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A STOCHASTIC MODEL FOR THE GROWTH OF CANCER TUMORS

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Abstract. In this paper we study a stochastic model for the behavior of cancer tumors, described by a stochastic differential equation with multiplicative noise term. We consider that the number of tumor cells is influenced by the drug therapy and by random perturbations. We study the existence of the solution process, as well as its behavior in the framework of stochastic inclusion problems and random dynamical systems (long time behavior). Computer simulations are also given.

1. Introduction

Different types of mathematical models of cancer progression and treatment have already been constructed. They simulate important elements of the complex process of tumor growth and response to the therapy, the effects and interactions between tumor cells and immune cells. For example, there are many papers written on the subject of optimal control for mathematical models in cancer chemotherapy, such as J.M. Murray [17], K.R. Fister and J.C. Panetta [11], L.G. de Pillis and A.E. Radunskaya [8], [9], L. G. Hanin, S. T. Rachev and A. Yu. Yakovlev [13] etc. In the last years, stochastic growth models for cancer cells were developed, we mention the papers of W.Y. Tan and C.W. Chen [20], N. Komarova [15], G. Albano and V. Giorno [1], L. Ferrante, S. Bompadre, L. Possati and L. Leone [10], A. Boondirek,

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Y. Lenbury, J. Wong-Ekkabut, W. Triampo, I.M. Tang, P. Picha [3]. Also stochastic optimal control problems in chemotherapy were investigated by A.J. Coldman and J.M. Murray [6].

Following the models developed by G. W. Swan [19] and continued by W. Krabs [16] we complete their results by studying a *growth model for tumor cells under the influence of random perturbations*. We especially study a growth model with multiplicative noise term for which we investigate the existence of the solution (Section 2). We consider that the size of the tumor is controlled by the function which is the drug dose and rewrite our control problem as a differential inclusion problem (Section 3). Furthermore we investigate the long time behavior of our model in the framework of random dynamical systems (Section 4). At the end we also give some computer simulations of the solutions and the solution-tube for different possible functions for the drug exposure (Section 5). This article is the starting point for further research on stochastic control problems in cancer growth models.

2. **The stochastic model**

We denote by $p(t)$ the number of cancerous tumor cells at time $t > 0$. In the book of G.W. Swan [19] the following model for the number of tumor cells in the absence of drugs is studied: $dp(t) = \lambda \ln\left(\frac{\mu}{p(t)}\right) p(t)dt,\ p(0) = p_0 > 0$, where $\lambda, \mu > 0$ are parameters. In [19] the following controlled cancer tumor growth model under influence of drugs is given

$$dp(t) = \left(\lambda \ln\left(\frac{\mu}{p(t)}\right) - G(v(t))\right) p(t)dt,\ p(0) = p_0 > 0, \tag{1}$$

where $v(t) > 0$ is the *dose of the drug* at time t, $G(v(t))$ is the *destroying rate* per tumor cell and time unit. W. Krabs uses in [16] the following monotone increasing and bounded function for G:

$$G(v) = \frac{k_1 v}{k_2 + v}, \tag{2}$$

where $k_1, k_2 > 0$ are constants. The optimal control problem of finding the control function $v > 0$ for which the drug exposure on the body is minimal is studied in [16]

$$\begin{cases} \int_0^T v(t) \to \min \\ p \text{ is a solution of (1) for } t \in [0,T] \\ p(T) = p_T, \end{cases}$$

where the values $T > 0$ and $p_T \in (0, \mu)$ are given. It is showed that the optimal control v has the form $v(t) = \sqrt{\frac{k_1 k_2}{D}} e^{\lambda t} - k_2,\ t \in [0,T]$, where D is a parameter. If $k_1 > D\, k_2$, then it is assured that $v(t) > 0$ for all $[0,T]$.

The aim of our paper is to generalize the model (1) to the stochastic case: Let $\Big(\Omega, \mathcal{F}, (\mathcal{F}_t)_{t\geq 0}, P\Big)$ be a filtered probability space and let $(W(t))_{t\geq 0}$ be a standard Wiener process adapted to the filtration $(\mathcal{F}_t)_{t\geq 0}$. We perturb (1) by a multiplicative noise term and consider the following stochastic differential equation with stochastic Itô integral

$$p(t) = p_0 + \int_0^t \left(\lambda \ln\left(\frac{\mu}{p(s)}\right) - G(v(s))\right) p(s)ds + \sigma \int_0^t p(s)dW(s), t \geq 0, \qquad (3)$$

where $p_0 > 0$ and $\sigma \in \mathbb{R}$ is a parameter. We assume that $G, v : \mathbb{R}_+ \times \Omega \to \mathbb{R}_+$ are processes that are measurable, adapted to the filtration $(\mathcal{F}_t)_{t\geq 0}$ and are a.s. locally bounded.

Theorem 1. *Equation* (3) *has a unique solution which has the following explicit form*

$$p(t) = (p_0)^{e^{-\lambda t}} \mu^{1-e^{-\lambda t}} \exp\left\{ -\int_0^t e^{\lambda(s-t)} G(v(s))ds + \sigma \int_0^t e^{\lambda(s-t)} dW(s) \right\} \qquad (4)$$

for a.e. $\omega \in \Omega$ *and all* $t \geq 0$.

