Mathematical Model of Rheumatoid Arthritis and its Treatment

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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. Herein, we present a novel mathematical model that describes the immunopathogenesis of rheumatoid arthritis using non-linear differential equations. A methodology for estimating the values of the coefficients contained in the model is discussed. The model explores the functional dynamics of cartilage destruction during disease progression, in which a system of differential equations deciphers the interactions between B and T lymphocytes. Immunomodulatory relation between pro-inflammatory and regulatory T cell subsets is also solved in these equations. Of importance, our model provides a mechanistic interpretation of targeted immunotherapy which deals with the intervention of pathophysiological immune processes in rheumatoid arthritis.

***Keywords**: Mathematical model, immune disorders, differential equations.*

Introduction

Formulation of relevant mathematical models is of profound importance in every field of research and, for its accuracy, represents the central focus in biomedical analyses. Immune system is a complex example of a network. It consists of various types of elements, which have different densities in different regions of the body, e.g., the blood or lymphatic system, the skin, liver, etc. The system is altered in time in healthy state or modulated in pathological conditions – immune mediated disorders.

Rheumatoid arthritis is a systemic autoimmune disease characterized by inflammation of the joints, bone loss, and cracking of cartilage tissue [1, 2]. The complex process of developing this disease involves the following stages of interaction between B and T lymphocytes: B lymphocytes are a subset of white blood cells, also termed leukocytes, which are characterized by their ability to synthesize and secrete antibodies. Antibodies specifically bind to the foreign antigen, allowing its removal. T lymphocytes are a subset of leukocytes which synthesize and secrete cytokines. Type and nature of cytokines guide the immune response by activating or suppressing other immune cells including B lymphocytes. T cell population is comprised of several subsets based on their phenotypic and functional features: Helper T cells (Th) - trigger the immune activation and, consequently, the prevention of immunodeficiency and cancer [3]. Regulatory T cells (Treg) - regulate the other immune cells by suppressing their activity [4]. Treg play a critical role in prevention of inflammation and autoimmunity through the establishment of immune tolerance [5, 6].

The balance between effector and regulatory cells establish immune homeostasis in the human body. If the B and T helper cells override the immune balance scales, then inflammatory and/or autoimmune diseases occurs, and if T regulatory cells are exterminated - immunodeficiency is prevailed [7]. In rheumatoid arthritis, the number of B lymphocytes goes beyond the norm and

along with T helper cells produces antibodies to the cells of the cartilage resulting in its structural destruction [8]. Treg 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 - Autoimmunity occurs [9].

In today's reality “Tocilizumab” (ant-IL6 receptor monoclonal antibodies) is the most promising immunotherapy for the management of rheumatoid arthritis. Resent preclinical and clinical trials show that “Tocilizumab” specifically blocks Th17 cell growth (a subset of T helper cells reported to be elevated in rheumatoid arthritis [10, 11]) and transforms them to regulatory T cells through the transcriptional plasticity of these subsets, i.e. restores Th/Treg balance [12, 13, 14]. Therefore, this drug represents the prospective novel therapy in rheumatoid arthritis. Current medical problem is the optimization of treatment dose and duration for its personalized administration in each individual patient. The wrong choice of the dose may lead to the serious side effects, enduring health complications and even a fatal outcome in patients, and there is no accurate biological test system that allows the prediction of such conditions. Based on this medical problem, we have created a mathematical model to describe the T cell plasticity in the immunopathogenesis of rheumatoid arthritis. By our knowledge, this is the first mathematical model, along with its computer program, which on a cell biology level describes the modulation of T lymphocyte balance in this disease. After simulation, the model may predetermine the drug dose and the drug administration frequency efficient for each patient individually. Therefore, this model creates an innovative approach in the management of patients with rheumatoid arthritis and has an immense potential to be implemented in the personalized healthcare of such patients.

Model assumptions

The main goal of our research is to develop a mathematical model that describes 1) immunopathogenesis of rheumatoid arthritis and 2) efficiency of targeted immunotherapy in this disease. Principal rational of the model is the establishment of a software product introduced in the present report for the first time. Of note, upon development of the mathematical model based on the immune parameters of rheumatoid arthritis, we made following assumptions regarding B lymphocytes, helper T lymphocytes, regulatory T lymphocytes and cartilage cells:

a) When B lymphocytes become higher than it is normal value they are considered as autoreactive B-cells and the destroy joint cells

b) B cells grow according to logistic model, helper T-cells activates growth and regulatory T-cells suppress growth. In the absence of disease amount of activated and suppressed B cells are equal.

c) Helper T cells grow logistically.

d) Source of regulatory T cells is outside of system and they appear with constant influx rate and with relatively rate.

e) Disease occurs when some rates of influx, death and cellular interaction are changed

