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CONTROL IN BIOLOGICAL SYSTEMS AND MEDICINE

The Energy Criterion for Quality of Immune Defence and Pathogenicity of Microorganisms[1]

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Abstract—Relationships between the energy cost of immune defence, the disease severity, and the properties of pathogens were investigated. The findings suggested a hypothesis explaining the observed distribution of microorganism pathogenicity. The mechanism supporting stability of this distribution explains emergence of new highly pathogenic strains of microorganisms.

1. INTRODUCTION

Analysis of the epidemiological data reveals a significant scatter in human resistance to infectious diseases: for any epidemics, the population has individuals who either do not fall sick at all or have illness in a much easier form than the others. Studies have demonstrated that these differences depend not only on the life style and the previous diseases, but also on heredity, that is, there exists a significant genetic deterministic scatter in the level of defence against infectious diseases [1].

Infectious diseases reduce fitness of individuals, and it would seem that the genes responsible for lower resistance must disappear from a population because their carriers have more chances to die out and leave no posterity. The fact that the individuals with a relatively low resistance to infections are nevertheless retained in the population indicates that high efficiency of the immune defence is accompanied by shifts in other physiological systems that offset the positive effect of higher resistance. This phenomenon is described in terms of resistance or defence "cost" [2–4]. A hypothesis of competition for limited resources is proposed to explain this phenomenon [5]. Its main point lies in the assumption that in different individuals the resources of an organism and the acquired resources can be distributed differently, which results in lower function of some systems upon increase of the resources consumed by other systems. Various substances can play the part of resource, but energy is the universal resource whose consumption characterizes activity of all physiological systems.

The smaller the energy consumed by the immune system, the more energy is left to the remaining systems. However, an inactive immune system cannot defend the organism against infectious diseases which lead to consumption of much energy for defence (fever, inflammation, and so on) and regeneration of the damaged tissue. Since reduction of the total energy consumption for both defence and disease is advantageous to the organism, this cost can be used as a measure of efficiency of the immune system.

Severity of disease and its outcome depend not only on the characteristics of the defence systems of an organism, but also on the properties of the microorganism inducing this disease. The organism interacts with a tremendous number of various microorganisms. One of the characteristics of the microorganisms parasitizing on human beings is their pathogenicity, that is, ability to damage the tissues and organs of the infected organism. The property of pathogenicity is distributed between the microorganisms very nonuniformly. There are tens of pathogen species causing severe and even

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extremely severe diseases, hundreds of species of infecting agents (with regard for their antigen variants) capable of causing easy and moderately severe diseases, and tens and hundreds thousands of species that are harmless to the human beings[2] [6, 7]. Studies have demonstrated that the main processes involved in the vital functions of microorganisms and the properties responsible for their pathogenicity are not rigidly related. In the present paper, the distribution of the microorganism pathogenicity is considered from the point of view of the energy cost of anti-infectious defence of the organism.

2. MATHEMATICAL MODEL OF ANTI-INFECTIOUS DEFENCE

The relationship between an individual and pathogens is described by the model of anti-infectious defence which assumes that the total number of different pathogens can be great and the immune system is capable of responding to any of them. During the interval under consideration, the individual is infected only by one pathogen, but infections can repeat depending on the level of the immune memory. It is believed that the pathogen is present permanently in the environment and enters the organism at the instant of infection, the dose of infection and the parameters of the immune system being constant. An individual can be in either of the two states: healthy or sick. The state of health is characterized by the zero concentration of the pathogen, and that of disease, by a nonzero concentration. In the state of health the individual can be immune to repeated infection.

The dependent variables of the model are as follows: $V(t)$ is the concentration of the pathogen in the target organ; $C(t)$ is the concentration of the specific lymphocytes in the lymphoid tissue; $C_m(t)$ is the concentration of the specific memory cells in the lymphoid tissue; $F(t)$ is the concentration of the antibodies in blood; and $m(t)$ is the fraction of cells of the target organ destroyed by the pathogen. We denote by t_0, $t_2, \ldots$, the instants of infecting and by t_1, $t_3, \ldots$, the instants of recovery. The dynamics of anti-infectious defence during infections (over the intervals $[t_{2k}, t_{2k+1}], k = \overline{0,n}$) obeys the equation system (1)–(4) of the basic model of the infectious disease [10] ($\tau = 0$):

