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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 nonspecific 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