# The Description of the Control Factors on the Complex Immune System

**Janar Yermekbayeva[1], Tolkynay Myrzakul[2], Onalsyn Dauletbakova[2] and Gulnara Abitova[1]**
**Department of System Analysis and Management[1]**
**Department of General and Theoretical Physics[2]**
**L.N. Gumilyov Eurasian National University**
**Astana, 010000, Kazakhstan**

## Abstract

This work discusses new applications of controlling population systems (cells in organism), in order to describe their dynamical features. In the first part of this work growth dynamics of the tumor cells are represented by a simple model. In the second part we apply the method for control dynamical models of the tumor cells with influence of the D-factor. On the basis of this procedure the obtained control parameters of the original system allows us to derive analytical relationships between cells of the original model. We can interpret these relationships together with control law as HIFU (High-intensity focused ultrasound) concentrations and influence of the considered process. By applying control law on steady mapping forms to the described model we show that control solutions of model equations are possible. We obtain an analytical solution for the modeling, controlling, engineering and simulation of processes.

## Keywords
Engineering Management, Control Theory, Structurally-steady mapping, Simulation process.

## Introduction

Every year, 200,000 children worldwide are diagnosed with cancer, and about 100,000 die, including 250 children daily, or 10 children - every hour. In 90% of all cases the cause of this high death rate is lack of access to modern treatment.

Today in the Republic of Kazakhstan according to official statistics, the number of cancer patients have increased annually by 50,000 people. Environmental factor in Kazakhstan is mainly from those that lead to cancer children. Points of the spread of radiation, as in the case of Baikonur and Semipalatinsk testing ground, annually increase the statistics of cancer mortality among children by 13-15%.

In the world of cancer risk over the period of childhood, one child in 450, while in adults the figure is ten times higher. The US Center for Disease Control predicts that new cases of cancer will double from 2002 rates, to 20 million cases per year by 2030 and it is shown schematically in Figures 1. Dynamics of disease shows the increasing progression.

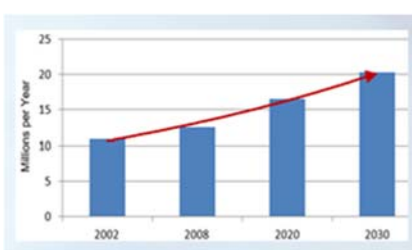


Figure 1. The predict of US Center for Disease Control.

The figure 2 demonstrates real facts from Oncology Center in Astana (Kazakhstan).The number of sick with mammalogy has steadily increased for the last 2 years.

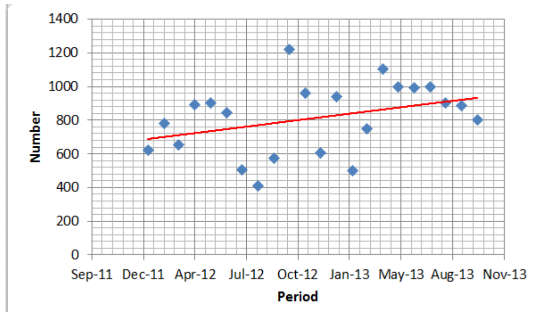


Figure 2. The facts from Oncology Center since Sept., 2011.

The control of factors, which influence the risk of oncological diseases, often attracts a constant interest. Over the past 10 years, activity in mathematical modeling of tumor has increased. A variety of modeling strategies have been developed, each focusing on one or more aspects of population of tumor cells. The control of special resources in medicine is important for the development of human and society. Interactions of mathematics, ecology, biophysics and medicine promote the development of the biosciences greatly in a certain extent (Nedorezov L.V and Omarov A.N, 1990). Since most of biological theories evolve rapidly, it is necessary to develop some useful mathematical models to describe the consequences of these biological models (Bazykin A.D 1998). However, today the control of complex mathematical models has not explored yet.

It is the purpose of the present paper to provide the new theoretical approach, where tumor cell population declined. 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. This results suggests that the control of tumor cells should be an essential component in the development of future therapies for cancer. Knowledge of mathematical model has a great importance in multidisciplinary science. A great number of research works (Slepkov V.A. and Khlebopros R.G 2004) and practical implementations have confirmed the interest of mathematicians in developing and applying the methods of theory of catastrophe. Many authors studied the dynamics of ecological models with infected prey, and their papers mainly focused on this issue (Slepkov V.A. and Khlebopros R.G 2007).

