UNIVERSITÀ DEGLI STUDI DI PALERMO

Meccanica dei Materiali e delle Strutture
Vol. VI (2016), no.1, pp. 131-138
ISSN: 2035-679X
Dipartimento di Ingegneria Civile, Ambientale, Aerospaziale, Dei Materiali
DICAM

DYNAMIC MATHEMATICAL MODELS OF THERAPY PROCESSES AGAINST GLIOMA AND LEUKEMIA UNDER STOCHASTIC UNCERTAINTIES

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Key words: Glioma, Leukemia, Therapy, Dynamic System, Control, Stochastic Uncertainty.

Abstract. *Nonlinear dynamic mathematical models of therapy processes against such cancer diseases as glioma and leukemia are considered. Negative effect of a therapeutic agent onto both malignant and benign cells is taken into account by using therapy functions. They depend on a time-varying concentration of a therapeutic agent and can be monotonic or nonmonotonic. In the deterministic case, laws of such dependencies are fixed. However, from the biomedical point of view, these laws are not precisely known and can be affected by individual characteristics of patients, cancer sub-types, drug agents, etc. Thus, it is reasonable to take stochastic uncertainties into account there. We propose an approach that accounts for stochastic uncertainties in the deterministic biomedical models. Moreover, influence of these uncertainties is demonstrated within the framework of Viability Theory.*

1 INTRODUCTION

Since cancer is one of the main causes of death, dynamic modeling of cancer cells' evolution and therapy planning is a promising field of Mathematical Biology[1]. Cancer progression (or regression) is estimated under various treatments such as chemotherapy, immune therapy, radiotherapy, etc., while choosing suitable dosages, durations and frequencies. In this paper, we consider nonlinear dynamic mathematical models of therapy processes for treating glioma and acute leukemia.

Glioma is a broad category of brain cancers that come from so-called glial cells[2]. It is characterized by a very high rate of penetration into surrounding tissues. Therefore, it often becomes almost impossible to separate malignant and healthy brain areas. Furthermore, some of the malignant cells can acquire drug resistant properties.

From the biomedical point of view, it is reasonable to introduce an upper limit restriction on the total number of malignant cells and a lower limit restriction on the total number of healthy cells at every instant of the observed time interval. This leads to state constraints in a controlled dynamic system (a control function usually represents amounts of a therapeutic agent applied to a patient at different time instants). Violations of such constraints mean in reality reaching critical near death conditions. Hence, there arises the problem to find a therapy strategy that provides maximum viability (survival) time without violating the imposed restrictions[3]. Note that such a problem statement is partially influenced by Viability Theory[4]. Even though, for modeling therapy of such terminal diseases as glioma, viability problems seem to be more natural than unconstrained dynamic optimization[5–7], their investigation often appears to be more complicated.

Leukemia is a cancer disease starting in the bone marrow and resulting in high numbers of abnormal white-blood cells also called leukemic cells. We are interested in modeling its rapidly progressive form called acute leukemia[8]. This is in principle a curable disease as opposed to glioma. Therefore, it is reasonable to estimate therapy quality by a suitable scalar criterion, rather than by using viability constraints[6, 9].

In the models of this paper, the fact that a therapeutic agent affects both type of cells negatively is taken into account by using so-called therapy functions. They depend on a time-varying concentration of a therapeutic agent and can be monotonic or nonmonotonic. The nonmonotonicity is usually related to existence of a threshold value after which efficiency of therapy decreases. In the deterministic case, laws of such dependencies are fixed. However, in biomedical practice, these laws are not precisely known and can be affected by individual characteristics of patients, cancer sub-types, drug agents, etc. Thus, it is reasonable to take stochastic uncertainties into account there. We propose an approach to develop a stochastic extension to the mentioned models of glioma and leukemia therapy. It can also be applied to dynamic models describing therapy of other cancer types. Moreover, we present the results of numerical simulations demonstrating influence of stochastic uncertainties with different noise intensities or the level of uncertainties.

2 PROBLEM STATEMENT

First, let us introduce deterministic models of glioma and leukemia therapy.

