Chapter 7

Fuzzy Logic and *S*-Lagrangian Dynamics of Living Systems: Theory of Homeostasis

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66473

Abstract

A key peculiarity of living organisms is their ability to actively counteract degradation in a changing environment or being injured by using homeostatic protection. In this chapter, we propose a dynamic theory of homeostasis based on a recently proposed generalized Lagrangian approach (*S*-Lagrangian). Following the discovery of homeostasis W. Cannon, we assume that homeostasis results from the tendency of the organisms to decrease the stress and avoid death. We show that the universality of homeostasis is a consequence of analytical properties of the *S*-Lagrangian, while peculiarities of the biochemical and physiological mechanisms of homeostasis determine phenomenological parameters of the Lagrangian. We show that plausible assumptions about *S*-Lagrangian features lead to good agreement between theoretical descriptions and observed homeostatic behavior.

Keywords: Homeostasis, *S*-Lagrangian, Dynamics, living systems, stress

1. Introduction

A primary difference between living creatures and non-living things is the capacity for reproduction. However, if one considers only individual life rather than the existence of species, the major paradox is that living things actively counteract degradation in a continuously changing environment or being injured through homeostatic protection. By homeostasis, we refer to the ability of living organisms to maintain viability and stability of physiological functions in a changing external environment. The system remains alive as a consequence of homeostasis maintaining system integrity in the presence of perturbing influences. Cessation of homeostasis leads to inevitable death. In living systems, the relationship between cause and effect is paradoxical: organisms are characterized by poorly predictable motility, which is supposedly managed by their internal motives. Homeostatic motivation transforms an object into a subject by virtue of its own behavior. Thus, the mystery of arbitrary actions may be disclosed by

exploring homeostasis [1]. It should be noted that homeostasis may evidently produce both maintenance of life and the will to act [2].

Although homeostasis is present in all living systems and relates to large numbers of different biochemical and physiological mechanisms, it reveals amazingly similar features and behavior. Such universality is not unique in the physical world. For example, physical systems, from crystals to large biomolecules, demonstrate universal behavior near critical points in spite of considerable differences in its structures and intermolecular interactions. This occurs due to the critical behavior of the systems being determined by the analytical properties of free energy near critical points, while the peculiarities of system structure and intermolecular interactions are "hidden" within the phenomenological parameters of the free energy.

We assume that the universality of homeostasis is a consequence of the analytical properties of the *S-Lagrangian*, which determines the dynamic equation associated with homeostasis, while peculiarities of the biochemical and physiological mechanisms determine phenomenological parameters of the Lagrangian. We show in Section 2 that plausible assumptions about *S-Lagrangian* properties lead to good agreement between theoretical descriptions and observed homeostatic features.

2. Biological background

2.1. Homeostasis levels

Living beings actively oppose their degradation in continuously changing environments by means of homeostasis [3] that supports the intrinsic bodily constants within acceptable limits. Maintenance of individual life requires evaluating and regulating its inner state. Homeostatic regularities can be traced to the level of particular cellular parameters, cells, in general, physiological systems of an organism, and an organism as a whole. In this study, we primarily focus on homeostasis of neurons and the nervous system. A cell, as a body, manifests complete homeostasis. This occurs not only to maintain biological constants but also to regulate physiological functions and motivational behavior. The behaving animal is sensitive to single neuronal spikes and even to their temporal patterning [4]. Moreover, a neuronal spike can serve as a tool of reaction for the whole animal [1]. Individual neurons act in concert to govern behavior [5].

At first glance, homeostatic mechanisms are not complicated. In theoretical research, the problem is often evaluated by the introduction of positive- and negative-feedback loops between the sensor and the metabolic flaw (e.g., [6, 7]). Attempts to model homeostatic regulation consider only simple homeostasis, with regulation of each variable described by the introduction of specific individual controllers. However, when homeostatic protection begins to work against a permanent environmental factor or severe injure, these mechanisms become ineffective and living systems utilize indirect paths to assign optimal parameters, depending on the situation.

Homeostatic function depends on sensors, which register deviations from the norm. Appearance of a metabolic flaw triggers the homeostatic device to compensate for the shortage.