Thus the research in this paper (development the control system with influence on tumor cells) is very important. It is represented interestingly not only as a basis for the solution of healthcare system, but also as independent theoretical research (Yermekbayeva J.J.,Omarov A.N.,2010). Engineering of control systems with control laws in a class of structural-steady mapping (D-factor form) wasn't studied before. The Multidisciplinary way of scientific health area will allow to find new methods in the theory of control in immunology.

Our main objective in this paper is to extend their results by introducing control variables. The paper is structured as follows: in Section 1, we summarize the main points of the mathematical model. Furthermore, we show state of the system on phase plane. In the Section 2 we create formulation of the Lyapunov function for stability. In Section 3 discuss and describe the influence of D-factor on model from point of physical properties. Last Section contains concluding remarks.

## 1. Mathematical modeling

First, we will use the Gompertz equation (1), that is an Ordinary Differential Equation (O.D.E) that shapes mathematically the population growth. In paper, we will describe the meaning of each one of its parameters.

$$\frac{dN}{dt} = aN - bN\log N = -bN\log(\frac{N}{K}) \tag{1}$$

Here, N: size of tumor, measured as total volume; K: carrying capacity; a: growth constant and b: decay rate. Graphs of Gompertz curves (Fig 3.), showing the effect of varying one of *a* and *b*, while keeping the constant growth.

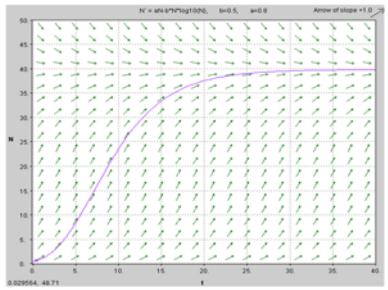

Figure 3. Gompertz model with *a*=0.8, *b*=0.5

In Next step, we illustrate through mathematical modeling the dynamics between tumor cells and effector cells. 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 (Yermekbayeva J.J., Beisenbi M, 2012). 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. We have studied and developed different mathematical models and methods of the study without and with special influence in works (Yermekbayeva J.J 2013).

To model (1), we add a synchronic controlling D-factor, which is a function of structurally steady mappings known as a "cusp catastrophe." One of the most important points in catastrophe theory is the behavior of smooth functions that depend on a parameter. The D-factor used here represents a cusp form (one of the 7 forms of catastrophe theory) (Beisenbi M.A 2011).

$$\dot{x}_1 = j - \beta x_1 x_2 - \gamma x_1 \cdot \frac{\alpha x_1 x_2}{1+x_2} - (D_{factor}) \quad or$$

$$\dot{x}_2 = x_2 - \frac{\mu x_2}{1+\delta x_2} - x_1 x_2 - (D_{factor})$$

$$\dot{x}_1 = j - \beta x_1 x_2 - \gamma x_1 \cdot \frac{\alpha x_1 x_2}{1+x_2} - x_1^4 - k_2 x_1^2 - k_1 x_1$$

$$\dot{x}_2 = x_2 - \frac{\mu x_2}{1+\delta x_2} - x_1 x_2 - x_1^4 - k_2 x_2^2 - k_1 x_2 \tag{2}$$

Here $x_1$ is the concentration of free cells (effector cells), $x_2$ is the concentration of tumor cells, $j$ is the growth rate of effector cells, $\beta x_1 x_2$ is the death rate of effector cells due to their interactions with tumor cells, $x_1 x_2$ is the death rate of tumor cells due to their interactions with effector cells, $\gamma$ controls the growth rate of effector cells due to interactions with tumor cells, $\alpha$ controls the growth rate of tumor cells, $\mu$ controls the natural death rate of effector cells, and $\delta$ controls the natural death rate of tumor cells. *D-factor* is presents in a view cusp form (catastrophe form). Negative values mean the specific influence on organism and parameter $k_1, k_2$ are control values.