For the glioma model, the following state variables are considered:

- C is the quantity of brain tumour (glial) cells;
- N is the quantity of normal cells;
- h is the concentration of a chemotherapeutic agent;
- g is the concentration of nutrients (oxygen, glucose, etc.).

Furthermore, the time variable is denoted by t, and amounts of the applied chemotherapeutic agent are represented by a function $u = u(t)$ which is also interpreted as an open-loop control strategy. Then dynamics of the state variables is described by the system of ordinary differential equations

$$\begin{cases} \dfrac{dC(t)}{dt} = r_1 g(t) C(t) \ln\left(\dfrac{C_\infty}{C(t)}\right) - k_1 f(h(t)) C(t), \quad C(0) = C_0, \\ \dfrac{dN(t)}{dt} = r_2 g(t) N(t) \ln\left(\dfrac{N_\infty}{N(t)}\right) - l_1 \dfrac{C(t) N(t)}{l_2 + C(t)} - k_2 f(h(t)) N(t), \quad N(0) = N_0, \\ \dfrac{dh(t)}{dt} = -\gamma_h h(t) + g(t) u(t), \quad h(0) = h_0, \\ \dfrac{dg(t)}{dt} = -\gamma_g g(t) + \alpha_g, \quad g(0) = g_0, \\ 0 \le u(t) \le R, \quad 0 \le t \le T, \end{cases} \tag{1}$$

where r_1, r_2, C_∞, N_∞, k_1, k_2, γ_h, γ_g, α_g, R are positive constants, l_1, l_2 are nonnegative constants, and $T > 0$ is a time horizon. Here the growth terms for glial and normal cells are Gompertzian with replication rates r_1, r_2 and limiting capacities C_∞, N_∞, while l_1, l_2 specify the rates and half-saturation constant in the term representing negative influence of glial cells on normal cells. Parameters γ_g and α_g describe degradation and constant positive flux of nutrients. Dissipation of the chemotherapeutic agent is determined by $\boldsymbol{\gamma_g}$, and its delivery rate is proportional to the concentration of nutrients (as well as the growth terms in the first two equations). There are also natural pointwise constraints on the function $u = u(t)$ (since the drug cannot be physically delivered with an arbitrarily high rate). Moreover, negative influence of chemotherapy on both glial and normal cells is represented by the factors $k_1 f(h)$ and $k_2 f(h)$, where $k_1 > k_2$ (the drug affects diseased cells stronger that normal ones) and $f(h)$ is a so-called therapy function. As was discussed in the introduction, the latter can be strictly increasing or having a threshold effect. For model (1), let us choose a monotonic therapy function[3]

$$f(h) = \frac{h}{\kappa + h}, \quad \kappa > 0. \tag{2}$$

Note that, as opposed to the model of Bratus et al. (2015)[3], system (1) includes the concentration of nutrients, which is more reasonable from the biomedical point of view.

For the model of acute leukemia, we consider such variables as the quantity of leukemic cells L, quantity of normal cells N, and chemotherapeutic agent concentration h. There is no any variable similar to the nutrient concentration g from the glioma model. The corresponding equations take the form[6, 9]

$$\begin{cases} \dfrac{dL(t)}{dt} = r_1 L(t) \ln\left(\dfrac{L_\infty}{L(t)}\right) - \gamma_1 L(t) - k_1 f(h(t)) L(t), \quad L(0) = L_0, \\ \dfrac{dN(t)}{dt} = r_2 N(t) \ln\left(\dfrac{N_\infty}{N(t)}\right) - \gamma_2 N(t) - c L(t) N(t) - k_2 f(h(t)) N(t), \quad N(0) = N_0, \\ \dfrac{dh(t)}{dt} = -\gamma_h h(t) + u(t), \quad h(0) = h_0, \\ 0 \le u(t) \le R, \quad 0 \le t \le T, \end{cases} \tag{3}$$

where the constants can be described similarly to the previous model. However, negative influence of diseased cells on normal cells becomes somewhat different. Now we take a nonmonotonic therapy function[9]:

$$f(h) = he^{-\beta h}, \quad \beta > 0. \tag{4}$$

For model (1), viability constraints (discussed in the introduction) can be written as

$$C(t) \le \hat{C}, \quad N(t) \ge \hat{N}, \quad 0 \le t \le T. \tag{5}$$

The control goal is to keep the system in the viability (survival) domain as long as possible.

