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Evolution of adaptation mechanisms: Adaptation energy, stress, and oscillating death

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HIGHLIGHTS

- We formalize Selye's ideas about adaptation energy and dynamics of adaptation.
- A hierarchy of dynamic models of adaptation is developed.
- Adaptation energy is considered as an internal coordinate on the 'dominant path' in the model of adaptation.
- The optimal distribution of resources for neutralization of harmful factors is studied.
- The phenomena of 'oscillating death' and 'oscillating remission' are predicted.

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ABSTRACT

In 1938, Selye proposed the notion of adaptation energy and published 'Experimental evidence supporting the conception of adaptation energy.' Adaptation of an animal to different factors appears as the spending of one resource. Adaptation energy is a hypothetical extensive quantity spent for adaptation. This term causes much debate when one takes it literally, as a physical quantity, i.e. a sort of energy. The controversial points of view impede the systematic use of the notion of adaptation energy despite experimental evidence. Nevertheless, the response to many harmful factors often has general non-specific form and we suggest that the mechanisms of physiological adaptation admit a very general and nonspecific description.

We aim to demonstrate that Selye's adaptation energy is the cornerstone of the top-down approach to modelling of non-specific adaptation processes. We analyze Selye's axioms of adaptation energy together with Goldstone's modifications and propose a series of models for interpretation of these axioms. *Adaptation energy is considered as an internal coordinate on the 'dominant path' in the model of adaptation.* The phenomena of 'oscillating death' and 'oscillating remission' are predicted on the base of the dynamical models of adaptation. Natural selection plays a key role in the evolution of mechanisms of physiological adaptation. We use the fitness optimization approach to study of the distribution of resources for neutralization of harmful factors, during adaptation to a multifactor environment, and analyze the optimal strategies for different systems of factors.

1. Introduction

Selye (1938a) introduced the notion of adaptation energy as the universal currency for adaptation. He published 'Experimental evidence supporting the conception of adaptation energy' (Selye, 1938b): adaptation of an animal to different factors (sequentially) looks like spending of one resource, and the animal dies when this resource is exhausted.

The term 'adaptation *energy*' contains an attractive metaphor: there is a hypothetical extensive variable which is a resource spent for adaptation. At the same time, this term causes much debate when one takes it literally, as a physical quantity, i.e. as a sort of energy, and asks to demonstrate the physical nature of this 'energy'. Such discussions impede the systematic use of the notion of adaptation energy even by some of Selye's followers. For example, in the modern 'Encyclopedia of Stress' we read: 'As for adaptation energy, Selye was never able to measure it…' (McCarty and Pasak,

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2000). Nevertheless, this notion is proved to be useful in the analysis of adaptation (Breznitz, 1983; Schkade and Schultz, 2003).

Without any doubt, adaptation energy is not a sort of physical energy. Moreover, Selye definitely measured the adaptation energy: the natural measure of it is the intensity and length of the given stress from which adaptation can defend the organism before *adaptability* is exhausted. According to Selye (1938b), 'during adaptation to a certain stimulus the resistance to other stimuli decreases.' In particular, he demonstrated that 'rats pretreated with a certain agent will resist such doses of this agent which would be fatal for not pretreated controls. At the same time, their resistance to toxic doses of agents other than the been adapted decreases below the initial value.'

These findings were tentatively interpreted using the assumption that the resistance of the organism to various damaging stimuli depends on its adaptability. This adaptability depends upon adaptation energy of which the organism possesses only a limited amount, so that if it is used for adaptation to a certain stimuli, it will necessarily decrease.

Selye (1938b) concluded that 'adaptation to any stimulus is always acquired at a cost, namely, at the cost of adaptation energy.' No other definition of adaptation energy was given. This is just a resource of adaptability, which is spent in all adaptation processes. The economical metaphors used by Selye, 'cost' and 'spending', were also seminal and their use was continued in many works. For example, Goldstone (1952) considered adaptation energy as a 'capital reserve of adaptation' and death as 'a bankruptcy in non-specific adaptation energy.'

The economical analogy is useful in physiology and ecology for analysis of interaction of different factors. Gorban et al. (1987) analyzed interaction of factors in human physiology and demonstrated that adaptation makes the limiting factors equally important. These results underly the method of correlation adaptometry, that measures the level of adaptation load on a system and allows us to estimate health in groups of healthy people (Sedov et al., 1988). For plants, the economical metaphor was elaborated by Bloom et al. (1985) and developed further by Chapin et al. (1990). They also merged the optimality and the limiting approach and used the notion of 'exchange rate' for factors and resources. For more details and connections to economical dynamics we refer to Gorban et al. (2010). For systems of factors with different types of interaction (without limitation) adaptation may lead to different results (Gorban et al., 2011). In particular, if there is *synergy* between several harmful factors, then adaptation should make the influence of different factors uneven and may completely exclude (compensate) some of them.

In order to understand why we need the notion of adaptation energy in modelling of physiology of adaptation, we have to discuss two basic approaches to modelling, *bottom-up* and *top-down*.

- The bottom-up approach to modelling in physiology ties molecular and cellular properties to the macroscopic behavior of tissues and the whole organism. Modern multiagent methods of modelling account for elementary interactions, and provide analysis how the rules of elementary events affect the macroscopic dynamics. For example, Galle et al. (2009) demonstrate how the individual based models explain fundamental properties of the spatio-temporal organization of various multicellular systems. However, such models may be too rich and detailed, and typically, different model assumptions comply with known experimental results equally well. In order to develop reliable quantitative individual based models, additional experimental studies are required for identifying the details of the elementary events (Galle et al., 2009). We suspect that for the consistent and methodical bottom-up modelling, we will always need additional information for identification of the microscopic details.
- Following the top-down approach, we start from very general integrative properties of the whole system and then add some details from the lower levels of organization, if necessary. It is much closer to the classical physiological approach. A properly elaborated top-down approach creates the background, the framework and the environment for the more detailed models. We suggest, without exaggeration, that all detailed models need the top-down background (like quantum mechanics, which cannot be understood without its classical limit). The top-down approach allows one to relate the modelling process directly to experimental data, and to test the model with clinical data (Hester et al., 2011). Therefore, the language of the problem statement and the interpretation of the results is generated using the top-down approach.
- To combine the advantages of the bottom-up and the top-down approaches, the *middle-out* approach was proposed (Brenner, 1998; Kohl et al., 2010). The main idea is to start not from the upper level but from the level which is ready for formalization. That is the level where the main mechanisms are known, and it is possible to develop an adequate mathematical model without essential extension of experimental and theoretical basis. Then we can move upward (to a more abstract integrative level) or downward (to more elementary details), if necessary. Following Noble (2003) we suggest that 'reduction and integration are just two complementary sides of the same grand project: to unravel and understand the 'Logic of Life'.'

Selye (1938b)and later Goldstone (1952) used the notion of adaptation energy to represent the typical dynamics of adaptation. In that sense, they prepared the theory of adaptation for mathematical modelling. The adaptation energy is the most integrative characteristic for the models of top level. In this work, we develop a hierarchy of top-down models following Selye's findings and further developments.

We follow Selye's insight about adaptation energy and provide a 'thermodynamic-like' theory of organism resilience that (just like classical thermodynamics) allows for economic metaphors (cost and bankruptcy) and, more importantly, is largely independent of a detailed mechanistic explanation of what is 'going on underneath'.

We avoid direct discussion of the question of whether the adaptation energy is a 'biological reality', a 'generalizing term' for a set of some specific (unknown) properties of an organism that provide its adaptation, or 'just a metaphor' similar to 'phlogiston' or 'ether', notions that were useful for description of some phenomena but had no actual physical meaning as substances.

Moreover, we insist that the sense of the notion of adaptation energy is completely described by its place in the system of models like the notion of mass in Newtonian mechanics is defined by its place in the differential equations of Newton's laws. Selye did not write the equation of the adaptation energy but his experiments and 'axioms' have been very 'mathematical'. He proved that (in some approximation) there is an extensive variable (adaptation resource) which an organism spends for adaptation. This resource was measured by the intensity and length of various stresses from which adaptation can defend the organism.

2. 'Axioms' of adaptation energy

Selye, Goldstone and some other researchers formulated some of their discoveries and working hypotheses as 'axioms'. These axioms, despite being different from mathematical axioms, are

used for fixing and securing sense. Selye's axioms of Adaptation Energy (AE) (following Schkade and Schultz (2003)) are:

1. AE is a finite supply, presented at birth.
2. As a protective mechanism, there is some upper limit to the amount of AE that an individual can use at any discrete moment in time. It can be focused on one activity, or divided among other activities designed to respond to multiple occupational challenges.
3. There is a threshold of AE activation that must be present to potentiate an occupational response.
4. AE is active at two levels of awareness: a primary level at which creating the response occurs at a high awareness level, with high usage of finite supply of adaptation energy; and a secondary level at which the response creation is being processing at a sub-awareness level, with a lower energy expenditure.