However, homeostatic resources may not be sufficient to restore disturbed functions. In these cases, living systems may try to change the environment, requiring the environment to be included in the interaction.[1]

The status of the internal environment is not sustainable for all life. Conditions remain stable only at intervals of time as compared to environmental variability. At these intervals, homeostasis counteracts weak disorders in the system and recovers initial conditions (*direct regulation*). Over time, adapting to strong external influences enables life to modify its parameters (*indirect regulation*). If the value of a deviated parameter is not restored, the organism may be able to maintain it by restructuring the optimum of other parameters. For example, stabilization of neuronal activity can be achieved by configuring both synapse efficiency and cell autonomous homeostasis [8]. Homeostasis readjusts to save some supreme quality criterion that distinguishes the living from the nonliving. The living entity keeps track of a special criterion the degree of remoteness from its destruction. This criterion determines the intensity of homeostatic protection. However, damage may reach such an extent that homeostasis is unable to overcome the irreversible destruction of the living system.

The nature of the general sensor for damage-recovery viability is unclear, though there are options that are significant to the survival of cells and the whole organism. These include energy (ATP level), excitability, intracellular pH levels, and concentration of certain proteins (caspases, cytokines, or antioxidants). These cannot be disregarded by the highest sensors, which could lead to death. For example, a supreme neuronal sensor might be excitability [1].

2.2. Protection generates action

Misalignment of homeostasis leads to damage, the increase in the activity, and leads to further aggravation of injury. As a rule, the response of neurons is proportional to the coming stimulation. However, superfluous stimulation and neuronal injury are intimately connected (excitotoxicity) [9]. Thus, the injured neurons generate spikes.

It should be noted that extensive damage of nerve tissue reduces excitability and violates its function, while protection temporarily restores excitability. Therefore, there is a region of the paradoxical states of excitable tissues, where excitation is reduced due to damage, but irreversible deterioration of the tissue has not yet occurred. In such a case, inhibition (or decreased excitation) counteracts the damage, paradoxically recovers the normal excitability, and promotes the generation of action (parabiosis, in accordance with N.E. Vedensky) [10]. Properties of homeostatic protection make it tempting to consider homeostasis as a driving force that induces actions directed against actual or anticipated damage. However, in cases where the damage cannot be completely compensated for by available resources, metabolic problems may be solved through actions directed at the environment.

To outside observers, the resulting behavior will resemble the emergence of motivation, will to live, and be match with conscious decision. The optimal state corresponds to such conditions that do not threaten the lives and do not evoke attempts to change structure and functioning of

[1]We do not consider this complicated form of homeostasis in this study; however, our approach is extendable to this case, as well.

the brain. A minimum of homeostatic load will serve as a criterion for this state. Joint behavior of a huge variety of such systems generates to complex forms of awareness. The neural tissue concentrates within itself the ability to evaluate its own state and endeavor to survive. A single cell, neurons in particular, can live, learn, want, suffer, delight, and try to survive [1]. Exertion of neuronal metabolism, leading to protection and goal-directed behavior, is rather appropriate for the description of conscious actions. Purposeful behavior corresponds to conscious decision and resembles a kind of generalized "pursuit of life." To the outside observer, this is reminiscent of intentional action and a manifestation of will.

2.3. Emergence of the feeling of a death threat

The essence of subjective feeling, goals, and will is still the amazing mysteries. The establishment of the theory of systems regulating optimal constants of their own state gives hope for understanding the problem of subjectivity, as homeostasis is the key tool that supports the system alive. The emergence of self as a state separated from the external environment is probably a direct consequence of the vitality of living systems. Alive system should assess its own vitality, and the phenomenon of maintaining its life is impossible to distinguish from instrumental actions. Probably, life appears along with the ability of an individual to evaluate its own integrity and health, and the homeostatic protection is a material manifestation of the pursuit of life.

Maintenance of vital activity resembles a manifestation of the mystical "vital force," which prevents disorder and violates the laws of thermodynamics. Homeostatic activities are so rational that their discoverer, W. Cannon, described them as "Wisdom of the body."

