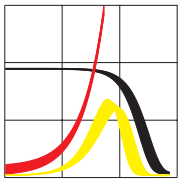

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Modeling of immune life history and body growth: The role of antigen burden

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Abstract

In this paper, a recently developed mathematical model of age related changes in population of peripheral T cells (Romanyukha, Yashin, 2003) is used to describe ontogenetic changes of the immune system. The treatise is based on the assumption of linear dependence of antigen load from basal metabolic rate, which, in turn, depends on body mass following the allometric relationship – 3/4 power scaling law (Kleiber, 1932; West, Brown, 2005). Energy cost of antigen burden, i.e. the energy needed to produce and maintain immune cells plus the energy loss due to infectious diseases, is estimated and used as a measure of the immune system effectiveness. The dependence of optimal resource allocation from the parameters of antigen load is studied.

Keywords: immune defense, energy cost, adaptation, antigen load, basal metabolic rate

1. Introduction

One of distinguished features of human immune system dynamics is the early onset of thymus atrophy – a primary lymphoid organ in which the development of bone marrow-derived progenitors into mature T cells takes place (Steinmann et al., 1985; Sapin, Etingen, 1996) (see Fig. 1). Such atrophy substantially restricts the ability of an adult organism to produce new T cells which, in turn, affects the strength and efficiency of an adaptive immune response. The evidence accumulates nowadays that some individuals maintain the ability to produce T cells throughout life (Douek et al., 1998; Franceschi et al., 1999). The results of longitudinal studies suggest that, in certain conditions, the thymic changes can be reversible (Mackall et al., 1995; Hakim et al., 2005). Taken together, these data argue for the existence of physiological mechanisms of dynamic adaptation of T cell population during the life course. In view of clonal selection theory (Burnet, 1959) one can assume that the adaptation strategy depends on the characteristics of antigenic milieu, the influence of which on the immune system is usually referred to as antigen load.

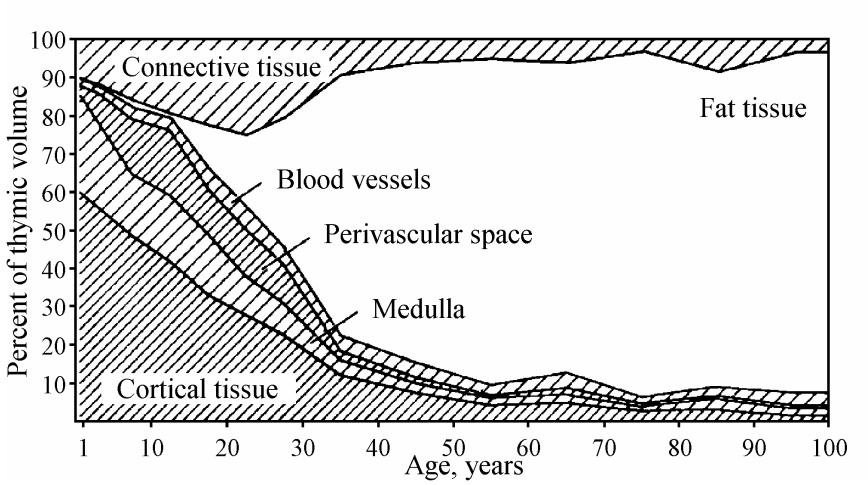

Figure 1. Thymic involution (Steinmann et al., 1985). After the age of 1, the volume of thymus, taken as 100%, remains relatively constant. The division of thymic precursor T cells takes place primarily in cortical tissue

The results of clinical and laboratory studies (De Martinis et al., 2005), as well as of mathematical modeling (Romanyukha, Yashin, 2003), show that the intensity of antigen load directly affects the dynamics of aging of the immune system. At the same time, the most pronounced changes in the population of T cells occur in childhood (Rufer et al., 1999; Zeichner et al., 1999) when the energy cost of infection burden is relatively high. Infections may stimulate an expansion of intact peripheral lymphoid tissue (IPLT) at an early age which affects the immune system learning capacity at later ages. Therefore, when studying aging in the immune system (immunosenescence), it is important to take the conditions and regularities of development of this system early in life into account.

Here, we address these issues using the extended mathematical model of age-related changes in population of peripheral T cells suggested by Romanyukha, and Yashin, (2003). The extended model, which adds one equation on age-related changes in body mass to the system of equations specified in Romanyukha and Yashin, (2003), exploits the new fundamental assumption that the value of antigen load is proportional to the intensity of basal metabolism. Resulting model allows for describing development of adaptive immunity during all postnatal life, including childhood and juvenile age. The dependence of basal metabolism on body mass is described using the Kleiber's 3/4 power scaling law (Kleiber, 1932; West, Brown, 2005).

2. Mathematical model

To describe the dynamics of T cell population on a life-long interval, including the period of postnatal development, it is necessary to take into account the following processes:

1. An increase of body mass, rate of energy metabolism, and, consequently, of total antigen load (Snyder et al., 1984);
2. Rapid shortening of stem cells' telomeres early in life (Rufer et al., 1999);
3. An expansion of IPLT during organism's growth and development (Sapin, Etingen, 1996).

It has been shown recently that the body mass dynamics of multicellular organisms can be described by the following equation (West, Brown, 2005):

$$\frac{dm}{dt} = \left(\frac{B_0 m_c}{E_c}\right) m^{3/4} - \left(\frac{B_c}{E_c}\right) m,$$

where m_c is the average mass of a cell, E_c the energy needed to produce a new cell, B_c metabolic energy needed for maintenance of a cell, and B_0 is the taxon-dependent normalization constant for the scaling of metabolic rate (West, Brown, 2005):

$$B = B_0 m^{3/4}. \qquad (1)$$

For mammals, this relationship was established experimentally in early 1930s (Kleiber, 1932).

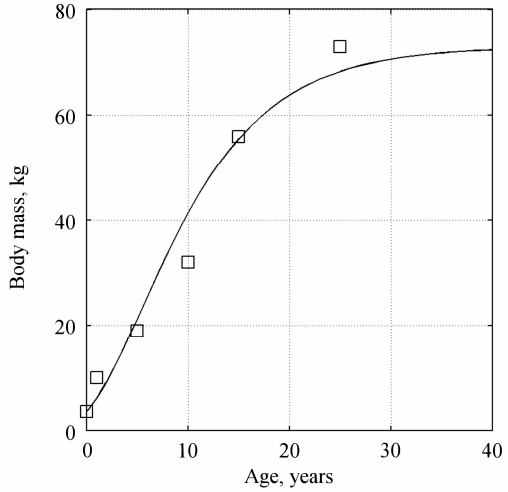

Figure 2. Body mass of reference man as a function of age

As compared to other vertebrates, the human growth is a relatively prolonged process, taking up more than a quarter of life expectancy. Typical plot of body mass versus age is shown in Fig. 2. Open squares correspond to the data on reference man (Valentin, 2002). Solid line represents approximate solution of the above equation with $B_0 m_c / E_c$ = 0,025 kg$^{1/4}$/day and horizontal asymptote $\overline{m}$ = 73 kg (body mass of reference man).

Assume that the rate of early IPLT expansion is proportional to specific antigen load (L/V) and the rate of body mass change (m). Then, an equation for $V(t)$ can be written as

$$\frac{dV}{dt} = \alpha_3 \frac{L}{V}\frac{dm}{dt} - k_V V.$$

The second term in the right-hand side of this equation describes slow shrinkage of $V(t)$ in old ages (Sapin, Etingen, 1996) due to age-dependent reduction of metabolically active body cell mass (Forbes, 1970).

Rapid telomere shortening of stem cells during the first and second years of life entails the similar changes in the length of telomeres of newly produced naive T cells in thymus (Rufer et al., 1999). Assume that the corresponding rate is proportional to the relative increase in body mass. Then, the rate parameter in equation for P^* can be written as a function of age: $k_P(t) = \bar{k}_P(dm/dt)/m + k_P$, where k_P is taken from the original model (Romanyukha, Yashin, 2003).

As previously, we assume the presence of physiological mechanisms responsible for maintenance of homeostatic concentration of T cells (C^*). Depending on the value of antigen load L, the term $\mu_M(C^* - N - M)$ in the right-hand side of the equation for memory cells can describe enhanced death rate or homeostatic proliferation of memory cells.