Proof. We consider two geometric Brownian motions (see [14, pg. 349]) starting at $x_0 = 1$ given by $B(t) = \exp\{\sigma W(t)\}$ and $\beta(t) = \exp\{-\sigma W(t)\}$, $t \geq 0$, which are the

solutions of the following linear equations

$$B(t) = 1 + \frac{\sigma^2}{2}\int_0^t B(s)ds + \sigma\int_0^t B(s)dW(s),\ t \geq 0, \tag{5}$$

$$\beta(t) = 1 + \frac{\sigma^2}{2}\int_0^t \beta(s)ds - \sigma\int_0^t \beta(s)dW(s),\ t \geq 0. \tag{6}$$

First, we prove that the solution of (3) is *unique*: Let $(p(t))_{t\geq 0}$ be a solution of (3). Applying the Itô formula for $Z := p \cdot \beta$ (see [14, Theorem 3.6]) we obtain from (3) and (6) that

$$Z(t) = p_0 + \int_0^t \left(\lambda \ln\left(\frac{\mu}{Z(s)}\right) - G(v(s) - \lambda\sigma W(s))\right) Z(s)ds,\ t \geq 0. \tag{7}$$

We denote $Y := \ln Z$, then $(Y(t))_{t\geq 0}$ satisfies the equation

$$Y(t) = \ln(p_0) + \int_0^t \left(\lambda \ln(\mu) - G(v(s)) - \lambda\sigma W(s) - \lambda Y(s)\right) ds,\ t \geq 0. \tag{8}$$

Obviously, the solution of (8) is unique (it is linear in Y), hence the solution of (3) must also be unique. Now, we prove the *existence of the solution* of (3). Note, that the solution of (8) has the explicit form

$$Y(t) = e^{-\lambda t}\ln(p_0) + \int_0^t e^{\lambda(s-t)}\left(\lambda \ln(\mu) - G(v(s)) - \lambda\sigma W(s)\right) ds,\ t \geq 0.$$

Then, $Z(t) = \exp\{Y(t)\}$ satisfies equation (7). By using the Itô formula for $Z \cdot B$ (see [14, Theorem 3.6]) we obtain from (7) and (5) that $Z \cdot B$ is a solution of (3). From the uniqueness of the solution of (3) it follows that

$$\begin{aligned} p(t) &= Z(t)B(t) = \exp\left\{Y(t) + \sigma W(t)\right\} \\ &= \exp\left\{e^{-\lambda t}\ln(p_0) + \int_0^t e^{\lambda(s-t)}\left(\lambda \ln(\mu) - G(v(s)) - \lambda\sigma W(s)\right) ds + \sigma W(t)\right\}. \end{aligned}$$

By calculations we get that the explicit form for p is given in (4). □

Remark 1. We introduce the set $\Omega^* \subset \Omega$ with $P(\Omega^*) = 1$ such that for all $\omega \in \Omega^*$ it hold:

- $e^{\lambda t}W(t) = \int_0^t e^{\lambda s}dW(s) + \lambda\int_0^t e^{\lambda s}W(s)ds$ for all $t \geq 0$;
- W has sublinear growth at $\pm\infty$, i.e. $\lim_{t\to\pm\infty} \dfrac{W(t)}{t} = 0$ for all $\omega \in \Omega^*$;
- the *Ornstein-Uhlenbeck process*

$$O(t) = \sigma\int_0^t e^{\lambda(s-t)}dW(s) \quad \text{for all } t \geq 0, \tag{9}$$

is well defined. ◊

Remark 2. Without loss of generality, we can say that (4) holds for all $\omega \in \Omega^*$. Since in the expression (4) appears the *Ornstein-Uhlenbeck process* $\Big(O(t)\Big)_{t\geq 0}$ which is a zero-mean Gaussian process with variance $\nu(t) = \mathrm{Var}(O(t)) = \dfrac{\sigma^2}{2\lambda}(1 - e^{-2\lambda t})$, we can compute the expected number of tumor cells at time $t > 0$ by

$$E(p(t)) = (p_0)^{e^{-\lambda t}}\mu^{1-e^{-\lambda t}}E\left(\exp\left\{-\int_0^t e^{\lambda(s-t)}G(v(s))ds + O(t)\right\}\right).$$

If, G and v are independent of the process W, then

$$E(p(t)) = (p_0)^{e^{-\lambda t}}\mu^{1-e^{-\lambda t}}E\left(\exp\left\{-\int_0^t e^{\lambda(s-t)}G(v(s))ds\right\}\right)E(\exp\{O(t)\}).$$

But, $E(\exp\{O(t)\}) = \exp\left\{\dfrac{\nu(t)}{2}\right\}$, then in this case we obtain

$$E(p(t)) = (p_0)^{e^{-\lambda t}}\mu^{1-e^{-\lambda t}}\exp\left\{\frac{\sigma^2}{4\lambda}(1 - e^{-2\lambda t})\right\}E\left(\exp\left\{-\int_0^t e^{\lambda(s-t)}G(v(s))ds\right\}\right).$$