The appearance of self-dissatisfaction plays a crucial role in triggering homeostatic protection, especially in the emergence of aware decisions. Nevertheless, it is difficult to provide a formal definition for the subjective feelings of discomfort that coincide with the appearance of damage. The assessment of general parameters is qualitative and is guided by the "injure-repair" scale. Living systems somehow regulate the avoidance of injury and the aspiration to life as it shifts toward death or life, that is, behaves as an object possessing minimum awareness. This mysterious variable may not be a function of the state and should depend on the previous history of the system, since homeostasis, as well as behavior, improves after exercise [1].

We have no possibility of determining how a neuron evaluates its own state, but we know that injury decreases positive feelings, while protection decreases distress. In any case, the approach of death increases cellular efforts to operate. A living system reacts to damage as if it is having a negative sensation. Homeostasis entails a relationship between physiology and mind. The problems of consciousness and the problem of life self-maintenance are inseparable. It is likely that the origin of life necessarily leads to the emergence of consciousness.

2.4. Homeostatic regulation

Theoretically, there are two explanations for homeostatic operation:

1. Rigid mechanistic programs that evaluate all options for possible injures.
2. Spontaneous relaxation, which minimizes injury.

http://dx.doi.org/10.5772/66473

If it is algorithmically predetermined by the Genetics, the body needs to recognize its own current state and select a genetically pre-tuned course of recovery. However, the number of possible optima can be as high as the number of non-lethal states of external environment and this would create invalid load on the genome. Besides, genetic defects often have limited impact on the relevant functional paths, since homeostasis is capable of compensating for many such defects [11, 12]. Therefore, it is reasonable to assume that spontaneous recovery to a sustained state is the main mechanism of homeostasis.

In general, a living system is open and its dynamics is irreversible. Living beings are somehow able to evaluate their remoteness or closeness to death. While this is beyond doubt, we cannot specify the exact mechanism of evaluation. Movement of a living being within the space of its parameters should minimize this global parameter, that is, proximity to death.

3. Theory of homeostasis

3.1. Dynamics equations of homeostasis

Consider a living organism, whose state is described by n variables, $\boldsymbol{q} = \{q_1, \ldots, q_n\}$. These variables can describe both behavioral and physiological or neurophysiological features and we consider them as coordinates of the abstract state space of the system.[2] As we have mentioned in Section 1.4, living organisms are somehow able to evaluate their level of discomfort or stress (see Ref. [1] for comprehensive discussion), so we consider this feature as additional scalar variable, S, and will call S as *stress-index* (*S-index*). It is a typical phenomenological variable, which cannot be directly measured,[3] but it should be emphasized that although S corresponds to the "feeling" quantity, it is an objective feature of the living beings [1].

In experiments with living organisms, many parameters that influence on the system's behavior are out of control, which leads to considerable deviations in *numerical* values of the experimental results. It means that small differences in the values of the experimental data became insignificant and the state of a system should be described by a *domain* of points rather than a *single* point in the state space. This kind of uncertainty does not have stochastic nature and L. Zadeh has introduced for its notion of the *fuzzy sets* [13] and theory of *possibility* [14–16].

We assume that the dynamics of the living systems satisfies causality principle in the form (see Ref. [1] for details):

- "If, at the time $t + dt$, the system is located in the vicinity of the point $\boldsymbol{x}$, then at the previous time t, the system could be near the point $\boldsymbol{x}' \approx \boldsymbol{x} - \dot{\boldsymbol{x}}' dt$, or near the point $\boldsymbol{x}'' \approx \boldsymbol{x} - \dot{\boldsymbol{x}}'' dt$, or near the point $\boldsymbol{x}''' \approx \boldsymbol{x} - \dot{\boldsymbol{x}}''' dt$, or …, and so on, for all possible values of the velocity $\dot{\boldsymbol{x}}$."

[2] We assume that the state space has trivial local topology, which means that any inner point of any small domain in the space belongs to the space as well.

[3] The phenomenological variables, which cannot be directly measured, are widely used in physics, for example "mechanical action" of the physical systems, order parameter of the superfluid phase transition, and so on.

where $\boldsymbol{x} = \{\boldsymbol{q},S\}$. Since velocities $\{\dot{\boldsymbol{q}},\dot{S}\}$ cannot be precisely obtained, we describe them by the function $Pos(\dot{\boldsymbol{q}},\dot{S};\boldsymbol{q},S,t)$,[4] which indicates *possibility* that the system has velocities $\{\dot{\boldsymbol{q}},\dot{S}\}$ near the point $\{\boldsymbol{q},S\}$ at the time t. The most possible velocities satisfy

$$Pos(\dot{\boldsymbol{q}},\dot{S};\boldsymbol{q},S,t) = 1 \tag{1}$$

and only this case will be considered in this chapter.