The complex interaction of parameters *k1,k2* 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 phase plane for system (2) with *D-factor* is shown in Fig. 4. The stationary points of the model are determined from the conditions $x_1 = 0$ and $x_2 = 0$.

Therefore, the model (1) has three equilibrium states:

$$x_{s1} = (0,0), x_{s2} = (M,0), \quad M = A - B$$

$$A = \sqrt[3]{\frac{J}{2} + \sqrt{Q}} \qquad B = \frac{\gamma + k_1 + k_2}{3A} \qquad Q = (\frac{\gamma + k_1 + k_2}{4})^4 + (\frac{j}{2})^2$$

The result of describing equilibrium gives following states:

when $(x_1, y_1) = (0,0); \lambda_1 = -5{,}5; \lambda_2 = 0.4$- it is a stem;

when $(x_2, y_2) = (1;2;0)$ $\lambda_1 = -48,9; \lambda_2 = -0,795$ – stable node

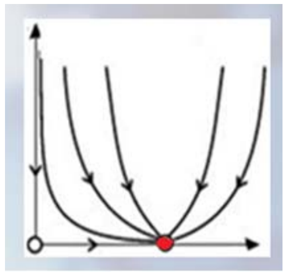

Figure 4. Phase Plane of System (2).The red point shows a stable node of model (2).

## 2. Analysis of the stability of control system

Stability is a fundamental notion in the qualitative theory of differential equations and is essential for many applications. In turn, Lyapunov functions are general instrument for studying stability. Nevertheless, in some special cases, a function can be constructed by applying special techniques (Abitova G., Beisenbi M. 2012).

We construct the Lyapunov function for system and then use geometric interpretation to find the region of stability. Lyapunov's theorem has a simple geometric interpretation (Polyak 2010). The geometric meaning of a Lyapunov function used for determining the system stability around the zero equilibrium and it is shown schematically in Figures 5.

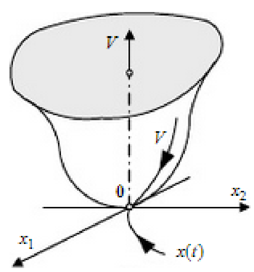


Figure 5. The geometric interpretation of Lyapunov function

Thus, from the geometric interpretation point of view the second method of Lyapunov, the study of stability is reduced to the construction of a family of closed surfaces surrounding the origin. As the integral curves have property to intersect each of these surfaces, then stability of the unperturbed motion will be set (Yermekbayeva J.J., Beisenbi M.A. 2012).

For $x_{s_2} = (M,0)$ the stationary point Lyapunov function's:

$V(x_1, x_2) = (\gamma + k_1 + 3M^2)x_1^2 + M(\beta - \alpha)x_1 x_2 + (k_2 + \mu + M - 1)x_2^2$

The positive detection condition of Lyapunov function:

$$\begin{cases} \gamma + k_1 + 3M^2 > 0 \\ M(\beta - \alpha) > 0 \\ k_1 + M + \mu - 1 > 0 \\ M > 0 \end{cases} \tag{3}$$

A found coefficients (3) can spot the structurally-steady area of the system (Beisenbi M, Yermekbayeva J.J 2013). Overall, the influence on the increment of tumor cells as constructed-steady image was revised as one of the controlling methods of immunological system. Lyapunov function is used to check the system to stability. The result is to repair the way to create the opportunities to control the increment of tumor cells within the organisms and the equalizer effect of renovation of immunological system on needed level. The proposed controlling method dilates the possibilities of analysis of dynamic models of immunological groups.

## 3. Description of the Control Factors

These relationships together with control law we interpreted as HIFU (High-intensity focused ultrasound) concentrations and influence of the considered process. The advantages of this kind of treatment that there is no need to introduce special conductors, i.e. the integrity of the skin is not broken unlike in the other types of ablation. HIFU- therapy is the distribution of energy in the form of ultrasonic waves through the medium of interest to us tissues. Since this method is completely non-invasive, it is of great interest to clinicians, inventors and medical companies, for that would use this method in the treatment of complex diseases, such as liver tumors, breast tumors, malignant tumors of bone and soft tissue and etc (Kim Y.S., Rhim H. 2008).