Moreover, if G and v do not depend on ω, then

$$E(p(t)) = (p_0)^{e^{-\lambda t}}\mu^{1-e^{-\lambda t}}\exp\left\{-\int_0^t e^{\lambda(s-t)}G(v(s))ds + \frac{\sigma^2}{4\lambda}(1 - e^{-2\lambda t})\right\},$$

while the variance is given by

$$\mathrm{Var}(p(t)) = (p_0)^{2e^{-\lambda t}} \mu^{2(1-e^{-\lambda t})} \exp\left\{ -2\int_0^t e^{\lambda(s-t)} G(v(s))ds + \nu(t) \right\} (\exp\{\nu(t)\} - 1).$$

$\Diamond$

3. **Random and stochastic differential inclusions**

We want to investigate (3) in the framework of differential inclusions (DIs), which are roughly speaking given by corresponding set valued differential equations.

Notations: Let (X, d) be a complete metric space.

- We denote by $\mathcal{K}(X)$ the set of all nonempty compact and convex subsets of X.
- In the set valued setting we use an appropriate concept for distance, namely the *Hausdorff semi metric* $d_H^*(\cdot,\cdot)$ and the *Hausdorff metric* $d_H(\cdot,\cdot)$. The Hausdorff semi metric for $A,\ B \subset X$ is given by $d_H^*(A,B) = \sup_{a\in A} \inf_{b\in B} d(a,b)$. Note, that $d_H^*(\cdot,\cdot)$ is only a semi metric, because in general $d_H^*(A,B) \neq d_H^*(B,A)$. We obtain the full metric by $d_H(A,B) := \max\{d_H^*(A,B), d_H^*(B,A)\}$.
- For $A,\ B \subset X$ and $\alpha \in \mathbb{R}$ we define $A + \alpha B := \{a + \alpha b \mid a \in A, b \in B\}$.
- For $x \in X$ and $\varepsilon > 0$ we denote by $B_\varepsilon(x) := \{y \in X | d(x,y) < \varepsilon\}$, the ε-ball for x.

Such as sets are characterized by their elements, set valued mappings are characterized by *selections*.

Definition 1. *Let $F : \mathbb{R}^+ \times \mathbb{R} \mapsto \mathcal{K}(\mathbb{R})$. A* selection *is a scalar valued mapping $f : \mathbb{R}^+ \times X \to X$ with $f(t,\cdot) \in F(t,\cdot)$ for a.e. $t \in [0,T]$.*

Let $(\Omega, \mathcal{F}, \mathbb{P})$ be a probability space. If we introduce DIs driven by random or stochastic processes over $(\Omega, \mathcal{F}, \mathbb{P})$, then we obtain *random differential inclusions* (RDI) and also *stochastic differential inclusions* (SDI) of Itô type having the form

$$\frac{d\varphi(t)}{dt} \in F(\theta_t\omega, \varphi(t)),\ t \geq 0, \quad \varphi(0) = x_0 \in \mathbb{R} \quad \text{(RDI)} \tag{10}$$

where θ is a metric dynamical system (see Definition 2 in Section 4) and

$$d\varphi(t) \in F(t,\varphi(t))dt + g(\varphi(t))dW,\ t \geq 0, \quad \varphi(0) = x_0 \in \mathbb{R} \quad \text{(SDI)} \tag{11}$$

respectively. Equation (11) is the symbolic notation for

$$\varphi(t) \in x_0 + \int_0^t F(\varphi(s))\,ds + \int_0^t g(\varphi(s))dW(s), \tag{12}$$

where the first integral is the so-called Aumann integral, defined as the set of the form

$$\int_0^t F(s,\cdot)\,ds = \left\{ \int_0^t f(s,\cdot)\,ds \mid f \in \mathcal{I}(F) \text{ for } t \in [0,T] \right\}$$

with the space of selectors

$$\begin{aligned} \mathcal{I}(F) \quad := \quad & \Big\{ f : [0,T] \times \mathbb{R} \mapsto \mathbb{R} \mid f(\cdot,x) \in L_1[0,T]\, \forall x \in \mathbb{R}, \\ & f(t,\cdot) \in F(t,\cdot) \text{ for a. e. } t \in [0,T] \Big\} \end{aligned}$$

and the second integral in (12) is a stochastic integral of Itô type.

We can interpret (3) as a SDI by writing, for example,

$$d\varphi(t) \in F(\varphi(t))dt + g(\varphi(t))dW(t), \quad t \geq 0, \quad \varphi(0) = x_0 > 0, \tag{13}$$

where $F : \mathbb{R} \mapsto \mathcal{K}(\mathbb{R})$ is the set valued mapping given by

$$F(\varphi(t)) := \left(\lambda \ln \left(\frac{\mu}{\varphi(t)} \right) - [0,\rho] \right) \varphi(t) \tag{14}$$

$g(\varphi(t)) := \sigma\varphi(t)$ and $\rho > 0$ is a parameter.

