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========== **MATHEMATICAL MODELING** ==========

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Mathematical model of the humoral immune response: focusing on Th17 autoimmunity

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Abstract. This work is devoted to development of mathematical model, describing processes of Th and B lymphocyte proliferation and differentiation, as well as IFN-γ, IL-2, IL-4 and IL-21 cytokine secretion. New approaches are suggested, allowing more accurate modelling. Special attention paid to Th17 lymphocyte impact to effect of plasma cells and IgM and IgG antibody level increasing.

Key words: *systems immunology, lymphocyte, cytokine network, IgM, IgG, IL-17.*

INTRODUCTION

Latest immunological researches require reconsidering traditional views on the structure of the immune system. High complexity, rich polymorphism, functional ambiguity, multilevel signalling system: all the parts of immune system are deeply penetrating one another. The building of solid picture of immune processes requires a qualitative generalizing synthesis of many facts of modern science. Unfortunately, such generalization is weakly presented in modern science and does not meet challenges of technological progress, obtaining the accurate experimental data in extraordinary rate. That is why in the last two decades an interest in the use of system approach and especially in its mathematical modelling tools in immunology significantly increased. The large number of studies in the area and the growing number of published reviews indicate the development of a new scientific branch [1]. However existing mathematical models consider the key immunological processes, such as cell differentiation and cytokine synthesis in simplified form, taking not attention of high complexity of the processes. Aim of this work is to generalize available data on Th and B lymphocyte differentiation by mathematical models, giving full and detailed description of the humoral immune response. For this purpose we provided original ideas, allowing detailed imitation of lymphocytes proliferation and differentiation by partial differential equations (PDE). Another processes, such as cells priming, antigen dynamics, etc. are described by nonlinear ordinary differential equations (ODE), following traditional approach in mathematical biology. Special attention is paid to Th17 differentiation modelling with the view of its impact to autoimmune processes development. Model is based on our previous works [2, 3].

GENERAL SCHEMA

Activation, proliferation and differentiation of Th and B lymphocytes during the immune response may show an affluent performance, depending on various factors. In particular, for a specific activation of Th lymphocytes antigen-presenting cells (APC) is needed. Our model is based on the schema, where B lymphocytes play the role of APC [4]. The advantage of this schema is that we don’t need to include additional cell types in the model, thereby reducing the number of equations and simplifying the process, however saving its qualitative part. The

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dynamics of interactions between Th and B lymphocytes in lymph node can be divided in 5 stages, see Fig. 1.

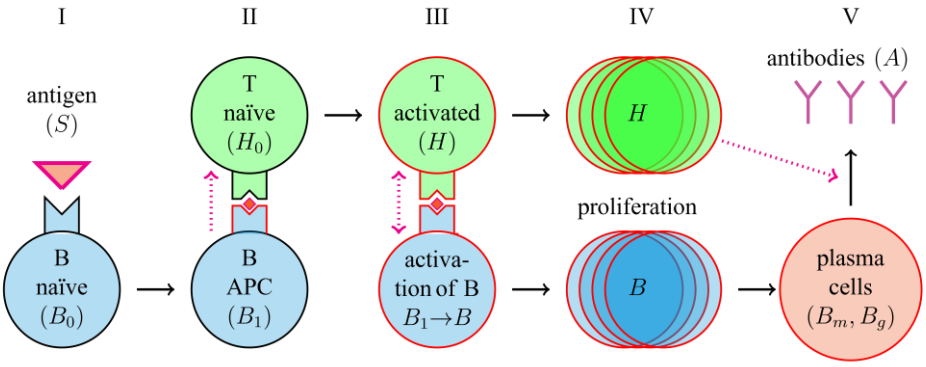

Fig. 1. Interactions between Th and B lymphocytes in lymph node divided in 5 stages: I – priming of B cells, their conversion to APC state; II – activation of Th cells by interaction with APCs; III – activation of B cells by interaction with activated Th cells; IV – proliferation and differentiation of Th and B cells; V – antibody synthesis by plasmocytes (differentiated B cells), switching from IgM to IgG class under influence of Th lymphocytes. The names of variables of the model are given in parentheses.

PROLIFERATION AND DIFFERENTIATION PROCESSES

In our model we take into account the fact, that naïve cells after activation did not become effector cells immediately, but maturing (differentiating) for a long time, going through several phases, gradually changing their cytokine profile and receptor repertoire on their surface [4]. These phases can be estimated by analyzing molecules presented on the membrane of cell (surface markers) [5].

According to empirical data, dynamics of cell differentiation is directly related to the number of divisions, which cells passed [6]. The proliferation rate also depends on the number of divisions [7–10]. Under these circumstances, an accurate model of proliferation during the immune response must take into account the number of divisions, passed by *every* cell. To follow the phenomenological approach a differential equations system was built:

$$\begin{cases} \dfrac{c_i^j - c_{i-1}^j}{\Delta t} = -p_j \dfrac{c_{i-1}^j}{\Delta z} - w_j c_{i-1}^j , & \text{if } j = 0, \\ \dfrac{c_i^j - c_{i-1}^j}{\Delta t} = -p_j \dfrac{c_{i-1}^j - c_{i-1}^{j-1}}{\Delta z} - w_j c_{i-1}^j , & \text{if otherwise.} \end{cases} \quad (1)$$

Here $\left\{c_i^j\right\}$ is a mash function: each value corresponds to concentration of cells at time $t = i\Delta t$ passed $z = j\Delta z$ cell cycles. Integer part of z describes the number of divisions passed, and the fractional part – current stage of cell cycle. We called Oz axis the proliferation line, since each unit segment corresponds to a full cell cycle, as shown in Fig. 2; p_j characterizes proliferation rate, w_j – death rate.

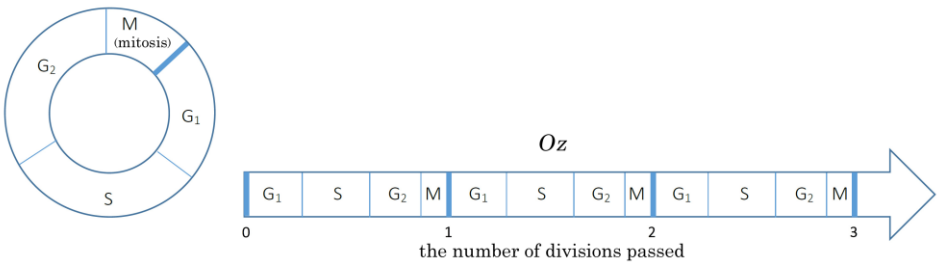

Fig. 2. On the left - a traditional scheme of the cell cycle. On the right - proliferation line: ratio of phases' lengths to each other is equal to the ratio of average time periods elapsed for phases.

Model (1) may be approximated by continuous equation. Here is a resulting PDE:

$$\frac{\partial C}{\partial t}(t,z) = -p(z)\frac{\partial C(t,z)}{\partial z} - w(z)C(t,z), \qquad (2)$$

where $C(t,z)$ is the concentration of precursor cells at time t passed z cell cycles, $p(z)$ is proliferation rate; $w(z)$ is rate of cell death. This equation is a modification of McKendrick-von Foerster age-structured population model proposed in 1926 [11, 12].