For model (3), the highest control (therapy) quality corresponds to the minimum of the integral functional

$$J(u) \quad = \quad E\left[\int_0^T \Phi(L(t), N(t))dt\right] \tag{6}$$

(the expectation sign disappears in the deterministic case), where

$$\Phi(L,N) \quad = \quad \begin{cases} L^{2,} & N \ge N_H, \\ L^2 + \alpha(N_H - N)^{2,} & N \le N_H, \end{cases} \tag{7}$$

with a constant N_H specifying a sufficiently healthy amount of normal cells. Such an additional policy function represents the goal not to reduce the amount of normal cells much lower than the suitable level N_H (low amounts of normal cells can also lead to death).

For the sake of convenience, some of the parameters appearing in models (1) and (3) have the same notations, but this does not mean their equality. Each of the models has its own independent parameters. Our aim is to build suitable stochastic extensions of deterministic models (1) and (3).

3 STOCHASTIC EXTENSION

One way of including stochastic uncertainties in model (1) is to replace the deterministic equation for the therapeutic agent with the stochastic equation

$$dh(t) \quad = \quad -\gamma_h h(t)dt + g(t)u(t)\sigma dw(t), \tag{8}$$

where $w(t)$, $t \ge 0$, is a one-dimensional standard Brownian motion, and constant $\sigma > 0$ is the noise intensity. For model (3), a similar modification can be made. Such a type of stochastic noise is often considered in mechanical systems and called internal[10]. In our biomedical systems, it describes uncertainty in drug delivery, because it is not known how much drug is actually delivered in different patients with different cancer's sub-types, especially in the case of glioma.

However, it is more interesting to consider uncertainty in laws specifying negative influence of a drug on diseased and normal cells. For this purpose, introduce a stationary Gaussian stochastic process $y(t)$, $t \ge 0$, with mean 1 and covariance function

$$E[(y(t)-1)(y(s)-1)] \quad = \quad \sigma^2 \exp(-k|t-s|). \tag{9}$$

One can easily verify that it satisfies the stochastic equation

$$dy(t) \quad = \quad -k(y(t)-1)dt + \sigma\sqrt{2k}dw(t). \tag{10}$$

Such a process is used in stochastic aerospace models[11]. Our approach is to include $\boldsymbol{y(t)}$ in the equations for diseased and normal cells as a factor near the therapy functions. This indeed

leads to random vibrations of actual therapy effects around theoretical deterministic laws (2) and (4). Thereby, model (1) is transformed into

$$\begin{cases} \dfrac{dC(t)}{dt} = r_1 g(t) C(t) \ln\left(\dfrac{C_\infty}{C(t)}\right) - k_1 f(h(t)) y(t) C(t), \quad C(0) = C_0, \\ \dfrac{dN(t)}{dt} = r_2 g(t) N(t) \ln\left(\dfrac{N_\infty}{N(t)}\right) - l_1 \dfrac{C(t) N(t)}{l_2 + C(t)} - k_2 f(h(t)) y(t) N(t), \quad N(0) = N_0, \\ \dfrac{dh(t)}{dt} = -\gamma_h h(t) + g(t) u(t), \quad h(0) = h_0, \\ \dfrac{dg(t)}{dt} = -\gamma_g g(t) + \alpha_g, \quad g(0) = g_0, \\ dy(t) = -k(y(t) - 1)dt + \sigma\sqrt{2k}\, dw(t), \quad y(0) = y_0, \\ 0 \le u(t) \le R, \quad 0 \le t \le T, \end{cases} \tag{11}$$

and model (3) is modified as

$$\begin{cases} \dfrac{dL(t)}{dt} = r_1 L(t) \ln\left(\dfrac{L_\infty}{L(t)}\right) - \gamma_1 L(t) - k_1 f(h(t)) y(t) L(t), \quad L(0) = L_0, \\ \dfrac{dN(t)}{dt} = r_2 N(t) \ln\left(\dfrac{N_\infty}{N(t)}\right) - \gamma_2 N(t) - cL(t) N(t) - k_2 f(h(t)) y(t) N(t), \quad N(0) = N_0, \\ \dfrac{dh(t)}{dt} = -\gamma_h h(t) + u(t), \quad h(0) = h_0, \\ dy(t) = -k(y(t) - 1)dt + \sigma\sqrt{2k}\, dw(t), \quad y(0) = y_0, \\ 0 \le u(t) \le R, \quad 0 \le t \le T. \end{cases} \tag{12}$$

