MODELLING AND SIMULATION OF THE IMMUNE PROCESS AT VIRAL HEPATITIS C

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Abstract. Mathematical model at viral hepatitis C is proposed as nonlinear system from ordinary differential equations. Based on clinical data of the immune process at viral Hepatitis C a numerical simulation is carried out. As a result of the simulation such values of the parameters in the kinetic model are obtained at which the experimental clinical values are maximal near to the theoretical results.

Key words: mathematical modeling, viral hepatitis C, kinetic variables, simulation.

1. INTRODUCTION

Development of the clinical and experimental immunology has gradually led to understanding of the leader weed immune protective mechanisms in the pathogenesis of infectious diseases, and together with perfection of computer facilities to creation of mathematical models. The part of models in these papers has enough a kind simple and convenient for analytical research that enables to study the generally laws of dynamics immune protection of an organism. Other problem for which decision models are used, the analysis of concrete mechanisms of immunity is, that inevitably leads to high dimension of vectors of dependent variables and parameters of such models. To traditional methods of research of the nonlinear multipleparameter problems imitating modelling is. One of most often solved within the limits of this approach problems is restoration of parameters according to supervision (standard identification of parameters). Data in a considered field of knowledge as a rule are characterized by incompleteness and discrepancy that complicates the analysis of models and interpretation of received results. Incompleteness of data creates a problem of validity estimations of parameters of models. Feature of existing mathematical models in immunology is that they are intended for research of transients in immune system (for example dynamics of immune response in case of sharp infections). It does not allow to carry out theoretical research such important problems of the contemporary immunology, as definition of norm of immune reaction and immunodeficiencies, together with studying of mechanisms of development and ways of the control of chronic infections and allergies. The specified reasons have led to necessity of search, a substantiation and application more the general laws of functioning of the immune protection of the organism, based on qualitative other principles in comparison with used earlier in this area.

Hepatitis C virus (HCV) was well adapted to emerge worldwide in the late 20th century. Transmitted primarily through percutaneous routes, it took advantage of tow emerging epidemics: an epidemic of recreational injection drug use in industrialized countries and an epidemic of unsafe injections primarily in developing countries, made possible by the expanded use of parenteral therapeutics and declining injection equipment prices after the World War II. The results at the beginning of the 21st century is a large pool of HCV-infected people, many of whom have asymptomatic, slowly progressing liver disease. The greatest burden from HCV infection will come from the long- term complications of this chronic liver disease, namely cirrhosis and hepatocellular carcinoma, which in any individual may take decades to develop. Fortunately, recognition of potential risk factors, changes in patterns of using injected drugs, and improved safety of the blood supply have led to a dramatic decline in the incidence of new HCV infections in recent years. However, since most acutely infected patients become and remain chronically infected, the overall prevalence of chronic infection has not fallen. Chronic liver disease due to HCV typically progresses slowly and usually does not result in major morbidity for many years. However, it is apparent that the large pool of patients with longstanding chronic hepatitis C is beginning to manifest the consequences of chronic infection and cirrhosis. In recent years pharmacological treatment has had good results in patients with HCV, with the virus being permanently eradicated in a large number of patients with a combination of interferon and ribavirin. This is a remarkable achievement in a chronic viral infection where spontaneous clearance is rare [1,2].

The viral hepatitis are a group of several acute viral infections, taking their course with manifestations of intoxication, damage of the liver, with or without icterus or other organic pathology. The most trivial manner of infection with hepatitis C virus (HCV) is the parenteral manner: post-transfusion, post-dental treatment, post-blood manipulations, and after sexual contact. The immunological reactivity of the organism (the immunity response) is different; however, it is genetically pre-conditioned and depends on the genotype of the individual, thus determining the broad range of manifestations of the disease. In cases of infection of persons with weak immunity response by an inferior (hollow, empty) virus, not possessing antigen variability, their organisms cannot get rid of the infection for a long period of time. The treatment of such cases may last for years. However, the most fatal consequences for such persons shall be observed, in case during the same period such persons become attacked with an infection caused by another variety of the hepatitis virus, which is capable to “capsulate” the HCV antigen; a combination thus occurring may bring to a lethal end [3,4,5,6].

