A HYBRID MODEL FOR TUMOR-IMMUNE COMPETITION

A. Ciancio[1], A. Quartarone[2]

In this work will be examined a model of the competition between the tumor cells and the immune system, starting from the Kuznetsov's model and using a hybrid model recently proposed in [21]. *The description of this phenomenon will be improved in a particular way in its initial phase. There will be considered both cases, the case in which tumor cells avoid the control of the immune system, as well as the stable case, pointing out that the tumor may have a long dormant stage.*

Keywords: dynamical systems, population models, stochastic dynamical systems, kinetic theory, nonlinearity.

MSC2010: 37C10, 37H20.

1. Introduction

Tumors which for some reason have their origin in a vertebrate, grow slowly for some time. In fact, sometimes it takes several months or even years for cancer to appear [1]−[2]. This semi-dormant state is described by many works in literature, because the dormant state cancer is a very well-known clinical phenomenon in which cancer cells can persist for an extended period of time, with a small (or no) increase in cancer cells. This state can occur naturally or after a seemingly effective therapy.

There are at least two independent explanations for this phenomenon:

a) The first one is due to the intrinsic properties of tumor cells and immune cells [3].
b) The second one is supposed due to a balance between the interactions between tumor cells and the immune system.

In both situations, the tumor seems eradicated.

But unfortunately the dormancy of the tumor is not necessarily a stable state, because many factors such as infection, stress, immuno-suppression can disturb this balance.

For this purpose Kuznetsov [3] proposed a mathematical model for tumor growth and its suppression, showing that this model can also describe the regrowth of dormant tumor following the occurrence of one of the two mechanisms discussed earlier:

a) The first mechanism is due to a modest decrease in immune system cells.
b) The second is the case in which it is assumed the presence of some tumor cell mutant that is resistant to the control of the immune system and thus grows

[1]Department of Mathematics, University of Messina, Viale F. Stagno d'Alcontres 31, 98166 I-Messina (ITALY), e-mails: aciancio@unime.it, quartaronea@unime.it

[2]Department of Mathematics, University of Messina, Viale F. Stagno d'Alcontres 31, 98166 I-Messina (ITALY), e-mails: quartaronea@unime.it

out of control, except for the limits imposed by the presence or absence of nutrients.

From the description of this model it will be seen that the tumor is reduced initially and then is kept in check by the constant presence of immune cells, but when the equilibrium relationship between tumor cells and cells of the immune system is properly disrupted, the cancer is no longer under control and escapes to grow in an uncontrolled manner.

However, as we shall see, this model is not suitable to describe the initial stage of the tumor competition because it does not take into account the fact that in the initial instants of growth the two populations have the same ability to learn, before they evolve over time. Moreover, the approach of [3] is developed at a supermacroscopic scale and neglects the heterogeneous behavior of cells.

To overcome this limitation we will follow the paper [21], where a very useful coefficient for describing the evolution of learning ability of the two populations is introduced. In [13] a different approach was proposed. They proposed a class of nonlinear integro-differential equations that at the mesoscopic level models the competition between a tumor and the immune system. And in [14] the asymptotic stability of the solutions of the mesoscopic equation in the case when the corresponding macroscopic equation is asymptotically stable is proved.

The contents of the paper are organized in six sections, which follow the above introduction.

Section 2 describes the model of Kuznetsov, and the significance of each parameter and shows an application of this model, both when the immune system fails to control cancer cells, which in the contrary case Section 3 describes the limits of the original model of Kuznetsov and introduces the paper [21], obtaining the coefficient will allow us to improve the description of the initial phase of tumor growth. Section 4 shows an application of the modified model obtained following the paper [21], when the immune system can control the cancer cells, and in the contrary case. Section 5 shows a comparison between the two models, when the immune system can control the cancer cells, and the contrary case.

The reader interested to understood more on the biology of cancer is addressed to the fundamental book of Weinberg, and specifically [15, chapter 11], devoted to the immune competition.

2. **Kuznetsov Model**

In the model for the regrowth of cancer proposed by Kuznetsov, is supposed that the encounters of killer cells with cancer cells cause:

1) suppression of tumor cells,

2) suppression or deactivation of the killer cells. By putting:

- $c = c(t)$ is the number of cancer cells at time t, measured in units of one million cells.
- $e = e(t)$ is the number of cytokines killers at time t, measured in units of one million cells.