It is also convenient to make the change of variables

$$c(t) = \ln\left(C_\infty / C(t)\right), \quad n(t) = \ln\left(N_\infty / N(t)\right) \tag{13}$$

in model (1) so as to write the first two equations in a simpler form:

$$\begin{cases} \dot{c} = -r_1 g(t) c(t) + k_1 f(h(t)) y(t), \quad C(0) = \ln\left(c_\infty / c_0\right) \\ \dot{n} = -r_2 g(t) n(t) + l_1 \dfrac{c_\infty e^{-c(t)}}{l_2 + c_\infty e^{-c(t)}} + k_2 f(h(t)) y(t), \quad n(0) = \ln\left(n_\infty / n_0\right) \end{cases} \tag{14}$$

Similarly, in model (3), the change of variables

$$l(t) = \ln\left(L_\infty / L(t)\right), \quad n(t) = \ln\left(N_\infty / N(t)\right) \tag{15}$$

leads to the new first and second dynamic equations

$$\begin{cases} \dot{l} = -r_1 l(t) + \gamma_1 + k_1 f(h(t)) y(t), \quad l(0) = \ln\left(l_\infty / l_0\right) \\ \dot{n} = -r_2 n(t) + \gamma_2 + c\, l_a e^{-l(t)} + k_2 f(h(t)) y(t), \quad n(0) = \ln\left(n_\infty / n_0\right) \end{cases} \tag{16}$$

4 NUMERICAL SIMULATIONS

In fact, our models are stated already in a form with dimensionless state and time variables[3, 6–9]. This is reasonable, since the key objective of such simplified mathematical models is to obtain only general qualitative results. They cannot serve for making accurate quantitative predictions because of tremendous complexity of real biological systems. However, we choose parameter values so that t can informally be interpreted as time in months.

For the glioma model, we choose the following parameters' values (which conform with the relevant orders of magnitude introduced by Bratus et al. (2015)[3]):

$$\begin{gathered} r_1 = 0.02,\ r_2 = 0.012,\ \ln C_\infty = \ln N_\infty = 19,\ k_1 = 4,\ k_2 = 1,\ l_1 = 0.1,\ l_2 = 4\cdot 10^7,\ \kappa = 1, \\ \alpha_g = 0.425,\ \gamma_g = 0.04,\ \gamma_h = 0.15,\ k = 0.05,\ \hat{C} = 4\cdot 10^7,\ \hat{N} = 5\cdot 10^7,\ R = 0.0075, \\ T = 30,\ C_0 = 10^7,\ N_0 = 10^8,\ g_0 = 12,\ h_0 = 0,\ y_0 = 1. \end{gathered} \tag{17}$$

Let us consider two deterministic open-loop therapy strategies as shown in Fig. 1. Both of them keep the deterministic system viable on the whole interval [0, T]. They also consume equal drug amounts. Influence of stochastic noise on the state trajectories as well as on the mean viability times is illustrated in Fig. 2.

For the leukemia model, we take

$$\begin{gathered} r_1 = r_2 = 0.1,\ \gamma_l = \gamma_n = 0.04,\ \gamma_h = 0.4,\ \beta = 0.01,\ k_1 = 2.5,\ k_2 = 1.4,\ c = 10^{-10}, \\ L_\infty = N_\infty = 10^{10},\ k = 0.05,\ N_H = 7.5\cdot 10^7,\ \alpha = 10,\ R = 1, \\ T = 10,\ L_0 = 1.8\cdot 10^8,\ N_0 = 10^8,\ h_0 = 0,\ y_0 = 1 \end{gathered} \tag{18}$$

(in compliance with the relevant orders of magnitude given by Bratus et al. (2012)[9], Bratus et al. (2013)[5]) and consider the deterministic open-loop therapy strategy indicated in Fig. 3. Dependence of the mean values

$$E\left[\overline{L}\right] = E\left[\frac{1}{T}\int_0^T L(t)dt\right],\quad E\left[\overline{N}\right] = E\left[\frac{1}{T}\int_0^T N(t)dt\right] \tag{19}$$

and functional (6) (opposite to mean therapy quality) on the noise intensity is shown in Fig. 4.