To understand this method of treatment we briefly describe the physical properties of ultrasound and its interaction with the biological tissues in the body .

Ultrasound is a mechanical elastic vibrations in the environment (gases, liquids and solids) outside the human hearing at a frequency $n$ = 20,000 Hz. The nature of the ultrasonic waves, though no different from the waves of the audible range, and subject to the same laws of physics, yet has specific features, which are the cause of such wide applications in science and engineering. Here are some of them: due to the small wavelength of the ultrasonic wave beam has a distribution pattern. Near the ultrasound transducer is distributed in the form of bundles to fit close to the size of the radiator. Getting on the heterogeneity in the environment, such a beam behaves like a light beam testing reflection, refraction, scattering, which allows you to create sound images in optically opaque media, using purely optical effects (focusing, diffraction, etc.) and small oscillation period, which allows to emit ultrasound pulses and carried out in an accurate timing selection signals propagate; lastly, the possibility of obtaining high-energy vibrations at low amplitude as oscillation energy is proportional to the square of the frequency .

This allows us to create ultrasonic beams with a high energy level , without the need for large equipment; in an ultrasonic field develop significant acoustic streaming . Therefore, the impact of ultrasound on the environment gives rise to specific effects: physical, chemical, biological, and medical. Such as cavitation, sound capillary effect, dispersion, emulsification, decontamination, disinfection, local heating , and many others; ultrasound inaudible and does not create discomfort to service personnel (Kennedy J.E, Haar GR, 2003).

And so all of these specific properties of ultrasonic waves was the reason of using it in a non-invasive ablation of damaged tissues. Illustration depicts extracorporeal high-intensity focused ultrasound therapy of intraabdominal tumor in figure 6.

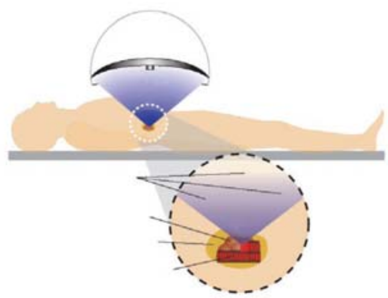

Figure 6. Extracorporeal HIFU therapy.

We describe three tumor tissue damage mechanism of high intensity focused ultrasound . Let's start with the first mechanism - thermal ablation. In thermal ablation during focusing high-energy ultrasound healthy tissue is not damaged. But in the area of the tumor through the lens emitter , for a very short time of about 1 sec. the temperature rises to 90C . In this zone starts to develop coagulate necrosis.

The second mechanism leading to tissue necrosis is the mechanism of acoustic cavitation. With this mechanism, focused ultrasound causes a vibration in the tissues , the molecular structure with the start alternately compress and decompress . During the next phase of expansion, the gas in the solution passes into the gaseous state and is converted into micro bubbles. Due to mechanical shock, when the size of the resonant frequency of the wave bubbles burst. Sound pressure during this process reaches several thousand Pa, the temperature of 2000-50000 C is reached, this leads to destruction of tissue (Mason T.J.2008). In this mechanism, the formation of cavitation depends on the length of the pulse, its frequency and intensity.

The third mechanism is damage to the blood vessels feeding the tumor , and the oxygen flow is stopped and disturbed trophic tissue. Coagulate necrosis caused by exposure to high intensity focused ultrasound , the biological effect is due to the total exposure to heat , cavitation and destruction of tumor tissue vessels .

## 4. Concluding Remarks

In the paper 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 and description of influence D-factor on model, their physical properties.

The sum up, results show three major points: first of them, it is study the model with one and two equations. We added special control law and research their influence. A Second offer is the construct of Lyapunov function and conditions for steady state. In general, properties of dynamic system are show following stationary state (Abitova G., Beisenbi M. 2012). The result represents cancer treatment that reduces the concentration of tumor cells to zero: complete recovery of the organism (effector cells in the immune system). It should be noted that this study has examined theoretical character now, and practical findings suggest that control laws will influence to system a positive (Myrzakul T.R. 2008).