Taking into account these considerations, the mathematical model of age related changes in population of peripheral T cells can be written as

$$\begin{aligned}
&\frac{dN^*}{dt} = -k_T N^*,\\
&\frac{dN}{dt} = \frac{N^*}{V} - \alpha_1 \frac{L}{V} N - \mu_N N - \frac{dV}{dt}\frac{N}{V},\\
&\frac{dM}{dt} = \rho_1\alpha_1 \frac{L}{V} N + \rho_2\alpha_2 \frac{L}{V} M + \mu_M(C^* - N - M) - \frac{dV}{dt}\frac{M}{V},\\
&\frac{dP^*}{dt} = -\left(\frac{\bar{k}_P}{m}\frac{dm}{dt} + k_P\right)P^*,\\
&\frac{dP_N}{dt} = (P^* - P_N)\frac{N^*}{NV},\\
&\frac{dP_M}{dt} = \rho_1\alpha_1(P_N - P_M - \lambda_N)\frac{L}{V}\frac{N}{M} - (\rho_2 + 1)\alpha_2\lambda_M \frac{L}{V},\\
&\frac{dV}{dt} = \alpha_3 \frac{L}{V}\frac{dm}{dt} - k_V V,\\
&\frac{dm}{dt} = \alpha_4 m^{3/4} - k_m m.
\end{aligned} \qquad (2)$$

The variables of this model depend on age t: $N^*(t)$ is the rate of naive T cells influx from thymus into IPLT, $N(t)$ the concentration of naive T cells in IPLT, $M(t)$ the concentration of memory T cells in IPLT, $P^*(t)$ the length of telomeres in naive T cells leaving thymus at the age t, $P_N(t)$ the length of telomeres in naive T cells,

$P_M(t)$ the length of telomeres in memory T cells, $V(t)$ the volume of IPLT, $m(t)$ the body mass. Initial conditions correspond to birth time:

$$N^*(0) = N_0^*, \quad N(0) = C^*, \quad M(0) = M_0^*, \quad P^*(0) = P_0^*,$$
$$P_N(0) = P_N^0, \quad P_M(0) = P_M^0, \quad V(0) = V_0, \quad m(0) = m_0. \tag{3}$$

Relying upon data on absence of memory T cells in the cord blood of human newborns (Hayward et al., 1989) we can suspect that at time of birth all T cells in IPLT are naive, i.e. were produced in thymus and did not interact with antigen ($N_0^* >> M_0^*$). The factor ($\rho_2 + 1$) instead of ρ_2 in the right-hand side of equation for P_M is a correction made to describe the balance of total length of telomeres in memory cells' population (Romanyukha et al., 2005). Physical meaning and initial estimates of model parameters are shown in Table 1.

Table 1: Initial conditions and initial parameters' estimates for simulation of age related changes in population of peripheral T cells

Para-meter	Physical meaning	Dimension	Value
α_1	Rate constant of naive T cells stimulation	ml/g	1.5×10^{4}
α_2	Rate constant of memory T cells stimulation	ml/g	1.5×10^{4}
α_3	Rate constant of the intact peripheral lymphoid tissue (IPLT) growth	$ml^2\times day/g$	3×10^{7}
α_4	Rate constant of body mass growth	$g^{1/4}/day$	2.5×10^{-2}
α_5	Parameter which relates antigen load and basal metabolic rate	$g^{1/4}/day$	2.8×10^{-10}
μ_N	Rate constant of natural death rate for naive T cells	one/day	1.3×10^{-4}
μ_M	Rate constant of competitive death (or homeostatic proliferation) for memory T cells	one/day	0.07
ρ_1	Number of memory T cells produced by one naive cell	—	100
ρ_2	Number of memory T cells produced by one memory cell	—	1.1
λ_N	Length of telomere repeats lost during transformation of naïve T cells to memory cell	base pairs (bp)	1400
λ_M	Length of telomere repeats lost during self replication of memory cells	bp	500
C^*	Low limit for normal concentration of memory T cells in intact lymphoid tissue	cell/ml	2.5×10^{9}
k_T	Rate of diminishing of naive T cells production with age	one/day	1.1×10^{-4}
k_V	Relative rate of reduction of the IPLT volume with age	one/day	2.7×10^{-5}
k_P	Relative rate of the telomere repeats reduction in the progenitor of naïve cells	bp/day	1×10^{-5}
$\overline{k}_P$	Relative rate of accelerated telomere shortening in the progenitor of naïve T cells in early childhood	bp/day	0.07

k_m	Rate parameter in the equation for body mass	one/day	1.5×10^{-3}
N_0^*	Rate of naive T cells release from thymus at birth	cell/day	8×10^{8}
N^0	Concentration of naive T cells in the IPLT at birth	cell/ml	2.5×10^{9}
M^0	Concentration of memory T cells in the IPLT at birth	cell/ml	2.5×10^{7}
P_0^*	Average length of telomeres in naive T cells leaving thymus at birth	bp	10370
P_N^0	Average length of telomeres in naive T cells in the IPLT at birth	bp	10370
P_M^0	Average length of telomeres in memory T cells at birth	bp	8970
V_0	Volume of intact lymphoid tissue at birth	ml	150
m_0	Body mass at birth	g	3500

Consider the value of antigen load *L*. When modeling age-related changes of T cell population in adults, a reasonable assumption was used about constancy of *L*. The direct quantitative data of this sort are not present, but it is clear that in general case the magnitude of antigen load depends on the intensity of metabolism. It can be assumed that $L = k_L B$, where *B* is the value of basal metabolism, and k_L the parameter which depends on a combination of various factors: ecological (level of environmental pollution, quality of consumable water and foods), epidemiological (infection morbidity), cultural and social (level of sanitation and hygiene), climatic, and other. From Eq. 1, it is clear that

$$L = \alpha_5 m^{3/4}, \tag{4}$$

where $\alpha_5 = k_L B_0$. So, we have derived an important empirical relationship between antigen load and body mass which is considered as the principal determinant of energy metabolism.

3. Generalized picture of T-cell population dynamics

The term *generalized picture* means coordinated quantitative description of typical variants of the process in terms of dependent variables of the mathematical model (Marchuk et al., 1991). When constructing generalized picture of the dynamics of T cell populations, which is shown on Fig. 4 by circles, we used the data (Rufer et al., 1999) on the dynamics of relative contents of naive and memory T cells in the blood, as well as the length of their telomeres, taking into account age dependence of T cell concentration (Hulstaert et al., 1994). We assumed that the ratio of naive and memory T cell populations in the blood and IPLT is equal. Also, the following assumptions were used:

1. The rate on naive T cells influx from the thymus (P^*) is proportional to the volume of thymic cortical tissue (Steinmann et al., 1985);

2. From the time of birth to the age of 1 year the thymic volume grows 2-fold (Sapin, Etingen, 1996), and not changes later on (Steinmann et al., 1985);
3. At the time of birth, the length of telomeres in newly produced naive T cells in thymus is assumed to be equal to those of peripheral naive T cells; at the subsequent time points this value was estimated indirectly using the data on the kinetics of telomere shortening in blood granulocytes (Rufer et al., 1999);
4. Age dependence of body mass *m* is taken to mirror the data on the reference man, whereas the volume of IPLT (*V*) is proportional to the number of lymphocytes in the body (Valentin, 2002).

The data on body mass and the number of lymphocytes are used to develop typical variant of energy metabolism changes during postnatal growth and development, aiming to provide adequate description of specific antigen load and proliferation rates of T cells in children's IPLT.

4. Parameters' estimation

The scheme of adjusting model parameters is shown in Fig. 3. Evidently, the parameters determining dynamics of a body mass $\overline{m}$ and the rate of T cells' influx from the thymus N^* can be adjusted first independently of other parameters, and so on. This scheme enabled us to construct initial estimates of model parameters (see Table 1).

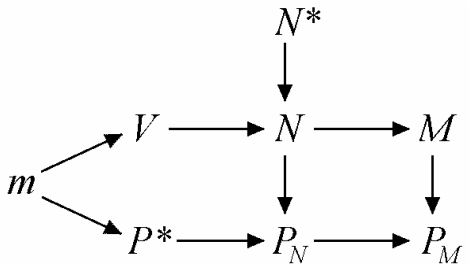

Figure 3. Consequence of steps for estimation of parameters

The solution to the initial problem is shown as solid lines on Fig. 4, which fits the data relatively well except for some data points. For quantitative description of the agreement between the model and the generalized picture data we considered an objective function

$$F(\alpha) = \sum_{i,j} \left(\lg \left(\frac{x^i(t_j, \alpha)}{X_j^i} \right) \right)^2$$

which characterize deviation of model solutions from the data , where α is the vector of model parameters, $x^i(t_j, \alpha)$ the value of the ith component of model solution at time t_j, and X_j^i is the corresponding data of generalized picture. An expression in the

right-hand side of this formula represents a least-squares objective function for logarithmically transformed data and model solutions.