$$\frac{dV}{dt} = \beta V - \gamma FV, \tag{1}$$

$$\frac{dC}{dt} = \alpha\xi(m)FV - \mu_c(C - C^*), \tag{2}$$

$$\frac{dF}{dt} = \rho C - \eta\gamma FV - \mu_f F, \tag{3}$$

$$\frac{dm}{dt} = \sigma V - \mu_m m. \tag{4}$$

In the absence of infection (over the time intervals $[t_{2k+1}, t_{2k+2}]$, $k = \overline{0,n}$), the anti-infectious defence obeys Eqs. (5)–(8) obtained from (1)–(4) for $V \equiv 0$, that is, in the absence of the pathogen, with addition of Eq. (6) for the concentration C_m of the memory cells:

$$\frac{dC}{dt} = -\mu_c(C - C^*), \tag{5}$$

$$\frac{dC_m}{dt} = -\alpha_m C_m, \tag{6}$$

$$\frac{dF}{dt} = \rho(C + C_m) - \mu_f F, \tag{7}$$

$$\frac{dm}{dt} = -\mu_m m. \tag{8}$$

[2] In particular, the degree of dependence of the microorganisms on the given host is an important factor affecting their pathogenicity. The point is that many pathogens infect several species and for many viruses and bacteria the human being is an occasional or rare host.

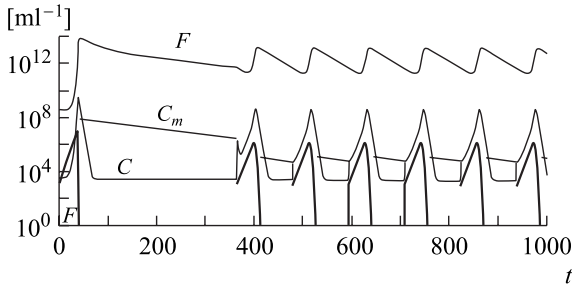

Fig. 1. Solution of the model of anti-infectious defence (1)–(8) for the parameters and initial conditions of Table 1. The concentrations of specific antibodies, memory cells, lymphocytes, and pathogens are plotted on the vertical axis; the time in days, on the horizontal axis. The pathogen entering a susceptible organism at time $t = 0$ causes acute infection of high severity. The memory cells C_m formed after recovery provide the antibody concentration at a level inhibitory to repeated infection. After diminishing of the level of immune memory and antibody concentration, infections of lesser severity occur repeatedly.

Systems (1)–(4) and (5)–(8) are related by the initial conditions. At the instant of the first infection,

$$V(t_0) = V_0; \quad C(t_0) = C^*; \quad F(t_0) = \rho C^*/\mu_f; \quad m(t_0) = 0.$$

At the instants of repeated infections, for Eqs. (1)–(4):

$$V(t_{2k}) = V_0; \quad C(t_{2k}) = C_m(t_{2k_-}) + C(t_{2k_-});$$
$$F(t_{2k}) = F(t_{2k_-}); \quad m(t_{2k}) = m(t_{2k_-}).$$

The initial conditions for Eqs. (5)–(8):

$$C(t_{2k+1}) = (1-\delta)C(t_{2k+1_-}); \quad C_m(t_{2k+1}) = \delta C(t_{2k+1_-});$$
$$F(t_{2k+1}) = F(t_{2k+1_-}); \quad m(t_{2k+1}) = m(t_{2k+1_-}),$$

where δ is the fraction of lymphocytes transforming into the memory cells at the instant of recovery ($0 < \delta < 1$). The condition for end of an infection at the time t follows $V(t) \le V_{\min}$, where $V_{\min}$ is the threshold of pathogen disappearance, that is, the concentration below which the pathogen is incapable of infecting a susceptible organism. The model parameters were established on the basis of the data presented in the literature and specified in the course of preliminary experiments for adjusting the model to the data of the generalized picture of disease in the case of pneumonia [8]. They are presented in Table 1. Figure 1 depicts a typical solution defined by the system of model Eqs. (1)–(8).

Depending on the parameter values and the initial conditions, there may be qualitatively different variants of solutions of (1)–(4) that are interpreted as acute form of disease with recovery, persistent infection, lethal disease, or abortive infection without development of disease ([9], Ch. 2). The variant of abortive infection corresponds in essence to the state of resistance to infection provided, for example, by the cells of immune memory. We assume here that infection occurs if the post-infection solution of the model corresponds to the acute infection. The condition of infection at the time t is $0 < F(t) < F_t$, where $F_t = \dfrac{\beta - \epsilon_c}{\gamma}$ is the threshold concentration of antibodies and $0 < \epsilon_c < \beta$ is the parameter estimated from the numerical experiments.

