Reduction of Dimensionality of a Dynamical Model of Aggressive Tumor Treated by Chemotherapy, Immunotherapy and siRNA Infusion. Part II. Application of the Tichonov’s Theorem

Nikolova E.

Institute of Mechanics and Biomechanics
Bulgarian Academy of Sciences
4 Acad. G. Bonchev Str., 1113 Sofia, Bulgaria
E-mails: elena@ibmb.bas.bg

Summary: The well-known Tichonov’s theorem for a quasi-steady state approximation is applied to a dynamical model of aggressive tumor treated by chemotherapy, immunotherapy and siRNA infusion. On the basis of this theorem the complete model, represented as a system of seven nonlinear ordinary differential equations, is reduced to a degenerate one, comprising only four ordinary differential equations. By qualitative analysis, it is established, that two of equations of the degenerate model, conjugated to form a two-dimensional dynamic system, are independent of the equation, representing dynamics of the tumor evolution. In addition the other variable, expressing siRNA drug dynamics is also determined as a independent one-dimensional system in the quasi-stationary model. In this way, the interaction between NK cells and a chemotherapy drug, and the siRNA infusion drug are identified to play a role of a drivers for the quasi-stationary behaviour of the tumor progress.

Keywords: Aggressive tumor, Combination of drug therapies, Tichonov’s theorem, Quasi-stationary approximation, Qualitative analysis

1. INTRODUCTION

It is well-known, that the concept of Michaelis-Menten kinetics is effectively used to model biological realities of tumors [1, 2]. The models constructed by this concept present nonlinear systems of autonomous ordinary differential equations. However, the complexity of these systems under consideration and the difficulties in generating experimental data requires search of other approaches in order to investigate their dynamics in details. Recently the reduction of dimensionality of such models is widely applied method for their simplification, including the area of cell biology too [3]. Exact relations are used for such a reduction, like conservation laws and different approximations [4, 5]. The reduction of dimensionality...
of the mathematical models, representing the biological events, helps us to receive information for their dynamical behaviour at the stationary stage. For instance, in [6-8] it is shown, that the stationary state of ERK signalling pathway, which is regulated by RKIP has private dynamical features, which were not observed at its initial stage. By analogy with the investigations, made in [8] the aim of this paper is to show how considerations of time hierarchy in tumor evolution allows us to reduce the number of differential equations of the mathematical model, representing the aggressive tumor process treated by combination of three therapies and to get additional information for the its quasi-stationary behaviour.

2. APPLYING OF TICHONOV’S THEOREM ON THE DYNAMICAL MODEL OF AGGRESSIVE TUMOR TREATED BY COMBINATION OF THREE THERAPIES

In [9] the scaling form of the model of aggressive tumor treated by chemotherapy, immunotherapy and siRNA infusion is presented by the following system ordinary differential equations:

\[
\frac{d\tau}{dt} = k_1\tau - \varepsilon^2 k_2\tau n - \varepsilon^4 k_3\tau l - \varepsilon^3 k_4\tau m + \varepsilon^5 k_5 r\tau
\]

\[
\frac{dn}{dt} = \varepsilon k_6 - \varepsilon k_7 n - \varepsilon^3 k_8 nm
\]

\[
\varepsilon^2 \frac{dl}{dt} = -\varepsilon^3 k_9 l - \varepsilon^5 k_{10} l m + \varepsilon^4 k_{11} l i + k_{12}
\]

\[
\varepsilon^6 \frac{dr}{dt} = k_{13}\tau - \varepsilon^6 k_{14} r - \varepsilon^9 k_{15} r s
\]

\[
\frac{dm}{dt} = -k_{16} m + d_m
\]

\[
\varepsilon^5 \frac{di}{dt} = -\varepsilon^5 k_{17} i + d_f - \varepsilon^9 k_{18} i r
\]

\[
\frac{ds}{dt} = \varepsilon d_s - k_{19} s
\]

where \(\tau, n, l, r, m, i\) and \(s\) are the scaling forms of state variables presenting dynamics of the tumor cell population, the total NK cell effectiveness, the total CD8 + T cell effectiveness, the total TGF - \(\beta\)
cytokines production, the chemotherapy drug concentration, the immunotherapy (IL-2) drug concentration and the cytoplasmic free siRNA concentration, respectively, and \( k_1 - k_{10} \) are rate constants (parameters) of the model. Moreover, the constant doses of chemotherapy, immunotherapy and siRNAs drugs are denoted by \( d_m, d_i \) and \( d_s \), respectively. In accordance with Tichonov’s terminology, presented in [9, 10], the presence of a small parameter \( \varepsilon \) in every term of this system determines its order. On the base of this terminology, in [9] the equations (2.3), (2.4) and (2.6) of the above given system, having \( \varepsilon \) in the numerator are determined to form an attached system, i.e. the variables \( l, r \) and \( i \) are fast varying with respect to the variables \( \tau, n, m \) and \( s \), considered as slow varying ones. The four equations, representing dynamics of the slow system components are considered as a degenerate system. Moreover, the last ones play a driving role with respect to the three subordinated fast variables. Next, in accordance with Tichonov’s conditions we will consider the attached system under condition that only the variables \( l, r \) and \( i \) are unknown functions of time. The system has stationary (steady state) solution in the form:

