Linking immune life history, body growth and aging: a modeling approach

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Abstract

In this work, a 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 is estimated and used as a measure of the immune system effectiveness. The dependence of optimal resource allocation in the immune system from the parameters of antigen load is studied.

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

The scheme of relating immune system aging and metabolism

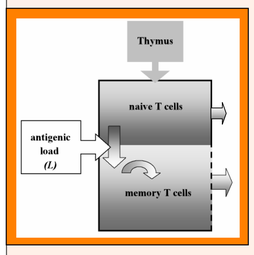


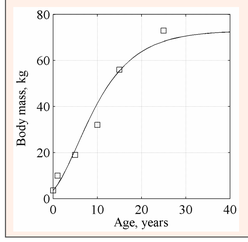
Fig. 1. The scheme of age-related changes in population of human peripheral T cells (Romanyukha, Yashin, 2003). Involution of thymic cortical tissue, where the production of naive T cells takes place, starts early in life at the age of 1 year (Steinmann et al., 1985)

Assumption 1. Antigen load is proportional to basal metabolic rate (BMR).

An empirical 3/4 power scaling law (Kleiber, 1932): BMR ~ (body mass)$^{3/4}$.

Assumption 2. Body mass can be used as a surrogate measure of antigen load: $L = \alpha_5 m^{3/4}$

"Working assumption" 3: $\alpha_5 = const$.



Theoretical prediction for body mass growth of multicellular organisms (West, Brown, 2005):

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

Fig. 2. Body mass of the Reference man as a function of age

Mathematical model

To describe the dynamics of age-related changes in population of peripheral T cells, the following model system was considered:

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

The model utilizes telomeric hypothesis of aging, clonal selection theory, and a concept of limited immunological space.

Model variables depend on age t: N^* - the rate of naive T cells influx from thymus into the intact peripheral lymphoid system (IPLT), N - the concentration of naive T cells in IPLT, M - the concentration of memory T cells in IPLT, P^* - the length of telomeres in naive T cells leaving thymus at age t, P_N - the length of telomeres in naive T cells, P_M - the length of telomeres in memory T cells, V - the volume of IPLT, m - the body mass.

Parameters' estimation

1. Logarithmic least-squares:

$$F = \sum_{i,j} (\lg(\frac{x_i(t_j)}{X_i^j}))^2 \to \min.$$

X_i^j – observational data; $x_i(t_j)$ – solution to the model system.

2. The principle of minimal energy dissipation (Romanyukha et al., 2006):

$$W = W_f + W_l \to \min.$$

Energy expenses on the immune system function (power units)

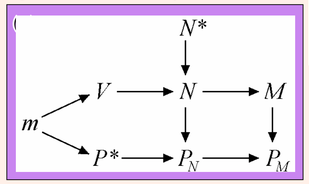
Energy loss due to infectious diseases (power units)

Energy cost of antigen load and of immune defense (estimates)

- Average power of immune defense (Reference Man): 2.4 W
- Energy cost of acute respiratory infection of intermediate severity: 2.5 MJ
- Total energy cost of acute infectious diseases (lifetime): 400 MJ
- Total energy cost of the immune defense (lifetime): 5.3 GJ
- Total power of the immune defense for mankind: 15 GW

Optimization technique

Differential evolution (DE) algorithm (Storn, Price, 1997)
http://www.icsi.berkeley.edu/~storn/code.html



Storn, R., Price, K., 1997 Differential evolution: a simple and efficient heuristic for global optimization over continuous spaces. J. Global Optimization 11, 341-359.

Fig. 3. "Natural" order of the model parameters' estimates

Results

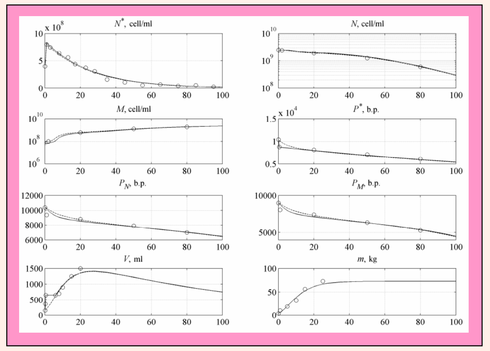


Fig. 4. The refined solutions to the model system

Compare: Primary immunodeficiencies in children impair or even arrest body growth (Bjorkander et al., 1984), so as HIV infection, depending on viral load (Arpadi et al., 2000)

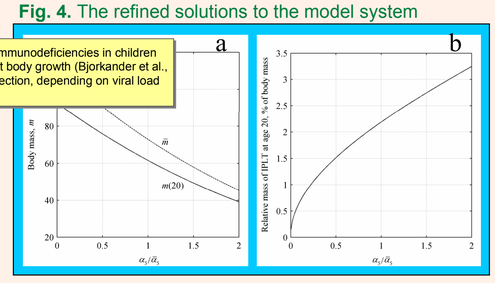
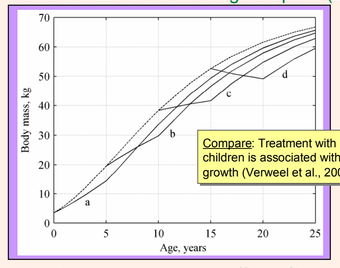


Fig. 5. The influence of antigen load on body mass (a) and relative mass of immunological space (b) at mature age



Compare: Treatment with HAART in HIV-infected children is associated with a sustained effect on growth (Verweel et al., 2002)

Fig. 6. An increasing age effect of temporal 2-fold increase in antigen load on body mass

Conclusions

A method of immune life history analysis is suggested which enables to study relationships between the immune system development, body growth, and infection load. Numerical experiments show stabilizing effect of body mass on the immune system dynamics, major contribution of infection load to total antigen burden in early childhood, and a decrease in the immune system "sensitivity" with growing antigen load. These observations agree with an "adaptionist" view on the immune system behavior in HIV infection (Grossman, Herberman, 1997) and may serve as a positive feedback in the progression of HIV infection to AIDS (possible mechanism of AIDS development).

Compare: As the frequency of infection increases it becomes more profitable to the immune system to tolerate pathogens in the body rather than attempt to eliminate them (Romanyukha et al., 2006)

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http://www.demogr.mpg.de/papers/working/wp-2006-042.pdf