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The New Approach of Complex Control Law on Immunological System

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Abstract: In this study, we investigate a new mathematical models and approach of the control of tumors in organism. We consider the Immunological Model for the population dynamics of cells with control-factors representing the influence on the disease. We analysed the impact of the "D-factor" on the steady states and their stability and determine a control value. In these models, we studied the "D-factor" in "Umbilical" from catastrophe theory to impose control on tumor growth. By adjusting parameters, the models shows stationary states at which the immune system is stabilized and the number of tumor cells is either driven to zero or remains constant. Numerical simulations are carried out to confirm the theoretical findings to investigate the impact of the control parameters on the dynamic of the disease. The offered results can be used at theoretical studies for stabilization immune system at predicted level. These results are particularly relevant as new method in mathematical modeling and their applied views and for the prevention and early diagnostics of cancer and health improvement.

Key words: Control theory, theory of catastrophe, structurally-steady mapping, lyapunov function, mathematical modeling, immune system, HIFU therapy

INTRODUCTION

Now a days in the Republic of Kazakhstan according to official statistics, the number of cancer patients in Kazakhstan annually increases by 50,000 people. The control of factors which influence the risk of oncological diseases, often attracts a constant interest.

The control of special resources in medicine is important for the development of human and society. In exploiting the biological research, both the medicine helpfulness and the environmental effects should be taken into account which initiates a new research area: Biomathematics. Interactions of Mathematics, Ecology and Medicine promote the development of the Biosciences greatly and the certain extent.

Since most of biological theories evolve rapidly, it is necessary to develop some useful Mathematical models to describe the consequences of these Biological models (Nedorezov and Omarov, 1990; Abrosov *et al*., 1988; Bazykin, 1998). However, so far the control of complex mathematical models has not been explored yet.

It is the purpose of the present paper to provide the new theoretical approach where tumor cell population had been dropped. For this we began to find the classical control techniques and methods and possibility for decrease of tumor appearance and to keep stability of organism.

These results are suggests that the control of tumor cells should be an essential component in the development of future therapies for cancer. This research also opens the way to other therapeutic opportunities, such as preventive anti-tumor vaccination.

Knowledge of mathematical model has a great importance in multidisciplinary science. A great number of research works and practical implementations have confirmed the interest of mathematicians in developing and applying the methods of theory of catastrophe. Predator-prey models with disease are a main problem and a main field of research. In subsequent years and currently many researchers Bazykin (1974), Ermekbayeva and Omarov (2010), Khlebopros *et al.* (2010) and Slepkov *et al*. (2007) studied the dynamics of ecological models with infected prey and their papers mainly focused on this issue. Our main objective in this study is to extend their results by introducing control variables.

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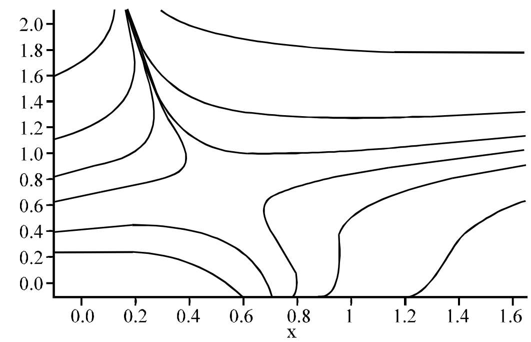

Fig. 1: Phase Portrait of System (1)

MATERIALS AND METHODS

To model cell populations, including their interactions and influence, we start with two dynamical variables: the concentration of tumor cells and the concentration of cells that have specific resistance to tumor growth (Slepkov *et al*., 2007; Khlebopros *et al*., 2004). Cells with natural resistance have some level of activity which is included in the model as a parameter. In particular, the temporal evolution of the two concentrations is modeled by these two differential equations (Bazykin, 1974; Ermekbayeva and Omarov, 2010):

$$\dot{x}_1 = j - \beta x_1 x_2 - \gamma x_1 + \frac{\alpha x_1 x_2}{1+x_2}$$
$$\dot{x}_2 = x_2 - \frac{\mu x_2}{1+\delta x_2} - x_1 x_2 \qquad (1)$$

