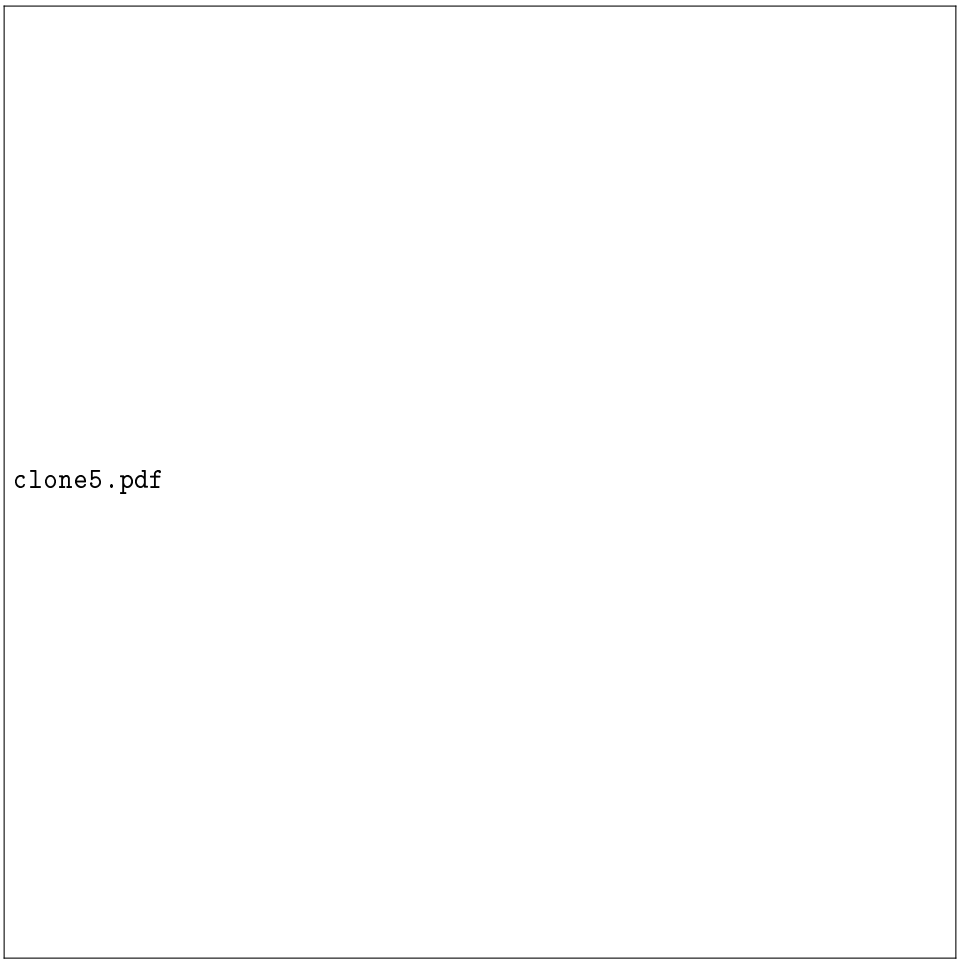

Figure 3: S.I. and tumor size of Clone 5 according to days [**?** **?**].

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

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

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 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 [**?** **?**] and moreover dynamic programming technique could also be applied to obtain Hamilton-Jacobi-Bellman equation [**?** **?**]. 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 [**?**].

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Competing Interests

The authors declare that they have no competing interests.

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