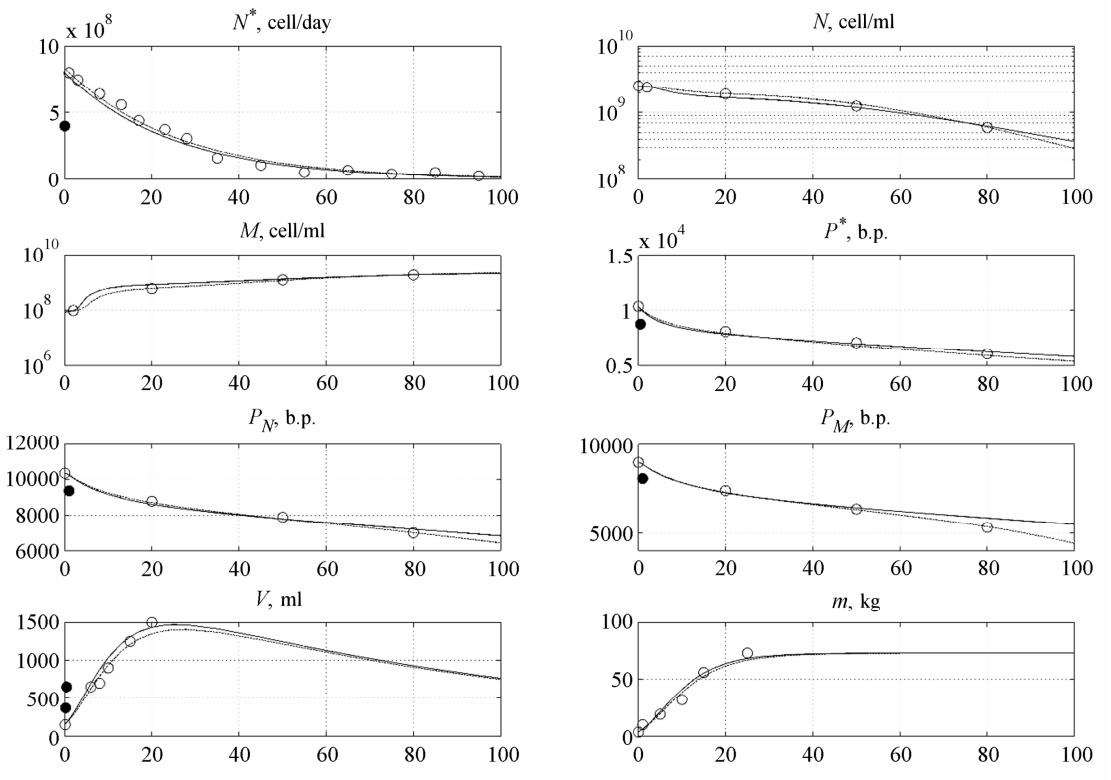

Figure 4. Solution to Cauchy's problem of the ODE system (solid lines). The values of model parameters are shown in Table 1. Dotted lines correspond to the solution of the optimization problem obtained using differential evolution algorithm (see Table 2). Along the x-axis is the age (years). Data of generalized picture are shown as open circles (°); other data represented as (•), were excluded.

The value $F = 0.85$ corresponds to the initial values of parameters shown in Table 1, it was calculated for the whole set of generalized picture data (see Fig. 4). As is follows from the analysis of model solutions, it is impossible to improve significantly the quality of data fitting without correction of model equations for N^*, P^* and V. Also, such a possibility may be associated with the refined description of the dynamics of naive T cells production in thymus (N^*) and, partially, of the kinetics of telomeres shortening of memory T cells (P_M) in adults. This is illustrated by the solution of the minimization problem $F \to \min$ on a subset of model parameters using differential evolution (DE) algorithm (Storn, Price, 1997).

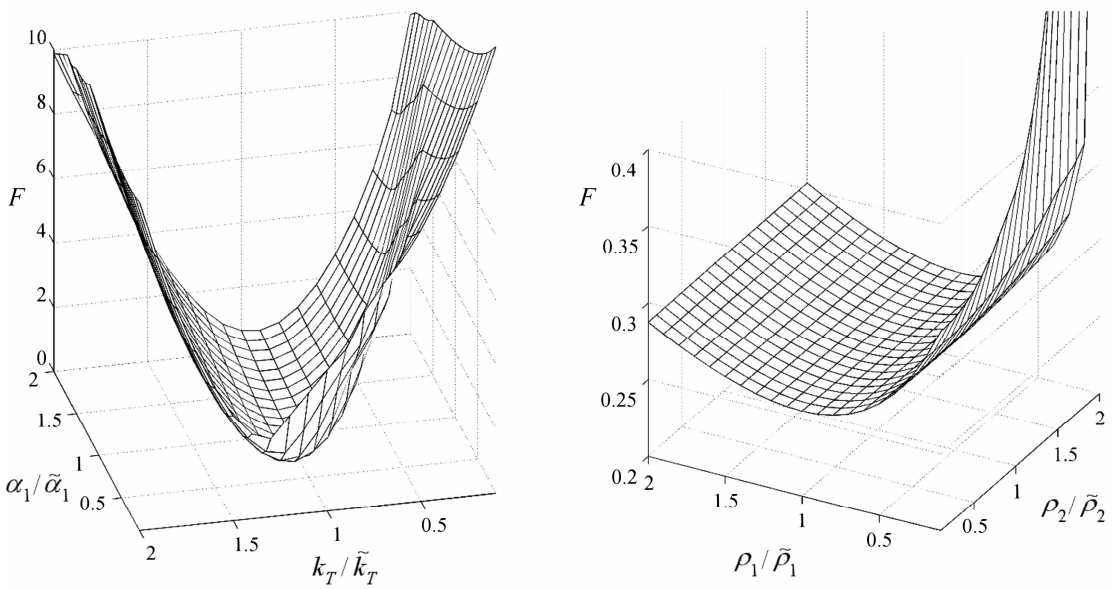

Figure 5. Dependence of function F on the parameters k_T, α_1, ρ_1 and ρ_2 in the vicinity of local minima. Parameters marked with tide correspond to the solution of minimization problem. It can be seen that 20-fold change of the parameters α_1 and ρ_2 exert a small influence on F.

Table 2: The results of sequential parameter estimation procedure for modeling age related changes in population of peripheral T cells using differential evolution (DE) algorithm. In our calculations the following parameters of the algorithm were used: $CR = 0.8$, $H = 0.8$, $D = 2, 4, 5$, $NP = 10 \times D$, *itermax* = 150, *strategy=DE/rand/*1/*bin*. Permissible boundaries for model parameters are shown as XVmin and XVmax. The values of residual function F are shown in the last row.

Parameter	XVmin	XVmax	Initial estimate	Refined estimate		
				1	2	3
N_0^*	4×10^8	10^9	8×10^8	8.34×10^8		
k_T	8×10^{-5}	2×10^{-4}	1.1×10^{-4}	1.06×10^{-4}		
α_4	0.01	0.04	0.025		0.023	
k_P	5×10^{-6}	2×10^{-5}	10^{-5}		1.3×10^{-5}	
$\bar{k}_P$	0.01	0.1	0.07		0.06	
α_3	10^7	5×10^7	3×10^7		2.8×10^7	
α_1	5×10^3	5×10^4	1.5×10^4			10^5
μ_N	10^{-4}	10^{-2}	1.3×10^{-4}			5×10^{-5}
ρ_1	10	1000	100			2000
ρ_2	1	100	1.1			324
μ_M	0.001	0.1	0.07			8.7
F			0.32	0.28	0.26	0.25

Solution to the minimization problem obtained on a subset of model parameters and of generalized picture data (open circles on Fig. 4) is shown in Table 2. The corresponding solution of model system is shown as dotted lines on Fig. 4. It can be seen that the adjustment of parameters for equations for N^*, m, V and P^* enabled for some improving of data fitting. Variation of other parameters resulted in insignificant decrease of the value of F (7%, see Table 2) and showed low sensitivity to variations of some parameters in the vicinity of local minima (Fig. 5).

In conclusion, the model solution satisfactorily describes the data on age-related changes in T cell populations on a whole age interval except for the first year of life. In order to fit well the whole set of generalized picture data let us describe some additions to the model.

5. Refined model

At the first 6 months of life, immune defense is provided mainly by maternal antibodies though it was shown recently that mature T-cell immune response against viral and macroparasitic infections can occur in prenatal conditions [(King et al., 2002; Marchant et al., 2003), cited from (Hazenberg et al., 2004)]. Along with increase in thymic volume, at that age total number of peripheral T cells and the volume of IPLT grow rapidly. According to data in (Valentin, 2002), the number of lymphocytes in the body between the ages of 0.5 and 6 years remains relatively stable and subsequently increases, approaching a maximum by 20 years (Fig. 4). The equation for the volume of intact peripheral lymphoid tissue $V(t)$ is

$$\frac{d}{dt}V(t) = \begin{cases} 8\times10^{-3}V, & if \quad 0 \le t/365 < 0.5, \\ 0, & if \quad 0.5 \le t/365 < 6, \\ \alpha_3 \frac{L}{V}\frac{dm}{dt} - k_V V, & if \quad t/365 \ge 6, \end{cases}$$

where t is the age (in days).

From similar considerations, an equation for the rate of naive T cells production in thymus (N^*) is modified:

$$\frac{d}{dt}N^*(t) = \begin{cases} 2\times10^{-3}N^*, & if \quad 0 \le t/365 < 1, \\ -k_T N^*, & if \quad t/365 \ge 1. \end{cases}$$

The results presented in Fig. 4 show that inadequate quality of approximation of the model solution components P_N and P_M to data on the first year of life can be a consequence of inaccurate description of the dynamics of telomeres' shortening in newly produced T cells in thymus. In view of the absence of direct quantitative data which characterize the number and the rate of proliferation of stem cells, we first assumed that the rate of change of the value P^* is proportional to the relative rate of

body mass change over time ($\dot{m}/m$). However, this assumption did not allow us to fit the data satisfactorily. So, we represented function P^* at an initial age interval as an exponent with an index chosen from the condition of agreement between the model and data[1]:

$$\frac{d}{dt}P^*(t) = \begin{cases} -9.5\times10^{-4}P^*, & if \quad 0 \le t/365 < 0.5, \\ -k_P P^*, & if \quad t/365 \ge 0.5. \end{cases}$$

The solution of the refined model is shown in Fig. 6. In view of the absence of model parameters in equation for P_N , it is interesting to see that the good agreement between the component P^* and the data turned out to be insufficient for the precise description of P_N behavior early in life (Fig. 6).

