Mathematical modeling of immune system development: connections to body mass growth and metabolic rate

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Abstract

To describe immune system development, a theoretical approach is considered based on the assumption about the availability of the immune system goal-seeking behavior – physiological adaptation. For this, we consider an extended mathematical model of age related changes in population of peripheral T cells (Romanyukha, Yashin, 2003). Energy cost of antigen burden is estimated and used as a measure of the immune system effectiveness. Our 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). The dependence of optimal resource allocation in the immune system from the parameters of antigen load is studied.

Fig. 1. Construction of Dnipro hydro plant (USSR, photo of 1934) An amount of energy produced there for 10 seconds (about 5 GJ) is a good estimate of energy expenses for human immune defense during life time

Relating immune system development and metabolism

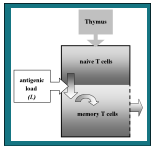


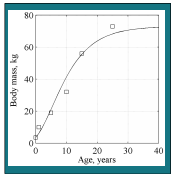
Fig. 2. The scheme of age-related changes in population of human peripheral T cells (Romanyukha, Yashin, 2003). Involution of thymus, an organ where the production of naive T cells takes place, starts early in life at the age of 1 year (Steinmann et al., 1985)

Main assumption: Antigen load is **proportional** to basal metabolic rate

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

Body mass can be used as a surrogate measure of antigen load:

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



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. 3. 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:

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

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

The 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, 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. Simple data fit: logarithmic least-squares

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

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

2. Strong immune system or effective reproduction? - the principle of minimal energy dissipation

$$W = W_{is} + W_d \to \min,$$

Romanyukha, A.A. et al., 2006. Energy cost of infection-burden: an approach to understanding the dynamics of host-pathogen interactions. J. Theor. Biol. 241, 1-13.

Energy expenses on the immune system function (power units) – maintenance and production of immune cells

Associated metabolic cost of infections and other diseases (power units)

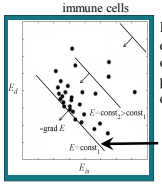


Fig. 4. Energy allocation into immune defense (E_{is}) and associated metabolic cost of infectious and other immune-controlled pathologic states (E_d) – various traits for different hosts

Equipotential lines = a fragments of 'circles' of the 1st Holder norm in P^2=(E_{is},E_d)

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
- 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 (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.

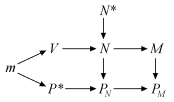


Fig. 4. Natural order of the model parameters' estimates

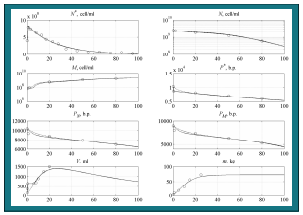
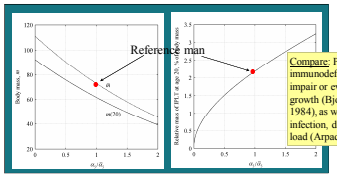


Fig. 5. The refined solutions to the model system

Results

- How the intensity of antigen load affects final body mass?



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

Fig. 6. The dependence of final body mass (left) and of baseline immunological space (right) from antigen load

- An importance of timely immune system learning

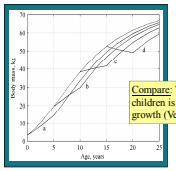


Fig 7. An increased age effect of temporal (2-fold) rise in antigen load on body mass

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

- Inverse relationship between the value of antigen load and the rate constant of immune (T) cells division. Interpretation: infection anergy (i.e., unresponsiveness) development as a result of increase in antigen load.

Conclusions

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. 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 the antigen load is determined by the BMR is crucial in this study.

Our results emphasize the importance of the exposure to pathogens at the early period of developing adaptive immunity. We obtained numerically a decrease in the immune system sensitivity to pathogens with growing antigen load as an adaptive trait in order to minimize energy cost of immune defense. This effect could be considered as a mechanism of positive feedback in the progression of HIV infection to AIDS and agrees well with an adaptionist view on the immune system behavior in HIV infection (Grossman, Herberman, 1997). Further studies are needed to clarify the nature and consequences of the observed trade-off between body growth and immune defense.

Literature cited

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For further information

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