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IMPLEMENTATION OF THE MATHEMATICAL MODEL OF RHEUMATOID ARTHRITIS

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Abstract. Mathematical models of immune mediated disorders provide an analytic framework in which we can address specific questions concerning disease immune dynamics and the choice of treatment. Such models are actively reported in the field of tumor immunology and immunotherapy by de Phillis et al [2, 3]. Herein, we present a novel mathematical model that describes the immunopathogenesis and the targeted immunotherapy of rheumatoid arthritis using non-linear differential equations. Of importance, based on this model, the software that solves the Cauchy problem for this system and visualizes the obtained solution is developed. Solutions are obtained for the case of each individual patient to decipher the disease progress and the absence of disease.

Keywords and phrases: Mathematical model, immune disorders, differential equations.

AMS subject classification (2010): 97M60.

1 Introduction. Rheumatoid arthritis is the chronic autoimmune inflammation of the joints associated with the disturbed counts and functions of the adaptive immune cells, B and T lymphocytes. Pathological (autoreactive) B cells are guided by the T cell subpopulations. In general, T helper 17 (Th17) cells promote the disease, whereas regulatory T cells (Treg) protect against its occurrence. In addition, rheumatoid arthritis is associated with the production of cytokine - IL-6. As it has been described in our previous study [1], IL-6 skews T cell differentiation towards Th17 instead of immunosuppressive Treg. While a targeted therapeutic drug - tocilizumab (monoclonal antibodies against IL-6 receptor) [1], is successfully emerging in medical practice in recent years, the clinical outcome is still not homogenous. Refined personalized analyses of T and B lymphocyte subsets in individual patients with rheumatoid arthritis are critically needed for rigorous disease management.

2 Model development. Following biological assumptions are applied to develop the mathematical model: a) Target cells grow according to logistical model and they are attacked by autoreactive B cells; b) B cells that are above of the normal level are considered as autoreactive B cells. B cells grow also logistically; c) Helper T cells grow logistically; d) Helper T cells stimulate the growth of autoreactive B cells; e) Source of regulatory T cells is considered outside of the system; f) Regulatory T cells suppress the growth of autoreactive B cells; g) The disease begins when, for some reasons, helper T

cells population become larger than normal value and regulatory T cells became less than normal value.

In the model we denote four cell populations:

$J(t)$ - Target cell population at time t. $B(t)$ - B cell population at time t. $T_h(t)$ - helper T cells population at time t. $T_{reg}(t)$ - Regulatory T cells population at time t. Also J^0, B^0, T_h^0, T_{reg}^0 denote population of corresponding cells at time t=0. Normal level of B cells is denoted by B^{norm}.

3 Model equations. According to list of assumptions we set the system with four differential equations where each equation describes rate of change of corresponding cell population.

$$\begin{cases} \dfrac{dJ(t)}{dt} = r_0 J(t)(1 - b_0 J(t)) - a_0 J(t)(B(t) - B^{norm}) & (1) \\ \dfrac{dB(t)}{dt} = r_1 B(t)(1 - b_1 B(t)) + c_1 B(t) T_h(t) - d_1 B(t) T_{reg}(t) & (2) \\ \dfrac{dT_h(t)}{dt} = r_2 T_h(t)(1 - b_2 T_h(t)) & (3) \\ \dfrac{dT_{reg}(t)}{dt} = s_2 - d_2 T_{reg}(t) & (4) \end{cases}$$

Equation (1) describes rate of change of target cells and is based on assumptions (a), (b). r_0 is target cell growth rate and $1/b_0$ is target cell carrying capacity. a_0 is rate at which target cells are destroyed by B cells. In cases when target cells do not grow (for example, in case of rheumatoid arthritis) r_0 is equal to 0. Equation (2) is based on assumptions (b), (d), (f) and describes rate of change of B cells. r_1 is B cell growth rate and $1/b_1$ is B cell carrying capacity, c_1 is rate at which B cells are stimulated to be produced by helper T cells and d_1 is B cell inactivation rate by regulatory T cells. Equation (3) is based on assumption (c) and describes helper T cell growth rate. r_2 is helper T cell growth rate and $1/b_2$ is helper T cell carrying capacity. And equation (4) describes regulatory T cell growth rate. It is based on assumption (e). s_2 denotes constant source of regulatory T cells and d_2 death rate of regulatory T cells.

We can add drug therapy equation to the model. The drug therapy must restore balance between helper and regulatory T cells. We make the next assumption for drug: (a) the drug kills part of the helper T cells thus reducing their number; (b) the drug transforms other part of helper T cells into regulatory T cells thus further reducing their number and increasing number of regulatory cells.