We denote by $U(\varphi, T) = \{V(t), F(t), C(t), C_m(t), m(t)\}$ the solution of the model of anti-infectious defence (1)–(8) over the interval $T = [t_0,\ t_e]$, $t_0 < t_1 < \ldots < t_i \le t_e$, where t_0 is the instant

Table 1. Values of the parameters of the anti-infectious defence model

Parameter	Value	Unit	Name and physical sense of the parameter
β	0.25	day^{-1}	rc* of pathogen multiplication
γ	8.5×10^{-14}	$\frac{\text{ml}}{\text{pt}\times\text{day}}$	rc of pathogen neutralization by antibodies
α	5×10^{-11}	$\frac{\text{cell}\times\text{ml}}{\text{pt}\times\text{molec}\times\text{day}}$	rc of lymphocyte multiplication
μ_c	0.5	day^{-1}	rc of lymphocyte natural death
ρ	7×10^3	$\frac{\text{molec}}{\text{cell}\times\text{day}}$	rc of antibody production by lymphocytes
η	20	molec/pt	Consumption of antibodies for pathogen neutralization
μ_f	0.05	day^{-1}	rc of antibody catabolism
σ	10^{-8}	$\frac{\text{ml}}{\text{pt}\times\text{day}}$	rc of destruction of the target organ cells by pathogen
μ_m	0.4	day^{-1}	rc of regeneration of the target organ
α_m	0.01	day^{-1}	rc of natural death of the memory cells
$V_{\min}$	1	pt/ml	Pathogen concentration corresponding to its elimination from organism
δ	0.1	—	Fraction of lymphocytes transforming into the memory cells upon recovery
C^*	2.8×10^3	cell/ml	Homeostatic level of lymphocytes
V_0	10^3	pt/ml	Dose of infection
ϵ_c	0.2	day^{-1}	Constant in the infection condition

* rc is the rate constant.

of first infection and φ is the vector of the model parameters. For nonnegative initial conditions and values of the parameters, solution of the model $U(\varphi, T)$ exists and is unique, continuous, and nonnegative over the interval T [10, 11].

3. SUBSTANTIATION OF USING THE ENERGY CRITERION FOR OPTIMALITY

Let us assume that efficiency of the anti-infectious defence system may be characterized by the energy consumption for the immune defence processes and pathological processes [8, 12]. Table 2 shows the estimated energy consumption for various processes of interaction with the pathogen. The parameter values used in the estimates in Table 3 were taken from two sources: experiments and literature. Let us consider as an example the estimate $E_3 = LN_sT(w_1 + e_2\mu_c)C^*$ of energy consumption for formation of lymphocytes in the bone marrow and their maintenance over the time T. This process supports the pool of the naïve cells of the immune system. A distinguishing feature of the pool of the naïve lymphocytes is the fact that it includes the lymphocytes capable of responding to diverse antigens. At that, for each antigen, a constant (homeostatic) concentration C^* of lymphocytes responding to it and only to it is maintained.

Let N_s denote the number of possible antigens ($N_s = 10^6$ for the humans) to which the immune system responds. The first term describes the energy for maintaining the homeostatic level LN_sC^* of the lymphocytes of N_s specificities over the time interval T. The second term describes the costs of lymphocyte population turnover. It is assumed that the lymphocytes of all specificities are uniformly distributed over the entire volume of the lymphoid tissue. We neglect their content in blood and also assume that C^* varies simultaneously for the lymphocytes of all specificities produced by the central organs of the immune system. This assumption can be grounded on the

Table 2. Main components of the energy cost of anti-infectious defence (a variant of notation for model (1)–(8))