Where:

x_1 = The concentration of free cells (effector cells)
x_2 = The concentration of tumor cells
j = The growth rate of effector cells
$\beta x_1 x_2$ = The death rate of effector cells due to their interactions with tumor cells
$x_1 x_2$ = The death rate of tumor cells due to their interactions with effector cells
γ = Controls the growth rate of effector cells due to interactions with tumor cells
α = Controls the growth rate of tumor cells
μ = Controls the natural death rate of effector cells
δ = Controls the natural death rate of tumor cells

Thus, the model is a system of two differential equations involving six parameters. The phase portrait for System (1) is shown in Fig. 1. On Fig. 2, we presented design simulink scheme of System (1). The stationary points of the model are determined from the conditions $\dot{x}_1 = 0$ and $\dot{x}_2 = 0$. Therefore from Eq. 1 has three equilibrium states:

$$x_{s1} = (0,0),\ x_{s2} = \left(0, \frac{\eta - 1}{\delta}\right), x_{s3} = \left(\frac{j}{\gamma}, 0\right)$$

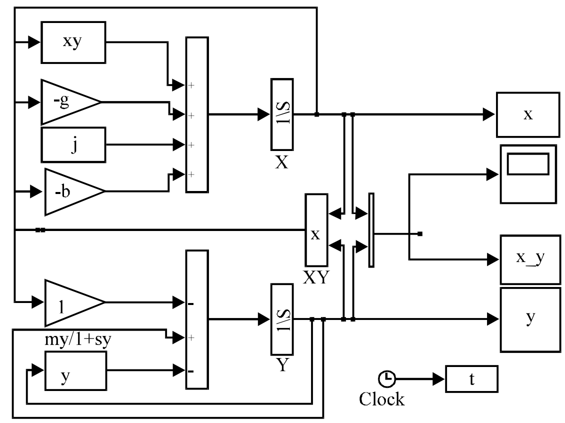

Fig. 2: Simulink scheme of System (1)

Phase portrait of Eq. 1 show than the state of system is not steady. In this research, we propose the promote for stabilization of the (system) organism's state on a predictable level.

RESULTS

The spasmodic changes arising in the form of the sudden reply of system on smooth change of external conditions are called as accidents. At accident under the influence of operating parameters, the steady state of system changes, i.e., it passes from one steady state into another.

R. Tom proved the important theorem in the theory of accidents which helped to classify catastrophes by type and entered so-called elementary or initial catastrophes. The Tom's theorem allows to classify all smooth potential functions. The most remarkable property of this classification is that it depends only on number of k of operating parameters which is considered final.

In this study, we present an extension of the model of Eq. 1 in which we made major change: addition D-factor (as umbilical form). Third, studying the stability state of models from construct Lyapunov functions.

The complex interaction of parameters k_1, k_2, k_3 in equations are describes as an immune response in the organism with two types of specialized immune system cells (regulatory T-cells and effector T-cells) which are particularly closely involved.

The Influence control law in "umbilical" form on dynamic model: We add a synchronic controlling D-factor which is a function of structurally steady mappings known as a "UMBILIC catastrophe" in to System (1). One of the most important points in catastrophe theory is the behavior of smooth functions that depend on a

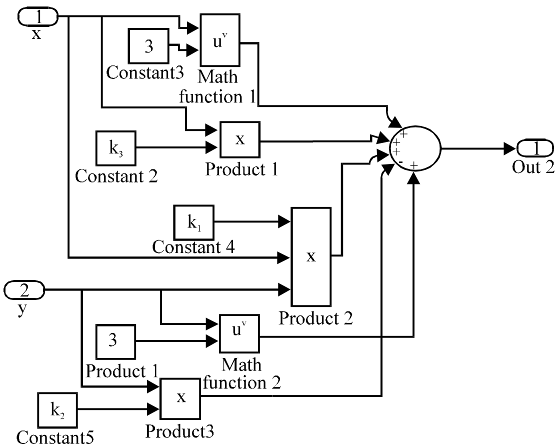

Fig. 3: Simulink scheme of Subsystem (1)

parameter. The D-factor used here represents a fold form (one of the 7 forms of Catastrophe theory) (Polyak and Scherbakov, 2002).