Model equations

To establish the basics for the mathematical model, we consider the model without drug intervene at first, and indicate it as “without drug” model. The mathematical model includes time (t) depended and also time independent variables. “Without drug” model consists of four nonlinear differential equations. We denote four cell populations: $J(t)$ - cartilage cell population at time t moment. $B(t)$ - B cell population at time t moment. $T_h(t)$ - helper T cells population at time t moment. $T_{reg}(t)$ - regulatory T cells population at time t moment, also coefficients $a_1, r_1, b_1, c_1, d_1, r_2, b_2, s_2, d_2$ and constant B^{norm}. All coefficients are positive numbers. System is shown below:

$$\begin{cases} \dfrac{dJ(t)}{dt} = -a_1 J(t)(B(t) - B^{norm}) & [1] \\ \dfrac{dB(t)}{dt} = r_1 B(t)\big(1 - b_1 B(t)\big) + c_1 B(t) T_h(t) - d_1 B(t) T_{reg}(t) & [2] \\ \dfrac{dT_h(t)}{dt} = r_2 T_h(t)\big(1 - b_2 T_h(t)\big) & [3] \\ \dfrac{dT_{reg}(t)}{dt} = s_2 - d_2 T_{reg}(t) & [4] \end{cases}$$

Let's consider each equation of the model:

1) Equation (1) describes change rate of cartilage. There is B cell number value for healthy human which is considered as norm. We assign it as B^{norm}. When $B(t) > B^{norm}$, rate is negative, and amount of cartilage is reduced (see assumption **a**.). According to equation when $B(t) < B^{norm}$, amount of cartilage will grow. But this is not so in reality. We impose a restriction $B(t) \geq B^{norm}$;

2) Equation (2) describes change rate of B cells. It consists of three parts. The first part $r_1 B(t)\big(1 - b_1 B(t)\big)$ determines logistically growth of B cells, the second pat $c_1 B(t) T_h(t)$ determines stimulated (by helper T cells) growth with rate c_1, and the third part $-d_1 B(t) T_{reg}(t)$ is suppressed (by regulatory T cells) fraction of B cells. Suppression rate is d_1. (see assumption **b**.)

3) Equation (3) is logistically growth of helper T cells (assumption **c**.)

4) Equation (4) describes rate of regulatory T cells change by simple model pattern with constant influx rate (assumption **d.**).

Now consider logistic model circumstantially. The logistic equation (sometimes called the Verhulst model or logistic growth curve) is a model of population growth first published by Pierre Verhulst [18]. The model is continuous in time, but a modification of the continuous equation to a discrete quadratic recurrence equation known as the logistic map is also widely used. The continuous version of the logistic model is described by the differential equation:

$$\frac{dN}{dt} = rN\left(1 - N\big/K\right)$$

where r is the Malthusian parameter (rate of maximum population growth) and K is the so-called carrying capacity (i.e., the maximum sustainable population). If $N(0) = N_0$, then

$$N(t) = \frac{N_0 K e^{rt}}{(K + N_0(e^{rt} - 1))} \to K$$

(Figure 1).

Then we add the effect of the drug on the system. We denote by $u(t)$ the amount of the drug in the blood at time t. We make the next assumptions about the drug:

a) The drug is completely eliminated (metabolism and excretion) from the body through the blood;
b) The drug is directly administered by an intravenous injection is immediately completely distributed into the bloodstream;

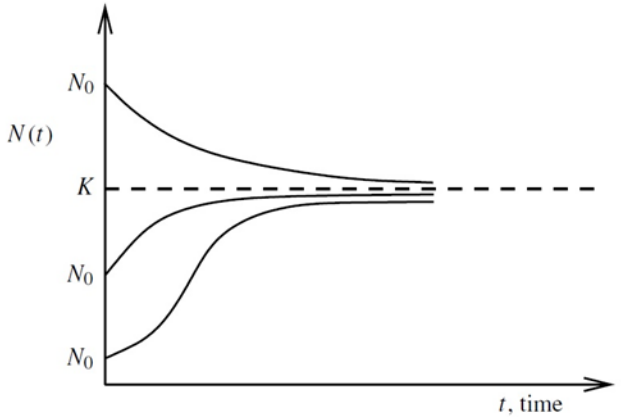

Figure 1: Logistic equation growth curve in time, starting from N_0 value and growing to K - carrying capacity value

c) Amount of the drug in the blood after injection is given by exponential reduce model pattern

d) The drug interacts with helper T cells and kills part of them. Fractional cell kill for an amount of drug u is given by an exponential

$$F(u) = k(1\, e^{-mu})$$

e) The drug also turns other part of helper T cells into regulatory T cells

Model "with drug" consists of five differential equations:

Additionally U (t) will be added as drug dose value at t time moment and new coefficients: k_1, m_1, k_2, m_2, d_3. System is shown below:

$$\begin{cases} \dfrac{dJ(t)}{dt} = -a_1 J(t)(B(t) - B^{norm}) & [5] \\ \dfrac{dB(t)}{dt} = r_1 B(t)\big(1 - b_1 B(t)\big) + c_1 B(t) T_h(t) - d_1 B(t) T_{reg}(t) & [6] \\ \dfrac{dT_h(t)}{dt} = r_2 T_h(t)\big(1 - b_2 T_h(t)\big) - k_1(1 - e^{-m_1 u(t)})T_h - k_2(1 - e^{-m_2 u(t)})T_h & [7] \\ \dfrac{dT_{reg}(t)}{dt} = s_2 - d_2 T_{reg}(t) + k_2(1 - e^{-m_2 u(t)})T_h & [8] \\ \dfrac{du(t)}{dt} = -d_3 u(t) & [9] \end{cases}$$

All new coefficients are positive.

Let's consider added items of the system:

1) Equation (5) determines amount of the drug in the blood at time t. It is assumed that drug injection was made at time $t = 0$;

2) Items in equation (4) $k_1(1 - e^{-m_1 u(t)})T_h$ and $k_2(1 - e^{-m_2 u(t)})T_h$ determine part of killed and transformed helper T cells, respectively. See assumption d and e. We set $m_1 = 1$ and $m_2 = 1$ in our preliminary study.

It is not possible to solve all equations of system with analytic method, so numerical solution is used.

Coefficient estimation

The model contains several coefficients, 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 analyses (for example, current numbers of B or T cells) or can be known from the state of the art for patients' groups (for example, normal sizes of B or T cell populations). But other coefficients are immeasurable (for example coefficients that determines speed of increasing/decreasing B cells, this is individual value for each patient). We have to correctly the estimate of their values from data of clinical analysis. Example: if for patient N1 B cells number has increased 1.5 times within a month and for patient N2 it has increased twice at the same time interval, then their coefficients are different values. A computer program was developed for individual coefficient calculation. With laboratory analysis data and coefficient calculation can properly predicting the behavior of cells within the next short or long time period.

For simplicity, we assume that drug does not change coefficients

$$a_1,\ r_1,\ b_1,\ c_1,\ d_1,\ r_2,\ b_2,\ s_2,\ d_2.$$

To calculate them, the data of clinical analyses of each cell population at time t_0 and at time t_n are required. In addition, normal values of lymphocytes must be available. The values of cell populations at these times are denoted by corresponding superscript: B^0, B^n, B^{norm}, $T_h^{\ 0}$, $T_h^{\ n}$, T_h^{norm}, etc.

For estimation of r_1 and r_2 two results of clinical analysis are required. We consider current values of lymphocytes as value that is reached asymptotically, i.e. for $t = \infty$. In logistic models (equations (2) and (3)) we take its inverse value as carrying capacity. We assume that α fraction of asymptotical value is achieved at current time. $\alpha \approx 1,\ \text{but}\ \alpha < 1$. For equation (2) we, additionally, have to make an assumption which part of the growth is due to logical growth and which part of it involves T lymphocytes. Let's denote by β part of growth that is caused by logistically growth. Therefore, $\bar{B} = B^n + \beta(B^n - B^0)$ is amount of B cells obtained by logistical growth. $\bar{B} = B^n + (1-\beta)(B^n - B^0)$ is amount of B cells obtained by action of T cell. When disease is absent $c_1 B(t) T_h(t) - d_1 B(t) T_{reg}(t)$ must be equal to 0. Therefore,

$$\frac{c_1}{d_1} = \frac{T_{reg}^{norm}}{T_h^{norm}} \equiv w\ . \qquad [10]$$

Summarizing the above, we obtain:

$$b_1 = \frac{1}{\bar{B}} \qquad b_2 = \frac{1}{T_h^n} \qquad r_1 = \ln\left(\frac{\alpha(\bar{B}-B^0)}{B^0(1-\alpha)}\right)\Big/ t_n \qquad r_2 = \ln\left(\frac{\alpha(T_h^n - T_h^0)}{T_h^0(1-\alpha)}\right)\Big/ t_n$$

Substituting (10) into system (1) - (5) and solving it numerically, the solution of B can be considered as a function of $w - B(t,w)$. Then we have to find numerical solution of equation

$$B(t_n, w) = B^n$$

For equation (4) asymptotically reached value is $\frac{s_2}{d_2}$. Analytic solution of (4) is:

$$T_{reg}(t) = \left(T_{reg}^0 - T_{reg}^n\right) e^{-d_2 t} + \frac{s_2}{d_2}$$

From conditions $T_{reg}(0) = T_{reg}^0$, $T_{reg}(\infty) = T_{reg}^0$ and $T_{reg}(t_n) = \alpha \cdot T_{reg}^n$ we obtain

$$d_2 = -\ln\left(\frac{(\alpha-1)T_{reg}^n}{T_{reg}^0 - T_{reg}^n}\right)\Big/ t_n\ .$$