From Fig. 2 and 4, one can see that, as the noise intensity increases, the mean viability time in the glioma model decreases, and functional (6) in the leukemia model increases. Thus, stronger uncertainty implies lower mean therapy quality and this dependence is nonlinear. In the leukemia model, the mean therapy quality decreases much faster for greater uncertainties.

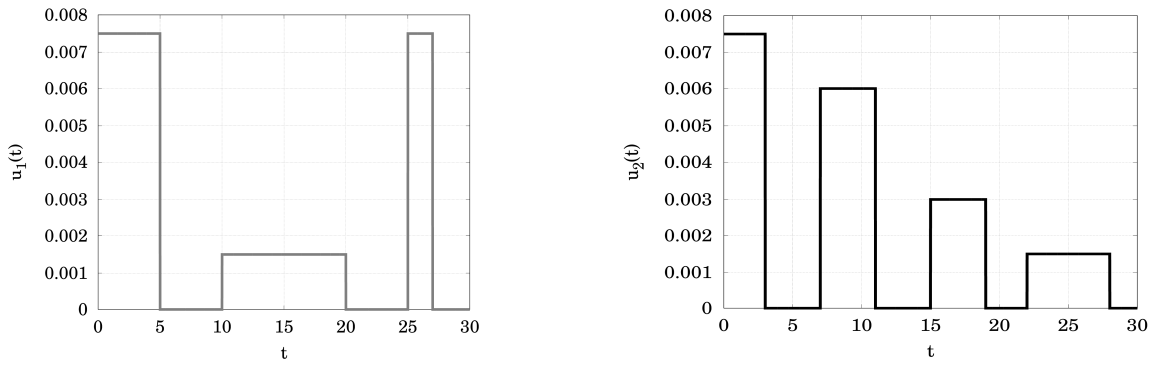

Figure 1:Deterministic therapy strategies $\boldsymbol{u_1(t)}$ and $\boldsymbol{u_2(t)}$ in the glioma model.

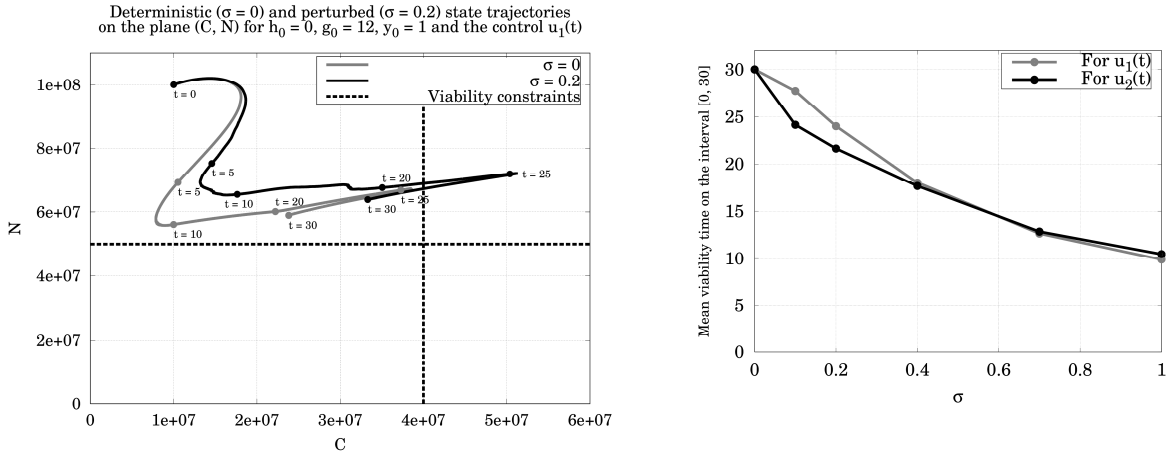

Figure 2: Glioma model. Left: Perturbation of the deterministic state trajectory under therapy strategy $\boldsymbol{u_1(t)}$ by stochastic noise with intensity $\boldsymbol{\sigma}$ = 0.2. Right: Mean viability times for therapy strategies $\boldsymbol{u_1(t)}$ and $\boldsymbol{u_2(t)}$ depending on noise intensity $\boldsymbol{\sigma}$.