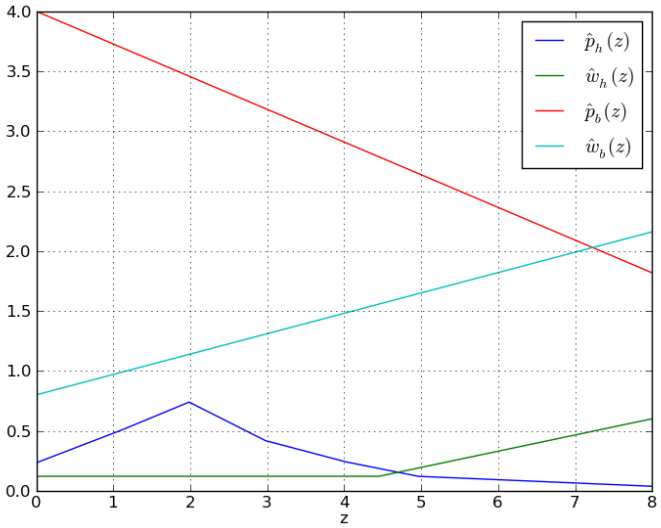

Fig. 3. Empirical functions of proliferation rate (p) and death rate (w) for Th (h) and B lymphocytes (b) depends on the number of divisions passed (z).

Recently a number of mathematical models of cell proliferation has been developed, which are also based on ideas of McKendrick-von Foerster [8–10]. These specialized models are designed to interpret data of flow cytometry, particularly to determine dynamical characteristics of proliferating cells such as a probability of division or death. We used the results of data analysis derived by these models to determine functions $p(z)$ and $w(z)$ (see Fig. 3).

The special feature of this model (2) is that the proliferation in it is considered as a process of movement of progenitor cells through several cell cycles. Assuming that division of one cell results in two identical cells, we continue to pursue cell-precursor as a single cell started a new cell cycle. The *Oz* axis position of precursor cell shows, how many divisions the cell passed. So we can find the resulting number of divided cells: let the number of precursors be H_0 and the number of divisions be z, then the number of divided cells is $2^z H_0$. For equation (2) total number N of cells divided for the time T will be:

$$N = \int_0^z 2^{\zeta} H(T,\zeta)d\zeta.$$

PARTICULARITIES OF CYTOKINE SYNTHESIS BY CELL

Cytokines are main mediators of immune reactions. Generally, the main purpose of cytokine synthesis is an autocrine or paracrine action. Despite the large number of data published, the dynamics of cytokines production by single cell still is badly known. Usually researchers measure cytokine level in peripheral blood, where there is only little portion of protein synthesized *in situ* (in lymph nodes or nidus of infection). Estimation of cytokine concentration and dynamics *in situ* and interpretation of such data is a very difficult problem,

because the level of cytokines in the place, where intensive dynamic processes occur, may vary by orders in a short time, and the number of cytokine-synthesizing cells is also not always possible to determine precisely. Nevertheless, on the basis of several works one can roughly approximate the rate of cytokines synthesis and its dynamics in time [6, 13–16].

The data of IL-4 and IFN-γ synthesis dynamics by differentiating T cells shows that the rate of particular cytokine synthesis depends on the number of divisions, which cells passed (this value stabilizes only after 4th division [6]). Dynamics of IL-2 synthesis by T cells also was investigated [14–16]. The features of cytokines synthesis are summarized on Fig. 4.

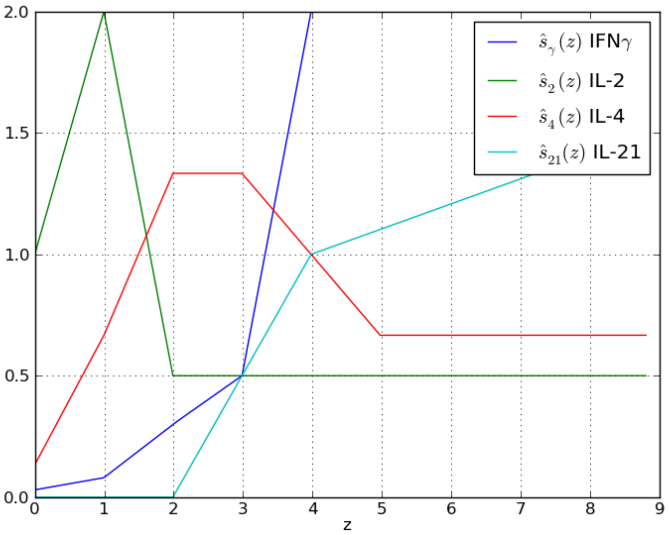

Fig. 4. Dynamics of cytokines production depending on number of divisions, which cell passed (*z*).

For proliferation equation (2) the cytokine concentration dynamics will be:

$$\frac{dI(t)}{dt} = \int_0^{\nu} 2^{\zeta} s(\zeta) H(t,\zeta) d\zeta - w_I I(t),$$

where $s(z)$ is the rate of cytokine synthesis by cell passed z divisions; w_I is rate of cytokine degradation.

FEATURES OF TH LYMPHOCYTE DIFFERENTIATION

During differentiation naïve Th0 cell may change its phenotype in several alternatives – this is the most important component of differentiation, a key stone for selecting the immune response type.

There are a few works devoted to mathematical modelling of Th0 lymphocytes differentiation to Th1 and Th2 phenotypes [17-19]. Most of them are based on the well-known theory of regulatory genes proposed by Jacob and Monod in 1962. In various areas of Mathematical Biology and Biophysics there are a large number of models of that type, e.g., genetic trigger model proposed by Chernavsky [20]. The main idea of this theory is that differentiation is managed by some of the leading gene-regulators.

However, our knowledge of Th lymphocyte differentiation mechanisms is not full. The recent discovery of complex cytokine network leading differentiation processes and the existence of other phenotypes, e.g. Treg, Th17, Th9, Th22, have questioned sufficiency of the genetic trigger model for this phenomenon. Therefore, we proposed the original model which describes the differentiation of T cells in three different phenotypes, that are Th1, Th2, Th17, taking into account the influence of cytokine network.

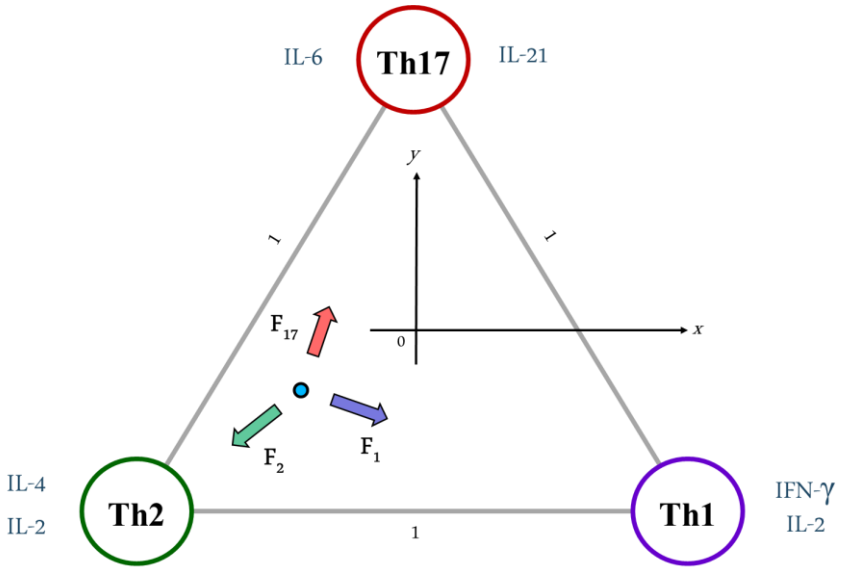

Fig. 5. Triangle of differentiation. The closer the point is to one of peaks, the more cells of such phenotype are in population. Magnitude of forces acting on point depends on concentrations of the proper differentiation factors, i.e. cytokines IFN-γ, IL-2, IL-4, IL-6, IL-21 and others.