For estimation a_1 we also use analytic solution of equation (1) and obtain

$$a_1 = \frac{-ln\left(\frac{J_n}{J_0}\right)}{\int_0^t (B(\xi) - B^{norm})d\xi)}$$

For example, let at time $t = 0$ initial value of lymphocytes are:

$$B^0 = B^{norm} = 300 \cdot 10^6, \quad T_h^0 = T_h^{norm} = 3.5 \cdot 10^6, \quad T_{reg}^0 = T_{reg}^{norm} = 4.5 \cdot 10^6 \quad [11]$$

After 200 days (at the moment $t_{200} = 200$) values are:

$$B^{200} = 450 \cdot 10^6, \quad T_h^{200} = 9 \cdot 10^6, \quad T_{reg}^{200} = 3.5 \cdot 10^6 \quad [12]$$

Since it is difficult to measure the size of the cartilage, we normalized this parameter and assume that its size when disease is absent is 1000 units. Let, after 200 days 25% of cartilage is destroyed. It means,

$$J^0 = J^{norm} = 10000 \qquad J^0 = J^{200} = 7500. \quad [13]$$

In "with drug" model we have additionally coefficients: k_1, m_1, k_2, m_2, d_3. No automatic calculation is performed for first four of them. k_1 and k_2 determining T cells shortening speed was chosen according to proximity to real results: k_1 = 0.005, k_2 = 0.025. m_1 and m_2 does not have a big impact on the outcome and their values is equal to 1. Analytical solution of (5) is: $U(t) = U_0 e^{-d_3 t}$, the initial value U_0 is dose of drug. We must take into account half-life period of drug. So

$$d_3 = -\ln(0.5)/\tau\,. \quad [14]$$

Where τ is half-life period of the drug.

Solving System Equation

Visualizing results of differential system equation solution, we introduce certain parameters and discuss results in point of them, however, both the model and the computer program allow these options to be varied. For input parameters upon establishment of the computer program, at least two results of laboratory analyses are required (together with time difference), to perform coefficient calculation for each patient and then to solve the system.

Take into account conditions (11), (12) and (13) and set $\alpha = 0.99$ and $\beta = 0.7$ we obtain the curves for the "Without drug" model (Figure 2). Value of β impacts on behavior of B and J curves (Figure 3).