The law that regulates the growth of the tumor population is given by the differential system:

$$\begin{cases} \dfrac{dc}{dt}(t) = k \cdot c(t)\,[1 - b \cdot c(t)] - a \cdot p \cdot e(t)\, c(t) \\ \dfrac{de}{dt}(t) = r + \left[\dfrac{\nu \cdot c(t)}{g + c(t)}\right] e(t) - d \cdot e(t) - a(1-p)c(t)e(t), \end{cases} \tag{1}$$

where

- $kc\,[1 - bc]$ =is the intrinsic rate of tumor cell growth;
- k =maximum rate of tumor growth, when $b = 0$, the tumor grows at a rate k;
- b =reciprocal of the maximum number of cells in the cell population i.e. $1/b$ =(maximum number of tumor cells permitted to arise)/10^6;
- p =is the probability that a tumor cell bound with a killer cells will be destroyed;
- a = is defined so that $a(1-p)$ is the rate of destruction of natural killer cells (after the encounter with tumor cells);
- ap =rate of destruction of tumor cells after encounter with a killer cell, is the constant "kinetic" which when multiplied by e and c forms the rate of destruction of the entire tumor;
- $a \cdot p \cdot e(t)\, c(t)$ =rate of destruction of tumor cells.

The rate of population growth killer (which varies in size when they are attracted new killer cells for the presence of cancer) is described by the second differential equation of system (1) where

- r =parameter that indicates the base number of killer cells, $\Rightarrow r = e_0 d$;
- $e_0 = 0,3$ million cells;
- d =natural rate of death of killer cells;
- $\dfrac{\nu c(t)}{g + c(t)}$ = logistic growth rate;
- ν = maximum rate of the logistic growth of the population killer, due to the tumor growth;
- u =amount of time it takes for the immune response before the new killer cells can attack the tumor;
- g =parameter g is the mid-point logistic parameter;
- $a(1-p)ce$ =killer-cell death or inactivation due to the induced by the tumor.

This model as already mentioned, is developed at a super-macroscopic scale. It is applied to the experimental data known in the literature related to tumor growth in mice used as test subjects. To evaluate the numerical values that define the tumor growth we have considered mice with an initial tumor of 0.5 million cells, not under the control of the immune system and therefore free to grow. While we applied this model in mice with an initial 0.5 million cancer cells under the control of the immune system.

From the results we have [6]:

Numerical Values	
$d = 0.591$	$a = 0.138$
$u = 28.054$	$k = 0.188$
$v = 0.524$	$b = 0.002$
$p = 0.998$	$g = 0.160$

With these parameter values and given as initial conditions:

$$c(0) = 0.5;\ e(0) = 0.3. \tag{2}$$

We have that tumor growth is suppressed and enter into a dormant state of equilibrium, apparently stable. Now we vary the value of the parameter p. From $p = 0.998$