Selye's Axioms 1–3 are illustrated in Fig. 1.

Goldstone (1952) proposed the concept of a constant production or income of AE which may be stored (up to a limit), as a capital reserve of adaptation. He showed that this concept best explains the clinical and Selye's own laboratory findings. According to Goldstone (1952), it is possible that, had Selye's experimental animals been asked to spend adaptation at a lesser rate (below their energy income), they might have been able to cope successfully with their stressor indefinitely. The whole systems of adaptation reactions to weaker factors were systematized by Garkavi et al. (1979). On the basis of this system, Garkavi et al. (1998) developed the activation therapy, which was applied in clinic, aerospace and sport medicine.

Goldstone's findings may be formulated as a modification of Selye's axiom 1. Their difference from Selye's axiom 1 is illustrated in Fig. 2 (compare to Fig. 1). We call this modification Goldstone's axiom 1′:

- AE can be created, though the income of this energy is slower in old age.
- It can also be stored as adaptation capital, though the storage capacity has a fixed limit.
- If an individual spends his AE faster than he creates it, he will have to draw on his capital reserve.
- When this is exhausted he dies.

3. Factor-resource basic model of adaptation

Let us start from a simple (perhaps, the simplest) model with two phase variables, the available free resource (AE) r_0 and the resource supplied for the stressor neutralization, r. There are also four processes: degradation of the available resource, degradation

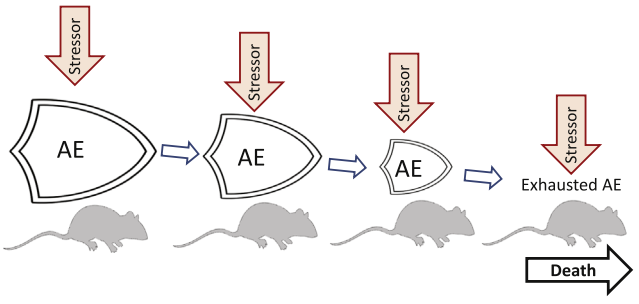

Fig. 1. Schematic representation of Selye's axioms. The shield of adaptation spends AE for protection from each stress. Finally, AE becomes exhausted, the animal cannot resist stress and dies (The rat silhouette is taken from Wikimedia commons, File:Rat_2.svg.)

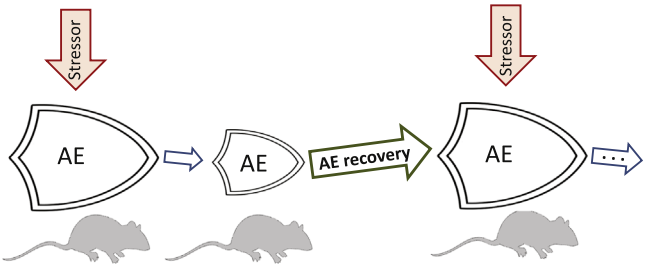

Fig. 2. Schematic representation of Goldstone's modification of Selye's axioms: AE can be recovered and adaptation shield may persist if there is enough time and reserve for recovery.

of the supplied resource, supply of the resource from the storage r_0 to the allocated resource r, and production of the resource for further storage (r_0). The equations are:

$$\frac{dr}{dt} = -k_d r + k r_0 (f-r) h(f-r);$$

$$\frac{dr_0}{dt} = -k_{d0} r_0 - k r_0 (f-r) h(f-r) + k_{pr}(R_0 - r_0), \quad (1)$$

where

- $k_d r$ is the rate of degradation of resource supplied for the stressor neutralization, where k_d is the corresponding rate constant;
- $k_{d0} r_0$ is the rate of degradation of the stored resource, where k_{d0} is the corresponding rate constant, we assume that $k_d \geq k_{d0}$;
- $k r_0 (f-r) h(f-r)$ is the rate of resource supply for the stressor neutralization, where k is the supply constant;
- $h(f-r)$ is the Heaviside step function;
- $k_{pr}(R_0 - r_0)$ is the resource production rate, where k_{pr} is the production rate constant.

Let us notice that:

- if $r_0 \geq R_0$ then $dr_0/dt \leq 0$,
- if $r_0 = 0$ then $dr_0/dt \geq 0$,
- if $r = 0, r_0 \geq 0$, then $dr/dt \geq 0$,
- if $r = f$ then $dr/dt \leq 0$.

Therefore, the rectangle D given by inequalities $0 \leq r \leq f$, $0 \leq r_0 \leq R_0$ is *positively invariant* with respect to system (1): if the initial values $(r(t_0), r_0(t_0)) \in D$ for some time moment t_0 then the solution $(r(t), r_0(t)) \in D$ for $t > t_0$.

For large f there exist a stable steady state in D with

$$r_0 \approx \frac{k_{pr} R_0}{kf}, \quad r \approx \frac{k r_0 f}{k_d} \approx \frac{k_{pr} R_0}{k_d}.$$

AE is never exhausted even when $f \to \infty$. Immortality at infinite load is possible. Something is wrong in the model. AE production should decrease for large non-compensated stressors $\psi = f - r$. Let us modify the production term in (1) and add a fitness (well-being) W. This fitness (well-being) is equal to one when the stressor load is compensated and goes to zero when the non-compensated value of the stressor load $\psi = f - r$ becomes sufficiently large. Let us choose the following form of W for one-factor model:

$$W(\psi) = \left(1 - \frac{\psi}{\psi_0}\right), \quad 0 \leq \psi \leq \psi_0. \quad (2)$$

Fitness $W(\psi)$ is a linear function on the interval $0 \leq \psi \leq \psi_0$. It takes its maximal value 1 at point $\psi = 0$ (completely compensated stressors) and vanishes at $\psi = \psi_0$ (Fig. 3).

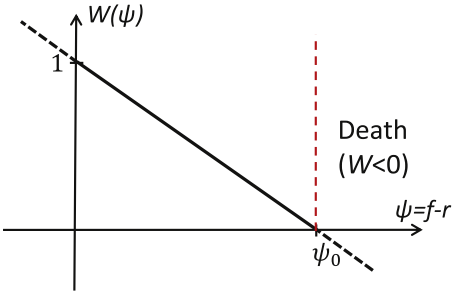

Fig. 3. The fitness function for system (3). ψ_0 is the critical value of stressor's intensity. If $f \le \psi_0$ then life is possible without adaptation: for zero AE supply W remains positive.

Formally, it may be continued to the whole line by constants: $W=1$ for $\psi<0$ and $W=0$ for $\psi>\psi_0$:

$$W(\psi)=\left(1-\frac{\psi h(\psi)}{\psi_0}\right)h\left(1-\frac{\psi h(\psi)}{\psi_0}\right).$$

Nevertheless, it is convenient to use the simplest linear function (2) and analyze the system at the borders $\psi=0$ and $\psi=1$ separately.

The modified system of equations has the form:

$$\begin{aligned}\frac{dr}{dt}&=-k_d r+kr_0(f-r)h(f-r);\\ \frac{dr_0}{dt}&=-k_{d0}r_0-kr_0(f-r)h(f-r)+k_{pr}(R_0-r_0)W(f-r),\end{aligned}\qquad(3)$$

where the fitness function $W(\psi)$ is given by (2).

4. Problems in definition of instant individual fitness

We use an individual's fitness W to measure the wellbeing (or performance) of an organism. Moreover, this is an instant value, defined for every time moment. Defining of the instant measure of an individual's performance is a highly non-trivial task. The term 'fitness' is widely used in mathematical biology in essentially another sense based on the averaging of reproduction rate over a long time (Haldane, 1932; Maynard-Smith, 1982; Metz et al., 1992; Gorban, 2007). This is Darwinian fitness. It is non-local in time because it is the average reproduction coefficient in a series of generations and does not characterize an instant state of an individual organism.

The synthetic evolutionary approach starts with the analysis of genetic variation and studies the phenotypic effects of that variation on physiology. Then it goes to the performance of organisms in the sequence of generations (with adequate analysis of the environment) and, finally, it has to return to Darwinian fitness (Lewontin, 1974). The physiological ecologists are focused, first of all, on the observation of variation in individual performance (Pough, 1989). In this approach we have to measure the individual performance and then link it to the Darwinian fitness.