Proliferating and differentiating cell with every division passed begins to synthesize more and more cytokines of particular profile, affecting the other dividing cells, forcing them to differentiate along the same way. We describe cells susceptibility to three differentiation ways by a point moving inside isosceles triangle, called the "triangle of differentiation" (Fig. 5). The closer the point is to one of its vertices, the greater is the fraction of cells differentiating in appropriate way. We assume that naïve Th cell after the activation has the equal predisposition to three main phenotypes, i.e. it corresponds to the point in the centre of triangle. The strength of forces $\mathbf{F_1}$, $\mathbf{F_2}$ and $\mathbf{F_{17}}$ depends on concentration of cytokines IFN-γ, IL-2, IL-4, IL-6, IL-21, so the point moves towards the vertex, which differentiation factor is prevailing. One can say that the point is moving in the triangle under the influence of cytokine fields (see Fig. 6).

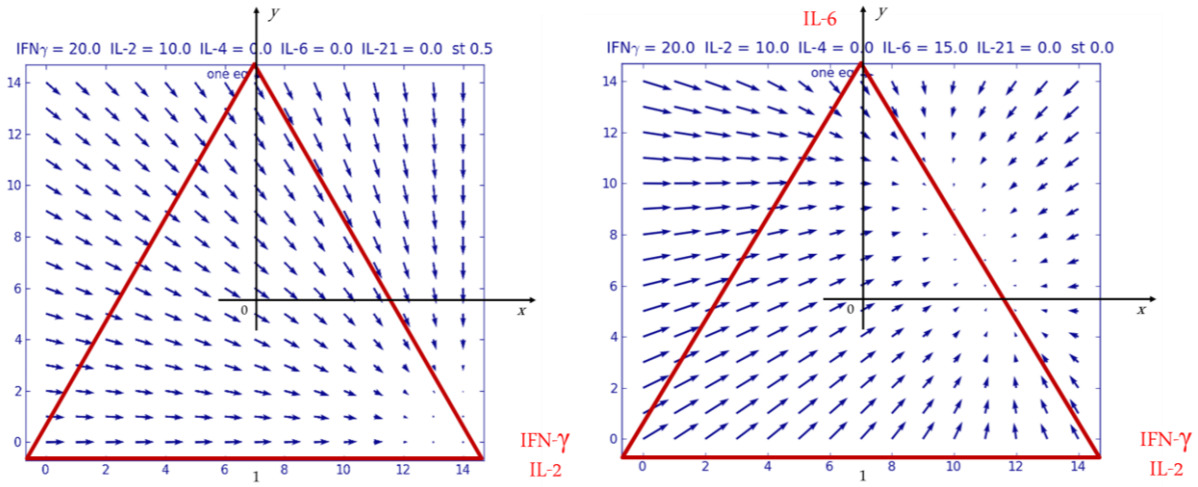

Fig. 6. Cytokine field produced inside the triangle of differentiation under influence of high concentrations of cytokines: a) IFN-γ and IL-2; b) IFN-γ, IL-6, IL-2.

If we take into account that differentiating cells also move on the proliferation line, then geometrical interpretation of the model will be as a triangle moving along the line with the point moving inside the triangle (see Fig. 7).

Another feature of differentiation process, which has also been modelled is the plasticity of Th lymphocytes. By plasticity we mean possibility of proliferating cells to switch to another phenotype, if environment's conditions changed. Certainly, plasticity of a cell decreases with each division [6, 19, 21]. In the model this is implemented so that the more divisions the cells have passed, the weaker are act at the appropriate point forces $\mathbf{F_1}$, $\mathbf{F_2}$ and $\mathbf{F_{17}}$, thereby the position of the dot is stabilized (see Fig. 7). On the basis of data obtained by Grogan et al. [6], we built the function of plasticity $\hat{b}(z)$ (Fig. 8).

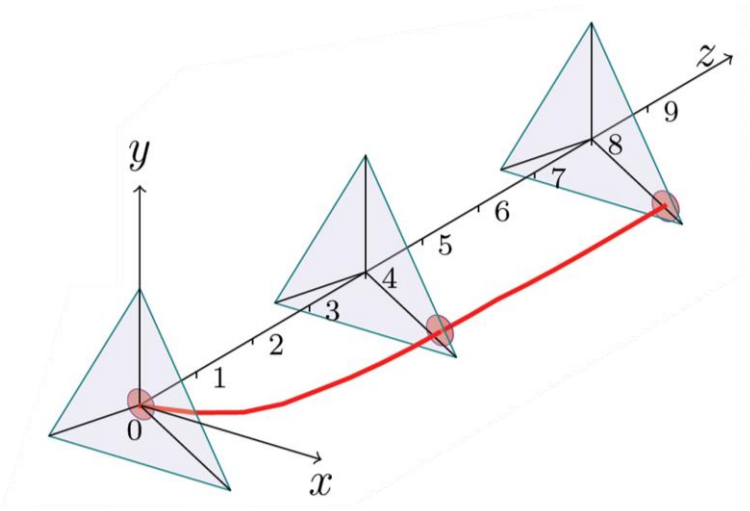

Fig. 7. Geometrical interpretation of the model: a point moves in triangle (of differentiation), and triangle moves along the line (of proliferation).

Th17 immune response was accurately modelled. Bettelli et al. observed a nonlinear dynamical effect of some cytokines on the Th17 differentiation [22]. For example, IL-6 is of greatest significance at the beginning of differentiation, whereas IL-21 is more important in the later stage (when IL-6 loses its relevance). Hence functions $\hat{g}_6(z)$ and $\hat{g}_{21}(z)$, which determine impact of IL-6 and IL-21 on the Th17 differentiation, were introduced into the model (see Fig. 8).

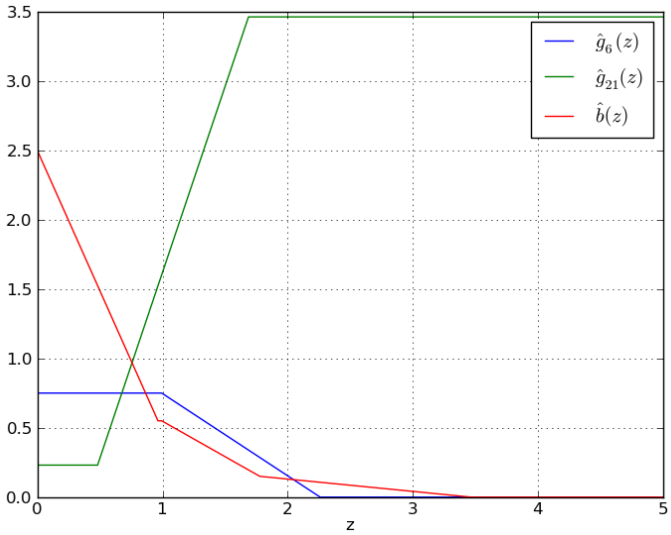

Fig. 8. Plasticity function and functions of the influence of IL-6 and IL-21 on the Th17 differentiation, depending on the number of divisions passed (z).