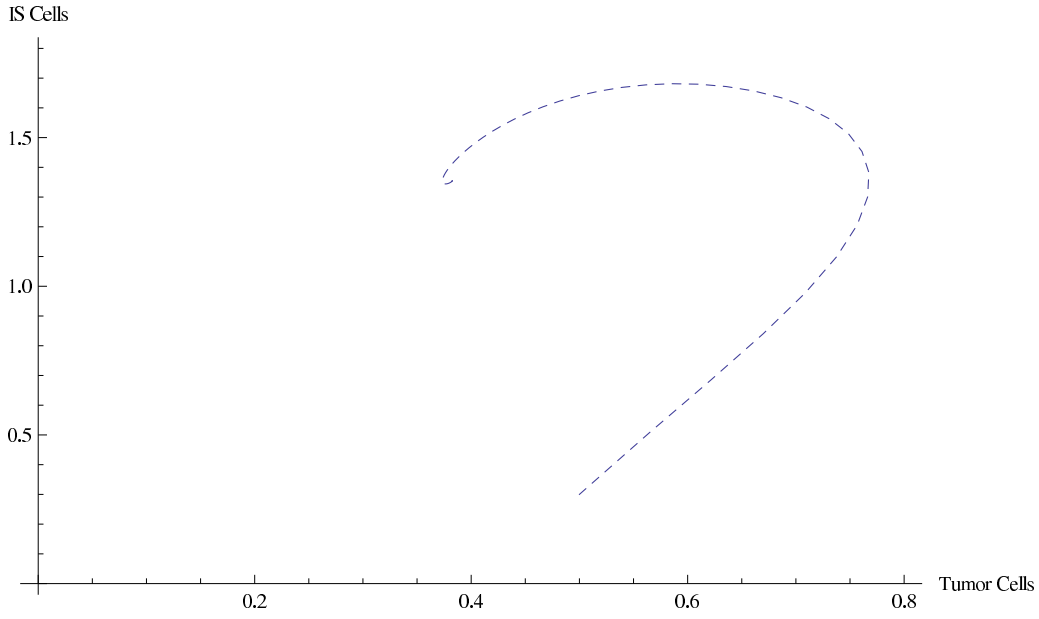

FIGURE 1. Phase diagram of the original model with $p = 0.998$

to $p = 0.498$ keeping the same initial conditions (2). We immediately notice that a small decrease in immune response means that the tumor grows in an uncontrollable way: as shown in Figure 2. This result indicates that a modest decrease in the immune response effectiveness, corresponding to a small increase in the proportion $1-p$ of killer lymphocytes being inactivated by tumor cells, dramatically changes the outcome of the disease: from a stable evolution (Figure 1) to an unstable evolution (Figure 2).

Note also that this phenomenon of re-growth there is also after a appropriate change of the parameters v,d,k, while there are no appreciable changes by varying the parameter g. Therefore, this model suggests that the regrowth of a dormant state may be associated with a decreased activity of the immune system, caused by multiple mechanisms.

3. **The Kuznetsov Model Revised by Cattani-Ciancio**

Since the parameters of the differential system do not depend on time and on the quantity of the cells, we can see that it is not suitable for describing the evolution of the competition between two species. To analyze the more realistic case, in which it is supposed that the learning ability of the both cell populations is the same, in the initial phase, with aim to tend to two different values during the evolution of the system, we must take into account that each cell population evolves in a different way and as consequence develops the capacity to avoid or to destroy another specie

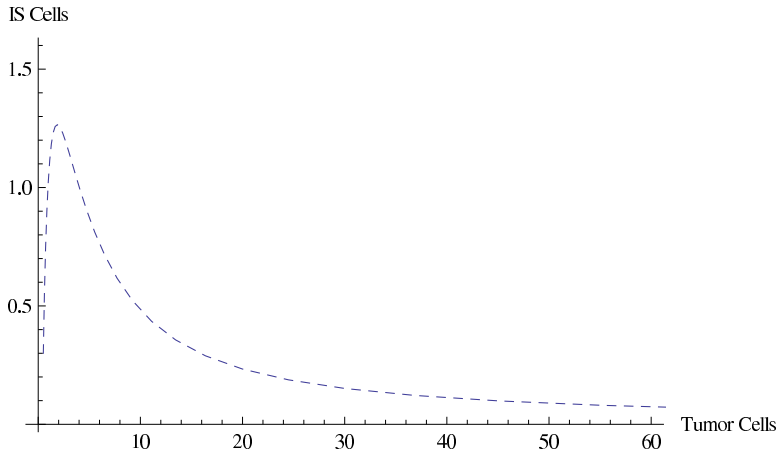

FIGURE 2. Phase diagram of the original model with $p = 0.498$

with different speed (generally, malignant cells develop the ability to hide from the immune system cells more quickly than the latter become able to locate and destroy the first).

To overcome this limitation following the work of [21]. Let us consider a system of two interacting and competing populations. Each population is constituted by a large number of individuals called active particles, and their microscopic state is called (biological) activity, as described in [7]−[12]. This activity enables the particle to organize a suitable response with respect to any information process. In absence of the external information, the activity reduces either to a minimal loss of energy or to a random process.

In active particle competitions the simplest model of binary interaction is based on proliferation-destructive competition. That is when, one of the population gets aware of the presence of the other competing population starting to proliferate and to destroy the competing cells. However, in this process an important step is the ability of the first population cells (tumor cells) to hide themselves from the second population cells (cells of the immune system), which tends to evolve with the aim to identify and to destroy the extraneous cells.

In details consider a physical system of two interacting populations each one constituted by a large number of active particles with sizes

$$n_i = n_i(t), (n_i(t) : [0, T] \to \mathbb{R}_+), \tag{3}$$

for $i = 1, 2$.