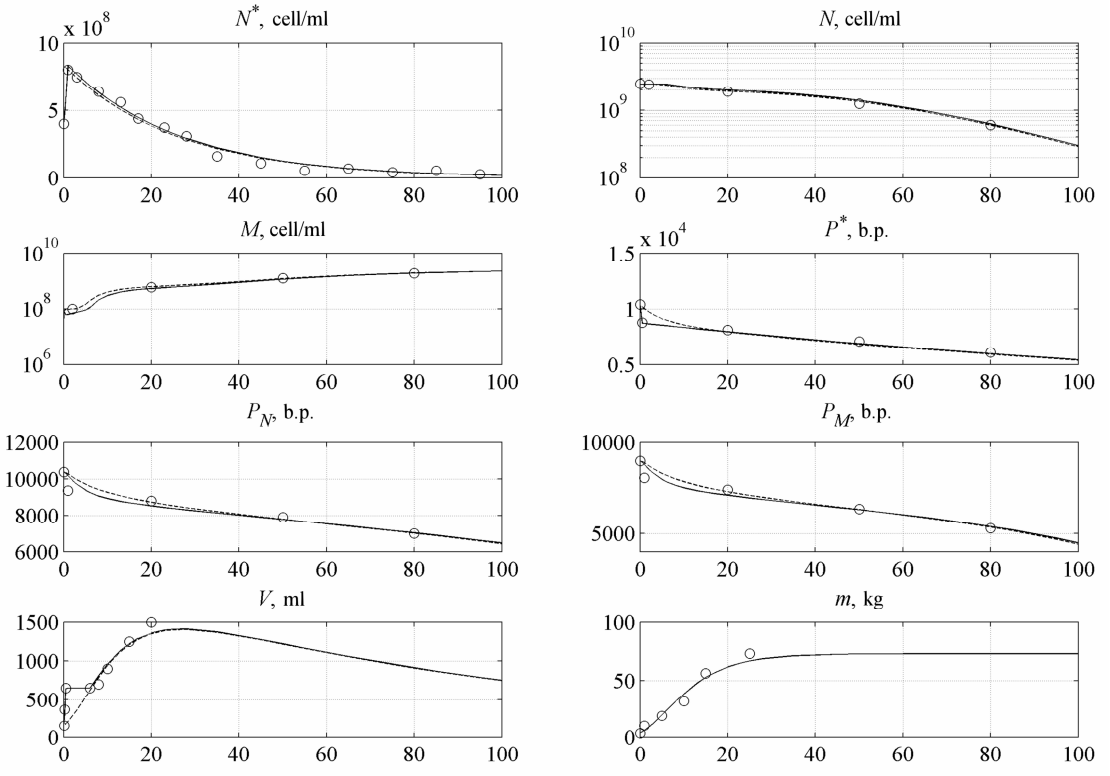

Figure 6. Solution to the refined model system (solid lines). Dotted lines represent the solution shown in Fig. 4 with the parameters corresponding to minimal value of *F*. Along the x-axis is age (years). Generalized picture data are shown as open circles. For refined model solution and all data set of generalized picture, $F = 0.32$.

One possible explanation involves the effect of naive T cells' *homeostatic proliferation* (Unutmaz et al., 1994). Such proliferation results in increased telomere shortening in naive T cells as compared with the rate induced by telomere shortage in

[1] Another possibility of the description of rapid shortening of peripheral T cells' telomeres at an early age could be associated with the consideration of power dependence in the form $\dot{P}^* \sim (\dot{m}/m)^p$, where $p > 1$. Unfortunately, simple physiological interpretation of this relation is difficult and requires additional study.

stem and/or precursor T cells, and, hence, can be accounted for in the equation for P_N. From Fig. 6, it can be seen that the rate of homeostatic proliferation of naive T cells is comparable with that of their production in thymus. Similar results were obtained in (Hazenberg et al., 2000, 2004; Ye, Kirschner, 2002; Dutilh, DeBoer, 2003) when modeling kinetic data on T-cell receptor excision circles (TREC) numbers.

6. "Initial reserve" of the immune system and infection burden

Fig. 7 shows the dynamics of relative antigen load L/V for the refined and initial models (the model solutions are represented in Fig. 6). One can see from this figure, the refined model is characterized by the significantly smaller values of L/V at the early ages. This can be interpreted as a formation of the immune system "reserve" owing to fast initial increase in the volume of IPLT.

An important part of the antigen load L is represented by the infection load, related to the impact of *multiplying* antigens. At present, it is difficult to obtain a quantitative estimate of relative contribution of the infection load to total antigen load, but, clearly, this contribution can be significant. The results of simulation of the impact of HIV infection on the rate of T-cell population aging suggest 2 to 8-fold increase in the fraction of divided naive T cells, and, hence, of total antigen load (Hazenberg et al., 2000; Sannikova et al., 2004).

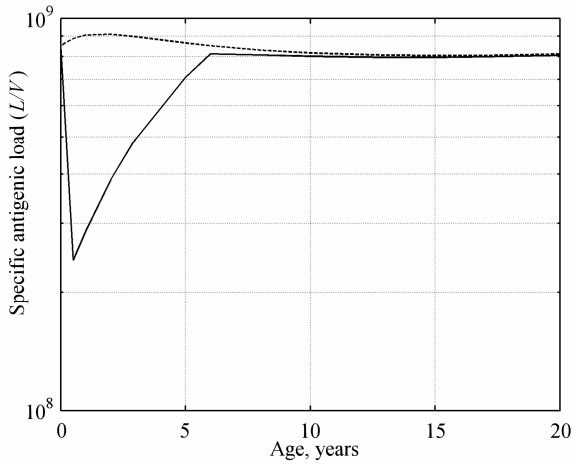

Figure 7. Specific antigen load L/V as a function of age for refined (solid line) and initial models (dotted line).

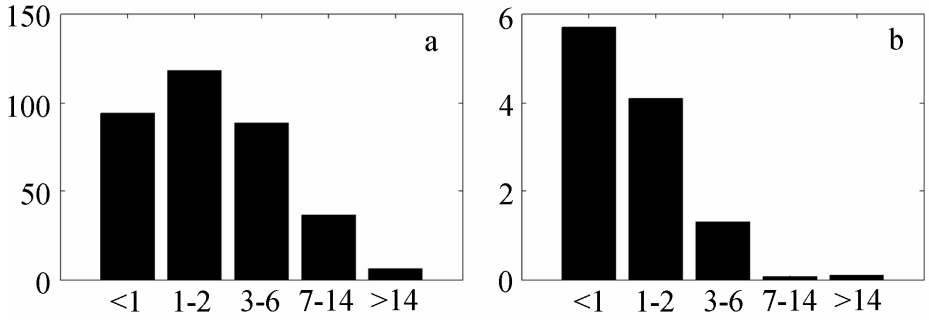

Figure 8. Morbidity due to (a) acute respiratory infections and (b) acute intestinal infections in Russia in 2004 for various age groups [elaborated from (Yasinski et al., 2005)]. Along the x-axes – age (years), along the y-axes – number of cases per 100 persons per year.

The magnitude of infectious pathogens multiplication in human body in case of acute infections can vary from 10^5-10^6 for bacterial pneumonia (Romanyukha, Rudnev, 2001) to 10^{10}-10^{11} for viral infections, such as influenza A or hepatitis B (Marchuk et al., 1991; Bocharov, Romanyukha, 1994). Fig. 8 shows converted averaged data on the frequency of acute respiratory and intestinal infections in 2004 for various age groups of Russian population (Yasinskii et al., 2005). These acute infections in Russia are most common.[2] The diagram at Fig. 8 shows that the frequency of acute infections is maximal during the first 5 or 6 years of life, and the absolute maximum falls at the age 1 or 2 (due to acute respiratory infections). At this age, extensive learning of the immune system occurs accompanied by the formation of immune memory against frequently encountered pathogens. Importantly, general population is essentially inhomogeneous in relation to infection morbidity. For instance, the so-called *frequently-ill children* can represent up to 20% of total with average incidence 10-15 acute infections per year (Albitskii et al., 2003).

Estimate of total antigen load L (see Eq. 4) was obtained under assumption of its linear dependence from basal metabolic rate. The high rate of infection diseases in childhood imply a significant excess by the value of L at this age of the value determined by the basal metabolic rate. One can assume that this "initial reserve" of the immune system is, in fact, consumed under the influence of infection load. As a result, the specific antigen load, L/V, can be significantly *higher* than the values suggested by the refined model (continuous line on Fig. 7). The comparison of graphs on Fig. 7 suggests that the initial reserve of the immune system early in life allows for 2-4-fold increase of total antigen load above the values permitted by the basal metabolic rate.

[2] Also, we must add here chicken pox with the incidence rate 0.005 year^{-1}. The maximal incidence rate falls at the age of 3-6 years, and in 2004 amounted to 6.3 cases per 100 children of this age group (Yasinskii et al., 2005).