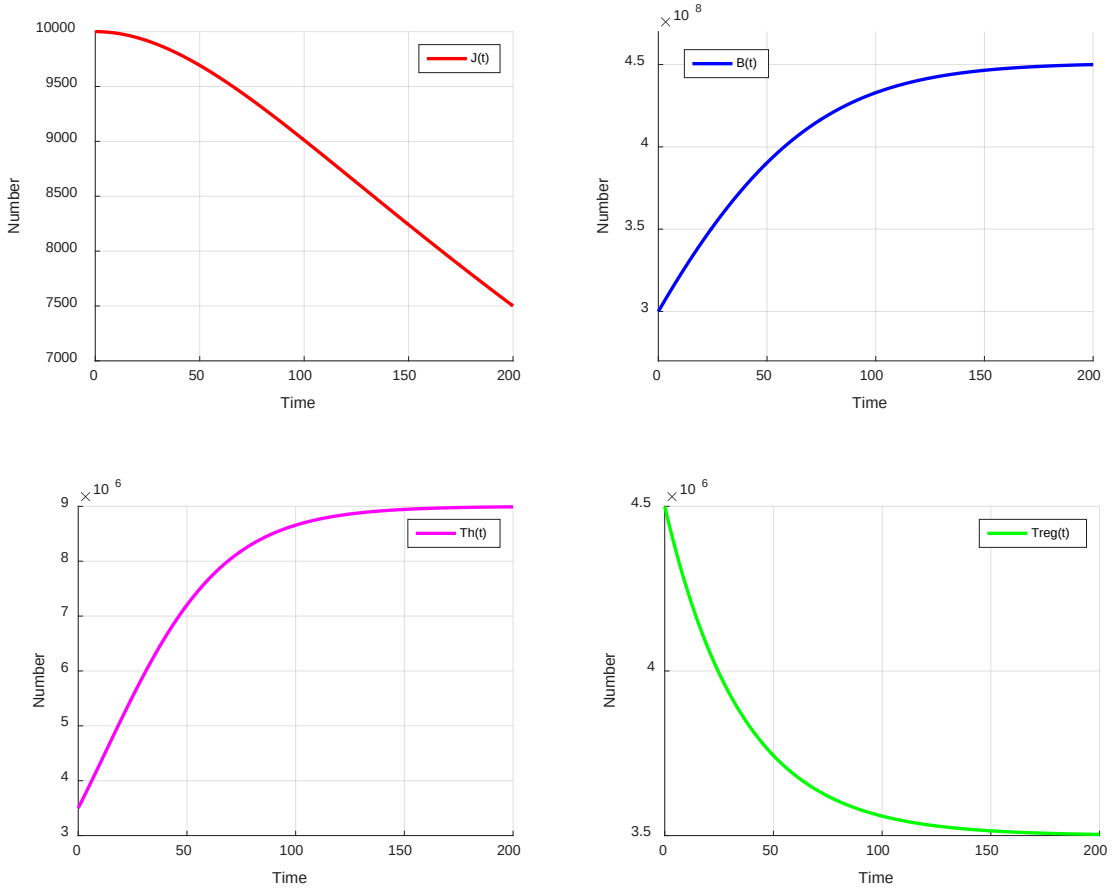

Figure 2: Dependence of J, B, Th, Treg cells on time.

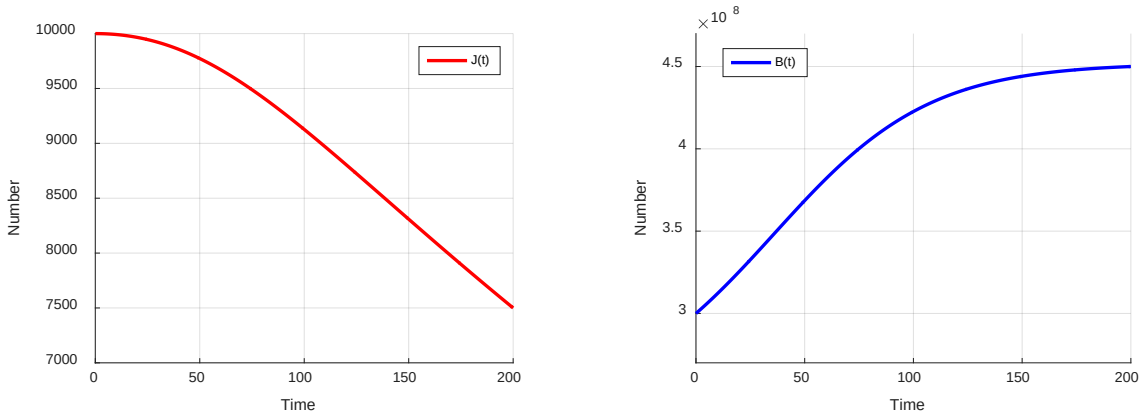

Figure 3: Case β=0.35. Dependence of J and B cells on time.

Importantly, the present mathematical model does not require the simultaneous acquisition of all immune parameters from a patient. Rather, this model can function using the patient's different parameters acquired at different time points. Let conditions (12) and (13) be replaced by

$$B^{100} = 450 \cdot 10^6, \quad T_h^{160} = 9 \cdot 10^6, \quad T_{reg}^{50} = 3.5 \cdot 10^6 \quad J^{140} = 7500$$

i.e. parameters of of lymphocytes and cartilage are measured after 100, 160, 50 and 140 days, respectively, after the first measurement. (Figure 4). Note that all coefficients of model are calculated automatically based on the results of clinical analyses.