MODEL

As a result, a system of equations (3)–(22), consisting of 4 PDE (7)–(10) and 16 ODE (3)–(6), (11)–(22), has been built:

$$\frac{dS}{dt} = \hat{\lambda}_s(t) - k\frac{A_m + A_g}{1+\delta_a(A_m + A_g)}S, \tag{3}$$

$$\frac{dB_0}{dt} = \sigma_b - \alpha_s\frac{S}{S + S^* B_0}B_0 - w_b B_0, \tag{4}$$

$$\frac{dH_0}{dt} = \sigma_h - \alpha_b\frac{B_1 + B_\sigma}{B_1 + B_\sigma + B^* H_0}H_0 - w_0 H_0, \tag{5}$$

$$\frac{dB_1}{dt} = \alpha_s\frac{S}{S + S^* B_0}B_0 - \alpha_h B_1\frac{\int_0^\nu 2^\zeta H(t,\zeta)d\zeta}{\int_0^\nu 2^\zeta H(t,\zeta)d\zeta + H^* B_1} - w_b B_1, \tag{6}$$

$$\frac{\partial H}{\partial t} = -\hat{p}_h(z)\frac{\partial H}{\partial z} - \left(\hat{m}_h(z) + \hat{w}_h(z)\right)H, \tag{7}$$

$$\frac{\partial B}{\partial t} = -\hat{p}_b(z)\frac{\partial B}{\partial z} - \left(\hat{m}_b(z) + \frac{\hat{w}_b(z)}{1+\gamma(t)}\right)B, \tag{8}$$

$$\frac{\partial X}{\partial t} = -\hat{p}_h(z)\frac{\partial X}{\partial z} + F_x^*(\mathbf{F_1}, \mathbf{F_2}, \mathbf{F_{17}}, z), \tag{9}$$

$$\frac{\partial Y}{\partial t} = -\hat{p}_h(z)\frac{\partial Y}{\partial z} + F_y^*(\mathbf{F_1}, \mathbf{F_2}, \mathbf{F_{17}}, z), \tag{10}$$

$$\frac{dB_m}{dt} = \left(\int_0^\nu 2^\zeta \hat{m}_b(\zeta)B(t,\zeta)d\zeta + 2^\nu \hat{p}_b(\nu)B(\nu,t)\right)\left(1 - \frac{H_\sigma}{H_g^* + H_\sigma}\right) - w_m B_m, \tag{11}$$

$$\frac{dB_g}{dt} = \left(\int_0^\nu 2^\zeta \hat{m}_b(\zeta)B(t,\zeta)d\zeta + 2^\nu \hat{p}_b(\nu)B(\nu,t)\right)\frac{H_\sigma}{H_g^* + H_\sigma} - w_g B_g, \tag{12}$$

$$\frac{dH_1}{dt} = \int_0^\nu 2^\zeta \hat{m}_h(\zeta)H(t,\zeta)\,f_{h1}(t,\zeta)d\zeta + 2^\nu \hat{p}_h(\nu)H(\nu,t) - w_h H_1, \tag{13}$$

$$\frac{dH_2}{dt} = \int_0^\nu 2^\zeta \hat{m}_h(\zeta)H(t,\zeta)\,f_{h2}(t,\zeta)d\zeta + 2^\nu \hat{p}_h(\nu)H(\nu,t) - w_h H_2, \tag{14}$$

$$\frac{dH_{17}}{dt} = \int_0^\nu 2^\zeta \hat{m}_h(\zeta)H(t,\zeta)\,f_{h17}(t,\zeta)d\zeta + 2^\nu \hat{p}_h(\nu)H(\nu,t) - w_h H_{17}, \tag{15}$$

$$\frac{dI_\gamma}{dt} = \rho_\gamma\int_0^\nu 2^\zeta H(t,\zeta)\,f_{h1}(t,\zeta)\hat{s}_\gamma(\zeta)d\zeta - w_\gamma I_\gamma, \tag{16}$$

$$\frac{dI_2}{dt} = \rho_2\int_0^\nu 2^\zeta H(t,\zeta)\left(f_{h1}(t,\zeta) + f_{h2}(t,\zeta)\right)\hat{s}_2(\zeta)d\zeta - w_2 I_2, \tag{17}$$

$$\frac{dI_4}{dt} = \rho_4 \int_0^{\nu} 2^{\zeta} H(t,\zeta)\, f_{\mathrm{h}2}(t,\zeta)\hat{s}_4(\zeta)d\zeta - w_4 I_4, \tag{18}$$

$$\frac{dI_6}{dt} = \hat{\lambda}_6(t) - w_6 I_6, \tag{19}$$

$$\frac{dI_{21}}{dt} = \rho_{21} \int_0^{\nu} 2^{\zeta} H(t,\zeta)\, f_{\mathrm{h}17}(t,\zeta)\hat{s}_{21}(\zeta)d\zeta - w_{21} I_{21}, \tag{20}$$

$$\frac{dA_m}{dt} = \rho_m B_m - k\frac{A_m}{1+\delta_a A_m} S - w_{a_m} A_m, \tag{21}$$

$$\frac{dA_g}{dt} = \rho_g B_g - k\frac{A_g}{1+\delta_a A_g} S - w_{a_g} A_g, \tag{22}$$

where

$$B_\sigma = \int_0^{c} 2^{\zeta} B(t,\zeta)d\zeta, \qquad H_\sigma = \int_d^{\nu} 2^{\zeta} H(t,\zeta)d\zeta, \qquad \gamma(t) = \delta_h \frac{\left(\int_d^{\nu} 2^{\zeta} f_{\mathrm{h}17}(t,\zeta) H(t,\zeta)d\zeta\right)^2}{\left(\int_d^{\nu} 2^{\zeta} f_{\mathrm{h}17}(t,\zeta) H(t,\zeta)d\zeta\right)^2 + \left(H_{17}^*\right)^2},$$

$$f_{\mathrm{h}i}(t,z) = \frac{|d_f - r_i|}{|d_f - r_1| + |d_f - r_2| + |d_f - r_{17}|}.$$

$$\mathbf{F}^* = (\mathbf{F_1} + \mathbf{F_2} + \mathbf{F_{17}})\hat{b}(z), \tag{23}$$

$$|\mathbf{F_1}| = \frac{I_\gamma}{I_\sigma}\left(1 + \frac{I_2}{I_\sigma + I_2}\right) h_1(t,z), \tag{24}$$

$$|\mathbf{F_2}| = \frac{I_4}{I_\sigma}\left(1 + \frac{I_2}{I_\sigma + I_2}\right) h_2(t,z), \tag{25}$$

$$|\mathbf{F_{17}}| = \left(\frac{I_4}{I_\sigma}\hat{g}_6(z) + \frac{I_{21}}{I_\sigma}\hat{g}_{21}(z)\right) h_{17}(t,z), \tag{26}$$

$$I_\sigma = I_\gamma + I_2 + I_4 + I_6 + I_{21}, \quad h_i(t,z) = \frac{r_i^{k_1}}{d_h + r_i^{k_2}},$$

where $r_i(t,z)$, i = 1, 2, 17, is a distance from the triangle vertex Thi to the point $(X(t,z), Y(t,z))$.