In particularly, from physical terms of values *k1,k2* in the system, we can explains as thermal influence, ultrasound ablation and zone of the cell periphery which explain a HIFU process (High-intensity focused ultrasound). More generally, this paper illustrates that the D-factor can be applied to control the growth of tumor cells in an organism, fixing the immune system at a predictable level. However, for this approach to be successful, intensive interactions with cell biologists, engineers and applied mathematicians are essential. Such an interdisciplinary approach appears to be necessary in order to control tumor cell population.

## 5. Acknowledgment

The authors thank Professor Beisenbi M.A., Professor Omarov A.N., Abitova G.A. for fruitful discussions on the biological and mathematical implications and possible extensions of the work.

## References

Nedorezov L.V., Omarov A.N. Stability and diversity in predator-prey systems. *Izvestiya Sibirskogo Otdeleniya Akademii Nauk SSSR, Seriya Biologicheskikh Nauk*, No 2, pp.63-67, 1990.

Abrosov N.S, Nedorezov L.V, Omarov A. Evaluation of the stability of the flow systems. Ecology of populations. *Proc. of All-Union Reports*, No 2, pp. 189-191, 1988.

Nedorezov L.V., Omarov A.N. A generalization of the Lotka-Volterra competition.*Zh.Obshch. Biol*, Vol 1,No 6,pp. 746–751,1989.

Bazykin A.D. Nonlinear Dynamics of Interacting Populations. *World Scientific*, Moscow, 450 p., 1998.

Khlebopros R. G., Okhonin V. A., Fet A. I., Catastrophes in Nature and Society,*USA,* 2010.

Slepkov V.A., Khlebopros R.G, Gabuda S.P. Phase portraits of multi-dimensional ecological systems. *Proceedings of the 6th European Conference on Ecological Modelling ECEM '07*, Trieste, pp. 263-269, 2007.

Khlebopros R.G, Slepkov V.A., Soukhovolsky V.G. Mathematical Model of Solid Tumor Formation.*Proceedings of the 8th World Multi-Conference on Systemics, Cybernetics and Informatics.Orlando*, Florida, USA, No 16, pp. 43-49, 2004.

Slepkov V.A., Khlebopros, R.G., Sukhovolsky, V.G., Mironov, Yu.V., Fedorov, V.E., Gabuda, S.P. Mathematical model of solid tumor formation. http://arxiv.org/abs/q-bio/0401032v1.

Yermekbayeva J.J.,Omarov A.N.. Compensatory effect in control of phytophage and entomophage population numbers. *Euroasian Entomological Journal*.Vol 9, No 2, Russian IF=0,241, 2010.

Yermekbayeva J.J., Beisenbi M., Omarov A, Abitova G.The Control of Population Tumor Cells via Compensatory Effect. *Proceedings of the ICMSCE 2012*, Kuala-Lumpur, Malaysia, pp. 46-51, 2012.

Yermekbayeva J.J. On the Influence of Structurally-SteadyMappings on Predator-Prey Model. *Proceedings of International Conference on Mathematical Methods and Models in Biosciences. Bulgarian Academy of Sciences in Sofia*, p.118, 2012.

Yermekbayeva J.J. Control of tumoral cages growth with the help of «compensatory effect». *Proceedings of the XVI All-Russia symposium «Complex systems in extreme conditions», Krasnoyarsk scientific center of the Siberian Branch of the Russian Academy of Science*, 155 p.,2012.

Yermekbayeva J.J., Saulet J., Kozhakhmetova A., Akhmetov A.The Mathematical Modeling of Influence Control Factor On Immunological System. *Proceedings of the International Conference on Applied Analysis and Mathematical Modeling*, 243 p., 2013.

Polyak B., Scherbakov P., 2002. Robust Stability and Control [in Russian], Nauka, ISBN 5-02-002561-5, Moscow, pp. 37–53.