The connection between individual performance and Darwinian fitness is not obvious. Moreover, the dependence between them is not necessarily monotone. This observation was formalized in the theory of r- and K-selection (MacArthur and Wilson, 1967; Pianka, 1970). The terminology refers to the equation of logistic growth: $\dot{N}=rN(1-\frac{N}{K})$ (K is the 'carrying capacity' and r the maximal intrinsic rate of natural increase). Roughly speaking, K measures the competitive abilities of individuals and r measures their fecundity. Assuming negative correlations between r and K, we get a question: what is better in the Darwinian sense: to increase individual competitive abilities or to increase fecundity? Earlier, Fisher (1930) formulated a particular case of this problem as follows: 'It would be instructive to know not only by what physiological mechanism a just apportionment is made between the nutriment devoted to the gonads and that devoted to the rest of the parental organism, but also what circumstances in the life-history and environment would render profitable the diversion of a greater or lesser share of the available resources towards reproduction.' The optimal balance between individual performance and fecundity depends on environment. Thus, Dobzhansky (1950) stated that in the tropical zones selection typically favors lower fecundity and slower development, whereas in the temperate zones high fecundity and rapid development could increase Darwinian fitness.

Nevertheless, the idea that the states of an organism could be linearly ordered from bad to good performance (wellbeing) is popular and useful in applied physiology. The coordinate on this scale is also called 'fitness'. Several indicators are measured for fitness assessment and then the fitness is defined as a composite of many attributes and competencies. For example, for fitness assessment in sport physiology these competencies include physical, physiological and psychomotor factors (Reilly and Doran, 2003). The balance between various components of sport-related instant individual fitness depends upon the specific sport, age, gender, individual history and even on the role of the player in the team (for example, for football).

Similarly, the notion 'performance' in ecological physiology is 'task-dependent' (Wainwright, 1994) and refers to an organism's ability to carry out specific behaviors and tasks (e.g., capture prey, escape predation, and obtain mates). Direct instant measurement of Darwinian fitness is impossible but it is possible to measure various instant performances several times and treat them as the components of fitness in the chain of generations. Arnold (1983) proposed several criteria for selection of the good measure of performance in the evolutionary study: (1) the measure should be ecologically relevant, i.e. it measures success in the ecologically important behavior significant for survival and reproductive output; (2) the measure should be phylogenetically interesting, i.e. it captures the differences between taxa and the difference between higher taxa is larger than for closed taxa, at least, for some types of performance. The relations between performance and lifetime fitness are sketched on flow-chart (Fig. 4) following Wainwright (1994) with minor changes. Darwinian fitness may be defined as the lifetime fitness averaged in a sequence of generations.

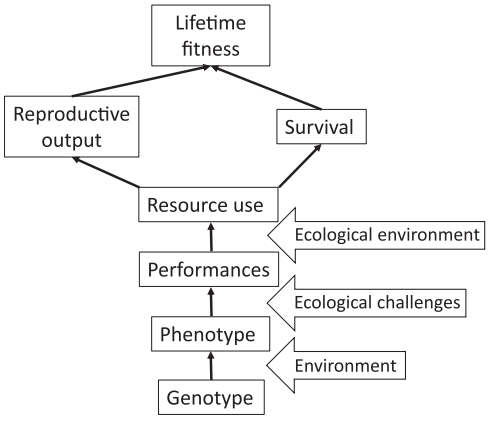

Fig. 4. Flow diagram showing the paths through from genotype to Darwinian fitness. Genotype in combination with environment determines the organismal design (the phenotype) up to some individual variations. Phenotype determines the limits of an individual's ability to perform day-to-day behavioral answer to main ecological challenges (performances). Performance capacity interacts with the given ecological environment and determines the resource use, which is the key internal factor determining r- and K-components of fitness, reproductive output and survival.

The idea of individual fitness is intensively used in conservation physiology (Wikelski and Cooke, 2006). An important problem is to determine how single intensive periods of stress influence individual fitness. Wikelski and Cooke (2006) stressed that when the link between baseline physiological traits and fitness is known, conservation managers can use physiological traits as indicators to predict and anticipate future problems. Ecological success is coupled to environmental conditions via the sensitivity of physiological systems (Seebacher and Franklin, 2012). Ideally, individual fitness is maximized when the organism can perform at a constant and optimal level despite environmental variability, but this is impossible in the changing world for several reasons: (i) adaptation requires time and there is a lag between the changes in environment and the adaptive response, (ii) adaptation has a cost and excessive adaptation load may decrease performance because of this cost, and (iii) adaptation has its limits and even in the most plastic organisms, the capacity to compensate for environmental change is bounded.

We use the instant individual fitness (wellbeing) W as a characteristic of the current state of the organism, reflecting the non-optimality of its performance: $W=1$ means the maximal achievable performance and $W=0$ means inviability (death). If the organism lives at some level of W then we can consider W as a factor in the lifetime fitness. Such a factorization assumes that the physiological state of the organism acts independently of other factors to determine fitness. This assumption follows the ideas of Fisher (1930). The basic assumptions of Fisher's model were analyzed by Haldane (1932). 'Independence' here is considered as multiplicativity, like in probability theory. Of course, the hypothesis of independence is never absolutely correct, but it gives a good initial approximation in many areas, from data mining (naïve Bayes models) to statistical physics (non-correlated states).

This is the qualitative explanation of the instant individual fitness W. It is the most local in time level in the multiscale hierarchy of measures of fitness: instant individual fitness *to* individual life fitness *to* Darwinian fitness in the chain of generations. The proper language for discussion of the individual fitness gives the idea of particular performances, these are abilities of the organism to answer various specific ecological challenges. The instant individual fitness aims to combine various indicators of different performances into one quantity.

The quantitative definition of the W scale is given by its place in the equations. The change of the basic equation will cause the change of the quantitative definition. Now, we are far from the final definition of W. Moreover, it is plausible that for different purposes we may need different definitions of W.

5. Dangerous borders

The fitness takes the maximal value $W=1$ if the factor is fully compensated, $f=r$. Due to Eqs. (3) if $f=r$ and $r\geq 0$ then $\mathrm{d}r/\mathrm{d}t=-k_d r\leq 0$ and $\mathrm{d}W\,\mathrm{d}t\leq 0$. Therefore, the fitness W cannot exceed the value 1 if it is initially below 1.

The line $W=0$ (i.e. $f-r=\psi_0$) is a *border of death*. If W becomes negative, it means death. On this border,

$$\text{If } r_0<k_d\frac{f-\psi_0}{\psi_0} \quad \text{then } \frac{\mathrm{d}r}{\mathrm{d}t}<0 \text{ and } \frac{\mathrm{d}W}{\mathrm{d}t}<0,$$

$$\text{If } r_0>k_d\frac{f-\psi_0}{\psi_0} \quad \text{then } \frac{\mathrm{d}r}{\mathrm{d}t}>0 \text{ and } \frac{\mathrm{d}W}{\mathrm{d}t}>0.$$

The situation when $W=0$ and $\mathrm{d}W/\mathrm{d}t<0$ leads to death. Therefore, this part of the border ($r_0<k_d(f-\psi_0)/\psi_0$) is called the *dangerous border*. On the contrary, if $W=0$ but $\mathrm{d}W/\mathrm{d}t>0$ it means survival and this border ($r_0>k_d(f-\psi_0)/\psi_0$) is safe. The intersection point of the border of death and the r-nullcline of system (3) separates the safe part of the border from the dangerous part (Fig. 5a).

If $f\leq\psi_0$ then the whole border of death belongs to the half-plane $r\leq 0$ (Fig. 5b). In this case, all the borders of the rectangle D ($0\leq r\leq f$, $0\leq r_0\leq R_0$) are repulsive and the motion remains in D forever, if it starts in D. Below we consider the case $0<\psi_0<f$. Let us analyze the system (3) in the rectangle Q given by the inequalities:

$$Q:\ 0\leq r,\quad f-\psi_0\leq r\leq f,\quad 0\leq r_0\leq R_0. \tag{4}$$

In the rectangle Q the Heaviside functions in system (3) could be deleted and this system takes a simple bilinear form

$$\begin{aligned}\frac{\mathrm{d}r}{\mathrm{d}t}&=-k_d r+kr_0(f-r),\\ \frac{\mathrm{d}r_0}{\mathrm{d}t}&=-k_{d0}r_0-kr_0(f-r)+k_{pr}(R_0-r_0)\left(1-\frac{f-r}{\psi_0}\right).\end{aligned} \tag{5}$$

Q is not necessarily positively invariant with respect to (5). The system may leave Q through the dangerous border.