Initial conditions

$$\begin{aligned} &S = S_0, \quad B_0 = B_0^*, \quad H_0 = H_0^*, \quad H_1 \equiv 0, \quad H_2 \equiv 0, \quad H_{17} \equiv 0, \\ &B_1 \equiv 0, \quad H \equiv 0, \quad B \equiv 0, \quad X \equiv 0, \quad Y \equiv 0, \quad B_m \equiv 0, \quad B_g \equiv 0, \\ &A_m \equiv 0, \quad A_g \equiv 0, \quad I_\gamma \equiv 0, \quad I_2 \equiv 0, \quad I_4 \equiv 0, \quad I_6 \equiv 0, \quad I_{21} \equiv 0. \end{aligned} \tag{27}$$

Boundary conditions

$$H(t,0)=\frac{\alpha_b}{\hat{p}_h(0)}\left(B_1+B_\sigma\right)H_0, \qquad X(t,0)=0,$$

$$B(t,0)=\frac{\alpha_h}{\hat{p}_b(0)}B_1\frac{\int_0^{\nu}2^{\zeta}H(t,\zeta)d\zeta}{\int_0^{\nu}2^{\zeta}H(t,\zeta)d\zeta+H^{*}B_1}, \qquad Y(t,0)=0. \tag{28}$$

Equation (3) describes concentration of antigen: the first term in the right describes the inflow of antigen, the second the waning due to elimination by antibodies.

Naïve B lymphocytes in (4): the first and last terms describe homeostasis of cells, the second is a converting to the antigen presenting cell (APC) due to encounter with pathogen (Fig. 1,I).

Naïve Th0 cells in (5): the first and last terms describe homeostasis of cells, the second – activation due interacting with APCs and activated B cells (Fig. 1,II).

B cells in APC state waiting for a signal from Th cells (6): second term is activation and proliferation beginning as a result of meeting with activated Th lymphocytes (Fig. 1,III).

Proliferation and differentiation of Th cells (7), described as a movement of cells through a series of cell cycles: $H(t,z)$ is concentration of cells at the time *t* with *z* divisions passed (one cell cycle equal to 1), $\hat{p}_h(z)$ is proliferation rate, $\hat{m}_h(z)$ is rate of migration from lymph node, $\hat{w}_h(z)$ is death rate of proliferating cells (Fig. 1,IV).

Proliferation and differentiation of B cells equation (8) is similar to equation (7), but also describes the impact of Th17 cells. Th17 is able to decrease apoptosis of proliferating B lymphocytes due to synthesis of IL-17 [23]. This ability is realized by the function $\gamma(t)$.

Internal phenotype changes in proliferating Th cells (9), (10). *X* and *Y* are the coordinates of point inside the triangle of differentiation that identify the distribution of cells on Th1, Th2, and Th17 subpopulations. The point moves under the action of forces $\mathbf{F_1},\mathbf{F_2},\mathbf{F_{17}}$ (Fig. 5).

The concentration of mature B cells (plasmocytes) synthesizing IgM and IgG antibodies, respectively (11) and (12): first multiplier in large brackets describes migration of mature B lymphocytes from lymph node, the second multiplier in large brackets describes influence of differentiated Th lymphocytes on isotype switching from IgM to IgG class, the last term describes death of cells due to apoptosis.

Equations (13)–(15) describe dynamics of mature Th cells (Th1, Th2, and Th17, respectively) on periphery: first two terms – migration of mature Th lymphocytes from the lymph node, the last term – apoptosis (natural death) of Th lymphocytes. Functions $f_{\mathrm{h1}}(t,z)$, $f_{\mathrm{h2}}(t,z)$, $f_{\mathrm{h17}}(t,z)$ define the percentage of total number of proliferating Th cells, being in the Th1, Th2 and Th17 state, respectively.

Dynamics of IFN-γ (16): the first term describes cytokine synthesis by Th1 lymphocytes, second term – degradation of cytokine. The function $\hat{s}_\gamma(z)$ determines rate of cytokine synthesis by cell, depending on the number of divisions passed.

Dynamic of IL-2 (17) described similarly to (16), but the source of cytokine is Th1 and Th2 cells.

Dynamic of IL-4 (18) described similarly to (16), but the source of cytokine is Th2 lymphocytes.

Dynamics of IL-6 (19): the first term describes the inflow of cytokine from external source, the second term – degradation of cytokine.

Dynamic of IL-21 (20) described similarly to (16), but the source of cytokine is Th17 lymphocytes.

Equations (21) and (22) describe synthesis, consumption and natural decay of IgM and IgG antibodies, respectively.

$B_\sigma(t)$ is concentration of centroblasts (in our case the fraction of proliferating B cells that passed no more than c divisions and whereby able to provoke activation of naïve Th0 cells).

$H_\sigma(t)$ is concentration of differentiating Th lymphocytes that passed more than d divisions and able to provoke the switching of B cells antibody's isotype from IgM to IgG.

The functions $\hat{p}_{h,b}(z)$, $\hat{m}_{h,b}(z)$, $\hat{w}_{h,b}(z)$, $\hat{b}(z)$, $\hat{s}_i(z)$, $\hat{g}_i(z)$ were taken from empirical data available in literature (see Fig. 3, 4, 8); $\hat{\lambda}_s(t)$, $\hat{\lambda}_6(t)$ are variable functions used for providing computational experiments.

Coefficients were determined on the basis of available data [23–37] or were picked up during performance of computational experiments (Table 1 shows values in case of Figures 14 and 15, in other cases parameters may vary to a little degree).

Table 1. Values of coefficients

Coeff.	Description	Value	Unit
α_b	effectiveness of recognition antigen-MHC complex by naïve CD4+ T lymphocytes	2	L day^{-1}
α_h	effectiveness of second activation signal of B cells, required for initiation of proliferation and differentiation processes	5.15	L day^{-1}
α_s	effectiveness of first activation signal for B cells, causing increased expression of B7 and MHC molecules and following transition into the state of APC (B_1)	20.25025	L day^{-1}
B_0^*	normal concentration of specific clone of B lymphocytes	6493	cell L^{-1}
B^*	mitigating factor	5	–
c	maximum number of divisions of B lymphocytes, where they still retain the function of the APC	3.3	cycles
d	number of divisions T cell must to go to have opportunity to effect the switching of immunoglobulin synthesis in B cells	4	cycles
δ_a	mitigating factor	10^8	L mole^{-1}
δ_h	magnitude of death rate decreasing in proliferating B lymphocytes due to action of the Th17	3	–
d_f	factor regulating Th lymphocytes phenotype distribution.	1.05	–
d_h	factor which determines the plasticity effect of differentiating Th lymphocytes	0.01	–
H_0^*	normal concentration of Th0 specific clones in the blood	5403	cell L^{-1}
H_g^*	concentration of activated specific Th cells in lymph nodes, at which 50% of B lymphocytes switching from IgM to IgG antibody synthesis	1000	cell L^{-1}
H_{17}^*	Th17 concentration at which their effect on B cells death rate reducing is half of maximum possible	10000	cell L^{-1}
H^*	mitigating factor	0.5	–
k	biochemical constant of antigen-antibody complex formation rate, efficiency of autoantigen neutralization by autoantibody (here is used data of dsDNA oligonucleotides as autoantigen and anti-dsDNA antibody as autoantibody in patients with systemic lupus erythematosus)	3.54×10^9	mole^{-1} day^{-1}