An analogical picture may be observed also under the development of a strong immune response, for persons having considerable HBV variety. In the latter case, the T-cytotoxic lymphocytes, which have “cleared out” the infected hepatocytes, start also destroying the non-infected cells of the liver (an autoimmune process), thus bringing to hypercytolysis to end with hepatic coma. The most preferable (by clinicists) variance of the disease is its cyclic form, developing with persons having moderate immunity response, which form usually undergoes three phases (pre-icteric, icteric, and reconvalescent) to end up

with a healing effect within a period of 15 to 25 days after the appearance of the symptoms. It is obvious that the rich variety of manifestations of viral hepatitis C (depending on the intensity of immunity response) necessitates its constant immunological supervision, the differential evaluation of each component of the immunological chain inclusive. However, this problem is practically impossible to solve from the medical point of view. The basic difficulties, striking our attention under the qualitative and quantitative evaluation of immunological processes of this type, are the insufficient knowledge of the specifics of the hepatitis virus, the prohibition of internal biopsy (as a method giving most exact answers for the changes in the main participants of the immune process), the absence of experimental data in the incubation period as well as in the period of delayed convalescence, etc. [7,8,9,10].

2. MATHEMATICAL MODEL OF IMMUNE RESPONSE AT VIRAL HEPATITIS C

The arrangement of our model is shown in Figure 1. During the resting state of an organism, there are only macrophages and precursors in the system; the resting small lymphocytes of both plasma B cell and killer T cell character. When the antigen enters the system, the specific process is initiated and the state of the system changes dramatically: due to its binding to specific receptors of the surface of sensitive cells the antigen triggers the activation of these. In this step the antigen works as a signal initiating the process. In the next step activated cells (already marked by the antigen) are waiting for the second signal – the message which confirms that also other populations of cells should take part in the response have been already activated [11,12,13].

Our model involved: antigen, T cells (activated and helper), B cells (activated and helper) T killer cells, B plasma cells, macrophages and antibodies. It is necessary to stimulated specifically three, functionally distinct, cell populations from antigen cells: macrophages, T and B helper cells. Those cells that have met the specific antigen to which they are susceptible become activated. This encounter results in preparation of the cells marked that way for accepting the second signal. Such a signal results from the interactions of the elements of the system necessary for the successful response. The preparation of a cell to accept a signal is supposed to be based on synthesis and appearance of specific receptor molecules on the cell surface [14,15,16,17]. Through his tracing of the specific features of the viral antigen in the process of development of viral hepatitis C, and through reporting of the main mechanics of the pathogenesis, which viral hepatitis C unlocks, It offers a mathematical model reproducing the development of antiviral immune response of the organism after it is penetrated by the hepatitis virus C. The author receives satisfactory results in the above, by applying the model to reproduce the dynamics of participants in the immune process as well as to reproduce the proliferation of the virus in hepatitis under the development of the cyclic form of the disease, where organic damage is least, and where the disease ends up with a healing effect. In this paper the immunological process at virus hepatitis C is investigated for primary immune response only. Because of that the influence of memory cells not bear in mind.