The nullclines of this system (5) in Q are plots of monotonic functions $r_0(r)$. The r-nullcline is, for $r<f$, monotonically growing convex function of r:

$$-k_d r+kr_0(f-r)=0,\ \text{or } r_0=\frac{k_d r}{k(f-r)}=\frac{k_d}{k}\left(\frac{f}{f-r}-1\right).$$

The r_0-nullcline is

$$-k_{d0}r_0-kr_0(f-r)+k_{pr}(R_0-r_0)\left(1-\frac{f-r}{\psi_0}\right)=0,\ \text{or}$$

$$r_0=\frac{k_{pr}R_0}{q\psi_0}\left(1-\frac{\frac{1}{q}(k_{d0}+k\psi_0)}{r-(f-\psi_0)+\frac{1}{q}(k_{d0}+k\psi_0)}\right),$$

where $q=\frac{1}{\psi_0}k_{pr}-k\neq 0$.

The product $q\psi_0=k_{pr}-k\psi_0$ is the difference between the adaptation energy production rate constant k_{pr} and the supply coefficient $k\psi_0$ at the critical value $f-r=\psi_0$ (the supply rate is $k(f-r)r_0$).

If $q=0$ then the r_0-nullcline is a straight line

$$r_0=\frac{k_{pr}R_0}{\psi_0}\frac{r-(f-\psi_0)}{k_{d0}+k\psi_0}.$$

Geometry of the phase portraits is schematically presented in Fig. 5b–d. The nullclines are monotonic, the r-nullcline is convex, and for the case $q>0$ the r_0-nullcline is concave. The area between the nullclines is positively invariant. The phase portrait transforms from Fig. 5b to c and d when the pressure of factor f increases starting from safe values $f\leq\psi_0$ to high values $f\gg\psi_0$.

6. Resource and reserve

Selye, Goldstone and other researchers stressed that there are different levels of the adaptation energy supply, with lower and higher energy expenditure. Garkavi et al. (1979) insisted that there are many levels at lower intensity of stressors, and created the 'periodic table' of the adaptation reactions. Nevertheless, we propose to formalize, first, the two-state hypothesis.

There are two storages of AE: resource (which is always available if it is not empty) and reserve (which becomes available when the resource becomes too low). The Boolean variable $B_{o/c}$ describes the state of the reserve storage: if $B_{o/c}=0$ then the reserve storage is closed and if $B_{o/c}=1$ then the reserve storage is open. There are two switch lines on the phase plane (r,r_0): $r_0=\underline{r}$ (the lower switch

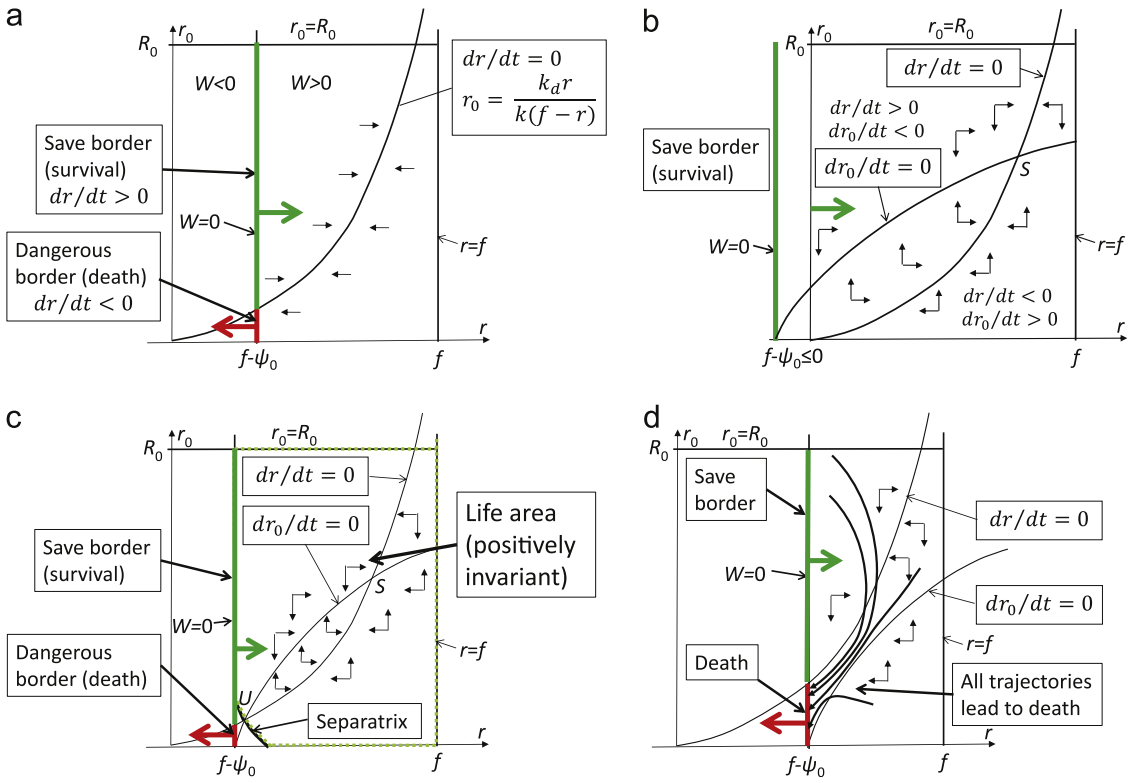

Fig. 5. Safe and dangerous borders for adaptation system (3) for $q>0$. The r-nullcline cuts the border of death $W=0$ ($r=f-\psi_0$) into two parts: $\dot{W}<0$ (dangerous border, red) and $\dot{W}>0$ (safe border, green) (a). The nullclines have in this case (a) unique intersection point S in D (that is the stable equilibrium). If $f<\psi_0$ then the whole border is safe (b). If the r- and r_0-nullclines have two intersections, the stable (S) and unstable (U) equilibria (c), then the separatrix of the unstable equilibrium U separates the area of attraction of the dangerous border (area of death) from the area of attraction of stable equilibrium (life area) (c). If there exists no intersection of the nullclines in the rectangle (d) then all the trajectories are attracting to the dangerous border. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

line that serves to opening the reserve storage) and $r_0=\bar{r}$ (the upper switch line that serves to closing the reserve storage). When the available resource r_0 decreases and approaches $\underline{r}$ from above then the supply or reserve opens (if it was closed). When the available resource $r_0<\bar{r}$ increases and approaches $\bar{r}$ from below then the supply of reserve closes (if it was open). For $r_0<\underline{r}$ the reserve is always open, $B_{o/c}=1$ and for $r_0>\bar{r}$ the reserve is always closed, $B_{o/c}=0$ (Fig. 6). These rules together with the following equations describe the system in $Q\times[0,R_{rv}]$ (4):

$$\frac{dr}{dt} = -k_d r + k r_0 (f-r);$$
$$\frac{dr_0}{dt} = -k_{d0} r_0 - k r_0 (f-r) + k_{rv} B_{o/c} r_{rv}(R_0-r_0) + k_{pr}(R_0-r_0)W;$$
$$\frac{dr_{rv}}{dt} = -k_{d1} r_{rv} - k_{rv} B_{o/c} r_{rv}(R_0-r_0) + k_{pr1}(R_{rv}-r_{rv})W, \quad (6)$$

where $W=1-\frac{f-r}{\psi_0}$ if we accept the particular simple form of fitness function (2).

For dynamics of r_0, the additional supply of AE from the reserve looks like the increase of the well-being W by $k_{rv}r_{rv}/k_{pr}$: after joining the last two terms in the second equation of (6) we get

$$\frac{dr_0}{dt} = -k_{d0} r_0 - k r_0 (f-r) + k_{pr}(R_0-r_0)\left(W + \frac{k_{rv} B_{o/c} r_{rv}}{k_{pr}}\right). \quad (7)$$

Let us analyze the impact of reserve on the dynamics of adaptation in the small vicinity of the border of death $W=0$. For simplicity, consider the case with sufficiently large reserve and fast reserve recovery.

There are three qualitatively different cases of the motion in the interval $\bar{r}\ge r_0\ge\underline{r}$ near the border $W=0$:

- $\bar{r},\underline{r}>r^*$ and the motion goes above both nullclines (Fig. 7a);

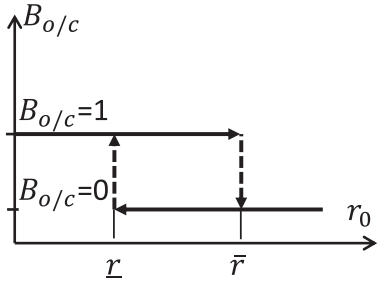

Fig. 6. Resource–reserve hysteresis. Hysteresis of reserve supply: if $B_{o/c}=0$ then reserve is closed and if $B_{o/c}=0$ then reserve is open. When r_0 decreases and approaches $\underline{r}$ then the supply or reserve opens (if it was closed). When $r_0<\bar{r}$ increases and approaches $\bar{r}$ then the supply of reserve closes (if it was open).