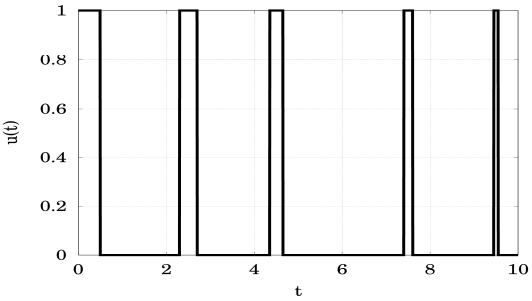

Figure 3: Deterministic therapy strategy $\boldsymbol{u(t)}$ in the leukemia model.

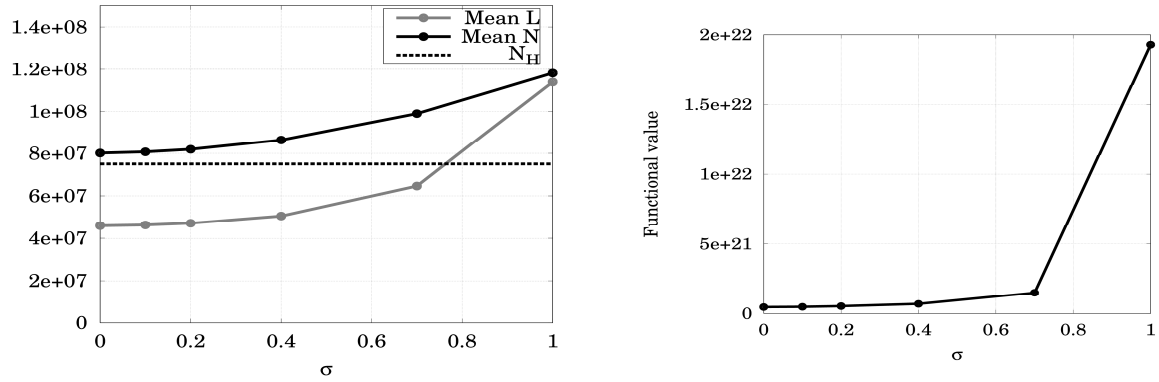

Figure 4: Leukemia model. Left: Mean values (19) depending on noise intensity $\boldsymbol{\sigma}$. Right: Functional (6) (opposite to mean therapy quality) depending on noise intensity $\boldsymbol{\sigma}$.

Note that stochastic uncertainties in our models are external according to the terminology of Bratus et al. (2016)[10]. Hence, our results conform with the property that stronger external uncertainties should decrease mean control quality[10]. This also leads to the hypothesis that these uncertainties may cause significant changes in the structures of optimal control strategies.

Furthermore, Fig. 2 indicates that, in the glioma model with a sufficiently small uncertainties, control $\boldsymbol{u_1(t)}$ leads to a greater viability time than control $\boldsymbol{u_2(t)}$ with consecutively decreasing dosages. For stronger noise, the results become almost the same.

CONCLUSION

In this paper, we proposed an approach to develop stochastic extensions of deterministic dynamic models arising in Biomedical Sciences. Two specific nonlinear models concerning glioma and leukemia therapy were formulated and then extended to the stochastic case by using the proposed approach. We also performed numerical simulations in order to obtain how the included stochastic uncertainties affect dynamics of the systems and, in particular, how much viability (survival) times or other criteria of therapy quality decrease with increasing uncertainties. For a future work, it is worth investigating to characterize influence of stochastic uncertainties on solutions to dynamic optimization problems for such biomedical models.

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