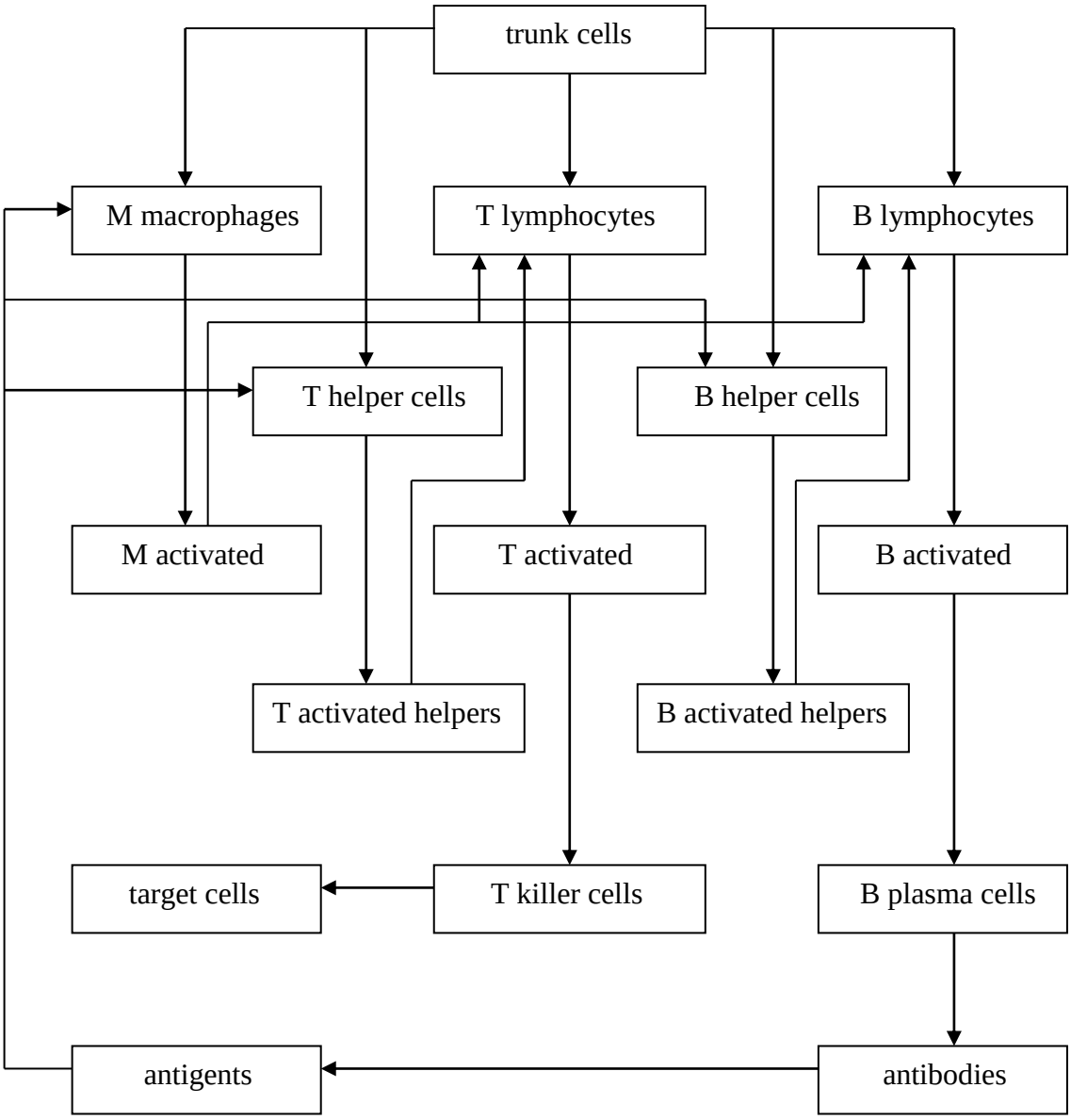

Figure 1. Scheme of the model.

Mathematical model of antiviral immune response at viral hepatitis C [18,19,20,21,22,23] as a system of ordinary nonlinear differential equations is presented in following form:

$$
\begin{aligned}
&dA_g/dt = K_1A_g - K_2A_gA_b \\
&dA_b/dt = K_3B_{pc} - K_4A_bA_g - K_5A_b \\
&dB_{pc}/dt = K_6B_a - K_7B_{pc} \\
&dT_{kc}/dt = K_8T_a - K_9T_{kc} \\
&dT_a/dt = K_{10}M_aT_0 - K_{11}T_a + K_{12}T_{ah}T_0 \\
&dB_a/dt = K_{13}M_aB_0 - K_{14}B_a + K_{15}B_{ah}B_0 \\
&dM_a/dt = K_{16}A_gM_0 - K_{17}M_a \\
&dT_{ah}/dt = K_{18}A_gT_{0h} - K_{19}T_{ah}
\end{aligned}
\tag{2.1}
$$

$$dB_{ah}/dt = K_{20}A_gB_{0h} - K_{21}B_{ah} ,$$

where the main components of the immune process vary in time, as follows:

- $A_g(t)$ - the concentration of "the free" virus (virus particles freely circulating in the organism and capable to proliferate in the cells of the body susceptible to a given virus type) *[mol]*;
- $A_b(t)$ - the concentration of antibodies [mol];
- $B_{pc}(t)$ - the concentration of plasma cells [mol];
- $T_{kc}(t)$ - the concentration of killer cells [mol];
- $T_a(t)$ - the concentration of activated T- lymphocytes [mol];
- $B_a(t)$ - the concentration of activated B- lymphocytes [mol];
- $M_a(t)$ - the concentration of activated macrophages (macrophages interacting with the free virus) [mol];
- $T_{ah}(t)$ - the concentration of T- activated lymphocyte- helpers, taking part in the cell response [mol];
- $B_{ah}(t)$ - the concentration of B- activated lymphocyte-helpers, taking part in humoral response [mol];
- K_1-K_{21} - kinetic parameters of the model;
- T_0, B_0, M_0, T_{0h} and B_{0h} – initial concentrations of T- lymphocytes, B- lymphocytes, macrophages, T- lymphocytes- helpers and B- lymphocytes- helpers [mol], respectively, are measured for a healthy organism and are constants.

Using substitutions $a_g=A_g/A_g^*$, $a_b=A_b/A_b^*$, $b_{pc}=B_{pc}/B_{pc}^*$, $\vartheta_{kc}=T_{kc}/T_{kc}^*$, $\vartheta_a=T_a/T_a^*$, $b_a=B_a/B_a^*$, $m_a=M_a/M_a^*$, $\vartheta_{ah}=T_{ah}/T_{ah}^*$ and $b_{ah}=B_{ah}/B_{ah}^*$ the system (2.1) at primary immune response for viral hepatitis C is obtained in the following non-dimensional form:

$$\begin{aligned}
da_g/dt &= k_1a_g - k_2a_ga_b \\
da_b/dt &= k_3b_{pc} - k_4a_ba_g - k_5a_b \\
db_{pc}/dt &= k_6b_a - k_7b_{pc} \\
d\vartheta_{kc}/dt &= k_8\vartheta_a - k_9\vartheta_{kc} \\
d\vartheta_a/dt &= k_{10}m_a - k_{11}\vartheta_a + k_{12}\vartheta_{ah} \\
db_a/dt &= k_{13}m_a - k_{14}b_a + k_{15}b_{ah} \\
dm_a/dt &= k_{16}a_g - k_{17}m_a \\
d\vartheta_{ah}/dt &= k_{18}a_g - k_{19}\vartheta_{ah} \\
db_{ah}/dt &= k_{20}a_g - k_{21}b_{ah}, ,
\end{aligned} \qquad (2.2)$$

where $k_1=K_1$, $k_2=K_2A_b^*$, $k_3=K_3B_{pc}^*/A_b^*$, $k_4=K_4A_g^*$, $k_5=K_5$, $k_6=K_6B_a^*/B_{pc}^*$, $k_7=K_7$, $k_8=K_8T_a^*/T_{kc}^*$, $k_9=K_9$, $k_{10}=K_{10}M_a^*T_0/T_a^*$, $k_{11}=K_{11}$, $k_{12}=K_{12}T_{ah}^*T_0/T_a^*$, $k_{13}=K_{13}M_a^*B_0/B_a^*$, $k_{14}=K_{14}$, $k_{15}=K_{15}B_{ah}^*B_0/B_a^*$, $k_{16}=K_{16}A_g^*M_0/M_a^*$, $k_{17}=K_{17}$, $k_{18}=K_{18}A_g^*T_{0h}/T_{ah}^*$, $k_{19}=K_{19}$, $k_{20}=K_{20}A_g^*B_{0h}/B_{ah}^*$, $k_{21}=K_{21}$. The concentrations of the kinetic variables T_a^*, B_a^*, M_a^*, T_{ah}^*, B_{ah}^* for a healthy organism are measured in the initial of the immune process ($T_a^*=T_0$, $B_a^*=B_0$, $M_a^*=M_0$, $T_{ah}^*=T_{0h}$, $B_{ah}^*=B_{0h}$). The concentrations of the kinetic variables A_b^*, B_{pc}^*, T_{kc}^* for a healthy organism are measured in the end of the immune process at a primary immune response. The concentration of A_g^* is measured in the initial of the immune process and is equal of the concentration of the virus on entrance its into a healthy organism.