Components of ec*	Description of the ec component
$E_1 = \sum\limits_k L_1 e_1 \beta \int\limits_{t_{2k}}^{t_{2k+1}} V dt$	ec of pathogen formation
$E_2 = \sum\limits_k L_2 e_2 \alpha \xi(m) \int\limits_{t_{2k}}^{t_{2k+1}} FV dt$	ec of immune response
$E_3 = L N_s T (w_1 + e_2 \mu_c) C^*$	ec of formation and maintenance of the naïve lymphocytes
$E_4 = L_2 w_1 \int\limits_{t_0}^{t_e} (C - C^*) dt$	ec of maintaining cells of the immune response
$E_5 = L_1 e_3 \mu_m m^* \int\limits_{t_0}^{t_e} m dt$	ec of regeneration of the target organ
$E_6 = w_2 \int\limits_{t_0}^{t_e} m dt$	Energy losses caused by violations of homeostasis
$E_7 = \sum\limits_k \left(L_2 w_1 \int\limits_{t_{2k+1}}^{t_{2k+2}} C_m dt \right)$	ec of maintaining the memory cells

* ec is the energy cost.

Table 3. Estimated values of the parameters of energy consumption for anti-infectious defence

Parameter	Value		Physical sense of the parameter
e_1	4×10^{-10}	J	ec of formation of one bacterium
e_2	2.6×10^{-9}	J	ec of formation of a lymphocyte
e_3	2.7×10^{-8}	J	ec of formation of a cell of the organ
w_1	3×10^{-13}	W	Energy for maintaining lymphocytes
w_2	~ 100	W	Losses caused by violation of organism homeostasis
L	1000	ml	Volume of the lymphoid tissue of the organism
L_1	300	ml	Volume of the target organ (lung)
L_2	15	ml	Volume of the lymphoid tissue of the target organ
N_s	10^6		Number of different specificities of lymphocytes
m^*	1.3×10^8	cell/ml	Normal concentration of the cells of the target organ

fact that formation of the antigen receptors is based on a random combinatory process going on at the level of the genom of the predecessor cells of lymphocytes in the marrow [13].

We introduce a cost equal to the mean energy consumed for anti-infectious defence over the time interval T:

$$W(\varphi, T) = \sum_{i=\overline{1,7}} E_i / T = \sum_{i=\overline{1,7}} E_i(U(\varphi, T))/T. \tag{9}$$

4. MINIMIZATION OF ENERGY CONSUMPTION FOR ANTI-INFECTIOUS DEFENCE

Let us see how the energy-optimal operation of the immune system depends on the properties of a pathogen. Efficiency of the anti-infectious defence depends on the following parameters of the anti-infectious defence model (1)–(8): α is the rate of development of the immune response; μ_c is the rate of natural death of lymphocytes; μ_m is the rate of regeneration of the target organ; α_m is the rate of death of the memory cells; C^* is the homeostatic level of lymphocytes; and δ is the

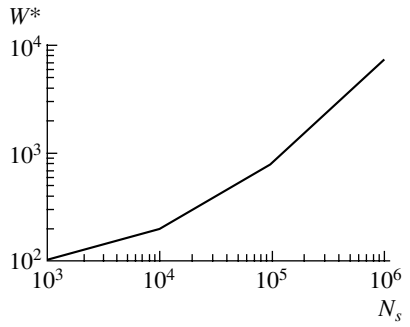

Fig. 2. Optimal value of the mean energy of anti-infectious defence W^* [J/day] vs. the number N_s of pathogen specificities.

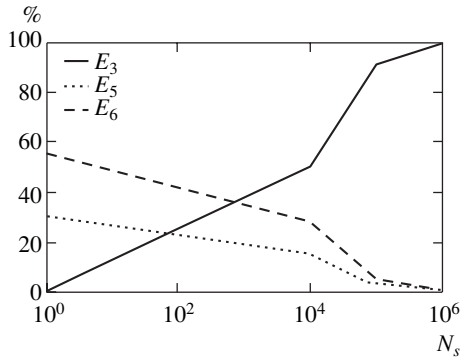

Fig. 3. Reallocation of energy for maintaining homeostasis (E_3) and compensating for violation of homeostasis and loss of fitness (E_6) as a function of the diversity of pathogens in the case of the optimal solution for $\sigma = 2 \times 10^{-9}$ ml/(pt day). Switching between the preventive defence (E_3) and defence in the course of disease (E_6) with the increase of the number of pathogens can be observed. With increase in the number of pathogens, the organism must maintain the level of energy consumption for the anti-infectious defence at least at a certain limit.