Particles are homogeneously distributed in space, while each population is characterized by a microscopic state, called activity, denoted by the variable u. The physical meaning of the microscopic state may differ for each population. We assume that the competition model depends on the activity by a function of the overall distribution

$$\mu = \mu [f_i(t, u)], (\mu [f_i(t, u)] : \mathbb{R}_+ \to \mathbb{R}_+) \tag{4}$$

such that $f_i(t,u)du$ denotes the number of particles of the i-th population, at the time t, that are in the interval $[u, u+du]$. Moreover,

$$\forall i, \forall t \geq 0 : 0 \leq f_i(t,u) \leq 1, \int_{D_u} f_i(t,u)du = 1. \tag{5}$$

Let

- G_i, $i = 1,2$ be a function of $n = n_1, n_2$;
- μ acts over $f = (f_1, f_2)$;
- A_i be a nonlinear operator acting on f;
- $\mu[f]$ be a functional $(0 \leq \mu \leq 1)$ which describes the ability of the second population to identify the first one.

The analysis developed in what follows is referring to a specific case where the second population attempts to learn about the first population which, instead, escapes by modifying its appearance. Specifically, the hybrid evolution equations can be formally written

$$\begin{cases} \dfrac{dn_i}{dt} = G_i\left(n_1, n_2; \mu[f]\right) \\ \\ \dfrac{\partial f_i}{\partial t} = A_i[f]. \end{cases} \tag{6}$$

As a consequence, (6) denotes a hybrid system of a deterministic system coupled with a microscopic system statistically described by a kinetic theory approach. In the following, the evolution of density distribution will be taken within the kinetic theory. The derivation of $(6)_2$ can be obtained starting from a detailed analysis of microscopic interactions. Specifically, consider binary interactions between a test, or candidate, particle with state u_* belonging to the $i-th$ population, and field particle with state u. belonging to the $j-th$ population. We assume that microscopic interactions are characterized by the following quantities:

- The encounter rate, which depends, for each pair of interacting populations on a suitable average of the relative velocity η_{ij}, with $i,j = 1,2$.
- The transition density function $\varphi_{ij}(u_*, u^*, u)$, denotes the probability density that a candidate particle with activity u_* belonging to the $i-th$ population, falls into the state $u \in D_u$, of the test particle, after an interaction with a field entity, belonging to the $j-th$ population, with state u^*. The probability density $\varphi_{ij}(u_*, u^*, u)$ fulfills the condition

$$\forall i,j, \forall u^*, u_* : \varphi_{ij}(u^*, u_*, u) > 0, \int_{D_u} \varphi_{ij}(u^*, u_*, u)\, du = 1.$$

Then, by using the mathematical approach, developed in [17], it yields the following class of evolution equations (for similar equations, see also [28])

$$\begin{aligned} \frac{\partial f_i}{\partial t}(t,u) = &\sum_{j=1}^{2} \int_{D_u \times D_u} \varphi_{ij}(u^*, u_*, u)\, f_i(t,u_*) f_j(t,u^*) du_* du^* \\ &- f_i(t,u) \sum_{j=1}^{2} \int_{D_u} \eta_{ij} f_i(t,u_*) du^* \end{aligned} \tag{7}$$

which can be formally written as $(6)_2$.

Since our model is based on the hiding-learning dynamics, one has to introduce the functional which takes into account the "distance" between the two distribution so that μ in (6) is defined as:

$$\mu\left[f_i, f_j\right](t) = \mu\left|f_i - f_j\right|(t) = 1 - \int_{D_u} \left(f_1 - f_2\right)^2 (t,u)du. \tag{8}$$

Notice that μ is the coupling term which links the macroscopic model $(6)_1$ to the microscopic model $(6)_2$.

In order to find some classes of solutions of (7), we assume that the transition density is the product of separable density functions

$$\varphi_{ij}\left(u^*, u_*, u\right) = (1 - \delta_{ij})\psi_i(u_*, u)\xi_i(u^*, u). \tag{9}$$

As an example, let us solve this system under the following hypotheses:

$$\psi_1(u_*, u) = \psi_2(u_*, u) = \delta(u - u_*), \xi_1(u^*, u) = \xi_2(u^*, u)\delta(u - u^*). \tag{10}$$

The system (7), by using $(9) - (10)$, becomes

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = \eta_{12} f_1 f_2 - \left(\eta_{11} + \eta_{12}\right) f_1 \\ \\ \dfrac{\partial f_2}{\partial t}(t,u) = \eta_{21} f_1 f_2 - \left(\eta_{21} + \eta_{22}\right) f_2. \end{cases} \tag{11}$$

