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Reduction of Dimensionality of a Dynamical Model of Aggressive Tumor Treated by Chemotherapy, Immunotherapy and siRNA Infusion.
Part I. Establishment of Time Hierarchy in the Model Dynamics

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Summary: The Tichonov's theorem for quasi-stationary approximation is considered as a basic approach for reduction of dynamical systems with time hierarchy. On the basis of previously determined parameters, seven ordinary differential equations of the dynamical model of tumor treated by chemotherapy, immunotherapy and siRNA infusion are written in a form appropriate to evaluate their terms for model reduction. In accordance with the terminology of the Tichonov's theorem, it is established that three of the system components are *fast varying* such that the corresponding kinetic equations form an *attached* system. The other four variables are *slow varying* and their kinetic equations form a *degenerate* system

Keywords: Ordinary differential equations, Reduction of dimensionality, Quasi-stationary Approximation, Tichonov's theorem

1. INTRODUCTION

Mathematical modeling of biological processes with different time scales leads to reduction of the governing equations to a quasi-stationary approximation (QSSA). In this paper, the term QSSA is used in a sense explained in the work of Schneider and Wilhelm [1]. Model reduction based on this approximation has found various applications in systems biology, including studies related to cell proliferation, and differentiation and the cell cycle [2]. The current work presents a more general approach to a QSSA based on the method of Tichonov's theorem proved in [3]. This is a new insight to the theorem and it essence is proposed here together with an elementary description of theorem application. Our aim is to demonstrate that the application of the method in this new form to the problems of tumors can be fruitful. On the other hand, we show that the QSSA theorem proved in the work of Tichonov [3] is very original and consistent from the pure mathematical point of view, but also effective in a computational sense, independently of the widespread time-scale procedure

2. TICHONOV'S THEOREM AS AN APPROACH FOR REDUCTION OF DYNAMICAL SYSTEMS WITH TIME HIERARCHY

Mathematical modeling of biological processes with different time scales leads in general to dynamical system in the form:

$$\varepsilon \frac{d\vec{x}}{dt} = \vec{f}(\vec{x}, \vec{y}) \quad (2.1)$$

$$\frac{d\vec{y}}{dt} = \vec{g}(\vec{x}, \vec{y}) \quad (2.2)$$

where $\vec{x} \in R^m, \vec{y} \in R^n, 0 < \varepsilon << 1$. The Tichonov's theorem [3] claims that

The solution of the **complete** *system (2.1-2) tends to the solution of the* **degenerate** *system (2.2) at* $\varepsilon \to 0$*, if the following conditions are satisfied:*

a) There is an isolated equilibrium (steady state) solution of the **attached** *system (2.1) (i.e. there is not other solution in its neighborhood).*

b) The existing equilibrium solution of the attached system is stable for every value of the **slow** *variables* $\vec{y}$*.*

c) The initial conditions (states) lie in a region of influence (a basin) of the equilibrium solution of the attached system.

d) The solution of the complete system is single-valued and its right hand sides are continuous.

It therefore follows that in every concrete case we can find the equilibrium solution of the attached system and to replace it in the degenerate one. Moreover, we should demonstrate that all requirements of the formulated theorem are satisfied.

Consider in general case the simplest example of two differential equations ($m = 1, n = 1$) or $\vec{x} \equiv x, \vec{y} \equiv y$. Then the system (2.1-2) takes the form

$$\varepsilon \frac{dx}{dt} = f(x, y) \quad (2.3)$$

$$\frac{dy}{dt} = g(x, y) \tag{2.4}$$

The essence of Tichonov's theorem claims that the character of the solution of system (2.3-2.4) does not change when the small parameter ε tends to zero. Thus we can assume $\varepsilon = 0$ in (2.3) and instead of differential equation obtain algebraic ones for the steady state value of fast variable x.