We replaced $G(v)$ by the set $[0,\rho]$. In our model $v(t) > 0$ denotes the dose of the drug at time t, while $G(v) > 0$ denotes the destroying rate of the cancer cells. It seems reasonable that G has to be a monotone increasing and bounded function (see [16]). In the special case mentioned in (2) we have $\lim_{v\to\infty} G(v) = \lim_{v\to\infty} \dfrac{k_1\, v}{k_2 + v} = k_1$. Therefore, we can take, for example, $\rho := k_1$.

Real therapy protocols are somehow periodic, drugs are given in periodic time intervals, and then a while no drugs are given, in order to allow the physical body of the

patient to recover after the drug exposure. The following type of control for the set valued mapping for the SDI (13) takes this fact better into account:

$$F(\varphi(t)) := \left(\lambda \ln\left(\frac{\mu}{\varphi(t)}\right) - [0,\rho]\left(\frac{1+\operatorname{sgn}(\sin(\alpha t+\beta))}{2}\right)\right)\varphi(t) \tag{15}$$

with α, $\beta \in \mathbb{R}$ are the parameter for the velocity and shifting of the protocol and $\operatorname{sgn}(x) = -1$, if $x < 0$ and $\operatorname{sgn}(x) = 1$, if $x \geq 0$.
Another further generalization is to consider the parameter ρ (i.e. the maximal destroy rate) as a stationary stochastic process $(\omega, t) \to \rho(\theta_t\omega)$.

4. **Random dynamical systems**

We give now a brief introduction into the theory of random dynamical systems. A complete survey can be found in [2]. Random dynamical systems are dynamical systems under random influences. Formally, they are given by two ingredients: a model for the underlying noise (*the metric dynamical system*) and a model, which describes the dynamics under the influence of that noise (*the cocycle*).

Definition 2. *Let $(\Omega, \mathcal{F}, \mathbb{P})$ be a probability space. A* metric dynamical system *(MDS) $\theta : \mathbb{R} \times \Omega \mapsto \Omega$ is a $(\mathcal{B}(\mathbb{R}) \otimes \mathcal{F}, \mathcal{F})$-measurable flow that fulfills the group property $\theta_0 = \mathrm{id}$, $\theta_{t+s} = \theta_t \circ \theta_s$ for all $s, t \in \mathbb{R}$. Moreover, we suppose that $(\theta_t)_{t\in\mathbb{R}}$ is continuous, i.e. $(t, \omega) \mapsto \theta_t\omega$ is continuous, and it is measure preserving, i.e. $\theta_t\mathbb{P} = \mathbb{P}$, for all $t \in \mathbb{R}$.*

Example 1. A well-known example of a MDS, which appears if we deal with stochastic differential equations, is the following: Let $(W_t)_{t\in\mathbb{R}}$ be a 1-dimensional two-sided standard *Wiener process* over the *canonical Wiener space* $(\tilde{\Omega}, \tilde{\mathcal{F}}, \tilde{\mathbb{P}})$, where $\tilde{\Omega} = \{\omega \in C(\mathbb{R}, \mathbb{R}) : \omega(0) = 0\}$, $\tilde{\mathcal{F}}$ is the Borel σ-algebra of $\tilde{\Omega}$ and $\tilde{\mathbb{P}}$ is the Wiener measure. Then, the *Wiener shift* $\theta_t\omega(\cdot) = \omega(\cdot + t) - \omega(t)$ defines a MDS. $\Diamond$

From now on let θ be an MDS over the probability space $(\Omega, \mathcal{F}, \mathbb{P})$. Let (X, d) be a complete metric space.

Definition 3. *We call (ϕ, θ) a* random dynamical system *(RDS) if $\phi : \mathbb{R}^+ \times \Omega \times X \mapsto X$ is a $(\mathcal{B}(\mathbb{R}^+) \otimes \mathcal{F} \otimes \mathcal{B}(X), \mathcal{B}(X))$-measurable mapping*

and satisfies for all $s,t\in\mathbb{R}^+$, $\omega\in\Omega$ *and* $x\in X$ *the* perfect cocycle property

$$\phi(0,\omega,x)=x,\quad \phi(t+s,\omega,x)=\phi\big(t,\theta_s\omega,\phi(s,\omega,x)\big).$$

An RDS can be generated for example by *random differential equations* or *stochastic differential equations*. An overview of typical generators of RDSs can be found in [2] and [5].

Definition 4. *A random variable* x^* *is called a* random fixed point *for a random dynamical system* (ϕ,θ), *if* $\phi(t,\omega,x^*(\omega))=x^*(\theta_t\omega)$ *for all* $\omega\in\Omega$ *and* $t\in\mathbb{R}^+$. *We say that a random fixed point* x^* *is* stable, *if it satisfies the pullback convergence relation* $\lim\limits_{t\to\infty}\phi(t,\theta_{-t}\omega,x)=x^*(\omega)$ *for all* $x\in X$ *and all* $\omega\in\Omega$.

The concept of pullback convergence was introduced in the 1990s by Crauel and Flandoli [7], Flandoli and Schmalfuß [12], and Schmalfuß [18].