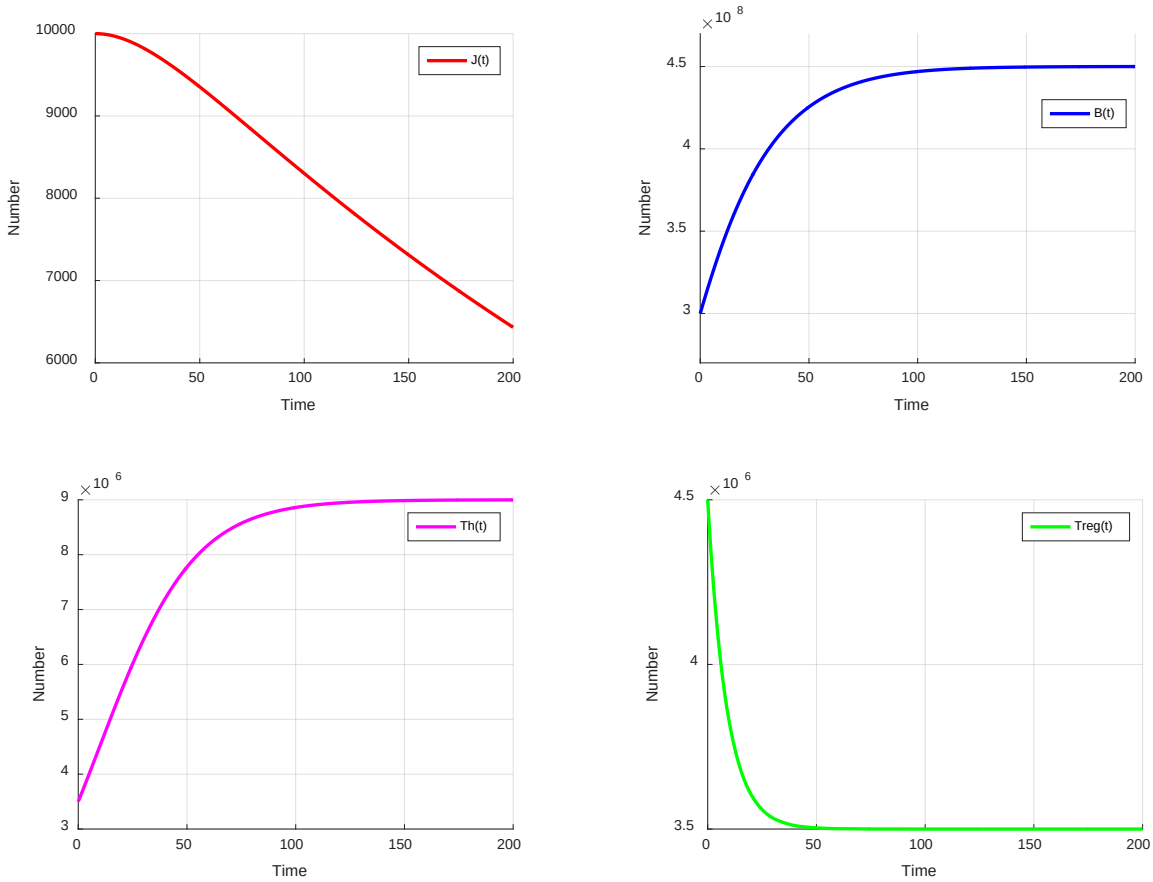

Figure 4: Case when cell values are measured after 100, 160, 50 and 140 days. Dependence of J, B, Th, Treg cells on time.

Table 1: Measured analysis data performed at 25th, 60th, 81st, 105th, 125th, 150th, 175th and 200th days after the first analysis

Number	Day	J(t)	B(t)	Th(t)	Treg(t)
1	0	1.00E+04	3.00E+08	3.50E+06	4.50E+06
2	25	9.80E+03	3.50E+08	3.70E+06	4.10E+06
3	60	9.50E+03	4.10E+08	4.00E+06	3.90E+06
4	81	8.70E+03	4.50E+08	4.20E+06	3.70E+06
5	105	8.50E+03	4.70E+08	4.30E+06	3.50E+06
6	125	8.30E+03	4.80E+08	4.40E+06	3.30E+06
7	150	8.10E+03	5.00E+08	4.45E+06	3.15E+06
8	175	7.50E+03	5.10E+08	4.70E+06	3.00E+06
9	200	7.30E+03	5.40E+08	4.75E+06	2.80E+06

If a series of analyzes are performed, the model can be solved for each time interval, taking values at the last time point of one interval as the initial value of the next interval. The next example outlines case with 9 clinical analyses. Cartilage and lymphocytes are measured at initial stage (t=0), when disease was absent, and other analysis were performed at 25th, 60th, 81st, 105th, 125th, 150th, 175th and 200th days after the first analysis (Table 1).

The coefficients were calculated for each time period. An interpolation spline was built based on these values, and it was applied as coefficients in the model. So, the coefficients become time dependent. Such a scheme of calculations enables the researcher to correct the model in the course of observation (Figure 5).

As it was demonstrated, the more result of laboratory analyses we have, the more accurate is the dynamics of cell increase/decrease.

Turning to "with drug" model, Let us take $\beta = 0.5$. Additional five coefficients must be chosen for this model: k_1, m_1, k_2, m_2, d_3; where $k_1 = 0.005$, $k_2 = 0.025$. $m_1 = 1$ and $m_2 = 1$. Dosage of Tocilizumab is 8 mg / kg and its half-life period is 13 days. We set the dose of drug as 0.8 and d_3 calculate from (14), where $\tau = 13$ [12] Patient gets drug every 4 weeks (Figure 6).