Polyak B. Introduction to optimization. Optimization Software*, Inc. Publications Division, New York*, 438 p., 2010.
Beisenbi M.A.*Methods of increasing the potential of robust stability control systems. L.N.Gumilyov Eurasian National University (ISBN 978-601-7321-83-3).* Astana, Kazakhstan, 352 p, 2011.
Abitova G., Beisenbi M., Nikulin V., Ainagulova A.Design of Control Systems for Nonlinear Control Laws with Increased Robust Stability. *Proceedings of the CSDM 2012*, Paris, France, *Springer, 2012.*
Beisenbi M, Yermekbayeva J.J. The research of the robust stability in Linear system. *Proceedings Engineering and Technology,* No 3, pp. 142-147, 2013.
Abitova G., Beisenbi M., Nikulin V., Skormin V., Ainagulova A., Yermekbayeva J.J. Control System with High Robust Stability Characteristics Based on Catastrophe Function. *Proceedings of the ICECCS 2012 (IEEE), Paris,* France, 2012.
Dubinsky T.J., Cuevas C., Dighe M.K., Kolokythas O., Hwang J.H.High-Intensity Focused Ultrasound: Current Potential and Oncologic Applications. American Journal of Roentgenology, 190: 191-1990.2214/AJR.07.2671,2008
Haar GT, Coussios C.High intensity focused ultrasound: physical principles and devices. *Int J Hyperthermia.*Vol 23(2), pp. 89-104, 2007.
Kim Y.S., Rhim H., Choi M.J., Lim H.K., Choi D. High-Intensity Focused Ultrasound Therapy: an Overview for Radiologists, Korean J Radiol.Vol 9(4),pp. 291–302.,doi:10.3348/kjr.2008.9.4.291,2008.
Kennedy J.E, Haar GR, Cranston D.High Intensity Focused Ultrasound: surgery of the future. *Brit J Radiol,*Vol 76; pp.90-99,2003.
Mason T.J. A sound investment. *Chem Ind, pp.*878-882, 1998.
Myrzakul T.R., Samners D.V.Application of mathematical model coupling to research a site - a specific recombination of DNA. *Bulletin of Al-Farabi University*, *Kazakhstan,* Biology Series. Vol. 1(36), pp. 174-176, 2008.
Raymkulov M.,Myrzakul T.R. Myrzakulov R. About dynamics of the coded molecule of DNA. *Bulletin of Al-Farabi University, Kazakhstan,* Physical Series.Vol. 2(26), pp.140-146, 2008.
Raymkulov M., Myrzakul T.R. Myrzakulov R. Phase trajectory of indignation of the coded molecule of DNA. *Bulletin of Al-Farabi University, Kazakhstan.* Physical Series.Vol. 2(26), pp.180-183, 2008.
Raymkulov M., Myrzakul T.R. Myrzakulov R. Model operation of genetic information of DNA.*Bulletin of Eurasian National University of L.N.Gumilyov, Kazakhstan.* Vol. 2, pp. 140-151, 2008.

## Biography

**Janar Yermekbayeva** is a Leading Researcher, PhD, Lecturer of Department System analyses and control L.N. Gumilyov Eurasian National University, she has published more than 30 research articles in USA, Kazakhstan, Russian Federation, Malaysia, Poland. She has taught courses in Digital Signal Processing for engineers.

**Tolkynay Myrzakul** is a Leading Researcher, PhD, Lecturer of Department General and Theoretical Physics L.N.Gumilyov Eurasian National University, she has published more than 15 research articles in USA, Kazakhstan, Russian Federation, India. She has taught courses in digital signal processing for engineers. She owner grants for interdisciplinary research program "Program in Mathematics and Molecular Biology" and "Burroughs Welcome Fund Interfaces Program". Passed scientific training in the Florida State University (Florida, USA ) and in the center of Nonlinear Dynamics at the University of Barasidasan (India).

**Onalsyn Dauletbakova** is a Ms. degree student in department General and Theoretical Physics L.N.Gumilyov Eurasian National University. Her scientific advisor is Tolkynay Myrzakul.

**Gulnara Abitova** is an Associate Professor in the Department of System Analysis and Control of the L.N. Gumilyov Eurasian National University in Kazakhstan. She received Ph.D in 2006 from Academic Research Institute of Metallurgy and Enrichment of the Ministry of Education and Science, Kazakhstan. She has been an invited to the Computer and Electrical Engineering Department in State University of New York (SUNY) at Binghamton for studying her research work. She has been an invited speaker at conferences and published more than 30 research articles in reputed international proceedings on mathematical and engineering sciences in the USA, Canada, France, Turkey, Malaysia, Bulgaria, and Hungary.