It has been shown in Ref. [17] that if a system's evolution satisfies the causality principle, the system's state space has trivial local topology, and if state can be described by a compact fuzzy set, then the most possible system's trajectories $\{\boldsymbol{q}(t), S(t)\}$ satisfy the generalized Lagrangian-like equations

$$\frac{d}{dt}\frac{\partial L}{\partial \dot{\boldsymbol{q}}_i} - \frac{\partial L}{\partial \boldsymbol{q}_i} = \frac{\partial L}{\partial S}\frac{\partial L}{\partial \dot{\boldsymbol{q}}_i}, \tag{2a}$$

$$\frac{dS}{dt} = L(\dot{\boldsymbol{q}},\boldsymbol{q},S,t), \tag{2b}$$

where $L(\dot{\boldsymbol{q}},\boldsymbol{q},S,t)$ is the solution of Eq. (1) with respect to $\dot{S}$. (We will call $L(\dot{\boldsymbol{q}},\boldsymbol{s},S,t)$ as "*most possible S-Lagrangian*" or *S*-Lagrangian for short. The equations of motion (2a) and (2b) are more general than the common Lagrangian equations. Since these equations can describe the dynamics of sets, they can be differential inclusion instead differential equations. The second extension is *dependence of the Lagrangian on S-variable*[5] (*S*-Lagrangian). In this case, the Lagrangian equations of motion acquire a non-zero right side, proportional to the derivative of the *S*-Lagrangian with respect to *S*. It has been shown in Ref. [17] that the equations of motion with *S*-Lagrangian lost time reversibility, the energy and momentum are not conserved even in closed systems. Note that *S*-Lagrangian is not an invariant under the addition of a function which is a total derivative with respect to time.[6] It should be emphasized that the derivation of these equations in Ref. [17] does not depend on any specific properties of the system or its Lagrangian. This means that Eqs. (2a) and (2b) give a reasonable method of applying the Lagrangian approach to non-physical systems. So, we believe that the dynamics of homeostasis can be described by Eqs. (2a) and (2b) with appropriate choice of the *S*-Lagrangian $L(\dot{\boldsymbol{q}},\boldsymbol{q},S,t)$.

Attempting to decrease stress and proximity to death is a basic feature of the living organisms. It is important that this feature exists already on a single-cell level (see Ref. [1] for comprehensive discussion). Deviation of the system's parameters from their ground values leads to increasing discomfort and the organisms try to decrease discomfort by generating the protection mechanisms. These mechanisms, in turn, generate the system's activity (see Section 1.3 or

[4] It should be emphasized that the function $Pos(\dot{\boldsymbol{q}},\dot{S};\boldsymbol{q},S,t)$ cannot be identified with any probability density $\rho(\dot{\boldsymbol{q}},\dot{S};\boldsymbol{q},S,t)$, because it has different mathematical features. Actually, $Pos(\dot{\boldsymbol{q}},\dot{S};\boldsymbol{q},S,t)$ is a *function*, while $\rho(\dot{\boldsymbol{q}},\dot{S};\boldsymbol{q},S,t)$ is a *functional* [17].

[5] In the classical mechanics, *S-variable* is nothing more than common mechanical action.

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http://dx.doi.org/10.5772/66473

[1]), which can be described by time derivatives of the variables, $\dot{\boldsymbol{q}}$. Following the discovery of homeostasis W. Cannon [3], we assume that homeostasis results from a tendency of the organisms to decrease the stress and avoid death and that the dynamics of the stress is determined by competition between damage and the protection mechanisms. So we write

$$\frac{dS}{dt} = L(\dot{\boldsymbol{q}},\boldsymbol{q},S,t) = -P(\dot{\boldsymbol{q}},\boldsymbol{q},S) + I(\boldsymbol{q},S,t), \tag{3}$$

where function $I(\boldsymbol{s},S,t)$ describes increasing of stress by deviation of the system's parameters, while $P(\dot{\boldsymbol{q}},\boldsymbol{q},S)$ corresponds to decreasing of stress by the protection mechanisms.