We study now the long time behavior of the solution p of equation (3) for different types of control functions v:

I. We consider the probability space $(\Omega,\mathcal{F},\mathbb{P})$ to be the Wiener space $(\tilde{\Omega},\tilde{\mathcal{F}},\tilde{\mathbb{P}})$ and the MDS θ the Wiener shift given in Example 1. Let $X=\mathbb{R}^+$ be the phase space. We define for all $x\in\mathbb{R}^+$ and all $t\geq 0$ the function

$$\phi(t,\omega,x)=x^{e^{-\lambda t}}\mu^{1-e^{-\lambda t}}\exp\left\{-\int_0^t e^{\lambda(s-t)}G(v(s))ds+\sigma\int_0^t e^{\lambda(s-t)}dW(s)\right\},\ \forall\omega\in\Omega^* \tag{16}$$

$$\phi(t,\omega,x)=x,\ \forall\omega\in\Omega\setminus\Omega^*,$$

where $\Omega^*\subset\Omega$ is the set of measure 1 that satisfies the properties from Remark 1.

Assume that $G\circ v$ is a strictly stationary process, i.e. $G\circ v(s,\theta_t\omega)=G\circ v(s+t,\omega)$ for all $s,t\in\mathbb{R},\omega\in\Omega$, which is also bounded $G\circ v(t,\omega)<M$ for all $t\geq 0$ and a.e. $\omega\in\Omega$.

One can check by calculations that in our case (ϕ,θ) is a RDS over $(\Omega,\mathcal{F},\mathbb{P})$ (the

Wiener space). In these calculations it is essential that the MDS θ is measure preserving with respect to P.

Example 2. Stationary processes $G \circ v$ are obtained for example when G is a non-random continuous function $G : \mathbb{R} \to \mathbb{R}^+$ which is continuous and $v(t,\omega) := z(\theta_t\omega)$ $t \in \mathbb{R}, \omega \in \tilde{\Omega}$, where z is a positive random variable. In our simulations we take $v(t,\omega) := \exp\{-z^*(\theta_t\omega)\}$, where $z^*(\omega) = -\sigma\lambda \int_{-\infty}^{0} e^{\lambda s} W(s)ds$ is the random fixed point of the *Ornstein-Uhlenbeck equation* $dO(t) = \lambda O(t)dt + \sigma dW(t)$, $t \geq 0$. For G we take the function given in (2). $\lozenge$

Theorem 2. *The solution of equation* (3) *has the following long time behavior: for each* $x \geq 0$ *it holds*

$$\lim_{t\to\infty} \phi(t, \theta_{-t}\omega, x) = \mu \exp\Big\{ - \int_{-\infty}^{0} e^{\lambda s} \Big(G(v(s)) + \sigma\lambda W(s) \Big) ds \Big\} \tag{17}$$

for all $\omega \in \Omega^*$.

Proof. For $\omega \in \Omega^*$ we take $\omega \mapsto \theta_{-t}\omega$ in (16) and analyze the expressions occurring in the formula. We have

$$\begin{aligned} \lim_{t\to\infty} \int_0^t e^{\lambda(s-t)} G(v(s, \theta_{-t}\omega))ds &= \lim_{t\to\infty} \int_{-t}^{0} e^{\lambda s} G(v(s+t, \theta_{-t}\omega)) \\ &= \int_{-\infty}^{0} e^{\lambda s} G(v(s,\omega))ds. \end{aligned}$$

For the expression containing the Ornstein-Uhlenbeck process we compute as follows: Using the notation introduced in (9) and the Wiener shift operator θ given in Example 1, we obtain $e^{-\lambda t} W(-t) = \dfrac{1}{\sigma} O(t, \theta_{-t}\omega) + \lambda \int\limits_{-t}^{0} e^{\lambda s} W(s)ds$ for all $t \geq 0, \omega \in \Omega^*$. We take into consideration that the process W has sublinear growth (see Remark 1), therefore,

$$\lim_{t\to\infty} O(t, \theta_{-t}\omega) = -\sigma\lambda \int\limits_{-\infty}^{0} e^{\lambda s} W(s)ds, \text{ for all } \omega \in \Omega^*. \tag{18}$$

The integral from the right-hand side of the above relation exists. Finally, we take $\omega \mapsto \theta_{-t}\omega$ in (16), then $t \to \infty$ and use (18) to get (17). $\square$

By calculations it is easy to prove that by the above result we obtained the *stable random fixed point* for (ϕ, θ)

$$x^*(\omega) = \begin{cases} \mu \exp\Big\{ - \displaystyle\int_{-\infty}^{0} e^{\lambda s}\Big(G(v(s)) + \sigma\lambda W(s)\Big)ds\Big\} \text{ for } \omega \in \Omega^* \\ \\ \mu \text{ for } \omega \in \Omega \setminus \Omega^* \end{cases}$$

which acts as a *random attractor* for our RDS. This means that other solutions are attracted by this random fixed point. Moreover, any ε-neighborhood $\overline{B_\varepsilon(x^*)}$, $\varepsilon > 0$ absorbs any other solution and any bounded solution set in finite time. Note, for every time t we have a finite well defined random variable.