Moreover, by assuming that

$$\eta_{11} = \eta_{12} = \eta_{21} = \eta_{22} = \eta \tag{12}$$

and putting

$$f(t,u) = f_1(t,u) - f_2(t,u) \tag{13}$$

from (11), one has

$$\frac{\partial f}{\partial t}(t,u) = -2\eta f(t,u). \tag{14}$$

The general solution of this equation is

$$f(t,u) = f(0,u)e^{-2\eta t}. \tag{15}$$

Assuming that

$$f(0,u) = \frac{1}{\sqrt{\eta}} e^{-u^2} \tag{16}$$

eq. (14) becomes

$$f(t,u) = \frac{1}{\sqrt{\eta}} e^{-(u^2 + 2\eta t)}. \tag{17}$$

And then from (8), by virtue of (13) and (17) we get the following time-dependent parameter, which takes into account the ability of competition of two species cellular (fig 3):

$$\mu(t) = 1 - \frac{e^{-4\eta t}}{\sqrt{2}}. \tag{18}$$

As can be seen this coefficient tends to 1 for a long time and therefore has no significant effect on the model, thus returning the classic model of Kuznetsov, which supposes that two populations have different learning abilities. So this coefficient is very useful to describe the evolution of competition from the initial moments, until

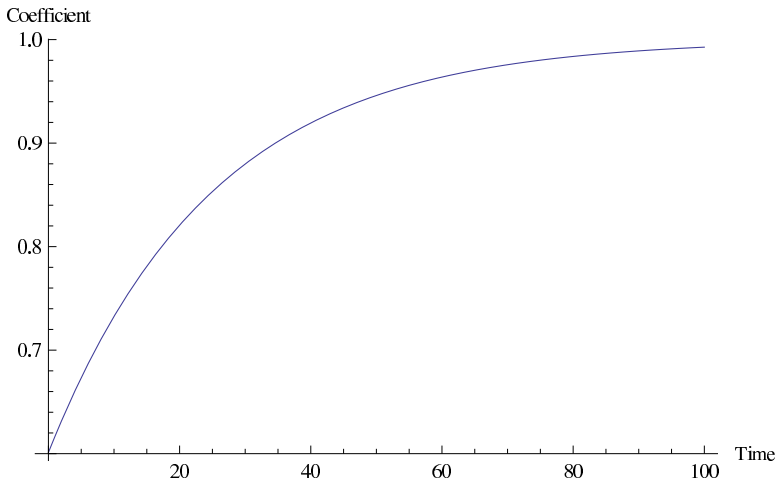

FIGURE 3. Coefficient (18)

a long time since that time has little influence on the model and describes well the initial transitional period, before to fading with increasing time. The classical model describes the evolution ignoring the initial phase.

We are able to describe the evolution of the phenomenon from the initial moment up to long periods.

4. **Model with Modified Coefficient**

By changing the model just seen, taking into account also the phenomena from the microscopic point of view, and then inserting the coefficient of the model obtained by [21], we obtain the hybrid system

$$\begin{cases} c^{'}(t) = kc(t)\left[1 - bc(t)\right] - ap\left[1 - \dfrac{e^{-4\eta t}}{\sqrt{2}}\right] e(t)\, c(t) \\ \\ e^{'}(t) = r + \left[\dfrac{\nu c(t)}{g + c(t)}\right] e(t) - de(t) - a\left(1 - p\left[1 - \dfrac{e^{-4\eta t}}{\sqrt{2}}\right]\right) c(t)e(t). \end{cases} \tag{19}$$

With this model the phenomenon description improves significantly as we can see from the following phase diagrams of figure 4. This diagram was obtained from the same initial conditions and the same values of the parameters of the first diagram shown above.

We see that initially the cancer cells grow slightly as being controlled by lymphocytes in that phase, which grow rapidly because of the presence of extraneous cells. While as time passes the immune system collapses so the tumor can grow in an uncontested way as it is shown in Figure 5.

5. **Comparison between Two Models**

Now we compare the phase diagrams for the two different models, first for the stable case where $p = 0.998$ and then the unstable case where $p = 0.498$

- Case 1: $p = 0.998$.

