STUDY OF COEFFICIENTS OF RHEUMATOID ARTHRITIS MODEL

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Abstract

Mathematical models of diseases caused by immune disorders allow to solve specific questions related to the disease immune dynamics and choice of relevant treatment. Here we consider the model of rheumatoid arthritis and discuss the evaluation of the coefficients of the model of their influence on the solution.

Анотация

Математические модели, описывающие болезни вызванные иммунным нарушениями, позволяют решать конкретные вопрсы, связанные с динамикой болезны и выбора соответствующего лечения. Здесь мы рассматриваем модель ревматоидного артрита и обсуждаем вопросы оценки коэффициентов модели их вляния на решение.

Introduction

The model based investigation of diseases is a complex and evolving field. We have introduced new mathematical model of immune mediated disorders [4]. The model describes progression of rheumatoid arthritis and the effect of treatment.

Rheumatoid arthritis is a systematic autoimmune disease characterized by inflammation of the joints, bone loss and cracking cartilage tissue [1, 2]. The disease is caused by violation of balance between B, regulatory T and helper T lymphocytes that are subset of blood cells. In rheumatoid arthritis B lymphocytes goes beyond the norm and along with T helper cells produces antibodies to the cell of the cartilage resulting in its structural destruction [3]. Regulatory T cells due to their reduced quantities fail to suppress B cells. The immune system fails to properly distinguish between “self” and “non-self” and attacks part of the body inducing strong inflammatory response against self-substances.

Mathematical model

Now we improve the model by adding treatment component. We concede “Tocilizumab” as drug for treatment. Mathematical model of rheumatoid arthritis with drug therapy is given below:

$$\frac{dJ(t)}{dt} = -a_1 J(t)(B(t) - B^{norm}) \tag{1}$$

$$\frac{dB(t)}{dt} = r_1 B(t)\big(1 - b_1 B(t)\big) + c_1 B(t) T_h(t) - d_1 B(t) T_{reg}(t) \tag{2}$$

$$\frac{dT_h(t)}{dt} = r_2 T_h(t)\big(1 - b_2 T_h(t)\big) - k_1(1 - e^{-m_1 u(t)})T_h - k_2(1 - e^{-m_2 u(t)})T_h \tag{3}$$

$$\frac{dT_{reg}(t)}{dt} = s_2 - d_2 T_{reg}(t) + k_2(1 - e^{-m_2 u(t)})T_h \tag{4}$$

$$\frac{du(t)}{dt} = -d_3 u(t) \tag{5}$$

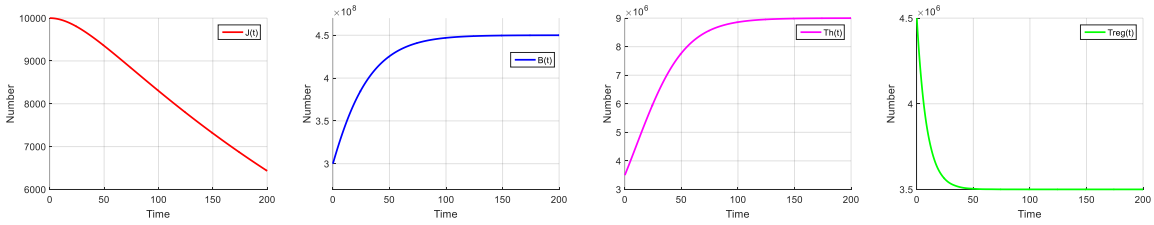
J(t) denotes cartilage cell population at time t moment, B(t) – B cell population at time t, $T_h(t)$ and $T_{reg}(t)$ – helper and regulatory T cells population, accordingly. Equations (1) and (2) are the same as for model without drug therapy. In equation (3) and (4) drug component is added. Equation (5) determines amount of the drug in the blood at time t. Drug action is the following: drug affects helper T and regulatory T cells. It kills part of helper T cells and turns other part of helper T cells into regulatory T cells. As a result, population of helper T cells is

decreased and population of regulatory T cells is increased. After a certain period B lymphocytes should start to decrease. The next assumptions are made about the drug:

1. The drug is completely eliminated (metabolism and excretion) from the blood.
2. The drug is directly administrated by an intravenous injection and is immediately completely distributed into the blood stream.
3. Amount of the drug in the blood after injection is given by exponential reduce model pattern: equation (5).
4. Fractional cells kill for an amount of drug u is given by exponential model $F(u) = k(1 - e^{-mu})$