k_1	coefficient that determines plasticity of T cells	2.2	–
k_2	coefficient that determines plasticity of T cells	2	–
ν	maximum number of cell cycles for proliferating Th and B cell in lymph node	8.3	cycles
ρ_2	rate of IL-2 synthesis by Th cell	0.022102	pg cell^{-1} day^{-1}
ρ_{21}	rate of IL-21 synthesis by Th cell	0.05	pg cell^{-1} day^{-1}
ρ_4	rate of IL-4 synthesis by Th cell	0.0565	pg cell^{-1} day^{-1}
ρ_g	rate of IgG synthesis by plasmocyte	2.43×10^{-11}	mole cell^{-1} day^{-1}
ρ_γ	rate of IFN-γ synthesis by Th cell	0.043	pg cell^{-1} day^{-1}
ρ_m	rate of IgM synthesis by plasmocyte	8.22×10^{-10}	mole cell^{-1} day^{-1}
S_0	average concentration of dsDNA autoantigen in blood of patients with systemic lupus erythematosus	2.12×10^{-10}	mole L^{-1}
S^*	mitigating factor, derived on the basis of average dsDNA concentration in healthy people blood	2.6×10^{-11}	mole cell^{-1}
σ_b	rate of natural increase of antigen-specific B cells level due to lymphopoiesis	297.0588	cell L^{-1}day^{-1}
σ_h	rate of natural increase of antigen-specific Th lymphocytes due to lymphopoiesis	27.72727	cell L^{-1}day^{-1}
w_0	death rate of naïve T cells due to reasons not related to the immune response	0.003229	day^{-1}
w_2	rate of natural degradation of IL-2	2.77	day^{-1}
w_6	rate of natural degradation of IL-6	2.77	day^{-1}
w_4	rate of natural degradation of IL-4	2.77	day^{-1}
w_{21}	rate of natural degradation of IL-21	2.77	day^{-1}
w_{a_g}	rate of natural degradation of IgG antibodies	0.046739	day^{-1}
w_{a_m}	rate of natural degradation of IgM antibodies	0.8	day^{-1}
w_b	death rate of non-activated B lymphocytes	0.04575	day^{-1}
w_g	death rate of plasmocytes, producing IgG antibodies	0.007639	day^{-1}
w_γ	rate of natural degradation of IFN-γ	4.10625	day^{-1}
w_h	death rate of mature Th cells	0.005131	day^{-1}
w_m	death rate of plasmocytes, producing IgM antibodies	0.266667	day^{-1}

NUMERICAL METHODS AND PROGRAM IMPLEMENTATION

The model has been used to make a number of computational experiments. Numerical procedures have been used as follows: for ODE solving the Euler-Cauchy method, for PDE solving the Lax-Wendroff method with elements of flow correction method [38] and the trapezoidal rule for integration. The methods have been implemented in Python programming language with the use of NumPy package (optimizing the work with large data sets) and Matplotlib package (2D and 3D results visualization).

RESULTS OF SIMULATION

Differentiation of B lymphocytes. Immunoglobulin classes switching

To study dynamics of IgM synthesis and further switching to IgG synthesis several computational experiments were prepared. At the first time only a single antigen dose was added (i.e. function $\hat{\lambda}_s(t) \equiv 0$). As a result, only IgM class antibodies formed (Fig. 9). Next time there was a permanent source of antigen ($\hat{\lambda}_s(t) = 1.5 \times 10^{-8}$ mole $L^{-1}day^{-1}$, see Fig. 10). In this case plasmocytes appeared to synthesize large amounts of IgM class antibodies on the third day. Then two days later a process started of their replacing by IgG synthesizing plasmocytes, thereby after two weeks IgG antibodies began to prevail.

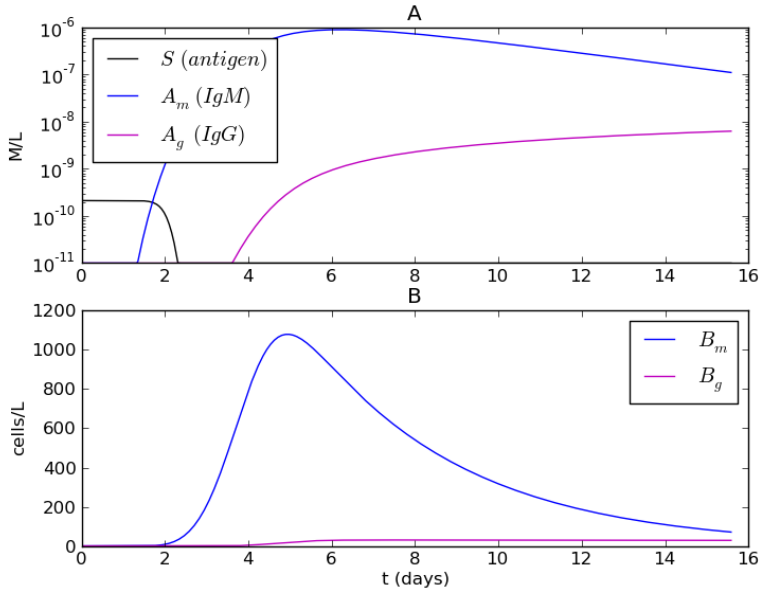

Fig. 9. A. Changes of antigen and antibody concentrations in blood after single injection of antigen: IgM antibodies prevail. B. Dynamics of different subpopulations of plasmocytes in peripheral blood.

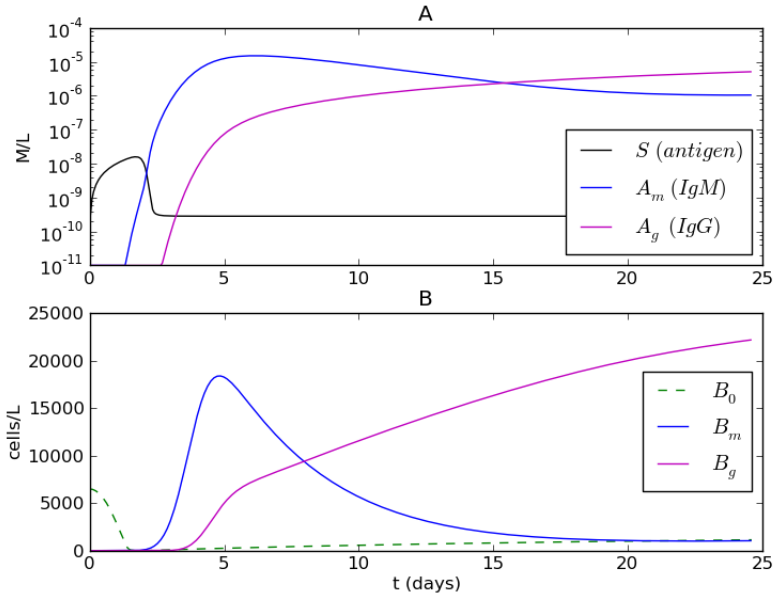

Fig. 10. A. Changes in concentration of antigen and antibody in the presence of external source of antigen. B. Dynamics of different subpopulations of plasmocytes in peripheral blood.