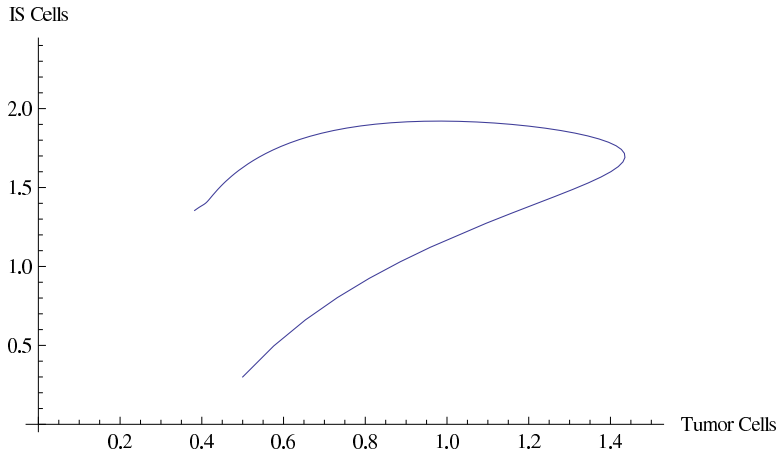

FIGURE 4. Phase diagram of the modified model with $p = 0.998$

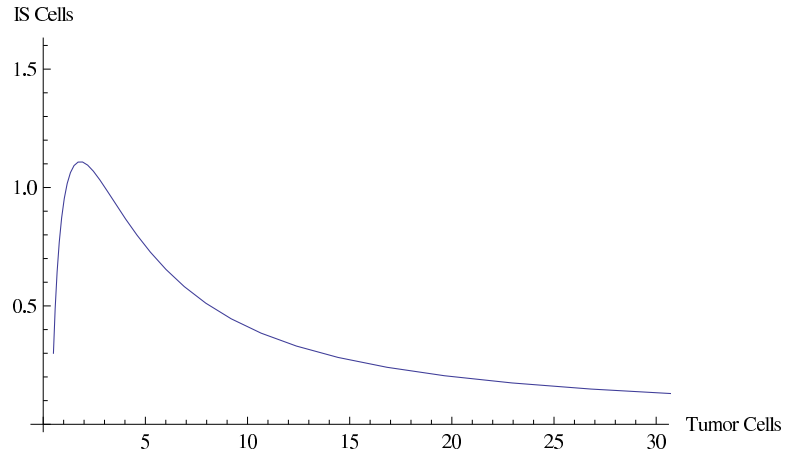

FIGURE 5. Phase diagram of the modified model with $p = 0.498$

With this value of p we obtain the following phase diagrams that we plot simultaneously: In this graph, the dashed line represents the phase diagram of the original system proposed by Kuznetsov, in which the two species are supposed to result already evolved, that means that we have already passed the phase "Hiding- Learning". So in this case the cells of the immune system have already developed the technique of identifying and destroying the tumor cells. For this reason we notice that these tumors grow slowly being destroyed by lymphocyte. While the solid line demonstrates the evolution of the Kuznetsov's model modified thanks to the coefficient described above. Certainly the initial point and the final one are the same because for $t = 0$ we have the same initial conditions, while for $t \to \infty$ the coefficient tends to one and thus provides no longer a significant contribution.

But the important result is found in the description of this evolution, because it illustrates the fact that initially the immune system is not able to identify and to destroy tumor cells. Comparing the two graphs we note in fact that for the same number of the cells (y axis), the solid line shows much more cancer cells than

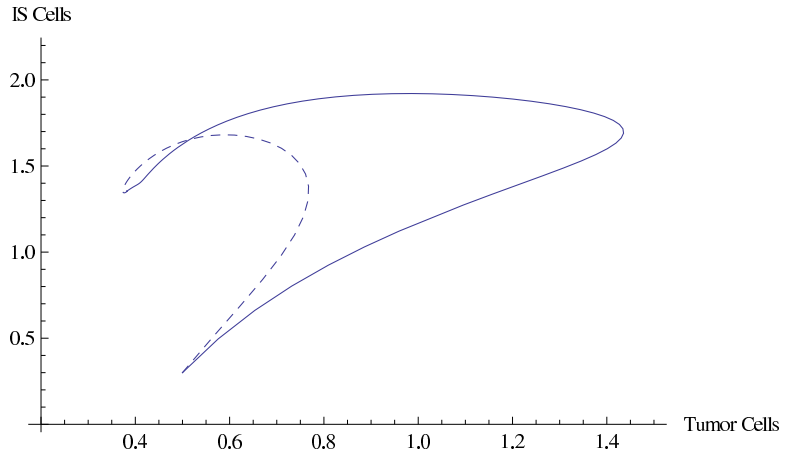

FIGURE 6. Phase diagram of the two models with $p = 0.998$ dashed line = Original Model , solid line = Modified Model

the dashed one, this is because the cancer in its early stage is not detected by the immune system and therefore can grow in a way less contrasted than when it is supposed that already at time $t = 0$ immune cells are capable to destroy tumor cells (original model, dashed line).