Experimental observations of homeostatic behavior (see Ref. [1] and references there) show that functions $I(\boldsymbol{q},S,t)$ and $P(\dot{\boldsymbol{q}},\boldsymbol{q},S)$ should satisfy the following:

i. Deviation of the system's variables from the ground states corresponds to injury or damage, even if *S-index* does not have the time to change.

ii. If stress is high, the same perturbation of the variables can strongly increase *S-index*, than its increasing at low levels of stress.

iii. Protection is reinforced by moderate stress, but if stress is very high, the protection mechanism becomes less effective.

Below, we consider time intervals, which is much shorter than the time of relevant changes in environmental conditions, so that we can neglect time dependence in Eq. (3) and write

$$L(\dot{\boldsymbol{q}},\boldsymbol{q},S) = -P(\dot{\boldsymbol{q}},\boldsymbol{q},S) + I(\boldsymbol{q},S), \tag{4}$$

and will call $I(\boldsymbol{q},S)$ as *Injure* and $P(\dot{\boldsymbol{q}},\boldsymbol{q},S)$ as *Protection* for short.

By using Eq. (4), we rewrite Eqs. (2a) and (2b) as

$$-\frac{d}{dt}\frac{\partial P}{\partial \dot{\boldsymbol{q}}_i} + \frac{\partial}{\partial \boldsymbol{q}_i}[P-I] = \frac{\partial P}{\partial \dot{\boldsymbol{q}}_i}\frac{\partial}{\partial S}[P-I] \tag{5a}$$

$$\frac{dS}{dt} = -P(S,\dot{\boldsymbol{q}},\boldsymbol{q}) + I(\boldsymbol{q},S). \tag{5b}$$

Equations (5a) and (5b) are the main *dynamic equations of homeostasis*. It should be noted that *S-index*

$$S = S_0 + \int_0^t [-P(S(t'),\dot{\boldsymbol{q}}(t'),\boldsymbol{q}(t')) + I(\boldsymbol{q}(t'),S(t'))]dt' \tag{6}$$

is not function of a state but depends on the system's history.

For small-to-moderate activity, we can expand $P(\dot{\boldsymbol{q}},\boldsymbol{q},S)$ with respect to $\dot{\boldsymbol{q}}$. We have[7]:

[7]Summating on the repeated indices (Einstein summation) is assumed.

$$P \simeq A(\boldsymbol{x},\xi,S) + a_i(\boldsymbol{x},\xi,S)\,\dot{\xi}_i + \frac{1}{2} m_{ij}(\boldsymbol{x},\xi,S)\dot{\boldsymbol{x}}_j\dot{\boldsymbol{x}}_i, \tag{7}$$

where we designate by the Latin symbol: $\boldsymbol{x}$ the variables with zero linear terms in Eq. (7) and by the Greek symbol: ξ the variables with non-zero linear terms[8] and keep in Eq. (7) only the terms with lowest order on $\dot{\xi}$ and $\dot{\boldsymbol{x}}$. For reasons that will be clarified later, we will refer to $\boldsymbol{x}$ as *stationary variables (C-variables)* and ξ as *running variables (R-variables)*.

The term $A(\boldsymbol{x},\xi,S)$ corresponds to short-term compensation of stress (e.g., by immediate releasing of the endorphins ("endogenous morphine"), which are quickly produced in natural response to pain [1]). The other terms correspond to long-term protection by generating the activity.[9] In the last terms, matrix m_{ij} determines character rates of changing of the variables $\boldsymbol{x}$: small m_{ii} corresponds to the fast-changing variables, while large m_{jj} corresponds to the slow-changing ones. The function $\boldsymbol{a}(\boldsymbol{x},\xi,S)$ determines the behavior of the *R-variables* (see page 13).