7. Energy cost of antigen burden

Let us consider total energy cost *E* of antigen burden. This value can be represented as the sum of energy expenditures on the immune system function (E_f) plus energy cost of infectious diseases (E_l):

$$E = E_f + E_l. \tag{5}$$

We can write E_f as

$$E_f = E_f^m + E_f^t + E_f^d,$$

where E_f^m is the energy cost of maintenance of peripheral T cells, E_f^t the cost of T cells production in thymus, and E_f^d is the cost of naive and memory T cells proliferation in IPLT. From the physical meaning of model equations it is follow that

$$\begin{aligned} &E_f^m = \beta_1 \int_0^T (M+N)V dt; \quad E_f^t = \beta_2 \int_0^T k_1 N^* dt; \\ &E_f^d = \beta_2 \int_0^T [k_2 \rho_1 \alpha_1 LN + k_3 \rho_2 \alpha_2 LM + \mu_M (C^* - N - M) h_{C^*-N-M} V] dt, \end{aligned} \tag{6}$$

where *T* is an individual's life span, β_1 is the power of maintenance of one T cell, β_2 is the energy needed for the production of one T cell, k_1 is the average ratio of the rates of T cell death and export from the thymus, k_2 and k_3 are the average ratio of maximal clonal size of specific T cells and of memory T cells arising from immune response, for naive and memory T cells, respectively, and h_{C^*-N-M} is the Heaviside function [the term $\mu_M (C^* - N - M)$ in the right-hand side of the equation for memory cells describes homeostatic proliferation, if $C^* - N - M > 0$, and cell death – otherwise].

The value of E_l can be represented as

$$E_l = E_l^n + E_l^e,$$

where E_l^n and E_l^e are energy losses due to interaction with new and already experienced antigens, respectively.

It is clear that, normally, the major part of E_l can be attributed to loss of energy due to acute infections, because just this type of infection represent the principal cause of morbidity and temporal disabilities in all age groups (WHO, 2004). For simplicity, we assume that all cases of acute infections in children are caused by

new antigens.[3] Consider piecewise constant function $0 \le f(t) \le 1$ which characterize the frequency of acute infectious diseases such that

$$\int_0^T f(t)dt = n/A,$$

where A is the maximal disease frequency, and n the characteristic of total number of acute infections per life time (specific form of f and the values of A and n can be estimated using data on infection morbidity, e.g., such as represented on Fig. 8. From the sensitivity analysis of basic mathematical model of infectious disease (Marchuk, 1997) it is follows that, other conditions being equal, the severity of infection is inversely proportional to the initial number of specific lymphocytes (data not shown). So, we can write E_l^n in the form

$$E_l^n = \int_0^T E_0 A \frac{C^* \overline{V}}{NV} \left(\frac{m}{\overline{m}} \right)^{3/4} f(t)dt. \qquad (7)$$

The factor $E_0(C^*\overline{V}/NV)/(m/\overline{m})^{3/4}$ describes empirical relationship between the severity of infection caused by new antigens, and the total number of naive T cells NV and body mass m. C^* is the normal concentration of T cells in IPLT, $\overline{V} = \overline{V}(t)$ the reference value of IPLT at age t, which corresponds to the refined solution of model system (parameters are shown in Table 2. It is known that metabolic cost of acute infection is proportional to basal metabolic rate (Long et al., 1979), which, in turn, is proportional to body mass scaled as 3/4 power (Eq. 4). To account for this relation, the term under the integral in Eq. 7 contains the correction factor $(m/\overline{m})^{3/4}$, which is equal to the ratio of metabolic costs of acute infection in man with body masses m and $\overline{m}$ (the body mass of reference man). E_0 is the energy cost of acute infection (provided that $NV = C^*\overline{V}$) adjusted for basal metabolic rate of reference man.

Assume that the decline in the frequency of acute infections in children, which is characterized by the function $f(t)$, reflects the rate of immune system learning, i.e. the decreasing exposure to the new antigens. Then, the value of E_l^e can be written, by analogy with Eq. 7, as

$$E_l^e = \int_0^T E_1 A \frac{C^* \overline{V}\,\overline{n}L}{MVn\overline{L}} \left(\frac{m}{\overline{m}} \right)^{3/4} (1 - f(t)) g(P_M)dt. \qquad (8)$$

We assume here that the value of E_l^e is proportional to antigen load L, and inversely proportional to the total number of memory cells MV. E_l is the adjusted metabolic

[3] Infectious diseases caused by opportunistic microorganisms (e.g., pneumonia) arise most often against a background of seasonal epidemics caused by the new serotypes of viruses, i.e. in absence or low level of specific immune memory (Marchuk, Berbentsova, 1989).

cost of interaction with experienced antigens (provided that $C^*\overline{V}\overline{n}L = MVn\overline{L}$) for the period $T/\overline{n}$, where $\overline{L} = \overline{L}(t)$ is the "reference" value of antigen load at age *t*, and $\overline{n}$ is the characteristic of total number of acute infections during life time provided that $L = \overline{L}(t)$.

The replicative potential of memory cells diminishes when the length of their telomeres (P_M) is shortening, and the magnitude of infection pathogens reproduction is increasing. This results in growing energy cost of infection diseases. This is accounted in Eq. 8 for E_l^e using the function $g(P_M) = (P_M^0 - P_H)/(P_M - P_H)$, where P_M^0 is the length of telomeres of memory T cells at birth, and P_H the Hayflick limit.

From the comparison of Eqs. 7-8 it is follows that the main part of energy cost of infection diseases at an early age is attributed to infection associated with the new antigens, and at the older ages with infections corresponding already known antigens.

In view of changing body mass and basal metabolic rate in childhood, it is convenient to consider, instead of the total energy cost of antigen burden *E*, the mean infection burden-related rate of energy loss and expenditures in organism (i.e., the mean power) adjusted for basal metabolic rate of reference man. Let us denote this value as *W*. Then, by analogy with Eq. 5,

$$W = W_f + W_l.$$

The components W_f and W_l can be defined using Eqs. 6-8, where the terms under the integrals contain an additional factor

$$\frac{1}{T}\left(\frac{\overline{m}}{m}\right)^{3/4}.$$

In this expression, $\overline{m}$ is the body mass of reference man, and $m = m(t)$ the body mass at age *t*. So, we can write

$$W_f^m = \frac{1}{T}\int_0^T \left(\frac{\overline{m}}{m}\right)^{3/4} \beta_1 (M+N)V dt;$$

$$W_f^t = \frac{1}{T}\int_0^T \left(\frac{\overline{m}}{m}\right)^{3/4} \beta_2 k_1 N^* dt;$$

$$W_f^d = \frac{1}{T}\int_0^T \left(\frac{\overline{m}}{m}\right)^{3/4} \beta_2 [k_2\rho_1\alpha_1 LN + k_3\rho_2\alpha_2 LM + \mu_M (C^* - N - M)h_{C^*-N-M}V]dt;$$

$$W_l^n = \frac{1}{T}\int_0^T E_0 A \frac{C^*\overline{V}}{NV} f(t)dt;$$

$$W_l^e = \frac{1}{T}\int_0^T E_1 A \frac{C^*\overline{V}\overline{n}L}{MVn\overline{L}}(1 - f(t))g(P_M)dt.$$

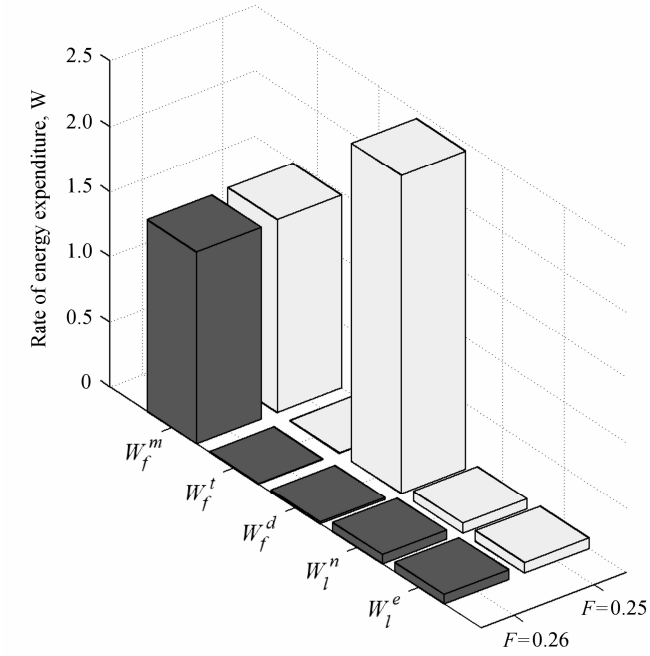

Figure 9. The structure of average power *W* of energy expenses on interaction with antigen load for two sets of parameters shown in Table 2 with F = 0.26 and F = 0.25, corresponding to *resistant* and *reactive* types of immune defense (see explanation in the text).