The D-factor used here represents in an "umbilical" form (Polyak and Scherbakov, 2002). Then, Eq. 1 becomes:

$$\begin{cases} \frac{dx_1}{dt} = J - \beta x_1 x_2 - \gamma x_1 + \frac{\alpha x_1 x_2}{1+x_2} - \\ -(x_1^3 + x_2^3 + k_1 x_1 x_2 - k_2 x_2 + k_3 x_1) \\ \frac{dx_2}{dt} = x_2 - \frac{\mu x_2}{1+\delta x_2} - x_1 x_2 - \\ -(x_2^3 + x_1^3 + k_1 x_1 x_2 - k_2 x_1 + k_3 x_2) \end{cases} \quad (2)$$

Then as an example, we define phase portrait of system for the following initial conditions. When the initial settings are follow: $j = 10$; $\alpha = 3$; $\beta = 1.3$; $\gamma = 5$; $\mu = 0.4$; $\delta = 0.04$; $k_1 = 1.9$; $k_2 = 3$; $k_3 = 3.5$.

Figure 3 shows a Simulink Block diagram of the subsystem with a control law on umbilical catastrophe function as per Eq. 2.

Overall, at the beginning our system was unstable. We can see it from found points. Then, we added controlling impaction of one-parameter image to the right side of the system and continued to research. We found equal point, then added the controlling impaction and we can see how given system becomes stable.

DISCUSSION

Stability is a fundamental notion in the qualitative theory of differential equations and is essential for many applications (Polyak, 2010; Beisenbi, 2011).

In turn, Lyapunov's functions are basic instrument for studying stability; however, there is no universal method for constructing Lyapunov's functions. Nevertheless in some special cases, a function can be constructed by applying special techniques (Abitova *et al.*, 2012a, b; Beisenbi and Yermekbayeva, 2013; Abitova *et al.*, 2012a, b; Beisenbi and Abdrakhmanova, 2013).

Method of Lyapunov's functions at research of control systems with an increased potential of robust stability: The law of management u(t) is set in the form of the sum three-parametrical structurally steady displays $x^3_2+x^3_1+k_1x_2x_1-k_2x_2+k_3x_1$ (hyperbolic umbilic catastrophe). We will determine by the following stage stationary conditions of system.

We will investigate stability of stationary states on the basis of the offered approach by a method of Lyapunov's function. Let us consider the general approach for stability for all a steady state. For this purpose, we will designate components of a vector of an anti-gradient components a vector $V_i(x)$ Lyapunov's functions. The full derivative on time from a vector Lyapunov's functions will be equal (Eq. 3):

$$\frac{dV}{dt} = \frac{\partial V}{\partial x} \times \frac{dX}{dt} \quad (3)$$

From Eq. 3, we receive that the full derivative on time from a vector Lyapunov's functions will be negative function, thus, the sufficient condition of asymptotic stability of system of rather steady state is satisfied.

On components of a gradient's vector a vector Lyapunov's functions, we build components a vector Lyapunov's functions in a view:

$$V_i(x) = (V_{i1}(x), V_{i2}(x), \ldots, V_{in}(x))$$

The next step is represent Lyapunov's Function in a scalar form. But, conditions of positive or negative definiteness of functions not obviously, thus, we will use the Mors lemma from theories of catastrophes.