Theorem 3. *The solutions of the SDI* (13) *satisfies the following property* $\phi_\rho(t, \omega, x) \leq \varphi(t, \omega, x) \leq \phi_0(t, \omega, x)$ *for all* $x > 0, \omega \in \Omega^*$, *where* ϕ_0 *and* ϕ_ρ *are the cocycles corresponding to* $G \circ v \equiv 0$ *and* $G \circ v \equiv \rho$, *respectively.*

Proof. The solution φ of (13) exists, since for each selection f of F (defined in (14)) the corresponding stochastic differential equation admits a solution $\varphi(t, \omega, x)$ given in (16) by $\phi(t, \omega, x)$, for which $G(v(\cdot)) \in [0, \rho]$. The stated inequalities follow from the fact that for each selection for the SDI we have in fact $G(v(\cdot)) \in [0, \rho]$. □

Remark 3. We see from this theorem that the solution tube for the SDI (13) is delimited by the two "extreme" solutions, namely ϕ_ρ and ϕ_0. Analogously we get that the set of random fixed points corresponding to the SDI (13) is delimited by the two random fixed points x_0^* and x_ρ^*, corresponding to $G \circ v \equiv 0$ and $G \circ v \equiv \rho$.

II. Now we consider that our equation is driven not only by the underlying noise term $\omega(t) = W(t)$ $\omega \in \tilde{\Omega}$ but also by nonrandom control functions $v \in C(\mathbb{R}, \mathbb{R}^+)$ (note, that v is the dose drug in the cancer growth model). In this case, the theory of RDS is embedded into the theory of *non-autonomous dynamical systems.*
Let $\hat{\Omega}$ be a nonempty set of elements. For each $t \in \mathbb{R}$ we consider $\hat{\theta}_t : \mathbb{R} \times \hat{\Omega} \mapsto \hat{\Omega}$ satisfying the group property $\hat{\theta}_0 = id$, $\hat{\theta}_{t+s} = \hat{\theta}_t \circ \hat{\theta}_s$ for all $s, t \in \mathbb{R}$.

Definition 5. *We call* $(\hat{\phi}, \hat{\theta})$ *a* non-autonomous dynamical system *(NDS), if* $\hat{\phi} : \mathbb{R}^+ \times \hat{\Omega} \times X \mapsto X$ *satisfies for all* $s, t \in \mathbb{R}^+$, $\hat{\omega} \in \hat{\Omega}$ *and* $x \in X$ *the* cocycle property $\hat{\phi}(0, \hat{\omega}, x) = x$, $\hat{\phi}(t+s, \hat{\omega}, x) = \hat{\phi}\big(t, \hat{\theta}_s\hat{\omega}, \hat{\phi}(s, \hat{\omega}, x)\big)$.

Let $(\tilde{\Omega}, \tilde{\mathcal{F}}, \tilde{\mathbb{P}})$ be the Wiener space and θ the Wiener shift MDS given in Example 1. Let $\tilde{\Omega}^*$ be the set of measure 1 which satisfies the properties from Remark 1.

For our problem (3) we consider the NDS: $\hat{\Omega} := \tilde{\Omega} \times C(\mathbb{R}, \mathbb{R}^+)$

$$\hat{\theta}_t(\omega, v)(\cdot) = (\theta_t\omega(\cdot), v(\cdot + t)) \text{ for all } \ (\omega, v) \in \tilde{\Omega} \times C(\mathbb{R}, \mathbb{R}^+),$$

and for $x \in \mathbb{R}^+$ the cocycle is given for each $(\omega, v) \in \tilde{\Omega}^* \times C(\mathbb{R}, \mathbb{R}^+)$ by

$$\hat{\phi}(t, (\omega, v), x) = x^{e^{-\lambda t}} \mu^{1-e^{-\lambda t}} \exp\left\{ -\int_0^t e^{\lambda(s-t)} G(v(s)) ds + \sigma \int_0^t e^{\lambda(s-t)} dW(s) \right\}, \quad (19)$$

while for $(\omega, v) \in (\tilde{\Omega} \setminus \tilde{\Omega}^*) \times C(\mathbb{R}, \mathbb{R}^+)$ by $\hat{\phi}(t, (\omega, v), x) = x$.

One can check by calculations that in our case $(\hat{\phi}, \hat{\theta})$ is a NDS over $\hat{\Omega}$. In these calculations it is essential that the MDS θ is measure preserving with respect to $\tilde{P}$.

Theorem 4. *If* $G, v \in C(\mathbb{R}, \mathbb{R}^+)$ *and* G *is bounded, then the solution of equation* (3) *has the following long time behavior: for each* $x \geq 0$ *it holds*

$$\lim_{t\to\infty} \hat{\phi}(t, \hat{\theta}_{-t}(\omega, v), p_0) = \mu \exp\Big\{ -\int_{-\infty}^0 e^{\lambda s} \Big(G(v(s)) + \sigma\lambda W(s) \Big) ds \Big\}$$

for all $(\omega, v) \in \tilde{\Omega}^* \times C(\mathbb{R}, \mathbb{R}^+)$.

The proof is similar to the proof of Theorem 2.