4 Coefficient estimation. The model contains several coefficient and their values may vary for different patients. It is the advantage of the model. The model can be set individually for each patient. So, it is very important to choose correct values of these coefficients. Some of them are measurable. They can be obtained from clinical blood analysis (for example, current number of B or T cells) or can be known from statistical data for patients groups (for example, normal sizes of B or T cell populations). But other

coefficients are immeasurable. We have to correctly estimate their values from data of clinical analysis.

In the logistic model $1/b$ is asymptotic value [5]. In our cases, as an asymptotic value we can assume normal value of cell population. So, as b_0, b_1, b_2 can take inverse number of cells in corresponding cell population. s_2/d_2 is also asymptotic value in equation (4). So, $s_2/d_2 = T_{reg}^{norm}$. For not sick patients we assume, $c_1 B(t) T_h(t) - d_1 B(t) T_{reg}(t) = 0$. It follows that $c_1/T_{reg}^{norm} = d_1/T_h^{reg}$. As r_0, r_1, r_2 coefficients indicate cell population growth rate for their evaluation we must have several clinical analysis data where corresponding cell population is changed. We developed software that calculates all these coefficients from clinical analysis data.

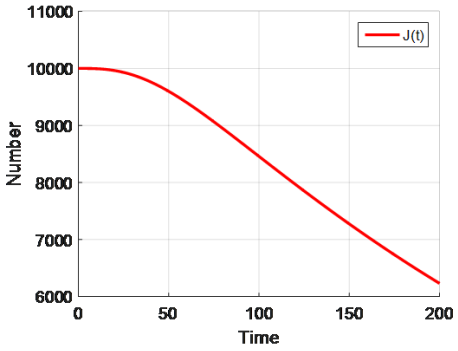

Figure 1: Cartilage volume change dynamics.

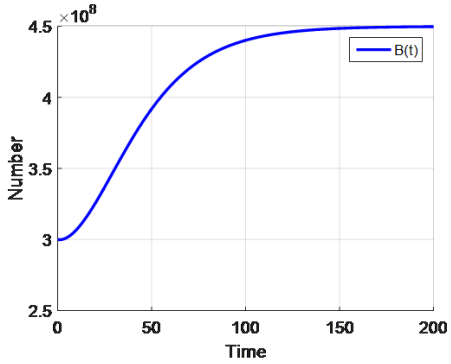

Figure 2: B cell population size change dynamics.

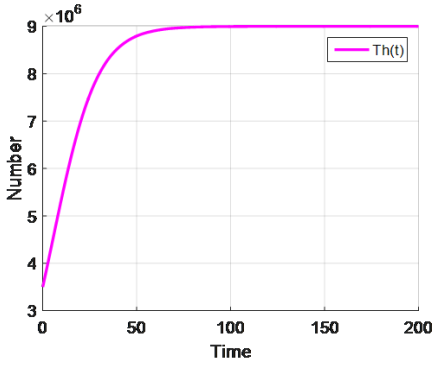

Figure 3: Helper T cells population size change dynamics.

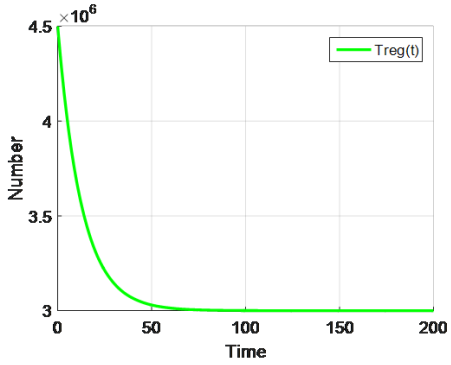

Figure 4: Helper T cells population size change dynamics.

Let as consider rheumatoid arthritis case. Let clinical analysis show: $T_{reg}^{norm} = 4.5 \cdot 10^6$, $T_h^{norm} = 3.5 \cdot 10^6$, $B^{norm} = 3 \cdot 10^8$. According to assumption (g) disease progresses when regulatory T cells become above normal value and helper T cells are less than normal value. Let, analysis also show the next dynamics in cell population changes during the disease: (a) regulatory T cell population decreases from normal size to $3 \cdot 10^8$ during 50 days, (b) helper T cells grow from normal value to $9 \cdot 10^6$ during 60 days, (c) B cells grow from normal value to $4.5 \cdot 10^8$ during 100 days, (d) cartilage volume decreases on 25%

during 140 days. As initial values we take normal values of cell populations. Fig. 1, 2, 3 and 4 represent the solution of the model.

5 Conclusions. There is no doubt that model-based investigation of diseases is complex and evolving field. We herein report the first attempt to establish the mathematical model and its computational implementation that, based on immune checkpoints, enable disease prognosis and aid therapeutic choices on the personalized patient care for rheumatoid arthritis. We believe that such models will help to predict the disease prognosis and to choose an effective approach for its therapeutic intervention.

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