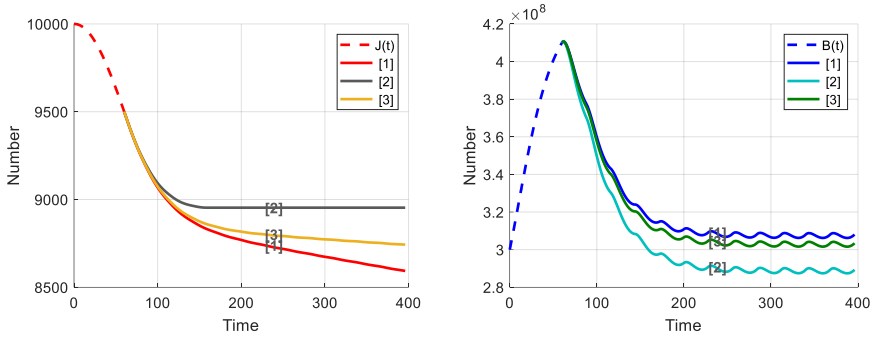
Coefficients of the model

The model contains several coefficients and their value may vary for different patients. So, it is important to choose correct values of these coefficients. Coefficient a_1 determines the rate of cartilage destruction. For healthy patient $B(t) = B_{norm}$ and a_1 may be ignored. r_1 and r_2 are cell amount rate and $1/b_1$ and $1/b_2$ are cells carrying capacity. s_2 denotes constant source of regulatory T cells and d_2 is death rate of regulatory T cells. c_1 and d_1 are rates of which B cells are stimulated to be produced by helper T cells and suppressed by regulatory T cells, accordingly [4]. These coefficients may be estimated if we have at least two clinical analysis of patient blood, taken in some time intervals. These analyzes should measure B lymphocytes, helper and regulatory T cell amounts, and estimate also cartilage size. We normalize size of the cartilage and normal size is assumed to be 10000 units. These values maybe measured at different time points. Figure 1 represents behavior of these 4 cells in case when at 100th day B lymphocytes value is $450 \cdot 10^6$, at 160th day helper T cells value is $9 \cdot 10^6$, regulatory T cells value is $3.5 \cdot 10^6$ at 50th day, and cartilage value is 7500 at 140th day. The next figure represents behavior of model functions $(J, B, Th, Treg)$ under the conditions described above.

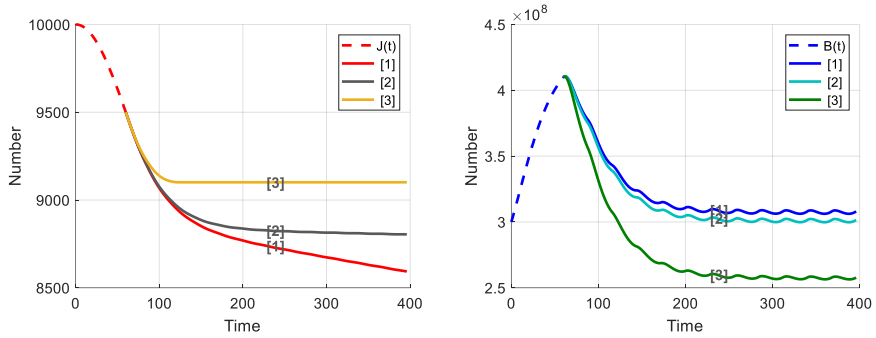


From these graphs, the condition of the cartilage may be presumed in 200 days. It is assumed that at initial time (t=0) all indicators were normal. Note that this figure is obtained from model that doesn't include treatment component. All coefficients of the model are calculated automatically based on the results of clinical analyzes.

Introduction of the drug component added another four coefficients (k_1, k_2, m_1, m_2) to the model. Correct selection of them is also very important. k_1 and k_2 denote fractional rate of killed and transformed by drug (Tocilizumab) helper T lymphocytes. The next figure shows effect of these coefficients on the progress of treatment. Dashed lines are values before drug treatment is started (60 days). Three different cases are considered: graph 1 represents case $k_1 = 0.005, k_2 = 0.025$, for graph 2 $k_1 = 0.005, k_2 = 0.03$ and for graph 3 - $k_1 = 0.007, k_2 = 0.025$. Here $m_1 = 1, m_2 = 1$



Coefficients m_1 and m_2 can be regarded as a scaling factor, and they can be included in the function u. Therefore, their values often are taken as 1. Figures below show effect of m_1 and m_2. For graph 1 $m_1 = 1, m_2 = 1$, for graph 2 – $m_1 = 2, m_2 = 1$, for graph 3 - $m_1 = 1, m_2 = 2$. Here $k_1 = 0.005, k_2 = 0.025$.



Another coefficient is introduced in equation (5). Coefficient d_3 can be calculated from half-life period (τ) of the drug: $d_3 = -\ln(0.5)/\tau$. The above results were obtained on condition that the drug disintegration time was 13 days, and the treatment of the disease started on the 60th day

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