- $\bar{r},\underline{r}<r^*$ and the motion goes below the r-nullcline but above the r_0-nullcline (Fig. 7b);
- $\bar{r}>r^*>\underline{r}$ and the motion intersects r-nullcline (Fig. 7c and d).

Here, r^* is the value of r_0, which separates the safe border from the dangerous border on the line $W=0$,

$$r^* = \frac{k_d f - \psi_0}{k - \psi_0}. \quad (8)$$

In all these cases the motion oscillates between the lines $r_0=\bar{r}$ and $r_0=\underline{r}$ (Fig. 7a). When the motion with closed reserve supply ($B_{o/c}=0$) reaches the line $r_0=\underline{r}$ then the reserve supply switches on ($B_{o/c}=1$), the value of r_0 goes up fast and quickly achieves $\bar{r}$ (because of the assumption of large reserve). The value of r does not change significantly during this 'jump' of r_0 from $\underline{r}$ to $\bar{r}$. When the motion with open reserve supply ($B_{o/c}=1$) reaches the line

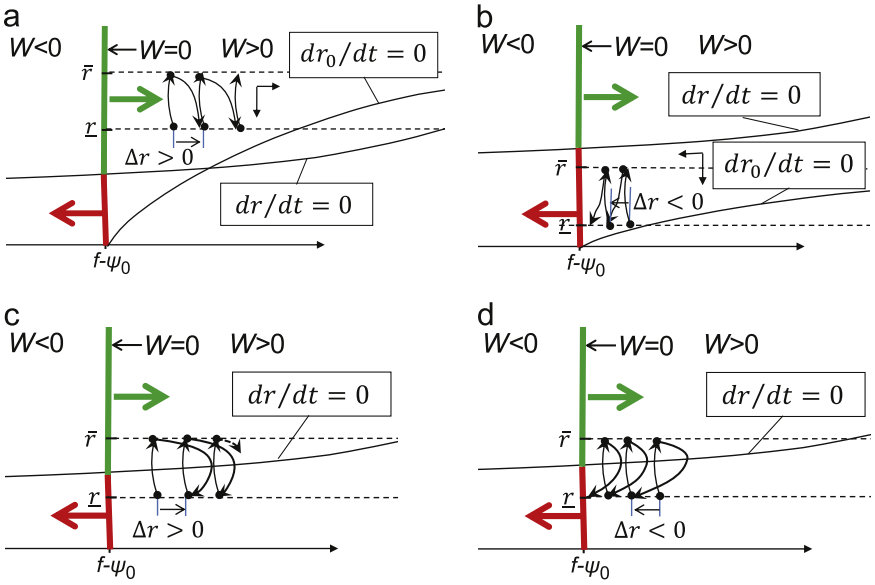

Fig. 7. Oscillating recovery ((a) and (c)) and oscillating death ((b) and (d)) near the border $W=0$ for the systems with large reserve. (Horizontally stretched sketch.) In case (a) both $\bar{r}, \underline{r} > r^*$, in case (b) both $\bar{r}, \underline{r} < r^*$, and in cases (c) and (d) $\bar{r} > r^* > \underline{r}$, where r^* is the value of r_0, which separates the safe border from the dangerous border on the line $W=0$ (8). The straight angles of possible velocities are presented for motions without research supply in cases (a) and (b).

$r_0 = \bar{r}$ then supply of reserve switches off ($B_{o/c} = 0$) and the value of r_0 decreases. (Note, that if the motion is sufficiently close to the border $W=0$ then it is above the nullcline of r_0 on the plane (r, r_0), Figs. 5 and 7).

Consider the motion which starts on the line $r_0 = \underline{r}$ with open reserve supply. The motion returns to the same line $r_0 = \underline{r}$ after the cycle: 'jump up' to the line $r_0 = \bar{r}$, switch reserve supply off and 'move down' without reserve supply to the line $r_0 = \underline{r}$, but the value of r may change. If this change $\Delta r > 0$ then the system moves from the border $W=0$ (oscillating recovery, Fig. 7a and c). If $\Delta r < 0$ then the system moves to the border $W=0$ (oscillating death, Fig. 7b and d).

If we combine the cases Fig. 7c (close to the border $W=0$) and d (at some distance from this border) then we can find the stable closed orbit for some combination of parameters in the limit of large reserve and fast reserve recovery. Such an orbit is presented in Fig. 8a (numerical calculation). If we decrease the reserve recovering constant k_{pr1} (and do not change other constants) then the closed orbit may become larger with longer time of reserve supply (Fig. 8b). The further decrease of k_{pr1} leads to destruction of the closed orbit and the oscillating death appears (Fig. 8d). The values of parameters were chosen just for numerical example.

Fig. 8 c demonstrates an important effect: the trajectories spend a long time near the places where cycles appear for different values of constants (see Fig. 8a and b) and go to the attractor (here it is death) after this delay. The delayed relaxation is a manifestation of the so-called 'critical retardation': near a bifurcation with the appearance of new ω-limit points, the trajectories spend a long time close to these points (Gorban, 2004).

The models based on Selye's idea of adaptation energy demonstrate that the oscillating remission and oscillating death do not need exogenous reasons. These phenomena have been observed in clinic for a long time and now attract attention in mathematical medicine and biology. For example, Zhang et al. (2014) demonstrated recently, on a more detailed model of adaptation in the immune system, that cycles of relapse and remission, typical for many autoimmune diseases, arise naturally from the dynamical behavior of the system. The notion of 'oscillating remission' is used also in psychiatry (Gudayol-Ferré et al., 2015).

7. Distribution of adaptation energy in multifactor systems

Usually, organisms experience a load of many factors, where the effect of one factor could depend on the loads of all other factors. We define a harmful factor or 'stressor' as a noxious stimulus and the 'stress response' of an organism as a suite of physiological and behavioral mechanisms to cope with stress (Wikelski and Cooke, 2006). Revealing and description of important factors may be a non-trivial task because any biological pattern is correlated with a large number of abiotic and biotic patterns. Some of them are known, though many are unknown. Correlations are not sufficient for extraction of main factors and the special effort and experimental study are needed to reveal causality (Seebacher and Franklin, 2012).

The effect of action of several factors may be far from additive. There are various mechanisms of interaction between factors in their action. The discovery of the first non-additive interaction between factors was done by Carl Sprengel in 1828 and Justus von Liebig in 1840 (van der Ploeg et al., 1999). They proposed 'the law of the minimum' (known also as 'Liebig's law'). This law states that growth is controlled by the scarcest resource (limiting factor) (Salisbury, 1992). It is widely known that not all systems of factors satisfy the law of the minimum. For example, some harmful factors can intensify effects of each other (effect of *synergy* means that the harm is superadditive). The *colimitation* effects are also widely known (Wutzler and Reichstein, 2008). Gorban et al. (2011) analyzed and compared adaptation to Liebig's and synergistic systems of factors. They formalized the idea of synergy for multifactor systems, introduced generalized Liebig's systems and studied distribution of AE for neutralization of the load of many factors. For this purpose, the optimality principle was used. Tilman (1980) studied resource competition. He developed an equilibrium theory based on classification of interaction in pairs of resources. According to Tilman (1980) they may be: (1) essential, (2) hemi-essential, (3) complementary, (4) perfectly substitutable, (5) antagonistic, or (6) switching. He also used the idea of optimality.