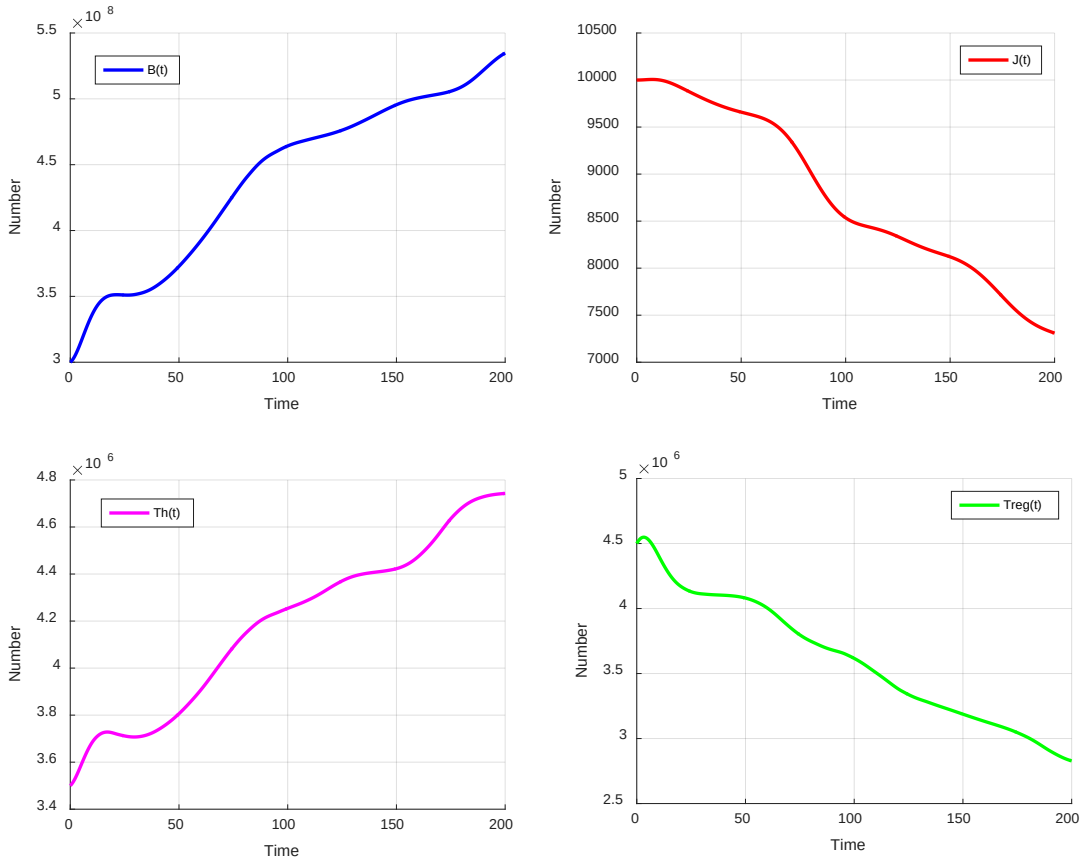

Figure 5: Case when model coefficients become time depended – they are calculated for each time period. Dependence of J, B, Th, Treg cells on time.

Let's consider previous case with (11)-(12)-(13) conditions, calculate coefficients from these conditions and then add drug effect which is taken in the 60th day (Figure 7).

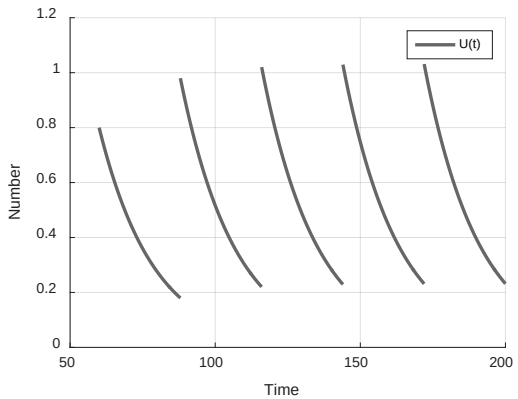

Figure 6: Case when patient gets drug every 4 weeks, Drug concentration in time.