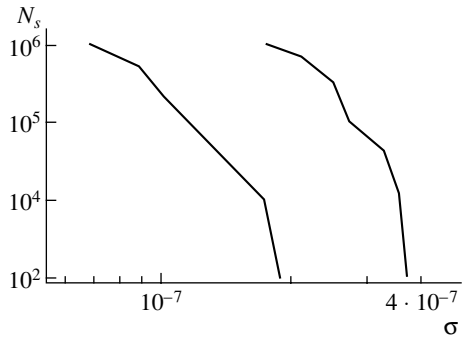

Fig. 4. Optimal value of the mean energy W^* used for anti-infectious defence vs. the pathogenicity of a microorganism σ [ml/(pt day)] and the number of specificities N_s for $\beta = 0.5$ day^{-1}. Left line—$W^* = 1000$ J/day, right line—$W^* = 2000$ J/day.

fraction of lymphocytes transforming into the memory cells at the time or recovery. The pathogen properties are described in the model by the rate of multiplication β and by the pathogenicity σ. The parameter N_s also can be attributed to the properties of the pathogen.

Let us evaluate the parameters of the anti-infectious defence model (1)–(8) minimizing the mean energy for defence against the pathogen. We denote by φ_c the vector of fixed model parameters

Table 4. Varied parameters of the model of anti-infectious defence

Parameter	Initial value	Range of variation
α	5×10^{-11}	$[5\times10^{-12},\ 5\times10^{-10}]$
μ_c	0.5	$[10^{-3},\ 5]$
μ_m	6×10^{-2}	$[10^{-2},\ 1]$
α_m	7×10^{-3}	$[10^{-5},\ 0.1]$
C^*	2.8×10^{3}	$[1,\ 2.8\times10^{4}]$
δ	0.1	$[10^{-3},\ 0.5]$

(Table 1); $\varphi_v \in \mathcal{D}_{\varphi_v}$ the vector of varied parameters; and $\mathcal{D}_{\varphi_v}$ the domain of their admissible values (Table 4). The values of the parameters of the energy consumption processes (Table 3) are fixed. For the given values φ_c of the parameters of the pathogen and the immune system, we determine the value φ_v^* of the vector of varied parameters such that

$$W^*(\varphi_v^*,\ \varphi_c,\ T) = \min_{\varphi_v \in \mathcal{D}_{\varphi_v}} W(\varphi_v,\ \varphi_c,\ T). \tag{10}$$

Let us see how the optimal values of the immune defence parameters depend on the pathogen parameters. The values α, μ_c, μ_m, α_m, C^*, and δ vary within the limits shown in Table 4, the rest of the values being constant. The length of the modeling interval is taken to be $T = 5000$ days. Figures 2–4 depict the characteristics of the minimal energy cost of the anti-infectious defence vs. the properties of the pathogen defined by the parameters σ and N_s.

The parameter α defines the rate of development of the immune response. Acceleration of the immune response and, consequently, accelerated recovery reduce the energy cost of the anti-infectious defence. Therefore, α tends to its upper limit. The cell death parameter μ_c tends to 5×10^{-2} day^{-1} lying on the boundary of the admissible range. It seems that the chosen value is a compromise between two species of consumptions such as formation and maintenance of the cells (Table 4). The value of μ_m tends to the upper limit. The optimal value of the mean energy consumption is low-sensitive to the parameters α_m, C^*, and δ, and their optimal costs do not manifest any pronounced dependence on σ and N_s.

5. RESULTS AND DISCUSSION

Let us see how the optimal level W^* of energy used by the organism for the anti-infectious defence varies as a function of the number N_s of different pathogens that can infect it. An example of such dependence is shown in Fig. 2: N_s varies within the interval 10^3–10^6 and the following parameters were used in calculations: $\beta = 0.25$ day^{-1} and $\sigma = 10^{-8}$ ml/(pt×day). One can see that W^* grows linearly with N_s. It is seen from the expressions for the components of energy cost (Table 2) that only the energy cost E_3 for formation and maintenance of the naïve lymphocytes depends on N_s. Consequently, for larger N_s the energy consumption consists mostly of the consumption for maintaining the homeostatic level of lymphocytes. To illustrate this assumption, we present in Fig. 3 the data on variation of the fractions of the three components E_3, E_5, and E_6 vs. N_s. The values of E_6 and E_5 reflect the fraction of energy used by the organism against the disease itself and regeneration of damage and E_3 characterizes readiness of the immune system to respond to various infections. The fraction of E_3 can be seen to become leading for $N_s > 10^4$, whereas the disease costs dominate for $0 < N_s < 10^4$.