Therefore, Eqs. (5a) and (5b) take the form:

$$m_{ij}\ddot{\boldsymbol{x}}_j + \left(W\frac{\partial m_{ij}}{\partial S} - \frac{\partial W}{\partial S} m_{ij}\right)\dot{\boldsymbol{x}}_j = -\frac{\partial}{\partial \boldsymbol{x}_i}(W - a_j\dot{\xi}_j), \tag{8a}$$

$$\Omega_{ij}^{-1}\dot{\xi}_j + \frac{\partial a_i}{\partial \boldsymbol{x}_j}\dot{\boldsymbol{x}}_j = \frac{\partial W}{\partial S} a_i - W\frac{\partial a_i}{\partial S} - \frac{\partial W}{\partial \xi_i}, \tag{8b}$$

$$\frac{dS}{dt} = -\frac{1}{2} m_{ij}\dot{\boldsymbol{x}}_j\dot{\boldsymbol{x}}_i + \left(W(\boldsymbol{x},\xi,S) - a_j\dot{\xi}_j\right). \tag{8c}$$

where we designated

$$W(\boldsymbol{x},\xi,S) = I(\boldsymbol{x},\xi,S) - A(\boldsymbol{x},\xi,S). \tag{9}$$

$$\Omega_{ij}^{-1} = \frac{\partial a_i}{\partial \xi_j} - \frac{\partial a_j}{\partial \xi_i} + a_i\frac{\partial a_j}{\partial S} - a_j\frac{\partial a_i}{\partial S}. \tag{10}$$

and in the first approximation with respect to $\dot{\boldsymbol{x}}$ and $\dot{\xi}$ we have omitted in Eqs. (8a) and (8b) the terms that are proportional to $o(\dot{\boldsymbol{x}}_k\dot{\boldsymbol{x}}_j, \dot{\boldsymbol{x}}_k\dot{\xi}_j)$.

Since Ω_{ij}^{-1} is an antisymmetric matrix, $\Omega_{ij}^{-1} = -\Omega_{ji}^{-1}$, Eq. (11b) may include the rotation of *R*-variables in the $\{\xi\}$ subspace. This means that even in the ground state, where *C*-variables possess stationary stable points $\dot{\boldsymbol{x}}_c = 0, \dot{S}_c = 0$, *R*-variables are functions of time (this is why we refer to these variables as *running variables*).

By using Eq. (8b), Eqs. (8a) and (8c) can be rewritten as

[8] In order to ensure that P would increase along with increasing activity, the matrix m_{ij} should be positively defined.

[9] Interestingly, various human activities, for example, aerobic exercise, stimulate the release of endorphins as well [18].

http://dx.doi.org/10.5772/66473

$$m_{ij}\ddot{\boldsymbol{x}}_j + \left[W\frac{\partial m_{ij}}{\partial S} - \frac{\partial W}{\partial S}m_{ij} + \frac{\partial}{\partial \boldsymbol{x}_i}\left(a_l\Omega_{lk}\frac{\partial a_k}{\partial \boldsymbol{x}_j}\right)\right]\dot{\boldsymbol{x}}_j = -\frac{\partial U}{\partial \boldsymbol{x}_i}, \tag{11a}$$

$$\dot{\xi}_j = \Omega_{ij}\left(\frac{\partial W}{\partial S}a_j - W\frac{\partial a_j}{\partial S} - \frac{\partial a_j}{\partial \boldsymbol{x}_k}\dot{\boldsymbol{x}}_k\right), \tag{11b}$$

$$\frac{dS}{dt} = -\frac{1}{2}m_{ij}\dot{\boldsymbol{x}}_j\dot{\boldsymbol{x}}_i + \left(a_i\Omega_{ij}\frac{\partial a_j}{\partial \boldsymbol{x}_k}\right)\dot{\boldsymbol{x}}_k + U(\boldsymbol{x},\xi,S), \tag{11c}$$

where

$$U = W\left(1 + a_j\Omega_{jk}\frac{\partial a_k}{\partial S}\right) + a_j\Omega_{jk}\frac{\partial W}{\partial \xi_k}. \tag{12}$$

Equations (11a) and (11c) represent *dynamic equations of homeostasis* for the systems with temperate activity.

3.2. Behavior near the stable states

In order for the running variables to not disturb the ground state, $S_c = 0$, $\boldsymbol{x}_c = \text{const.}$, we should assume that

$$\frac{\partial}{\partial \boldsymbol{x}_{kc}}a_j(\boldsymbol{x}_c,\xi,S_c) = 0;\ \frac{\partial}{\partial S_c}a_j(\boldsymbol{x}_c,\xi,S_c) = 0;\ \frac{\partial}{\partial \xi_k}W(\boldsymbol{x}_c,\xi,S_c) = 0. \tag{13}$$

(see Eqs. (11a) and (12)).