- Case 2: $p = 0.498$.

With this value of p we obtain the following phase diagrams that we plot simultaneously: Where the dashed line represents the phase diagram of the original model,

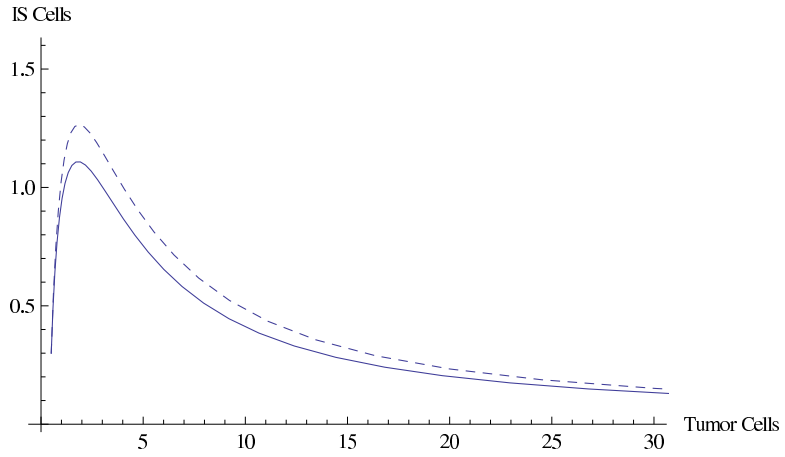

FIGURE 7. Phase diagram of the two models with $p = 0.498$ solid line = Modified Model, dashed line = Original Model

while the solid one concerns the model modified by the coefficient. We see that in this case the trend of the two curves is the same as well as the initial point and the point toward which both curves tend for $t \to \infty$ are the same, but once again we have a better description of the evolution of the system.

We note, in fact, that the curve for the original model shows a greater increase in lymphocytes, already from the earliest moments of the evolution of the tumor, as if the body had the innate ability to identify malignant cells reacting with an increased production of antibodies. But it is more realistic to think that the body does not have this ability and therefore (see solid line) initially reacts with a lower production of lymphocytes. While as time goes on the behavior of the two graphs in effect is the same, as during more prolonged periods both of them take in account the evolution of the both species.

REFERENCES

[1] J. W. Uhr, R. H. Scheuermann, N. E. Street and E. S. Vitetta, "Cancer dormancy: Opportunities for new therapeutic approaches", Nature Med. 3, 505−509, (1997).

[2] E. S. Vitetta, T. F. Tucker, E. Racila, Y. W. Huang, R. Marches, N. Lane. R. H. Scheuermann. N. E. Street. T. Watanabe and J. W. Uhr, "Tumor dormancy and cell signalling. V. Regrowth of the BC:Ll tumor after dormancy is established". Blood 89. 4425−4436. (1997).

[3] V. A. Kuznetsov, G. D. Knott, "Modeling tumor regrowth and immunotherapy", Math. Comp. Mod., 33 (2001) 1275−1287.

[4] V. A. Kuznetsov, "A mathematical model for the interaction between cytotoxic T lymphocytes and tumor cells. Analysis of the growth. stabilization, and regression of a B-cell lymphoma in mice chimcric with respect to the major histocompatibility complex", Biomedical Science 2, 465−476. (1991).

[5] V. A. Kuznetsov, I. A. Makalkin. M. A. Taylor and A. S. Perelson. "Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis", 8 11. Math. Biol. 56, 95−119, (1994).

[6] H. Sui, E. S. Vitetta, R. D. May and J.W. Uhr, "Tumor dormancy I: Regression of BCLi tumor and induction of a dormant tumor state in mice chimeric at the major histocompatibility complex", J. Immunol. 137, 1376−138. (1986).