Evolutionary approach aims to give a universal key to the problem of optimality in biology (Haldane, 1932; Maynard-Smith, 1982; Gorban and Khlebopros, 1988). The universal measure of optimality is Darwinian fitness, that is the reproduction coefficient averaged in a long time (Gorban, 2007) with some analytic simplifications, when it is possible (Karev and Kareva, 2014), and with

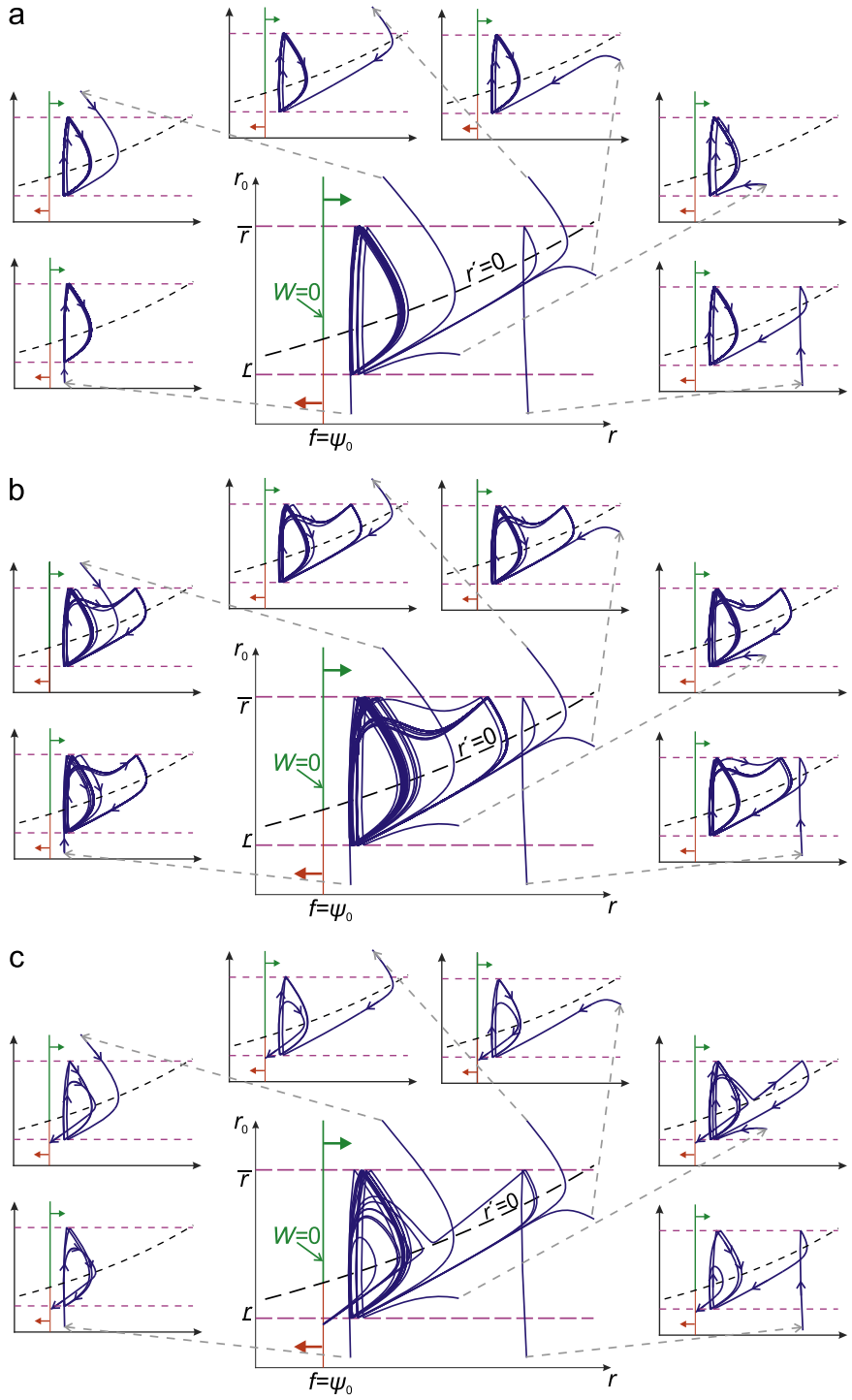

Fig. 8. Oscillations near the border of death for system (6) in projection onto the (r, r_0) plane (the reserve coordinate r_{rv} is hidden). For each case (a)–(c) several trajectories are plotted together (central plots) and separately (side plots). At the initial points of all trajectories the reserve is full, $r_{rv} = R_{rv}$. For all cases $\overline{r} = 2$, $\underline{r} = 0.5$, $R_0 = 10$, $R_{rv} = 5$, $k_d = 1$, $k_{d0} = 0.1$, $k_{d1} = 0.1$, $k = 0.5$, $k_{pr} = 2$, $k_{rv} = 2$, $\psi_0 = 7$, and $f = 10$. For case (a) $k_{pr1} = 18$ (stable oscillation), for case (b) $k_{pr1} = 7$ (stable oscillations with longer orbit), for case (c) the closed orbit vanishes and the trajectories cross the borders of death ($k_{pr1} = 3.6$).

known generalizations for vector distributions (Gorban, 1984; Metz et al., 1992). However, there is no universal rule to measure various traits of organisms by the changes in the average reproduction coefficient, despite exerted efforts, development of special methods, and gaining some success (Haldane, 1954; Waxman and Welch, 2005; Kingsolver and Pfennig, 2007; Shaw et al., 2008; Karev and Kareva, 2014). There may be additional difficulties because the evolutionary optimality is not necessarily related to organisms, and the non-trivial question arises: 'what is optimal?' Another difficulty is caused by possible non-stationarity of the optimum: selected organisms change their environment and become non-optimal on the background of the new ecological situation (Gorban, 1984). Nevertheless, the idea of fitness is proved to be very useful. Fitness functions are defined for different situations as intermediates between the (observable) traits of the animal and the average reproduction coefficient.

The factors-resource models with the fitness optimization allow us to translate the elegant dynamic approach of the

mathematical theory of evolution into physiological language. The key idea is to use statistical properties of physiological data instead of the data themselves. Correlations and variances are often more reliable characteristics of stress and adaptation than the values of physiological indicators (Gorban et al., 1987, 2010, 2011; Censi et al., 2011; Bernardini et al., 2013).

For formal definitions of Liebig's and synergistic systems of factors the notion of individual and instant fitness is used. We consider organisms that are under the influence of several factors F_i with intensities f_i $(i=1,\dots q)$. For definiteness, assume that all the factors are harmful (this is just the sign convention plus monotonicity assumption). AE supplied for neutralization of ith factor is r_i and fitness W is a smooth function of q variables $\psi_i = f_i - r_i \geq 0$. This means that the factors are measured in the general scale of AE units. Comparability of stressors of different nature was empirically demonstrated and studied by Selye (1938b). It was a strong argument for introduction of AE. The value $f_i - r_i = 0$ is optimal (the fully compensated factor), and any further compensation is impossible.

Assume that the vector of variables $(\psi_1,\dots,\psi_q)$ belongs to a convex subset U of the positive orthant $\mathbb{R}^q_+$, and W is defined in U. Harmfulness of all factors means that

$$\frac{\partial W(\psi_1,\dots,\psi_q)}{\partial \psi_i} < 0 \quad \text{for all } i=1,\dots,q \text{ and } (\psi_1,\dots,\psi_q)\in U.$$

Definition 1. A system of factors is *Liebig's system*, if there exists a function of one variable $w(\psi)$ such that

$$W(\psi_1,\dots,\psi_q) = w\left(\max_{1\leq i\leq q}\{f_i - a_i r_i\}\right). \tag{9}$$

A system of factors is *anti-Liebig's system*, if there exists a function of one variable $w(\psi)$ such that

$$W(\psi_1,\dots,\psi_q) = w\left(\min_{1\leq i\leq q}\{f_i - a_i r_i\}\right). \tag{10}$$

In Liebig's systems fitness depends on the worst factor pressure. In anti-Liebig's systems fitness depends on the easiest factor pressure and the factors affect the organism only together, in strong synergy.

To generalize these polar cases of Liebig's and anti-Liebig's system, recall the notions of *quasiconvex* and *quasiconcave* functions. A function F on a convex set U is *quasiconvex* (Greenberg and Pierskalla, 1971) if all its sublevel sets are convex. It means that for every $X, Y \in U$

$$F(\lambda X + (1-\lambda)Y) \leq \max\{F(X), F(Y)\} \quad \text{for all } \lambda\in[0,1] \tag{11}$$

In particular, a function F on a segment is quasiconvex if all its sublevel sets are segments.

A function F on a convex set U is *quasiconcave* if $-F$ is quasiconvex. Direct definition is as follows: A function F on a convex set U is *quasiconcave* all its superlevel sets are convex. It means that for every $X, Y \in U$

$$F(\lambda X + (1-\lambda)Y) \geq \min\{F(X), F(Y)\} \quad \text{for all } \lambda\in[0,1] \tag{12}$$

In particular, a function F on a segment is quasiconcave if all its superlevel sets are segments.

For Liebig's system the superlevel sets of W are convex, therefore, $W(\psi_1,\dots,\psi_q)$ is quasiconcave.

For anti-Liebig's system the sublevel sets of W are convex, therefore, $W(\psi_1,\dots,\psi_q)$ is quasiconvex.

Definition 2. A system of factors is generalized Liebig's system if $W(\psi_1,\dots,\psi_q)$ is a quasiconcave function.

A system of factors is a synergistic one, if $W(\psi_1,\dots,\psi_q)$ is a quasiconvex function.