The diagrams which characterize quantitative relations between various components of *W* for two sets of model parameters, which corresponds to F=0.26 and F=0.25, respectively (see Table 2), are shown in Fig. 9. The parameters of energy cost of antigen burden used in these calculations are shown in Table 3 and are discussed in the Appendix. It follows from Fig. 4 that these sets of parameters give approximations to the generalized picture data with virtually equal precision. However, as it is clearly seen in Fig. 9, these sets of parameters' values are characterized by different structures of energy expenditures on immune defense: F=0.26 is responsible to the *resistant type* of immune defense with the prevalence of energy expenditures on maintenance of immune cells, and F = 0.25 – to the *reactive type* of defense with the prevalence of energy expenditures on lymphocytes proliferation. For the former case, the powers of peripheral T cells proliferation (W_f^d) and of production of naive T cells in thymus (W_f^t) are small and comparable (0.02 W and 0.004 W, respectively). For our sets of model parameters, in view of appropriate choice of the parameter E_1 (see Appendix), the rates of energy losses due to interaction with new (W_l^n) and already experienced antigens (W_l^e) are similar, and equals 0.07 W and 0.08 W, respectively. The resulted values of $W_l = W_l^n + W_l^e$ (0.14 W and 0.16 W) agree well with the constructed theoretical estimate of average (per life) rate of energy expenditures on infectious disease (0.12 W, see the Appendix). Note that the considered sets of model

parameters are characterized by the relatively low average energy expenditures due to infectious diseases compared to direct cost proliferation and maintenance of immune cells (10% and 4% respectively). This is also in accordance with theoretical estimate derived in the Appendix, which is equal 5%.

Table 3: Energy cost of the immune defense: estimation of parameters

Parameter	Physical meaning	Dimension	Value
β_1	Power of the maintenance of one T cell	J/(cell×day)	4.1×10^{-8}
β_2	Energy cost of the production of one T cell	J/cell	2.7×10^{-8}
k_1	Relative rate of precursor T cells death in thymus, compared to the rate of naive T cells export	—	25
k_2	Relative proportion of memory T cells dying from apoptosis during clonal replication of naïve cells	—	20
k_3	Relative proportion of memory T cells dying from apoptosis during clonal replication of memory cells	—	20
T	Life span	day	3.65×10^{4}
$2\bar{n}$	Average number of acute infectious diseases per life	—	170
$\bar{m}$	Body mass of the Reference Man	g	7.3×10^{4}
A	Maximal frequency of acute infections in childhood	one/year	10
E_0	Energy cost of acute infection	J	1.25×10^{6}
E_1	Energy cost of infections caused by already experienced antigens for the time period $T/\bar{n}$	J	10^{5}
P_H	Hayflick limit	bp	4×10^{3}

Fig. 9 shows that, under given values of external parameters, the set of model parameters, which corresponds to the resistant type of immune defense, is energetically profitable. In contrast, the other set of model parameters can be considered as inadequate since the ratio of powers on proliferation and maintenance of lymphocytes will be disproportionately large ($W_f^d / W_f^m = 2.44\,\mathrm{W}/1.48\,\mathrm{W} = 1.65$ versus theoretical estimate 0.05).

8. Antigen burden and optimal resource allocation

Because of high rates of infection morbidity and mortality all over the world, the human immune system is the subject for strong selection pressure. So, the relation between energy cost of immune defense and losses of energy due to infectious diseases can be regarded as a typical example of trade-offs which are traditionally studied in framework of the theory of evolutionary life history (Stearns, 1992). This enables to pose the problem of searching for effective strategies of the immune system provided that environmental conditions are given. In our case, "environment" can be characterized as a vector-function $\beta = (L, f, n, A)$, where $L = \alpha_5 m^{3/4}$ is the total antigen load, *f* is the function of infectious diseases frequency, *n*, and *A* is the vector of respective parameters (see Eq. 7).

Let us consider the adjusted average power of energy expenditures *W* as a measure of immune system effectiveness. Define immune system *strategy* as a specified set of the model parameters which characterize the properties of the immune system. Let α' and α'' be such sets of parameters. We say that, for given environmental conditions, β, the strategy α' is *more efficient* than the strategy α'', if $W(\alpha', \beta) < W(\alpha'', \beta)$. We shall refer to some strategy $\tilde{\alpha}$ as *optimal* under such conditions, if:

$$W(\tilde{\alpha}, \beta) = \min_{\alpha} W(\alpha, \beta).$$

For simplicity, let us consider special case of this optimization problem in which only parameters α_1 and α_3 are vary describing the rate of naive T cells proliferation, and of the IPLT growth, respectively. As earlier, we assume that $\alpha_1 = \alpha_2$.

Fig. 10 shows the optimal structure of *W* for various values of total antigen load *L* (Fig. 10a) and of the adjusted energy cost of acute infection E_0 (Fig. 10b) (here, we additionally assume that E_0 is inversely proportional to the constant rate of T cells proliferation). It can be seen that an increase in total antigen load *L* leads to increase of all components of *W* (except for W_f^t), and mainly W_f^m which is the rate of energy expenditures on maintenance of T cells.

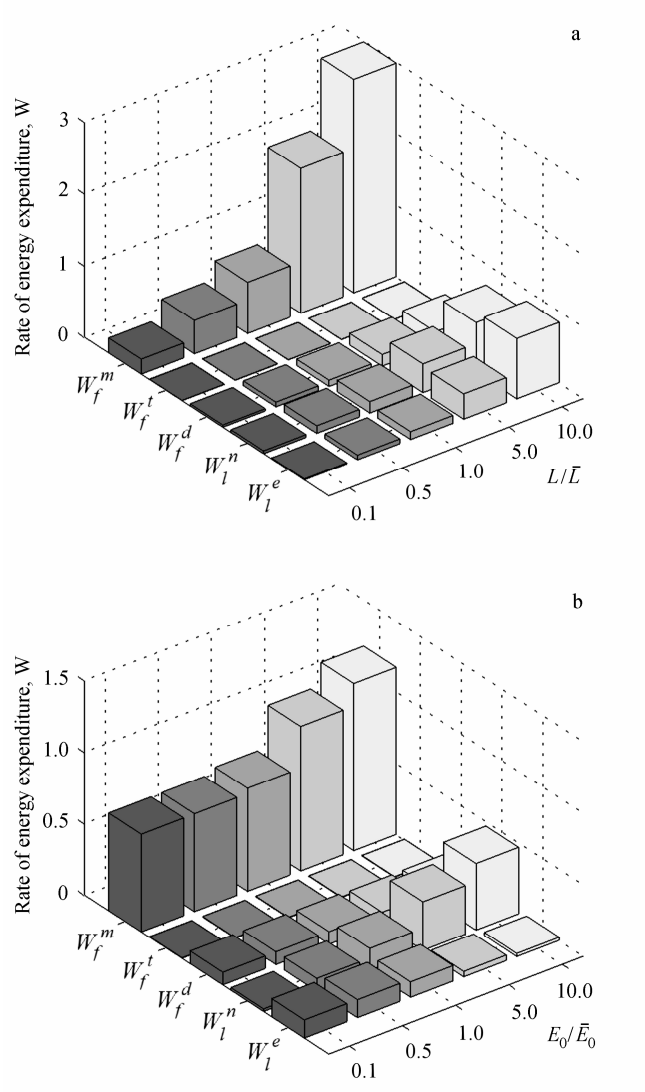

Figure 10. Optimal structure of average power on interaction with antigens for various values of a) antigen load (L), b) energy cost of infectious disease (E_0).

This occurs due to increase in the rate of the IPLT growth, where the maximal value of $V(t)$ corresponds to data on reference man (1500 ml) at 5-fold increased value of L compared to the value shown in Table 1. At the same time, an increase in the total antigen load leads to the decrease in the rate of peripheral T cells proliferation. This means that the *sensitivity* of the immune system to antigen load declines (data not shown).

An increase in E_0 results in growing ratio W_l^n / W_l^e, as well as fraction W_l / W of total energy cost of infectious diseases (Fig. 10b). However, the energy cost of T cells proliferation practically did not change at the considered interval of changes in E_0. In all cases, the resistant type of immune defense with the predominant energy expenses on T cells maintenance turned out to be optimal.

The results of modeling show that the energy cost of interaction with infectious pathogens grows linearly with the increase of antigen load *L*. Hence, a species living under conditions of higher infection load must necessarily spend more energy on the immune defense and less to the reproduction. This relation explains, in particular, the phenomenon of successful species' invasion of new territories (Keane, Crowley, 2002; Lee, Klasing, 2004). When a species find itself in a territory free of common pathogens, it can reduce energy expenditures on immune defense and invest the reserve to reproductive capacity.

9. Discussion

In contrast to other biological tissues and organs, the immune system aging starts early in life and can be irreversible in character. To study this phenomenon we modified the mathematical model of age related changes in population of peripheral T cells suggested by Romanyukha and Yashin, (2003) by including in it the dynamics of T cell populations during the postnatal life.

Human growth and development are accompanied by the increase in basal metabolic rate. The metabolism involves contact with environment, and all pathogenic microorganisms in it. That is why the assumption that antigen load is determined by the basal metabolic rate is crucial in this study.

The results of our analyses show an important potential of naive T cells' homeostatic proliferation in the maintenance of T cell homeostasis during the life course. Such proliferation also explains the observed effect of sharp increase of the volume of the IPLT as a result of increased antigen load caused by frequent infections with the “new” antigens.

The growing body of evidence from animal and human studies supports the idea about existence of trade-off between immune defense and organism’s growth. For example, data from gnotobiology (i.e., the study of organisms, or conditions that are either free of germs, or associated only with known or specified germs) show that the infection of germ-free chicken impairs their body growth by 15-30% (Lochmiller, Deerenberg, 2000). Primary immunodeficiencies in humans can also result in growth impairment and even growth failure (Bjorkander et al., 1984). This holds true for the HIV infection, depending on the extent of a viral load (Arpadi et al., 2000) which, presumably, reflects a rise of energy deficit caused by gradually increasing antigenic pressure.