The numerical values of the kinetic parameters k_1-k_{21} in the model (2.2) with dimension [*1/day*] are determined in Chapter 3 at the following initial conditions:

$$a_b=b_{pc}=\vartheta_{kc}=\vartheta_a=b_a=m_a=\vartheta_{ah}=b_{ah}=0,\ a_g=1 . \qquad (2.3)$$

3. SIMULATION OF THE IMMUNE RESPONSE AT VIRAL HEPATITIS C

After the dimensionless of the system (2.1) the obtained parameter values $k_1 \div k_{21}$ are used as basic ones at the solved of the system ordinary differential equations (2.2) using the method of Runge-Kutta from the RKGS program of the SSP package. As a result of that at different combinations of the parameter values $k_1 \div k_{21}$ near to the basic ones, theoretical curves are obtained for the different kinetic variables. The theoretical obtained curves are compared with the experimental curves for the different kinetics variables taken from [24]. From the carried out numerical simulation it is seen that for one concrete combination of the parameters values $k_1 \div k_{21}$, the difference between theoretical and experimental values of the kinetic variables is least. The final values of $k_1 \div k_{21}$ are demonstrated in Table 1 (column 2). The non-dimensional model (2.2) of antiviral immune response for viral hepatitis C describes the changes of the following kinetic variables: a_g (free virus), a_b (antibodies), ϑ_{kc} (killer cells), b_{pc} (plasma cells), ϑ_a (T activated lymphocytes), b_a (B activated lymphocytes), m_a (M activated macrophages), ϑ_{ah} (T activated lymphocytes- helpers), b_{ah} (B activated lymphocytes- helpers).

Clinical data about changes in the concentrations of the above variables is provided in [24]. Such data reports about the process of development of a cyclic form of hepatitis C for a period of 30 days. The veracity of data is confirmed by analogous investigations made in the Academy of Military Medicine of the City of Sofia. The experimental clinical curves of the different patients are framing theoretically, as a result of that the smooth experimental curves are obtained for the each kinetic variables using the fuzzy sets apparatus [25]. For our convenience data has been provided in non-dimensional form using (2.2) and (2.3). As a result the non-dimensional smooth clinical curves of each kinetic variable for 15 intervals of time (15 intervals of 2 day) are obtained. Their theoretical analogues are derived after solving the system of ordinary differential equations (2.2). The initial values of the parameters $(k_1 \div k_{21})$ are taken from [12] and comply with the specifics of the disease (Table 1, column 1).

4. CONCLUSION

The immune system can be seen as a parallel, information processing system that learns through examples and constantly adapts itself to new situations and possesses a distributive memory for patterns. For theoretical immunology, immune system simulations can be used to gain more insight in how various interactions together result in immunological phenomena. The immune system as a whole is a complex special purpose system.Therefore, a model that accurately simulates the immune system is no natural solver for arbitrary problems. However, particular theories about the immune system can be used to inspire new problem solving methods. Implementing processes of the immune system may lead to useful natural solving algorithms, but studying the general operations of the immune system may also lead to identification factors that have relevance in areas different than immunology. We believe that immune system models are useful because they reveal interesting behaviour that may lead to the discovery of new problem solving techniques.

This paper proposed generalized mathematical model, expressed through a system of 9 ordinary differential equations (2.1). The model represents the dynamics of the main

participants in immunity response upon development of the cyclic form of viral hepatitis C. The proposed numerical simulation allowed us to derive the numerical values of the parameters (constants) of the model (2.2), which render it as close to the real process as possible. Under the parametric values derived hereof, the numerical simulation of the system (2.2) as made for 15 intervals of time (30 days) shows out that the difference between the results obtained theoretically, and the clinical curves obtained through experiment, is only minimal (10%).

Table 1

In the first column - the initial parameter values $(k_1 \div k_{21})$; in the second column - the final parameter values $(k_1 \div k_{21})$.

№	1.	2.
k_1	0,5	0.520
k_2	0.05	0.047
k_3	0.5	0,540
k_4	0.05	0.053
k_5	0.1	0.094
k_6	0.3	0.312
k_7	0.1	0.088
k_8	0.3	0.306
k_9	0.1	0.089
k_{10}	0.2	0.255
k_{11}	0.05	0.059
k_{12}	0.1	0.111
k_{13}	0.2	0.192
k_{14}	0.05	0.059
k_{15}	0.1	0.078
k_{16}	0.1	0.116
k_{17}	0.05	0.042
k_{18}	0.1	0.115
k_{19}	0.05	0,040
k_{20}	0.1	0.089
k_{21}	0.05	0,061

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