Proposition 1. *A system of factors is generalized Liebig's system, if and only if for any two different vectors of factor pressures* $\boldsymbol{\psi} = (\psi_1, \dots \psi_q)$ *and* $\boldsymbol{\phi} = (\phi_1, \dots \phi_q)$ $(\boldsymbol{\psi} \neq \boldsymbol{\phi})$ *the value of fitness at the average point* $(\boldsymbol{\psi}+\boldsymbol{\phi})/2$ *is greater, than at the worst of points* $\boldsymbol{\psi}$, $\boldsymbol{\phi}$:

$$W\left(\frac{\boldsymbol{\psi}+\boldsymbol{\phi}}{2}\right) > \min\{W(\boldsymbol{\psi}), W(\boldsymbol{\phi})\}. \tag{13}$$

Proposition 2. *A system of factors is a synergistic one, if for any two different vectors of factor pressures* $\boldsymbol{\psi} = (\psi_1, \dots \psi_q)$ *and* $\boldsymbol{\phi} = (\phi_1, \dots \phi_q)$ $(\boldsymbol{\psi} \neq \boldsymbol{\phi})$ *the value of fitness at the average point* $(\boldsymbol{\psi}+\boldsymbol{\phi})/2$ *is less, than at the best of points* $\boldsymbol{\psi}$, $\boldsymbol{\phi}$:

$$W\left(\frac{\boldsymbol{\psi}+\boldsymbol{\phi}}{2}\right) < \max\{W(\boldsymbol{\psi}), W(\boldsymbol{\phi})\}. \tag{14}$$

Distribution of the supplied AE between factors should maximize the fitness function W which depends on the compensated values of factors, $\psi_i = f_i - r_i$. The total amount r of the allocated AE is given:

$$\begin{cases} W(f_1 - r_1, f_2 - r_2, \dots f_q - r_q) \to \max; \\ r_i \geq 0,\ f_i - r_i \geq 0,\ \ \sum_{i=1}^q r_i \leq r. \end{cases} \tag{15}$$

Analysis of this optimization problem (Gorban et al., 1987, 2010) leads to the following statements (Gorban et al., 2011) which sound paradoxical (if law of the minimum is true then the adaptation makes it wrong; if law of the minimum is significantly violated then the adaptation decreases these violations):

- *Law of the minimum paradox*: If for a randomly selected pair ('State of environment–State of organism'), the law of the minimum is valid (everything is limited by the factor with the worst value) then, after adaptation, many factors (the maximally possible amount of them) are equally important.
- *Law of the minimum inverse paradox*: If for a randomly selected pair, ('State of environment–State of organism'), many factors are equally important and superlinearly amplify each other then, after adaptation, a smaller amount of factors is important (everything is limited by the factors with the worst non-compensated values, the system approaches the law of the minimum).

These properties of adaptation are illustrated in Fig. 9.

Adaptation of an organism to Liebig's system transforms the one-dimensional picture with one limiting factor into a high dimensional picture with many important factors. Therefore, the well-adapted Liebig's systems should have less correlations between their attributes than in stress. The variance (fluctuations) increases in stress. The large collection of data which supports this property of adaptation in Liebig's system was collected since the first publication (Gorban et al., 1987) and was reviewed by Gorban et al. (2010).

Let us mention several new findings. Censi et al. (2011) proposed using the connectivity of correlation graphs in gene regulation networks as an indicator of analysis of illnesses and demonstrated the validity of this approach on patients with atrial fibrillation. Bernardini et al. (2013) studied mitochondrial network genes in the skeletal muscle of amyotrophic lateral sclerosis patients and found correlations of gene activities for ill patients higher than in control. Kareva et al. (2015) found signs of this general effect in their study of consumer–resource type models and analysis of population management strategies and their efficacy with respect to population composition. Bezuidenhout et al. (2012) used this effect to measure the health of soil and validated this approach. Pareto correlation graphs, including only the highest 20% of correlation coefficients, were particularly

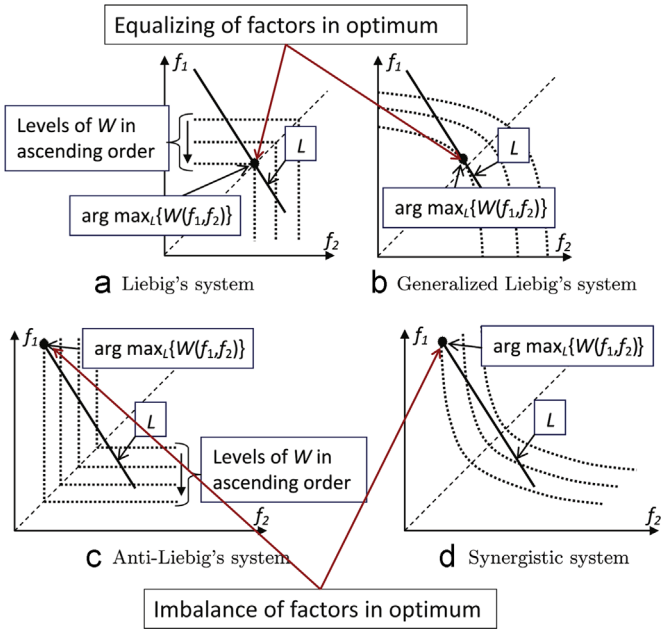

Fig. 9. Distribution of AE for neutralization of several harmful factors for different types of interactions between factors: (a) Liebig's system (the fitness W depends monotonically on the *maximal* non-compensated factor load only), (b) generalized Liebig's system (the fitness W is a *quasiconcave* function of non-compensated factors loads), (c) anti-Liebig system (the fitness W depends monotonically on the *minimal* non-compensated factor load only), and (d) synergistic system (the fitness W is a *quasiconcave* function of non-compensated factors loads). Interval L represents the area of optimization. 'Harmful' means that $\partial W/\partial f_i < 0$ for all factors.

useful in depicting the larger aggregated manageability and measurability of soils. Pokidysheva and Ignatova (2013) used analysis of dimension of the data cloud in evaluation of human immune systems for patients with allergic disease, either complicated or not complicated by clamidiosis. The patterns of population fluctuations are considered as leading indicators of catastrophic shifts and extinction in deteriorating environments (Dakos et al., 2010; Drake and Griffen, 2010). The integration level in the redox in a tissue was systematically studied (Costantini, 2014).

Chen et al. (2012) analyzed microarray data of three diseases and demonstrated that when the system reached the pre-disease state then:

1. There exists a group of molecules, i.e. genes or proteins, whose average correlation coefficients of molecules drastically increase in absolute value.
2. The average standard deviations of molecules in this group drastically increase.
3. The average correlation coefficients of molecules between this group and any others drastically decrease in absolute value.

The observation 1 (increase of the correlations in the dominant group) and 2 (increase of the variance in the dominant group) is in agreement with many of our previous results for different systems and with results of Censi et al. (2011), whereas the interesting observation 3 (decrease of the correlations between the dominant group and others, i.e. isolation of the dominant group) seems to be less universal (see, for example, the correlation graphs published by Gorban et al. (2010)).

Rybnikova and Rybnikov (2012) applied the method of measurement of stress based on the Liebig's paradox to assessing of societal stress in Ukraine. They diagnosed significant stress and dysadaptation increase before the obvious critical events occur (the report was published in 2012, a year before crisis). Some earlier applications to social, economical, and financial systems were reviewed by Gorban et al. (2010).

The theoretical basis of these applications can be found in the *quasistatic* theory of optimal resource allocation for different factors. It analyzes the optimal distribution of the total allocated AE between factors. In the previous sections of our work we develop and analyze dynamical models of adaptation to one-factor load. We have to go ahead and create the plausible dynamical model of adaptation to multifactor load. It is very desirable to introduce as little new and non-measurable details as possible.

Let us start from the models (6). First of all, we propose to use for the total AE supply $kr_0(1-W)$ instead of $kr_0(f-r)$. For one factor with the simplest fitness function it is just redefinition of constant $k \leftarrow k\psi_0$. Second, the AE distribution should optimize W and the simplest form of such an optimization is the gradient descent. Immediately we get a simple system (perhaps the simplest one) which is the direct generalization of (6) and follows the idea of distribution of the resource between factors for fitness increase.

$$\frac{dr_i}{dt} = -k_d r + kr_0(1-W)\frac{\frac{\partial W(\psi_1,\ldots,\psi_q)}{\partial \psi_i}}{\sum_i \frac{\partial W(\psi_1,\ldots,\psi_q)}{\partial \psi_i}};$$

$$\frac{dr_0}{dt} = -k_{d0}r_0 - kr_0(1-W) + k_{rv}B_{o/c}r_{rv}(R_0-r_0) + k_{pr}(R_0-r_0)W;$$

$$\frac{dr_{rv}}{dt} = -k_{d1}r_{rv} - k_{rv}B_{o/c}r_{rv}(R_0-r_0) + k_{pr1}(R_{rv}-r_{rv})W, \qquad (16)$$

where $\psi_i = f_i - r_i$; changes of the Boolean variable $B_{o/c}$ follow the rules formulated above (see Fig. 6).