The model, suggested and investigated in this paper, allows for evaluating possible consequences of such a trade-off for the immune system dynamics under the assumption of linear dependence of body growth from antigen load. More precisely, we assumed the following relationship between model parameters:

$$\alpha_4 = \alpha_{41} - \alpha_{42}\alpha_5,$$

where, as previously, α_4 is the rate constant of body mass growth, and α_5 is the parameter which relates antigen load and basal metabolic rate. The parameter α_{41} in the above formula characterizes a maximal rate of body growth in the absence of antigen load (i.e., under condition $\alpha_5 = 0$), and α_{42} describes the detrimental effect of antigen load on body growth.

It is well known, that the development of HIV infection in children can result in significant impairment of body growth and growth failure. Earlier we have shown (Sannikova et al., 2004) that the HIV infection leading to the development of acquired immunodeficiency syndrome is accompanied by the 8 times higher than normal value of the antigen load. These data are in agreement with observation that the immune hyperactivation during the HIV infection describes experimentally observed reduction in the expansion of the naive and memory T-cell pools better than it does thymic impairment (Hazenberg et al., 2004).

For illustrative purposes, we assumed that the arrest of body growth takes place when the value of antigen load is 10-fold greater than the normal. From this condition, and under additional assumption that the above relationship between model parameters holds true when using the model values of α_4 and α_5, the parameters α_{41} and α_{42} can be determined uniquely.

The results of our analysis suggest the stabilizing effect of body growth rate on the immune system with antigen load 1.5 times higher than normal insignificantly influencing the dynamics of model variables apart from the rate of body mass change and the stationary level of body mass in adulthood (changed from 73 to approximately 60 kg, data not shown). Further increase of antigen load resulted in more pronounced effect on the immune system dynamics with the involvement of volume of intact peripheral lymphoid tissue. Both the increase and the decrease of antigen load resulted in detrimental effect on the volume of intact peripheral lymphoid tissue with mild unidirectional effect on the dynamics of naïve and memory cells and opposite effect on the telomere's dynamics. Clearly, this result reflects non-linear nature of model equations. The decrease of antigen load resulted in increase of stationary adult body mass reaching a maximum of 115 kg in absence of antigen load (Fig.11). The results presented in Fig. 12 show an increasing effect of antigenic load on body mass with age.

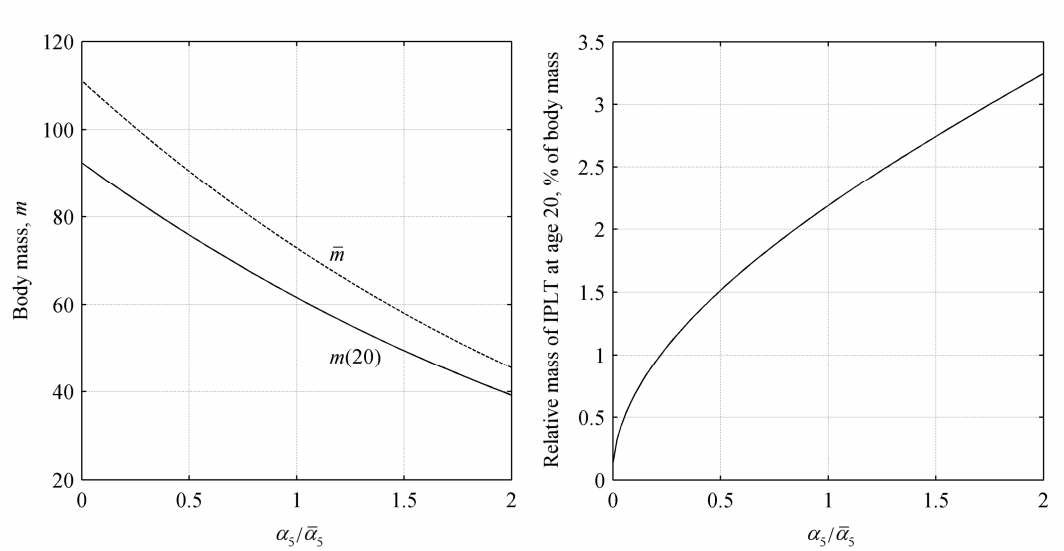

Figure 11. The influence of antigen load on the body mass at age 20 (left panel), and on the relative mass of IPLT (right panel)

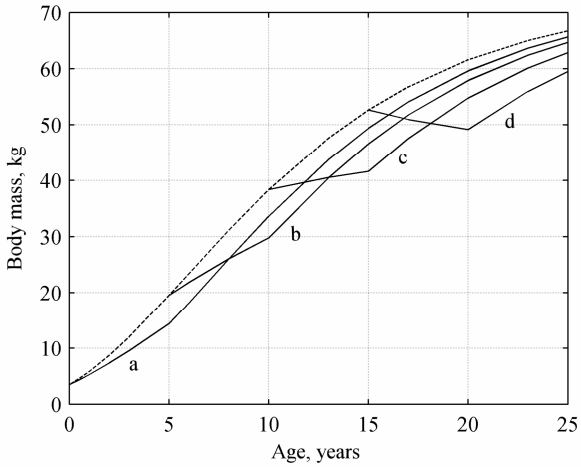

Figure 12. The influence of 2-fold increase in antigen load at the age intervals [0,5 years] (a), [5,10 years] (b), [10,15 years] (c) and [15,20 years] (d), respectively, on the dynamics of body mass. The normal age-related changes of body mass are shown as dotted line.

The preliminary results obtained in our analyses indicate that the mathematical and computer model of immunosenescence described in this paper captures important features of the processes dealing with development of adaptive immunity. The estimates of various components of the energy cost of immune system interaction with infectious pathogens are constructed and respective connections are verified. These relationships are considered from the evolutionary viewpoint assuming "optimality" of the immune defense. Additional analysis of interrelations between metabolic costs of various physiological processes and energy homeostasis at different stages of ontogenesis is needed to evaluate broader consequences of aging in the immune system for other physiological systems in aging organism. From the

mathematical modeling perspective, such an analysis must also include thorough testing and refinement of the hypotheses underlying model equations. Further investigations are needed to clarify the nature and consequences of the observed trade-off between body growth and immune defense.

The potential of using this approach to study mechanisms of infectious diseases can be illustrated by the following example. The development of HIV infection is usually accompanied by an *increase in the frequency and severity of opportunistic infections*. Traditionally this phenomenon is explained by the decrease in the number of peripheral T cells capable to mount an immune response. The results obtained suggest that *a decrease in the immune system's sensitivity* to antigenic challenge in HIV infection could be an additional factor responsible for this effect (see also (Romanyukha et al., 2006)).

This "adaptionist" view on the decline in immune functioning in HIV infection was also discussed by Grossman and Paul, (1992) and Grossmann and Herberman (1997). It is also supported by the evidence on down-regulation of cell surface CD4 on monocyte-derived dendritic cells in HIV infection (Kawamura et al., 2003), by the data on the reconstitution of immune responses in HIV-infected patients treated with highly active anti-retroviral treatment (HAART) (Schluger et al., 2003), as well as by observation of the sustained effect of treatment with HAART on body growth in HIV-infected children (Verweel et al., 2002). Our analysis showed that the observed effects could result from physiological adaptation aiming to reduce physiological (energy) cost of immune defense.

The results obtained in this paper emphasize the importance of the exposure to pathogens at the early period of developing adaptive immunity. More work has to be done to establish connection between inadequate exposure to pathogens in early childhood and immunity related diseases later in life, as well as evaluate evolutionary "optimal" exposure to pathogens which guarantees "healthy aging" of the immune system.

Appendix. Estimation of parameters for the energy cost of antigen burden

The analysis of energy cost of acute respiratory infections, such as pneumonia, show that more than 90% of this value can be attributed to the increase in body temperature (Romanyukha et al., 2006). A typical duration of the acute infection of upper airways of intermediate severity usually is about 5-7 days regardless of etiology, with fever lasting for 2-4 days and body temperature about 38-38,5^{o}C. An increase in the body temperature per each centigrade degree over a threshold of sub-febrile temperature (37^{o}C) leads to 10%-increment in basal metabolic rate (Long et al., 1979). The power

of energy expenditures in the reference man is about 80 W (Snyder et al., 1984). Taking this into account, we obtain that maximal power of energy expenditure in acute infection of upper airways of intermediate severity comprise as much as 10-15% of resting energy expenditure, or 8-12 W, whereas total energy cost of single acute infection ($\overline{E}_0$) can be estimated as 30-40% of daily resting energy expenditure, or

$$\overline{E}_0 = (0.3-0.4)\times 80\,\mathrm{W}\times 24\times 60\times 60\,\mathrm{s} \approx 2.5\times 10^6\ \mathrm{J}.$$

Recalling that E_0 is the adjusted energy cost of infection disease at $NV = C^*\overline{V}$, and assuming that, for adult individual, the condition $NV = C^*\overline{V}/2$ applies, while the energy cost of acute infection caused by the new infection antigens is inversely proportional to naive T cells concentration, we obtain that

$$E_0 = \overline{E}_0/2 \approx 1.25\times 10^6\ \mathrm{J}.$$

To estimate the parameter E_1, we assume that the energy costs of infections, caused by the new and already experienced infections, are equal for the solution of the refined model shown by dotted lines on Fig. 4:

$$W_l^n = W_l^e.$$

As an estimate for the parameter $\overline{n}$ we use a half of total number of infectious diseases per life span.