[7] N. Bellomo, A. Bellouquid, M. Delitala, "Mathematical Topics on the Modelling Complex Multicellular Systems and Tumor Immune Cells Competition", Math. Mod. Meth. Appl. Sci., 14 (2004) 1683−1733.

[8] N. Bellomo, G. Forni, "Looking for new paradigms towards a biological-mathematical theory of Complex Multicellular Systems", Math. Mod. Meth. Appl. Sci., 16, (2006). 1001−1029.

[9] N. Bellomo, A. Bellouquid, "On the onset of nonlinearity for diffusion models of binary mixtures of biological materials by asymptotic analysis", Int. J. Nonlinear Mechanics, (2006), 41, (2006) 281−293.

[10] N. Bellomo, A. Bellouquid, J. Nieto, J. Soler, "Multicellular biological growing systems - Hyperbolic limits towards macroscopic description", Mathematical Models and Methods in Applied Sciences, 17, (2007).

[11] N. Bellomo, N. Delitala, "From the mathematical kinetic, and stochastic game theory to modelling mutations, onset, progression and immune competition of cancer cells", Phys Life Rev. 5, 6, (2008) 183−206.

[12] N. Bellomo, "Modeling complex living systems - Kinetic theory and stochastic game approach", Birkhaeuser - Springer, Boston, 2008.

[13] M. Lachowicz, A. Quartarone, A general framework for modeling tumor immune system competition at the mesoscopic level, Appl. Math. Letters 25, 2118 2122 (2012).

[14] M. Lachowicz, A. Quartarone, T.V. Ryabukha, Stability of the solutions of the mesoscopic equation that corresponds to the replicator equation, Kinetic and Related Models, to appear.

[15] Weinberg RA. "The biology of cancer" New York: Garland Sciences, Taylor and Francis 2007.

[16] C. Cattani, A. Ciancio, B. Lods, "On a Mathematical Model of Immune Competition", Applied Mathematics Letters, 19, 7 (2006), 686−691.

[17] C. Cattani, A. Ciancio, "Hybrid Two Scales Mathematical Tools for Active Particles Modelling Complex Systems with Learning Hiding Dynamics", Mathematical Modelling and Methods in Applied Sciences 17 (2007) 171−187.

[18] C. Cattani, A. Ciancio, "Third Order Model for Tumor-Immune System Competition", Proc. of the 4-th International Colloquium Mathematics in Engineering and Numerical Physics, October 6-8, 2006, Bucharest (Ro), (2007) 30−37.
[19] C. Cattani, A. Ciancio, "Qualitative Analysis of Second Order Models of Tumor-Immune System Competition", Mathematical and Computer Modelling, 47, (2008), 1339−1355.
[20] C. Cattani, A. Ciancio, A. d'Onofrio, "Metamodeling the learning-hiding competition between tumours and the immune system: A kinematic approach", Mathematical and Computer Modelling, 52, (2010), 62−69.
[21] C. Cattani, A. Ciancio, "Separable transition density in the hybrid model for tumor-immune competition" Hindawi Publishing Corporation, Computational and Mathematical Methods in Medicine, Volume 2012, Article ID 610124, 6 pages, doi:10.1155/2012/610124.
[22] A. d'Onofrio, "A general framework for modeling tumor-immune system competition and immunotherapy". Mathematical analysis and biomedical inferences, Phys. D 208 (2005) 220−235.
[23] A. d'Onofrio, "Tumor-immune system interaction: modelimg the tumor-stimulated proliferation of effectors and immunotherapy", Math. Mod. Meth. Appl. Sci., 16, (2006) 1375−1401.
[24] A. d'Onofrio, "Tumor evasion from immune system control: strategies of a MISS to become a MASS", Chaos solitons and Fractal, 31, (2007), 261−268.
[25] A. d'Onofrio, "Metamodelling tumor-immune system interaction, tumor, evasion and immunotherapy", Math Comp Modelling, 47, (2008), 614−637.
[26] N. V. Stepanova, "Course of the immune reaction during the development of a malignant tumor", Biophysics, 24 (1980) 917−923.
[27] Y. Tao, H. Zang , "A parabolic-hyperbolic free boundary problem modeling tumor treatment with virus", Mathematical Models and Methods in Applied Sciences, 17, (2007) 63−80.
[28] V. Catană , "The heat equation for the generalized Hermite and the generalized Landau operators", Integr. Equ. Oper. Theory, 66, (2010) 41−52.