The fitness function should satisfy the following requirements: it is defined in a vicinity of $\mathbb{R}^q_+$, $0 \le W \le 1$, $W(0)=1$, $\partial W/\partial \psi_i \le 0$, grad $W = 0$ in $\mathbb{R}^q_+$ if and only if $W=1$, if $\psi_i < 0$ then $\partial W/\partial \psi_i = 0$.

The proposed model of the adaptation to the load of many factors needs further analysis and applications. The well-studied quasistatic model appears as a particular limiting case of (16) for slow degradation and fast resource redistribution.

The supply of AE to neutralization of each (ith) factor is in (16)

$$kr_0(1-W)\frac{\frac{\partial W(\psi_1,\ldots,\psi_q)}{\partial \psi_i}}{\sum_i \frac{\partial W(\psi_1,\ldots,\psi_q)}{\partial \psi_i}}.$$

Here, the value of the factor at kr_0 is always between zero and one. In (1) and (3) we used $k_0 r_0(f-r)$. This expression should be corrected by saturation at large $f-r$ because the rate of AE supply cannot be arbitrarily large: 'there is some upper limit to the amount of AE that an individual can use at any discrete moment in time' (Selye's Axiom 2). In (16) we get this saturation from scratch.

8. Conclusion and outlook

In this paper we aim to develop a formal interpretation of Selye–Goldstone physiological theory of adaptation energy. This is an attempt at top-down modelling following physiological ideas. These ideas were well-prepared by their authors for formalization and were published in the form of 'axioms'.

The hierarchy of two- and three-dimensional models with hysteresis is proposed. Several effects of adaptation dynamics are observed as oscillations in death or remission. These oscillations do not require any external reasons and have intrinsic dynamic origin. Observation of such effect in the clinic was already reported for some diseases.

The dynamic theory of adaptation when the organism is subject to a load of several factors needs further development. Goldstone

(1952) formulated a series of questions for the future dynamical theory of adaptation. More precisely, there was one question and several apparently contradictory answers supported by the practical observations:

'How will one stimulus affect an individual's power to respond to a different stimulus? There are several different and apparently contradictory answers; yet, in different circumstances each of these answers is probably true:

1. If an individual is failing to adapt to a disease he may succeed in doing so, if he is exposed to a totally different mild stimulus (such as slight fall of oxygen pressure).
2. In the process of adapting to this new stimulus he may acquire the power of reacting more intensely to all stimuli.
3. As a result of a severe stimulus an individual may not be able to adapt successfully to a second severe stimulus (such as a disease). If he is already adapting successfully to a disease this adaptation may fail when he is exposed to a second severe stimulus.
4. In some diseases (those of adaptation) exposure to a fresh severe stimulus may cure the disease. Exposure to an additional stressor will bring him nearer to death but the risk may be justifiable if it is likely to re-mould the adaptive mechanism to a normal form.'

Future theoretic development should help to predict, which of these contradictory answers will be true for a given patient. Currently we are still unable to give such a prediction for individual patients but the quasistatic theory achieves some success in predictions for groups and populations (Gorban et al., 1987; Sedov et al., 1988; Karmanova et al., 1996; Pokidysheva et al., 1996; Svetlichnaia et al., 1997; Vasil'ev et al., 2007; Razzhevaikin and Shpitonkov, 2008; Gorban et al., 2010, 2011; Censi et al., 2011; Razzhevaikin and Shpitonkov, 2012; Bezuidenhout et al., 2012; Rybnikova and Rybnikov, 2012; Pokidysheva and Ignatova, 2013; Bernardini et al., 2013). These authors proposed and tested a *universal rule* to investigate in practice the amount of stress sensed by the system (and thus the danger of catastrophic changes). The apparent universality of the top-down models of adaptation could sometimes help in the solution of the important general problem of anticipation of critical transitions (Scheffer et al., 2012) and we should also try to apply these models in general settings.

It is necessary to validate predictions of the models. Perhaps, some further improvements are needed. For example, the classical description of the physiological reaction to a noxious stimulus includes three phases (Selye, 1936): alarm–resistance–exhaustion (the general adaptation syndrome, GAS). The alarm phase could be described more precisely than it is done in the model (6) if we introduce an activation threshold. One Selye's axiom requires a threshold for activation of the AE supply: 'There is a threshold of AE activation that must be present to potentiate an occupational response.' We introduced a threshold for the activation of reserve but did not use a threshold for the activation of the start of AE supply (thus, in our models there are two levels of AE supply). Perhaps, such a threshold of initial AE activation could help in the precise description of the alarm phase. This threshold was even included by Chrousos and Gold (1992) in a general definition of the stress system: 'The stress system coordinates the generalized stress response, which takes place when a stressor of any kind exceeds a threshold.' There is some empirical evidence of the existence of a hierarchy of many activation thresholds (Garkavi et al., 1998). Construction of the models with a hierarchy of thresholds does not meet any formal difficulty but increases the number of unknown parameters.

Another improvement may be needed for the description of a dynamic response of the instant fitness to changes of factors. In the proposed models, the fitness reacts immediately. This seems to be an appropriate approximation when the intensities of the factors change slowly but in a more general situation we have to add a differential equation for the fitness dynamics.

There also remains a theoretical (or even mathematical) challenge: the systematic and exhaustive analysis of the phase portraits of the system (6) over the full range of parameters.

Many data about physiological, biochemical, and psychological mechanisms of adaptation and stress were collected during decades after Selye's works (Chrousos and Gold, 1992; McEwen, 2007). The published schemes of the stress systems and regulations include many dozens of elements. Mathematical models of important parts of homeostasis have been created (Pattaranit and Van Den Berg, 2008). In this situation, the simple models based on the AE production, distribution and spending have to prove their usefulness.

The adaptation models introduced and analyzed in this work exploit the most common phenomenological properties of the adaptation process: homeostasis (adaptive regulation), price for adaptation (adaptation resource), and the idea of optimization (for the multifactor systems). The developed models do not depend on the particular details of the adaptation mechanisms.

These models, which are independent of many details, are very popular in physics, chemistry, ecology and many other disciplines. They aim to capture the main phenomena. In order to clarify the status of these models, we use the classification of models elaborated by Peierls (1980). He introduced six main types of models:

- Type 1: Hypothesis ('Could be true'),
- Type 2: Phenomenological model ('Behaves as if…'),
- Type 3: Approximation ('Something is very small, or very large'),
- Type 4: Simplification ('Omit some features for clarity'),
- Type 5: Instructive model ('No quantitative justification, but gives insight'),
- Type 6: Analogy ('Only some features in common').

At a first glance, we have to attribute our models to Type 4 or even to Type 5. Many famous models belong to these types: the Van der Waals model of non-perfect gases, the Debye specific heat model (Type 4); the mean free path model for transport in gases, the Hartree–Fock model for nucleus, and the Lotka–Volterra model of predator–prey systems (Type 5).

Nevertheless, is seems to be possible to attribute the models of adaptation elaborated in this framework of the top-down approach to the second or even to the first type. Different biological systems that have evolved can have structures with analogous forms or functions but without close common ancestor or with different intrinsic mechanisms. This is convergent evolution (McGhee, 2011). Some famous examples are: evolution of wings, eyes, and photosynthetic pathways. The number of evolutionary pathways available to life may be quite limited, and the functional response to the similar environmental challenges may be similar without homology (no close common ancestor) and even with different mechanisms.

Adaptation is a universal property of life and there are many mechanisms of adaptation. Different detailed mechanisms may produce the same phenomenological answer at the top level because of convergent evolution. Let us call this hypothesis the *Principle of phenomenological convergence*. The term 'phenomenological convergence' was used in the analysis of synthetic biology by Schmidt (2016) (phenomenological convergence of nature and technology).

The principle of phenomenological convergence results in the conclusion that the general dynamic properties of adaptation may be much more universal than the particular biochemical and

physiological mechanisms of adaptation. This manifested independence of the top phenomenological level from the bottom level (detailed mechanisms) is the result of convergent evolutions. This allows us to use AE models without solid knowledge of the intrinsic mechanism (behave as if it is true, Type 2) or even to accept them as the truth (temporarily, of course, Type 1).

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