$$0 = f(x, y) \tag{2.5}$$

$$\frac{dy}{dt} = g(x, y) \tag{2.6}$$

From the equation (2.5) the fast variable x can be expressed as a function of y, i.e. $x = \varphi(y)$ and substituted in (2.6). As a result (2.6) becomes

$$\frac{dy}{dt} = g[\varphi(y), y] \tag{2.7}$$

In this way the complete system of two equations (2.3-4) is reduced to the degenerate system of one equation (2.7). Moreover the stationary values of the fast variable x depend only on the current values of the slow variable y, but not on final stationary values. In this sense the variable y plays role of a *driver* of the *subordinated* variabl*e* x.In accordance with the Tichonov's theorem, when the stationary solution of the attached system is isolated and stable, then the solution of the degenerate system depends only on the initial values of the slow variables. Therefore, the presence of a small parameter is a necessary condition of dimensionality *reduction* of the complete system. A preliminary dimensionless procedure is necessary to apply on the corresponding system, however, in order to appear such parameter. The last one expresses rather in *normalization* (or scaling) of the terms in the right hand sides of the systems equations. In this way only ε is considered as a dimensionless parameter, drawing attention also that it has not any physical sense.

3. SCALING OF THE DYNAMICAL MODEL OF AGGRESSIVE TUMOR TREATED BY CHEMOTHERAPY, IMMUNOTHERAPY AND SIRNA INFUSION

We consider the dynamical model of aggressive tumor treated by chemotherapy, immunotherapy and siRNA infusion developed in [4]. The model is presented by the following system of nonlinear differential equations:

$$\frac{dT}{dt} = K_1 T - K_2 TN - K_3 TL - K_4 TM + K_5 RT \quad (3.1)$$

$$\frac{dN}{dt} = K_6 - K_7 N - K_8 NM \quad (3.2)$$

$$\frac{dL}{dt} = -K_9 L - K_{10} LM + K_{11} LI + K_{12} \quad (3.3)$$

$$\frac{dR}{dt} = K_{13} T - K_{14} R - K_{15} RS \quad (3.4)$$

$$\frac{dM}{dt} = -K_{16} M + D_M \quad (3.5)$$

$$\frac{dI}{dt} = -K_{17} I + D_I - K_{18} IR \quad (3.6)$$

$$\frac{dS}{dt} = D_S - K_{19} S \quad (3.7)$$

where T, N, L, R, M, I and S are state variables presenting dynamics of the tumor cell population, the total NK cell effectiveness, the total CD8 + T cell effectiveness, the total TGF-β cytokines production, the chemotherapy drug concentration, the immunotherapy (IL-2) drug concentration and the cytoplasmic free siRNA concentration, respectively, and $K_1 - K_{19}$ 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 [5-10] the following numerical values for system parameters are given:

$$
\begin{aligned}
&K_1 = 0{,}58;\ K_2 = 5{,}2.10^{-10};\ K_3 = 7{,}11.10^{-9};\\
&K_4 = 0{,}62;\ K_5 = 2{,}7.10^{-8};\ K_6 = 0{,}82.10^{4};\\
&K_7 = 5{,}08.10^{-2};\ K_8 = 0{,}53;\ K_9 = 0{,}01;\\
&K_{10} = 0{,}42 : K_{11} = 0{,}28;\ K_{12} = 5{,}2.10^{5};\\
&K_{13} = 3.10^{-4};\ K_{14} = 10;\ K_{15} = 0{,}004;\\
&K_{16} = 0{,}9;\ K_{17} = 10;\ K_{18} = 10^{-3};\ K_{19} = 0{,}66;\\
&D_M = 2.10^{-6} mg/ml \ \ per\, day;\\
&D_I = 5.10^{6} IU/pulse \ \ per\, day;\\
&D_S = 0{,}125.10^{-12} mh/mg \ \ per\ day
\end{aligned}
\tag{3.8}
$$

In addition in [7, 9, 10-13] the following stationary values for state variables are given:

$$
\begin{aligned}
&T^* = 10^8 cells/ml;\ N^* = 10^5 cells/ml;\\
&L^* = 10^2 cells/ml;\ R^* = 10^{-8} mg/ml;\\
&M^* = 3{,}5.10^{-6} mg/ml;\ I^* = 5.10^{-4} mg/ml;\\
&S = 5.10^{-10} mg/ml;
\end{aligned}
\tag{3.9}
$$

On the base of above given numerical values (3.9) for the variables of the considered system (3.1-3.7), analogically to investigations made in [14, 15] we form the following substitutions:

$$
\begin{aligned}
&T = \tau/\varepsilon^4;\ N = n/\varepsilon^3;\ L = l/\varepsilon;\ R = \varepsilon^4 r;\\
&M = \varepsilon^3 m;\ I = \varepsilon^3 i;\ S = \varepsilon^6 s;
\end{aligned}
\tag{3.10}
$$