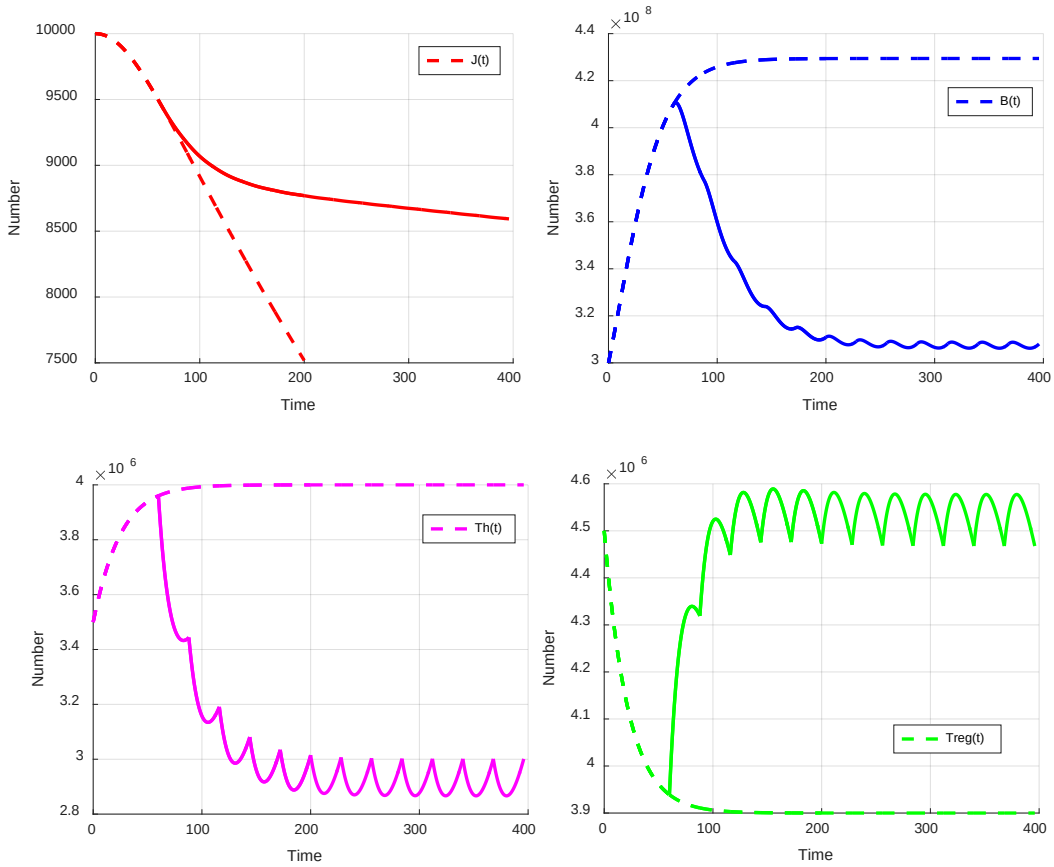

Figure 7: Dependence of J, B, Th, Treg cells in time. Solid lines correspond drug treatment (after 60th day) condition, dashed shows lymphocytes and cartilage levels for "without drug" case.

Discussion

Mathematical models of immune processes are very important tools for fundamental exploration of pathogenesis of the diseases and for optimization of their treatment. Drug delivery, its dosage and treatment duration are often managed by the monitoring systems involving mathematical models and related computer simulation software. Since the immune system is very complex, which consists of multiple dynamic populations of cells, the abridged assumptions have to be applied for the creation of a model. Numerous mathematical models of the immune system have been reported as the original studies and the reviews [21, 22, 23, 24, 25]. Mathematical models are widely applied in the field of cancer immunology and immunotherapy [26, 27]. Studies of various authors are also devoted to the modeling of inflammatory processes and autoimmune disorders. Iwami et al. proposed a general, minimalistic model including only T-cells, tissue damage, and the level of target cells [28]. Several authors have extended the self-immune response/target cell model to incorporate regulation by Tregs. A model of T cell-based immunotherapy for experimental autoimmune encephalomyelitis is reported by Borghans et al. [29]. Models of different mechanisms of Treg function are deciphered by Alexander and Wahl [30]. Few studies explore type 1 diabetes using mathematical models [31, 32]. Some aspects of mathematical model of rheumatoid arthritis are discussed in [33].

In the present study we aimed to establish a basic model of pathogenesis and treatment of autoimmune processes in rheumatoid arthritis. Frequencies and interactions between helper and regulatory T cells, B lymphocytes and target cells define the main parameters of the model. Correct selection of these measurable parameters allows investigators to configure it for an individual patient. Thus, adaptable nature is of a great advantage of the model and may take a rapid pace to be implicated in personalized care of the patients with rheumatoid arthritis. The application of our

mathematical model to create an optimal personalized treatment scheme is the subject of further investigations.

Conclusions

In this paper we report on a novel mathematical model of progression and treatment of rheumatoid arthritis, which easily can be adapted to the other autoimmune diseases. The model is based on assumptions using abridged immune parameters of the disease pathogenesis: helper and regulatory T cells, B lymphocytes, target cells, drug components. Coefficients of equations allow the adaptation of the model to an individual case of patients and the most accurate matching of the mathematical model to the clinical data of a patient can be achieved using the correct selection of the parameters. Such approach facilitates the prediction of the course of disease and the choice of the appropriate treatment regimens. Based on the model, friendly-interface software can be developed which will allow an optimal selection of the treatment dose, drug administration intervals and treatment duration. Of consequential limitation, the complex nature of the disease pathogenesis cannot be covered by this model in its complete extend. Nevertheless, up to now, this is the first system of non-linear differential equations that may most accurately reflect the key mechanism of rheumatoid arthritis - T lymphocyte plasticity (precisely Th17/Treg balance) in patients during active disease and after treatment. The validation of the model using patients' data should be followed as further investigations.

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