The considered system let is in a condition of stable or unstable equilibrium which are Mors's points. The system is in stationary points x_s where gradient from Lyapunov's function (potential function):

$$\nabla V = 0 \text{ and if } \det V_{ij} = \left| \frac{\partial^2 V(x)}{\partial x_i \partial x_j} \right|_{x_s} \neq 0$$

That in these stationary conditions of system the Mors's lemma is fair and guarantees existence of smooth replacement of variables such that Lyapunov's function can be locally presented by a square form.

Positive definiteness of Lyapunov's function will be defined by signs of coefficients of a square form (λ_i>0, i = 1,...n), i.e., signs of own values of a Hess's matrix (matrix of stability) (Khlebopros *et al*., 2004).

Therefore, it is necessary to define Hess's matrix in a point of balance. We will calculate Hess's matrix for Lyapunov's function in a stationary point and elements of a matrix of Hess.

On the Mors's lemma locally, we can present Lyapunov's function in steady state area in the form of a square form.

The necessary condition of stability of a steady state will be defined by system of inequalities when performing positive conditions of inequalities.

These data indicate that Lyapunov function which is using on the system for stability for System (2), we can apply the same (approach) algorithms which define stable conditions (Beisenbi and Uskenbayeva, 2014). Therefore, found coefficients can define the structurally-steady area of the system and decreasing tumor which represented as one of the controlling methods of immunological system.

The transient-response curve of system shows on Fig. 4 and 5. Overall the transition process of the system (stability focus) shows on Fig. 6.

The proposed controlling method dilates the possibilities of analysis of dynamic models of immunological groups. We can control the increment of tumor cells within the organisms on needed level with the help of special control law model and it might lead to the better life standard of people. Healthy well-being sphere is the most important problems all over the world.

In the study, we attempted to analyze the conditions that make model more steadily. The study has addressed the questions of new theoretical method of robust stability for nonlinear system for the designing more effective control systems (Beisenbi and Abdrakhmanova, 2014; Yermekbayeva, 2012; Yermekbayeva *et al*., 2012).

It should be noted that this study has examined theoretical character now and practical findings suggest that control laws will influence to system as a positive (Yermekbayeva, 2012, 2013; Yermekbayeva *et al*., 2013).

In particularly, from physical terms of values k_1, k_2, k_3 in the model, we can represents as thermal influence, ultrasound ablation and zone of the cell periphery which explain a HIFU process (High-intensity focused ultrasound).

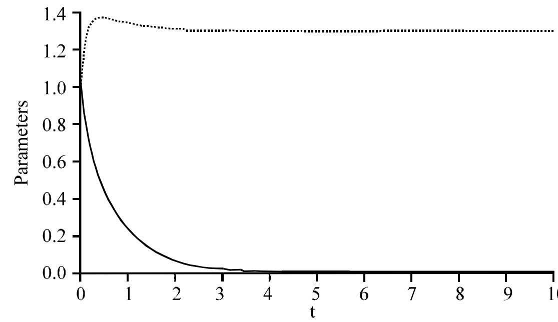

Fig. 4: The transient-response curve of System (2)

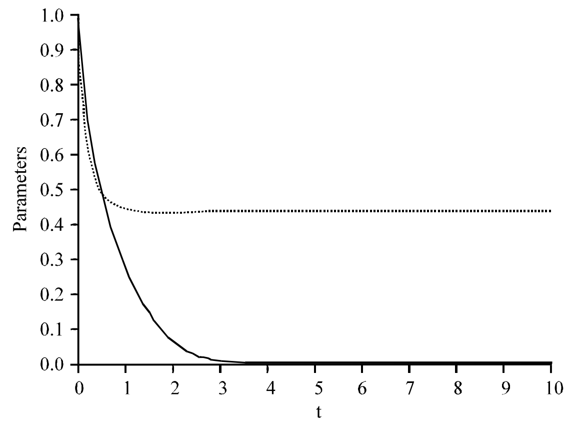

Fig. 5: The transient-response curve of System (2)