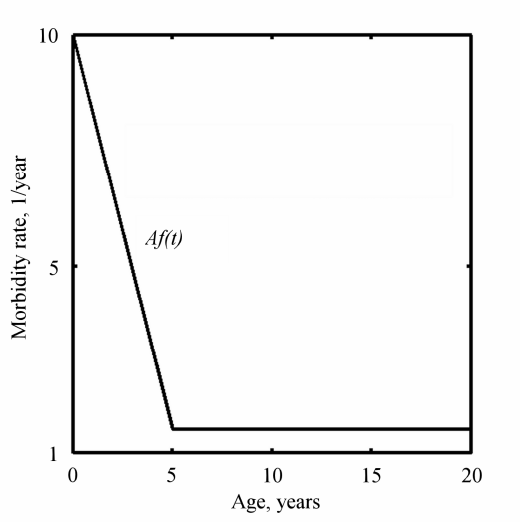

Figure 13. Empirical function *Af*(*t*) of the rate of infectious diseases as a function of age, *A*=10.

Let us estimate average rate of energy expenditure in the immune system of reference adult (W_i). To describe metabolically active tissues, at the beginning of 1950s a concept of body cell mass (BCM) was introduced by the American physician and physiologist Francis Daniels Moore (Moore et al., 1963). BCM of reference man comprise as much as 30 kg (Heymsfield et al., 2005), and the mass of lymphocytes

equals 1.5 kg (Snyder et al., 1984). Recalling that resting energy expenditure of reference man amounts to 80 W, we conclude that

$$W_i = (1.5/30)\times 80\,\mathrm{W} = 4\,\mathrm{W}.$$

This is a rough estimate of W_i since the rate of energy consumption by the different components of BCM (per the unit of body mass) significantly varies. For instance, the brain, liver, heart and kidneys, the total mass of which in adults approximately amounts to 6% of the body mass, is accounted for 60% of basal metabolic rate (Rolfe, Brown, 1997). So, for more precise estimation of W_i, it will be better to use the *in vitro* data on the intensity of cellular breathing.

Energy expenses of *blood leukocytes* comprise $(3\text{-}8)\times 10^{-3}$ W/g (Ivanov, 1990). More than a half of these cells is represented by neutrophils (Johnson, 1991) – relatively large (the mass of a neutrophil is approximately three time as much as of lymphocyte) and short-lived cells (the life span is 1 or 2 days) with relatively low metabolism per the unit of mass. For lymphocytes, an appropriate estimate is even smaller, amounting to 4.4 nmol O_2/(min×mg protein) in adults (Sariban-Sohraby et al., 1983). As it is known that the average protein content in eukaryotic cells comprises about 10% of cell mass (Spector, 1956; Gunsalus, Schuster, 1961), and the oxygen density is 1.43 kg/m^3 (Babichev et al., 1991), then the mentioned estimate of the intensity of lymphocytes breathing can be scaled as 4.7 microliters O_2/(min×g), or 1.6×10^{-3} W/g. Taking into account that the total mass of lymphocytes in reference man is equal to 1500 g (Snyder et al., 1984), then we obtain the more realistic estimate of W_i:

$$W_i = 1.6\times 10^{-3}(\mathrm{W/g})\times 1500\,\mathrm{g} = 2.4\,\mathrm{W}.$$

So, average energy expenditures of the immune system account for 3% of basal metabolic rate. At the same time, we established that the lymphocytes' population consumes energy at a relatively low rate per unit of BCM.

The incidence of acute respiratory infections among children under 5 years in average 4-fold higher than in the remaining part of population, amounting to 6-8 cases per capita for urban, and 4-6 cases for rural population annually in most countries irrespective of level of development (PHO, 1995). But the predominant type of infections can differ, with viral infections prevailing in the developed countries, and bacterial infections in the developing countries.

Assume that the frequency of acute respiratory infections in children younger than 5 years is linearly decreasing function of age (Fig. 13) leading, on average, to 6 cases per capita annually, and is constant after 5 years on the level 1.5 year^{-1}. We shall use this rough approximation of age dependence of infectious diseases' incidence rate for the description of decreasing intensity of antigen load by the new antigens, as well

as for counting the cost of infectious diseases (Eqs. 7-8). Fig. 13 represents an empirical dependence of diseases incidence *Af(t)* from age with the maximal incidence rate

$$A = 10\,\text{years}^{-1}$$

and total number of infectious diseases per life time

$$2\bar{n} \cong 170.$$

The value $\bar{n}$ was determined as a half area under the curve *Af(t)* on the stipulation that the life span *T* is equal to 100 years. If we assume that the average duration of fever in acute infection is equal to 2-4 days (as for influenza), then the total duration of fever throughout life can be estimated as 1-1.5 years.

Using the above estimate of maximal rate of energy loss during acute phase of infection (8-12 W), one can conclude that the average rate of energy loss due to infectious diseases throughout life amounts to (8-12)×(1-1.5)/100 ≈ 0.12 W, or about 5% of total power of the immune system expenditures.

Recalling that the morbidity of younger children approximately 4 times higher than in the remainder population, we obtain that in children with frequent and prolonged illness the loss of energy in infectious diseases is comparable to the rate of energy expenses on the maintenance and proliferation of lymphocytes!

Since the mass of one lymphocyte approximately equals 3×10^{-10} g (Johnson, 1991; Flindt, 1988), then, from the data on the intensity of lymphocytes' breathing (1.6×10^{-3} W/g) the *upper bound* for the energy cost of lymphocyte maintenance follows:

$$\bar{\beta}_1 = 4.1\times10^{-8}\ \text{J/(day}\times\text{cell)}.$$

The energy consumed by the cells of the immune system is a sum of expenses for their *maintenance* (W_m^i) and *proliferation* (W_i^d):

$$W_i = W_i^m + W_i^d.$$

Therefore, to estimate specific (per cell) energy cost of lymphocyte maintenance (β_1), it is sufficient to evaluate the ratio of mentioned energies taking the advantage of known estimate of $\bar{\beta}_1$.

We shall estimate the energy needed for the production of one lymphocyte using the data on the bacteria *S.aureus* assuming the similar relative content of major biochemical compounds of dry weight of eukaryotic and prokaryotic cells (Gunsalus, Schuster, 1961). Energy cost of the production of 100 mg of the bacterial dry weight amounts to 9×10^3 μmol ATP (Gunsalus, Schuster, 1961), or 30 J, since the hydrolysis of 1 mole of ATP gives, on average, 8 kcal (Lehninger, 1971). The dry weight of

lymphocytes represents about 30% of total. From this, recalling the mass of a lymphocyte, we can estimate specific energy β_2 needed to produce a lymphocyte:

$\beta_2 = 30\,\text{J}/(100/0.3\,\text{mg}) = 2.7\times10^{-8}$ J/cell.

If we assume that the percentage of dividing lymphocytes in the IPLT amounts normally to 1% (Hazenberg et al., 2000), and the duration of cell cycle equals to 8 hours, then, using an estimate of β_2 we obtain that total power of energy expenses on proliferation of lymphocytes amounts to 0,035 W, or about $0.0015\times W_i$. So, we have established that the major part of W_i is represented by the rate of energy expenses on the maintenance, but not proliferation, of lymphocytes:

$W_i^m >> W_i^d$.

So, we can assume that

$\beta_1 = \overline{\beta}_1$.

It is known that, during selection and proliferation in thymus, 95-97% of precursor T cells die. So, the appearance of each T cell in the peripheral pool is accompanied by the loss of 20-30 cells in thymus. This is accounted for in the Equation for E_f^t using the parameter k_1. In our calculations we used the value

$k_1 = 25$.

Table 4: Some energy characteristics of the human immune defense compared to various physiological and industrial costs

Characteristics	Dimension	Value
Energy cost of one acute respiratory infection of intermediate severity	MJ	2.5
Total energy cost of acute infectious diseases (life time, assumed 150-170 acute infections per life span)	MJ	400
Compare: energy cost of pregnancy	MJ	320
Average power of immune defense (reference man)	W	2.4
Compare: average power of basal metabolic rate (reference man)	W	80
Total energy cost of the immune defense (life span)	GJ	5.3
Compare: An 18-minutes amount of electric energy produced at the world-first nuclear power plant (Obninsk, USSR, electric power 5 MW), or 10-s amount of electric energy produced at the Dnieper hydroelectric power station (Ukraine, electric power 560 MW)	GJ	5.3
Total power of the immune defense for mankind	GW	15
Compare: Total BMR power of mankind	GW	500

The parameters k_2 and k_3 in Eqs. 6 describe an average ratio of maximal clonal size of specific T cells and of memory T cells arising from immune response, for naive and memory T cells, respectively. In acute infections, a major part of newly produced lymphocytes die from apoptosis, and the remainder (about 5%) form a population of long-lived memory cells (De Boer et al., 2001). From this, we obtain an estimates for k_2 and k_3 (see Table 3).

Our estimates of some energy cost characteristics of human immune defense compared to various physiological and industrial costs are summarized in Table 4.

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