It is known that individuals with a low threshold for activation of B lymphocytes are susceptible to autoimmune diseases [39]. Computational experiment with reduced activation threshold leads to a strong immune reaction even in the case of single injection of low dose of antigen. However, the model shows that immune reaction may be moderate, if some initial concentration of specific antibodies is presented (data not shown).

Features of Th lymphocytes differentiation

A situation where an external source of IL-6 leads to Th17 immune response development was modelled (Fig. 11). The presence of IL-6 at the beginning of differentiation results in secreting of large amounts of IL-21 by differentiating cells (Fig. 11,A), so the differentiation of T cells in the direction of Th17 phenotype is prevailing (Fig. 11,B).

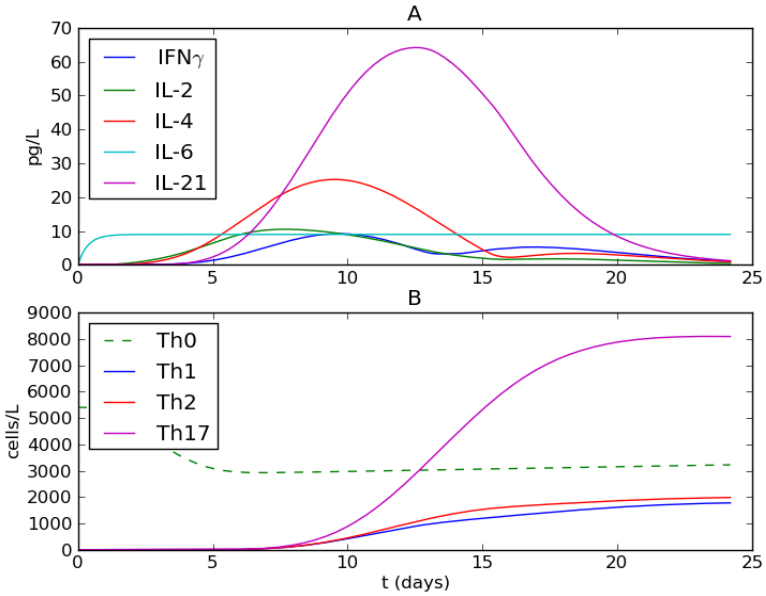

Fig. 11. **A**. Dynamics of cytokine synthesis by differentiating Th lymphocytes in presence of external source of IL-6. **B**. Issue of differentiated Th lymphocytes in peripheral blood.

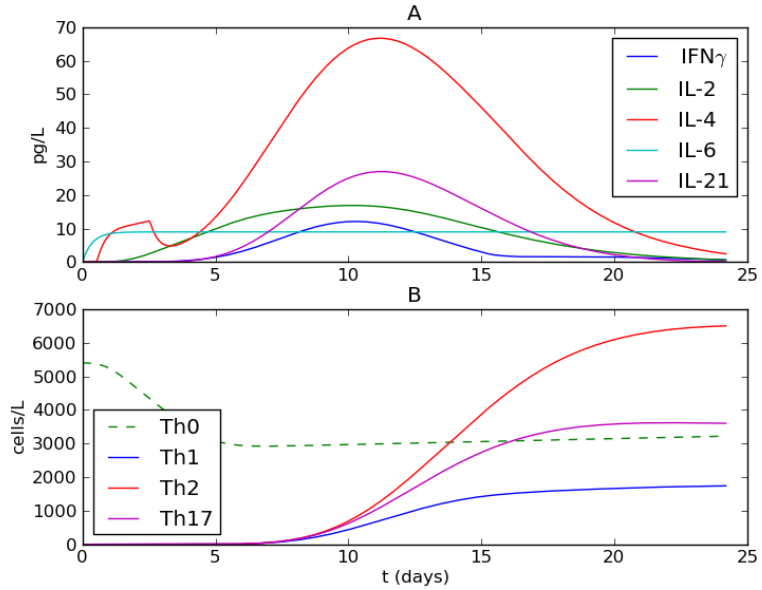

Fig. 12. **A**. Dynamics of cytokine synthesis by differentiating Th lymphocytes in the presence of external source of IL-6 and short-time IL-4 administration. **B**. Issue of differentiated Th lymphocytes in peripheral blood.

In the next experiment there were the same initial conditions, but in the period from 12 to 60 hours after the start of simulation an external source of IL-4 was added, which level was comparable with IL-6 source level (see Fig. 12). The changes are dramatic: short-time administration of IL-4 at the beginning switched immune response to Th2 way, despite permanent presence of IL-6. As a result, there are 55% of Th2, 30% of Th17 (which is supported by the external source of IL-6) and 15% of Th1. Such effect occurs, because differentiation of Th17 is inhibited by IL-2, which is synthesized by Th1 and Th2 lymphocytes.

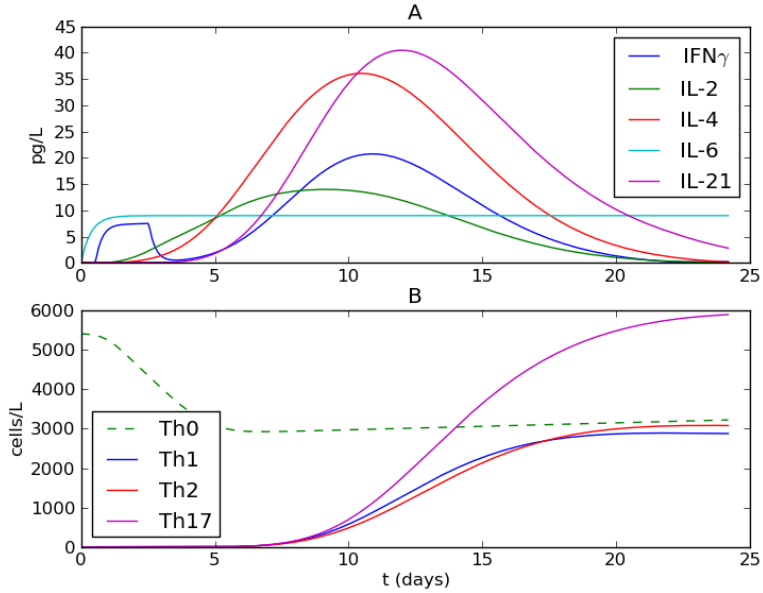

Fig. 13. **A**. Dynamics of cytokine synthesis by differentiating Th lymphocytes in the presence of external source of IL-6 and short-time IFN-γ administration. **B**. Issue of differentiated Th lymphocytes in peripheral blood.

The next experiment repeated the previous one, but IFN-γ instead IL-4 administration was used in the same dose (Fig. 13). Result is surprizing: 51% of Th17, 25% of Th2, 24% of Th1. This happens because the lifetime of the IFN-γ (according to available experimental data) is much less than the lifetime of IL-4. When administration of IFN-γ was stopped, a natural competition between Th1 and Th2 occurs. More durable IL-4 inhibited Th1 differentiation. As a result, the short-time administration of IFN-γ in the background of IL-6 did not switch the type of immune response. This example shows significance of cytokine dynamics at the early stage of differentiation, when specific parameters, such as the lifetime of cytokines, are of the great importance.