Here from (3.9) we select the value ε=0.01 to be characteristic dimensionless values of state variables. In this way the new variables τ, n, l, r, m, i and s have an order of 1 (i.e. they change in the interval between 0.1 and 10). This is in accordance with the principle of non-dimensionality. In the same way the coefficients (3.8) can be expressed in the form:

$$
\begin{aligned}
&K_1 = k_1;\ K_2 = \varepsilon^5 k_2;\ K_3 = \varepsilon^5 k_3;\ K_4 = k_4;\ K_5 = \varepsilon^4 k_5;\\
&K_6 = k_6/\varepsilon^2;\ K_7 = \varepsilon k_7;\ K_8 = k_8;\ K_9 = \varepsilon k_9;\ K_{10} = k_{10};\\
&K_{11} = k_{11};\ K_{12} = k_{12}/\varepsilon^3;\ K_{13} = \varepsilon^2 k_{13};\ K_{14} = k_{14};\\
&K_{15} = \varepsilon^2 k_{15};\ K_{16} = k_{16};\ K_{17} = k_{17};\ K_{18} = \varepsilon^2 k_{18};\\
&K_{19} = k_{19};\ D_M = \varepsilon^3 d_M;\ D_I = d_I/\varepsilon^3;\ D_S = \varepsilon^6 d_S;
\end{aligned}
\tag{3.11}
$$

where the new coefficients k_i $(i = 1,2,...,19), d_M, d_I, d_S$ have the same order (i.e. they change in the interval between 0.1 and 10). After replacing (3.10) and (3.11) in (3.1-3.7) we obtain the following system in Tichonov's form

$$\frac{d\tau}{dt} = k_1\tau - \varepsilon^2 k_2 \tau n - \varepsilon^4 k_3 \tau l - \varepsilon^3 k_4 \tau m + \varepsilon^8 k_5 r\tau \tag{3.12}$$

$$\frac{dn}{dt} = \varepsilon k_6 - \varepsilon k_7 n - \varepsilon^3 k_8 nm \tag{3.13}$$

$$\varepsilon^2 \frac{dl}{dt} = -\varepsilon^3 k_9 l - \varepsilon^5 k_{10} lm + \varepsilon^4 k_{11} li + k_{12} \tag{3.14}$$

$$\varepsilon^6 \frac{dr}{dt} = k_{13}\tau - \varepsilon^6 k_{14} r - \varepsilon^9 k_{15} rs \tag{3.15}$$

$$\frac{dm}{dt} = -k_{16} m + d_M \tag{3.16}$$

$$\varepsilon^5 \frac{di}{dt} = -\varepsilon^5 k_{17} i + d_I - -\varepsilon^9 k_{18} ir \tag{3.17}$$

$$\frac{ds}{dt} = \varepsilon d_S - k_{19} s \tag{3.18}$$

The presence of a small parameter ε in every term of this system determines its order. This means in accordance with the terminology of Tichonov's theorem we can say that the equations (3.14), (3.15) and (3.17) form an *attached* system, and the other four form a *degenerate* one. The set of both systems is referred to as the *complete* system. Certainly, Tichonov's theorem can be applied separately to every two groups of equations mentioned. It's worthy to note that the presence of epsilon terms in the right hand sides of more of equations does not influence on the order of corresponding derivatives in the left hand sides. This is in view of the circumstance that they can be just neglected in comparison of the other terms in the right sides, when estimating the order of derivatives. These considerations are essential for understanding and applying Tichonov's theorem.

4. CONCLUSION

The main conclusion from the considerations made in this paper is that time hierarchy exists in the dynamical model of aggressive tumor treated by combination of three therapies. By appropriate scaling of the model mentioned above the small parameter ε is derived in its equations. In accordance with terminology of Tichonov's theorem it is established that concentrations of the CD8+ T cells, the TGF-β cytokines and the immunotherapy (IL-2) drug are *fast varying* with respect to concentrations of the tumor cells, the NK cells, the chemotherapy and the siRNA drugs, which are *slow varying* system components. The separation of fast and slow system variables, made here is needed for further application of the Tichonov's theorem, presented in the paper.

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