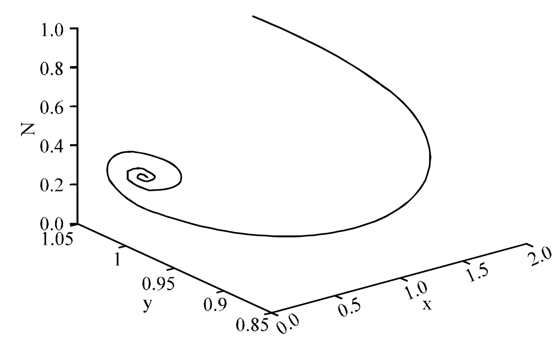

Fig. 6: Phase Portrait of System (2)

More generally, this study, illustrates that the "compensatory effect" can be applied to control the growth of tumor cells in an organism, fixing the immune system at a predictable level (Yermekbayeva *et al*., 2014).

These findings suggest that simulation of control systems plays a major role in area of prevention and early intervention of cancer. Furthermore, this new approach may form the foundation of future studies on treatment.

HIFU therapy: In this study, we briefly describe a relatively new type of cancer treatment therapy HIFU. HIFU therapy is the use of focused, high-intensity beam of ultrasound for local destruction of damaged or diseased tissues. Although, this method was discovered almost 60 years ago, its intensive use in the treatment of cancer began only in the 90's of last century. Since, this method of treatment is comparatively not expensive and has a number of advantages, currently the world's scientists, clinicians and companies producing medical equipment show great interest to HIFU therapy. The advantage of this method is that it is a non-invasive method for the meeting does not require any surgical instruments, procedures carried out without bleeding, the recovery period after HIFU therapy an average of 7 days. It can also be used as an alternative form of treatment or in combination with radiotherapy and chemotherapy.

Method of ultrasound ablation is indicated in the treatment of malignant tumors of various localization (liver, pancreas, kidney, mammary gland, etc.). Except brain damage, lung, intestine, bones of the skull and spinal column.

To conduct HIFU therapy necessary to clearly define the damaged tissue area in which to focus the beam of ultrasound and the desired frequency and intensity of the ultrasound. Since throughout therapy, high intensity ultrasound exposure process must be monitored, it is necessary to determine which imaging technique is used. Currently used two methods of visualization in planning and tracking the actions of HIFU: Magnetic Resonance-guided Focused Ultrasound (MRgFU or MRgHIFU) and Ultrasound-guided Focused Ultrasound (USgFUS or USgHIFU).

Now briefly describe three mechanisms of action HIFU. In the first mechanism, thermal ablation focussed by lenses of high-intensity ultrasound emitter passes through the tissue part thereof reflected (about 20-40%) and the remainder (60-80%) heats the tissue temperature in a very short period of time, about one second to 50-90°C. Thus there is a local extinction of tissue, i.e., coagulation necrosis. Where in adjacent tissues remain unharmed. The second damage mechanism tissue necrosis occurs due to mechanical and thermal stress on the tissue. Ultrasound causes cavitation in the tissue, in which the formed bubbles are burst, the temperature in this location reaches 2000-5000°C and the acoustic pressure of several thousands of Pascal. In a third mechanism, via HIFU damage vessels feeding the tumor, the oxygen supply is interrupted which also lead to the destruction of tumor tissue. The advantages of this method is that this method is non-toxic, it is not poisonous to the body. Focused ultrasound does not damage healthy tissue and acts directly on the tumor. It can be repeated several times at intervals of about 7 days. The recovery time of patients after HIFU action is very short, about 7 days. It can be used as an alternative form of treatment as well as complex therapy in addition to radiation and chemotherapy.

CONCLUSION

In conclusion, it is obvious that results show two major points: first of them, it is study the model with control law and their changing. A second offer is the define of Lyapunov function and conditions for steady state. In general, properties of dynamic system are represent following stationary states. The first represents cancer treatment that reduces the concentration of tumor cells to zero: complete recovery of the organism (effector cells in the immune system).

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