Increased expansion of B lymphocytes under the action of Th17 cells

IL-17 produced by Th17 cells increases the survival rate of B lymphocytes in 3 or 4 times [23, 35]. Two scenarios were simulated: Th2 immune response (Fig. 14) and Th17 immune response (Fig. 15). In both experiments similar parameters of the model was used, but in the case of Th17 an external source of IL-6 was added to initiate Th17 differentiation. The resulting B cell responses were compared. One can see that in the second case the expansion of B lymphocytes increased twofold.

Recently genome-wide association studies have identified predisposition to Th17 immune response in patients with systemic lupus erythematosus (which is a severe autoimmune disease) [39]. To examine the role of Th17 in this disease a special extension of the model has been made. The data of 295 patients of St. Petersburg First Pavlov Medical Institute and the City's Rheumatological Centre were used to make a number of simulations of systemic lupus

erythematosus development during a period of 200 days. It has been found that Th17 immune response increases the level of plasma cells and autoantibodies up to 6 times (in comparison to Th2 immune response in the same conditions) [40, 41].

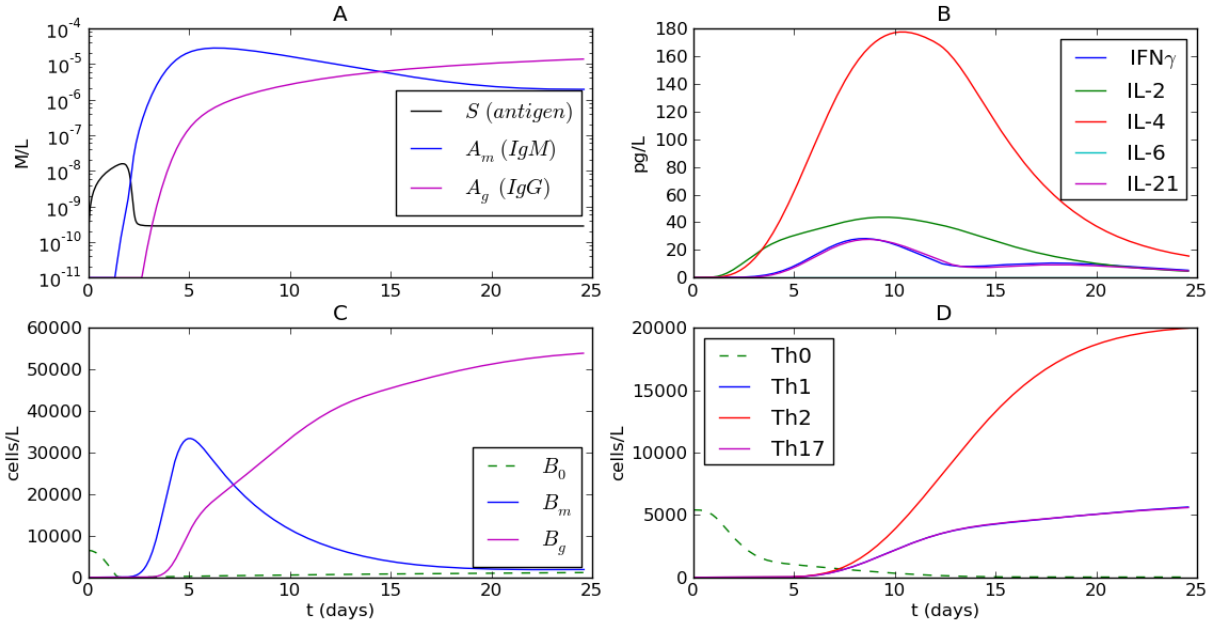

Fig. 14. **A**. Dynamics of antigen and antibody in peripheral blood. **B**. Dynamics of cytokine synthesis by Th lymphocytes in lymph node: Th2 immune response development. **C**. Dynamics of different subpopulations of plasmocytes in peripheral blood. **D**. Antigen-specific Th lymphocytes in peripheral blood.

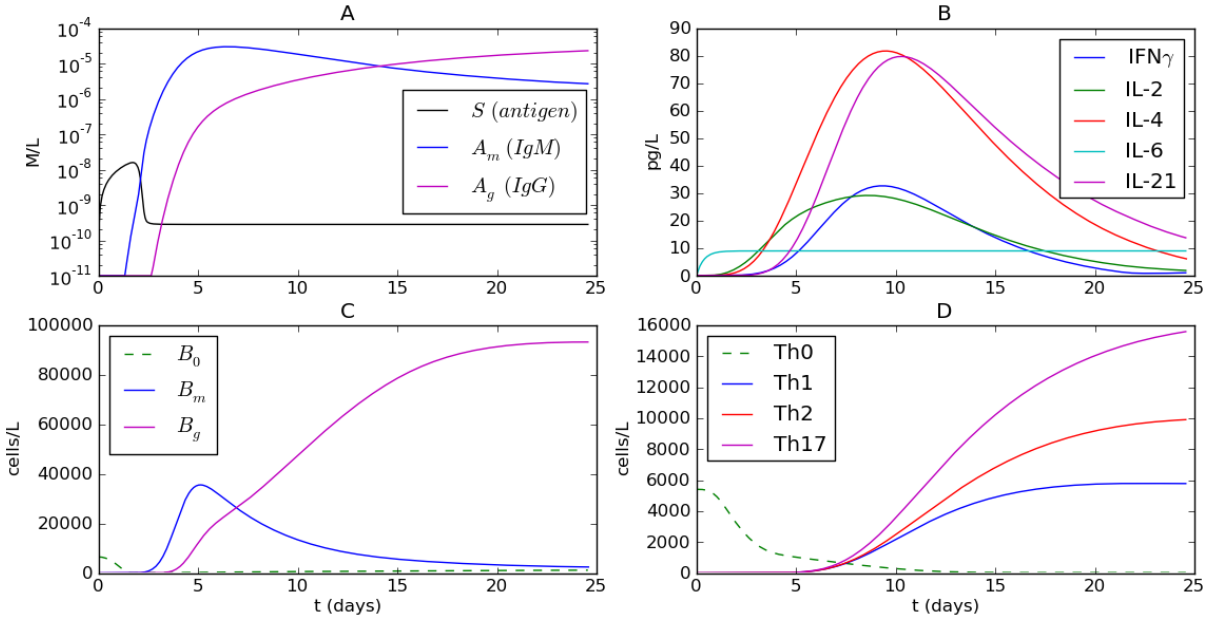

Fig. 15. **A**. Dynamics of antigen and antibody in peripheral blood. **B**. Dynamics of cytokine synthesis by T-lymphocytes in lymph node: Th17 immune response development. **C**. Dynamics of different subpopulations of plasmocytes in peripheral blood. **D**. Antigen-specific Th lymphocytes in peripheral blood.

CONCLUSION

The model provides detailed description of immune response, however maintaining the holistic view on entire system. Latest achievements of immunology have been used to make it possible to simulate the differentiation of Th1, Th2 and Th17 lymphocytes. The model considers differentiation like a process of continuous alterations affecting all related cellular processes in particular cytokine synthesis dynamics. The PDE equations allow exploring the lifetime of every cell in population. The model can be applied to research the broad range of problems, e.g. investigation of immune system mechanisms, complex diseases pathogenesis, medicaments testing, etc.

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