This result shows, that there exists a *stable random fixed point* for the NDS $(\hat{\phi}, \hat{\theta})$

$$x^*((\omega, v)) = \begin{cases} \mu \exp\left\{ -\displaystyle\int_{-\infty}^0 e^{\lambda s} \left(G(v(s)) + \sigma\lambda W(s) \right) ds \right\} \\ \qquad \text{for } (\omega, v) \in \tilde{\Omega}^* \times C(\mathbb{R}, \mathbb{R}^+) \\ \\ \mu \text{ for } (\omega, v) \in (\tilde{\Omega} \setminus \tilde{\Omega}^*) \times C(\mathbb{R}, \mathbb{R}^+). \end{cases}$$

There is a strong relation between a large set of DIs and set valued dynamical systems. Like differential equations often generate dynamical systems, DIs generate set valued

dynamical systems. That is, we can use the numerical methods for the approximation of dynamical systems also for DIs by taking the set valued nature of the inclusions into account. We can interpret (13) also as a *set valued random dynamical system*. If we replace the cocycle mapping ϕ with a set valued nonempty compact and convex cocycle mapping Φ (see [4]) we can define set valued random dynamical systems.

Definition 6. *We call* (Φ, θ) *a* set valued random dynamical system *(SVRDS) if* $\Phi : \mathbb{R}^+ \times \Omega \times X \mapsto \mathcal{K}(X)$ *is measurable and satisfies for all* $s, t \in \mathbb{R}^+$, $\omega \in \Omega$ *and* $x \in X$ *the* perfect set valued cocycle property $\Phi(0, \omega, x) = \{x\}$, $\Phi(t + s, \omega, x) = \Phi(t, \theta_s\omega, \Phi(s, \omega, x))$ $\forall s, t \in \mathbb{R}^+$.

In addition, we make also the following assumptions on Φ: We assume the *continuity in time* i.e. $\lim_{t\to s} d_H(\Phi(t, \omega, x), \Phi(s, \omega, x)) = 0$ $\forall$ $\omega \in \Omega$ and *upper semi-continuity* in parameter and initial value i.e. for $x, y \in \mathbb{R}$ we have

$$\lim_{x\to y, \omega_1 \to \omega_2} d_H^*(\Phi(t, \omega_1, x), \Phi(t, \omega_2, y)) = 0$$

uniformly in t, where t belongs to any compact interval from $[0, \infty)$ and for all $\omega \in \Omega$. A *trajectory* of a SVRDS is a single valued mapping $\phi : \mathbb{R}^+ \mapsto \mathbb{R}$ which for all $\omega \in \Omega$ satisfies $\phi(\omega, t) \in \Phi(t - s, \theta_s\omega, \phi(\omega, s))$, where $0 \leq s \leq t$.
As mentioned before SVRDS are generated for example by RDI (10) or SDI (11). Of course in this cases the trajectories of the SVRDS correspond to selections of the inclusion. The SDI (13) with (14) generates a SVRDS, while the SDI (13) with (15) generates set valued non-autonomous dynamical system.

5. **Simulations**

In this section we want to give some numerical results for (3). Note that our model is qualitative and not quantitative, the values given on the axes are not realistic. However it is possible to scale the model to any desired situation.

In our simulations we will use the parameters $k_1 = 1$, $k_2 = 1$, $\lambda = 1$, $\mu = 1$. In Figure 1 we can see the stochastic model without control functions. We used three different initial conditions. The existence of the random fixed point x_0^*, which is the

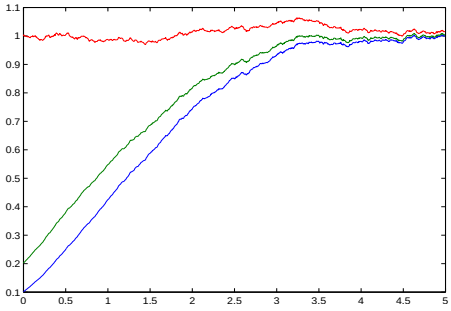

FIGURE 1. Simulation of three initial conditions for the control free system ($G \circ v = 0$).

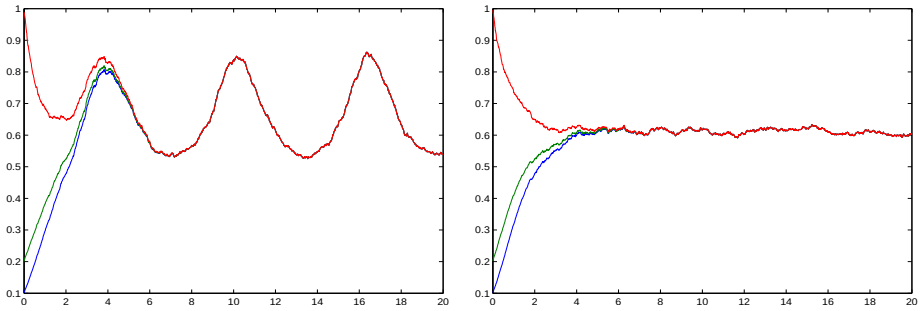

FIGURE 2. Simulations with different controls.

bound for the maximal tumor size is well visible.