\[
\begin{align*}
  l^0 &= \frac{k_{12} (\varepsilon^4 k_{14} k_{17} + \varepsilon^6 k_{15} k_{17} s + \varepsilon^7 k_{16} k_{18} \tau)}{\varepsilon k_9 + \varepsilon^5 m - \varepsilon^4 k_{11} k_{17} d_i - \varepsilon^7 k_{11} k_{15} d_i s} > 0 \\
  r^0 &= \frac{k_{13} \tau}{\varepsilon^6 k_{14} + \varepsilon^9 k_{15} s} > 0 \\
  i^0 &= \frac{d_i (k_{17} + \varepsilon^3 k_{18} s)}{\varepsilon^4 k_{14} k_{17} + \varepsilon^5 k_{15} k_{17} s + \varepsilon^7 k_{13} k_{18} \tau} > 0
\end{align*}
\]  

(2.8)

In order to analyze the stability of the steady state (2.8) we introduce the substitutions

\[
l = l^0 + \lambda; \quad r = r^0 + \rho; \quad i = i^0 + j
\]

(2.9)

in the attached system of equations (2.3), (2.4) and (2.6) As a result we obtain the variation equations

\[
\frac{d\lambda}{dt} = -\varepsilon k_9 \lambda - \varepsilon^3 k_{10} m \lambda + \varepsilon^2 k_{11} i^0 \lambda + \varepsilon^2 k_{11} i^0 j
\]

(2.10)
\[
\frac{d\rho}{dt} = -k_{14}\rho - \varepsilon^3 k_{15}\rho
\]
\[
\frac{dj}{dt} = -k_{17}j - \varepsilon^4 k_{18}r^0 - \varepsilon^4 k_{18}i^0 \rho
\]

The corresponding characteristic equation has the form:
\[
\begin{vmatrix}
-\varepsilon k_y - \varepsilon^3 k_{10}m + \varepsilon^2 k_{11}i^0 - \mu & 0 & \varepsilon^2 k_{11} l^0 \\
0 & -k_{14} - \varepsilon^3 k_{15} - \mu & 0 \\
0 & -\varepsilon^4 k_{14} l^0 & -k_{17} - \varepsilon^4 k_{18} r^0
\end{vmatrix} = 0
\]
(2.13)

and its solution can be written in the following manner:
\[
\mu^3 + p\mu^2 + q\mu + u = 0
\]
(2.14)

where

\[
p = \varepsilon k_y + \varepsilon^3 k_{10}m - \varepsilon^2 k_{11}i^0 + k_{14} + \varepsilon^3 k_{15} + k_{17} + \varepsilon^4 k_{18} r^0
\]
\[
q = (\varepsilon k_y + \varepsilon^3 k_{10}m - \varepsilon^2 k_{11}i^0)(k_{14} + \varepsilon^3 k_{15} + k_{17} + \varepsilon^4 k_{18} r^0) +
+ (k_{14} + \varepsilon^3 k_{15})(k_{17} + \varepsilon^4 k_{18} r^0)
\]
\[
u = (\varepsilon k_y + \varepsilon^3 k_{10}m - \varepsilon^2 k_{11}i^0)(k_{14} + \varepsilon^3 k_{15})(k_{17} + \varepsilon^4 k_{18} r^0)
\]
(2.15)