This regularity can be explained in part by the fact that the optimization problem modeled the introduction of infection by one of the N_s pathogens to which after the first infection an immune memory had been formed and then reduced severity of disease and, consequently, W^* at the subsequent introductions of infection. During their lives, the human beings suffer from tens to

a hundred of infectious diseases with apparent clinical symptoms of which majority occurs for the first time. In this case, one should consider about 10–20 infections for the 5000 day interval, and the graph intersection point in Fig. 3 shifts to the right by one order.

The numerical experiments demonstrated that W^* grows with the pathogenicity parameter σ. This could be expected because the variable m which defines $E_D = E_5 + E_6$ (see Table 2 and [9]) depends on σ. The parameters σ and N_s are independent; the results of studying their influence on W^* can be conveniently represented in the coordinates σ and N_s as curves along which W^* does not vary. Figure 4 depicts two curves calculated in this way and corresponding to $W^* =$ 1000 J/day (left) and $W^* = 2000$ J/day (right). We notice that, depending on the pathogenicity of microorganisms, the organism can control different numbers of their species while consuming the same energy.

This result can be interpreted as follows. During the life time the defence system encounters infections of various strengths. At that, the number of dangerous infecting agents producing grave diseases and requiring much energy for suppression is very small; the number of less pathogenic agents is greater; and finally, the majority of microorganisms are conditionally pathogenic and do not damage noticeably the organism [14]. The properties of the microorganisms with various levels of pathogenicity differ significantly, and their efficient suppression requires different properties of the immune system. As the result, the compromise values of the parameters and properties of the immune system turn out to be optimal for combatting the community of microorganisms with a wide pathogenic spectrum, which reduces efficiency of defence against each class of pathogens and improves adaptation of the microorganisms.

The energy consumed by the immune system is defined by the number of cells of the immune system, it is a stable and genetically controllable value constituting an appreciable part of the energy consumed for anti-infectious defence. Its increase usually leads to lower adaptation and growth of mortality [15]. An increase in the number of pathogen species above the level defined by the dependence of Fig. 4 for a constant level of energy also reduces adaptability and increases mortality. In turn, this reduces adaptation of the microorganisms owing to a lower number of the potential hosts to be used.

If the number of species—for example, in the class of dangerous infections—decreases, then the released energy of the immune system can be used for more active combat against the pathogens of other classes, which reduces their adaptation. Therefore, the natural selection among the pathogens must lead to filling all pathogenicity classes of microorganisms. The recent studies of the genetic processes defining pathogenicity of bacteria established that this property is defined by a few tightly linked genes, the so-called pathogenicity islands [16, 17]. These groups of genes can be rapidly transferred from one variant or species to another. Therefore, from the point of view of the genetic mechanisms, the number of highly pathogenic species and strains of bacteria can rapidly grow owing to the low pathogenic bacteria acquiring the corresponding genes. Similar processes were described for viruses as well.

The progress of medicine, epidemiology, and sanitation and the emergence of new efficient preparations brought down the pressure of some infectious diseases, but other diseases occupy their place, and sometimes the previous diseases—as was the case with tuberculosis—return. This manifests itself, for example, in that over the last 70 years the rate of infectious diseases in Moscow actually did not change despite substantial ecological changes and new methods of control and treatment of infections. The human immunodeficiency virus, which appeared some time after elimination of smallpox, exemplifies a new infection agent. The advent of antibiotic-resistant strains of tuberculosis and highly pathogenic strains of streptococcus and staphylococcus [18, 19] and the increase of clamidiosis infectivity also corroborate the assumption that there are selection processes sustaining occupation of the entire pathogenicity spectrum of the microorganisms.

Complex changes in pathogenicity of microorganisms come down to the above hypothesis, but the importance of taking into account the interaction between pathogens infecting one host raises no doubts. This rise was investigated in both experimental and theoretical studies [20] majority of which paid attention to the competitive relationships between the microorganisms within one pathogenicity class, pathogen lethality being used as the measure of action on the host [21]. The present paper uses energy as the characteristic of individual's response to its infecting pathogens. The cost of the generalized basic rate of reproduction $\overline{R}_0$ characterizing the mean rate of multiplication of microorganisms in the given host (by analogy with R_0 in [22, 23]) or the host energy used to synthesize new pathogenic microorganisms can be used as a characteristic of the pathogen strategy.

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