In Figure 2 we have simulated our stochastic model for different control functions. We used $v(t) = 1 + \cos(t)$ (nonrandom case) and $v(t) = e^{-z^*(t)}$ (stationary process). Also in these cases the random fixed point exists. However such controls are only of theoretical interest but they support the results of the theory given in Section 2.

From the theoretical results it is clear that we have to use drugs with a high enough destroying rate for the cancer cells. Our simulations support this assertion. Let us interpret our model as an SDI (13) with (14). The approximations in Figure 3 show the reachable set of the inclusion for different maximal destroying rates with the same selection strategy. Of course the simulation takes into account that we can use the maximal destroy rate for all t, which is obviously not possible because this destroy

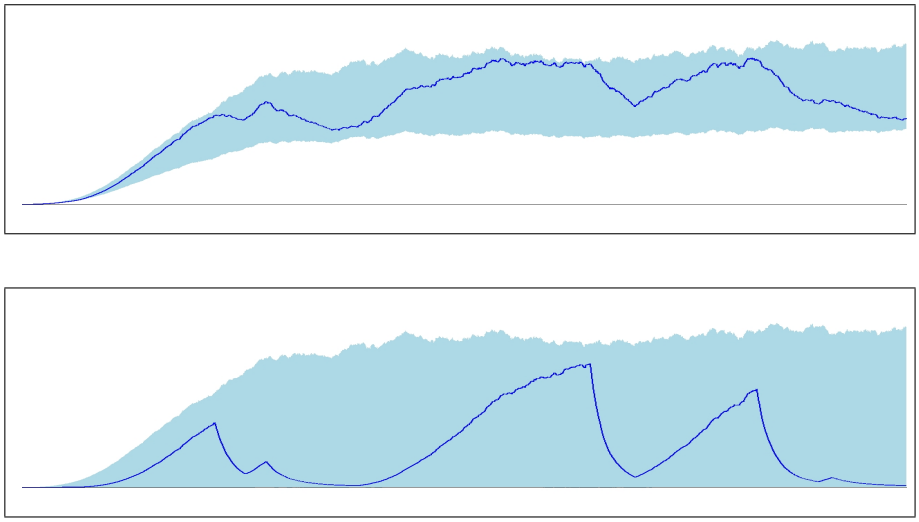

FIGURE 3. Simulations for different maximal destroy rates for the SDI (13) with (14).

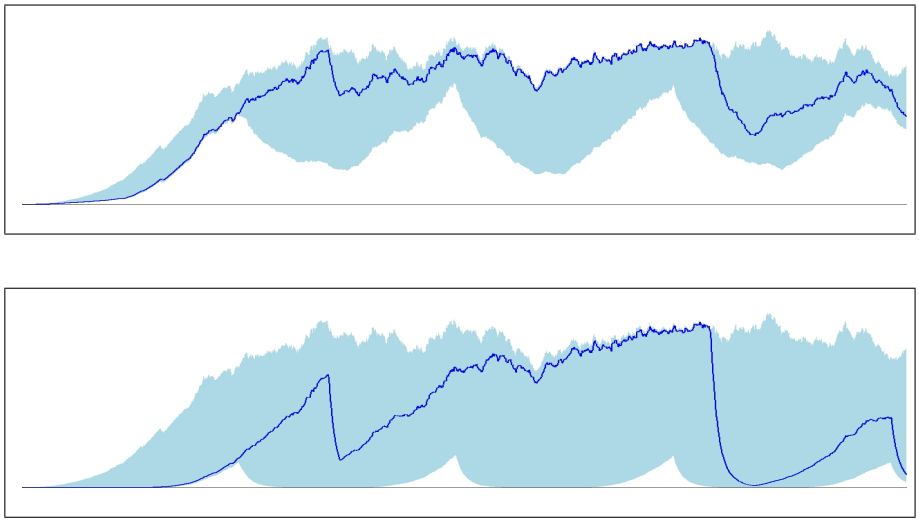

FIGURE 4. Simulations for different maximal destroy rates for the SDI (13) with (15).

rate damages also good cells. However the inclusion for (14) includes this very optimistic but unrealistic case.

It is clear from real world examples that realistic controls have to be some kind of periodic functions, because the drugs are given in intervals. It is not possible to control the concentration of the drugs for every time t and it is surely not possible to shorten the interval arbitrary.

We get a more appropriate model, if we use (15) in the SDI (13). Note, we have made the assumption that v has to be some kind of periodic function, where the time span for the therapy and the time span for rest has the same size. Also in this case we need a high enough destroying rate to get a successful procedure. In the time span, where we do not use drugs the tumor is again growing but the patient has the chance to improve his health for the new therapy session. The simulations are shown in Figure 4.

We point out that we are not experts in the topic of real healing procedures. The mathematical strategies used here are probably not realistic. But it is easily possible to extend these ideas to other more appropriate strategies.

However, the numerical results imply that it seems not possible to use a gentle procedure for the drug disposal. To get a successful procedure it seems to be necessary to use an aggressive strategy depending of the strength and health of the patient.

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