The coefficients \(p, q\) and \(u\) have positive values, in view of the fact that inequality
\[
\varepsilon k_y > \varepsilon^2 k_{11}i^0
\]
(2.16)
is numerically verified. In accordance with Routh–Hurwitz criterion, this means, that the equilibrium state (2.8) is stable. The last fact allow us to apply the Tichonov’s theorem. Next, by substituting the formulas (2.8) in the equations (2.1), (2.2), (2.5) and (2.7) the following quasi-stationary approximation of the model is derived:

\[
\frac{d\tau}{dt} = A\tau^2 + B\tau \\
\frac{dn}{dt} = \varepsilon k_6 - \varepsilon k_5 n - \varepsilon^3 k_8 nm \\
\frac{dm}{dt} = -k_{16} m + d_m \\
\frac{ds}{dt} = \alpha d_s - k_{19} s
\]

where

\[
A = \frac{\varepsilon^3 k_4 k_{13}}{k_{14} + \varepsilon^3 k_{15}} - \frac{\varepsilon^6 k_3 k_{12} k_{13} k_{18}}{k_9 - \varepsilon^4 k_{16} m - \varepsilon^3 k_{17} d_s (k_{17} + \varepsilon^3 k_{15} s)}
\]

\[
B = k_1 - \varepsilon^2 k_2 n - \varepsilon^3 k_4 m - \frac{\varepsilon^3 k_i k_{12} (\varepsilon^4 k_i k_{17} + \varepsilon^3 k_i k_{17} s)}{k_9 - \varepsilon^4 k_{16} m - \varepsilon^3 k_{17} d_s (k_{17} + \varepsilon^3 k_{15} s)}
\]

It is seen that the variables \(n, m\) and \(s\) take part in the expressions (2.21). Moreover, we must note that the last expressions have a very complicated analytical form, but their numerical form is very simpler in view of the fact that there are numerical values of the coefficients \(k_i\) (\(i = 1, 2, \ldots, 19\)). It is obvious, that the quasi-stationary system (2.17-2.20) will hold in some later (post-initial) period from the beginning of the considered process. This is in view of fact, that the complete system (2.1-2.7) takes a finite time in order to establish the assumed quasi-steady state. The numerical simulations of solutions of the complete and reduced systems show that the coincidence between both systems will observe after the 300-th day from beginning of the tumor evolution.
3. A CONSEQUENCE OF THE QUASI-STATIONARY SYSTEM ON THE TUMOR DYNAMICAL BEHAVIOUR

In this section we will demonstrate the advantages from the made quasi-steady state approximation for understanding of the main reaction mechanism in aggressive tumor treated by combination of three therapies in details. Here we pay attention to qualitative features of the system (2.17-2.20). It is seen that the equations (2.18) and (2.19) of the reduced system are independent of the other two and are conjugated to form a two-dimensional system. The variable $\tau$ is only dependent on these variables, which variation equations can be written, as it follows:

$$\frac{d\eta}{dt} = -\epsilon^3 k_8 m^0 \eta - \epsilon^3 k_8 n^0 \sigma$$
$$\frac{d\sigma}{dt} = -k_{16} \sigma$$

where $\eta$ and $\sigma$ are small perturbations about the stationary state $(n^0, m^0)$. In order to concretize the type of behaviour of (3.1-3.2) we should calculate the coefficients of the Routh-Hurwitz conditions

$$p_1 = k_{16} + \epsilon^3 k_8 m^0 > 0;$$
$$q_1 = \epsilon^3 k_{16} (k_7 + \epsilon^3 k_8 m^0) > 0$$

As it is well known from the standard theory, the positive signs of $p_1$ and $q_1$ determine the stable character of the stationary state $(n^0, m^0)$. This means, that we can consider the interaction between the NK cells and the chemotherapy drug as a driver in quasi-stationary approximation (2.17-2.20). In addition, the variable $s$ is also independent from the other components of the model (2.17-2.20) and forms a independent one-component system, which variation equation can be expressed in the form:

$$\frac{d\chi}{dt} = -k_{19} \chi$$
where \( \chi \) is a small variation about the stationary state \( s^0 \). It is seen, that the variation \( \chi \) tends asymptotically to zero. This means, that the stationary state of \( s \) has a stable character. In this way, it appears to be a second driver in quasi-stationary approximation (2.17-2.20).

4. CONCLUSION

In this paper it is shown that the consideration of time hierarchy in the dynamical model of aggressive tumor treated by combination of three types of therapies allows us to reduce the number of its differential equations and determine the driving reactions in the tumor dynamics. For this purpose the Tichonov’s theorem for the quasi-stationary approximation (the expression of the equilibrium values of fast varying variables by the slow- varying ones) is applied. The qualitative analysis of the reduced system is carried out. As a result of that, the two-component interaction between the concentrations of NK cells and a chemotherapy drug is identified as a driver of the dynamical behavior of the quasi-stationary tumor progress. In addition, the siRNA influx concentration also plays a driving role for control of the tumor process near its quasi-stationary state.

ACKNOWLEDGMENTS

This work was supported financially by ESF, OP “Human Resources Development”, grant № BG051PO001/07/3.3-02 -55/17.06.2008.

REFERENCES