Stable states of Eqs. (11a) and (11c) are defined by

$$W(\boldsymbol{x}_c,S_c) = \quad = 0, \tag{14a}$$

$$\frac{\partial W}{\partial \boldsymbol{x}_{ci}} = 0. \tag{14b}$$

There are two types of solutions for Eqs. (14a) and (14b), which could be called as ground states (*GSSs*) and as local stable states (*LSSs*). At *GSS*, the injure reaches its global minimum $I(\boldsymbol{x}_{c1},S_{c1}) = 0$ that leads to

$$A(\boldsymbol{x}_{c1},S_c) = 0. \tag{15}$$

In order for Eq. (15) to be valid for any set of $\boldsymbol{x}_{c1}$ that satisfy Eq. (14a), the function $A(S_c,\boldsymbol{x}_{c1})$ should be factorized as

$$A(\boldsymbol{x}_{c1},S) = S\Psi(\boldsymbol{x}_{c1},S), \tag{16}$$

given that $\Psi(\boldsymbol{x}_{c1},S)\neq 0$ (see Eq. (22)).

Unlike at *LSS*, where the system remains injured

$$I(\boldsymbol{x}_{c2},S_{c2}) > 0, \tag{17}$$

S-index is non-zero, because

$$A(\boldsymbol{x}_{c2},S_{c2}) > 0 \Rightarrow S_{c2} > 0. \tag{18}$$

This means that near *LSS*, the system is stressed, but its state is stable.

Consider the case where $m_{ij} = m_{ij}(\boldsymbol{x},S)$ and $W = W(\boldsymbol{x},S), \boldsymbol{a} = \boldsymbol{a}(\xi)$. If deviations from the stable state

$$\boldsymbol{y} = \boldsymbol{x}-\boldsymbol{x}_c, \tag{19a}$$

$$w = S-S_c, \tag{19b}$$

are small, we can expand Eqs. (11a) and (11c) with respect to $\boldsymbol{y}$ and w. In the first-order approximation, we obtain[10]

$$\ddot{y}_i + \gamma_c \dot{y}_i = -K_{ij}y_j, \tag{20a}$$

$$\dot{w} = -\gamma_c w. \tag{20b}$$

where

$$\gamma_c = -\frac{\partial W_c}{\partial S_c},$$

$$K_{ij} = m_{ik}^{-1}(\boldsymbol{x}_c,S_c)\frac{\partial^2 W_c}{\partial \boldsymbol{x}_{ck}\partial \boldsymbol{x}_{cj}}.$$

Equations (20a) and (20b) are simple and can be easily solved:

$$y_j = e^{-\gamma_c t/2}\sum_{\alpha}(Q_{j\alpha}e^{i\omega_\alpha t} + Q_{j\alpha}^{*}e^{-i\omega_\alpha t}), \tag{21a}$$

$$w = w_0 e^{-\gamma_c t}. \tag{21b}$$

where

$$\omega_\alpha = \sqrt{\lambda_\alpha - \frac{\gamma_c^2}{4}},$$

$w_0, Q_{j\alpha}$ are constants and λ_α are eigenvalues of the matrix, K_{ij}. We see that in order for the stationary state, $\boldsymbol{x}_c$, to be stable, it needs to be

[10]The terms that are proportional to w in Eq. (20a) and to y in Eq. (20b) have vanished because of conditions (14a) and (14b).

http://dx.doi.org/10.5772/66473

$$\frac{\partial W_c}{\partial S_c} < 0. \tag{22}$$

Additionally, matrix K_{ij} should be positively defined. The ground states correspond to zero damage and *S-index*, while the disturbed stationary states correspond to the local minimums of $W(\boldsymbol{x},S)$.

Consider the behavior of *R*-variables near the ground state with $\boldsymbol{a} = \boldsymbol{a}(\xi)$. In accordance with Eqs. (11b) and (14a), we have

$$\dot{\xi}_i = -\gamma_c(\boldsymbol{x}_c,S_c)\Omega_{ij}(\xi)\ a_j(\xi), \tag{23}$$

so the behavior of the *R*-variables is determined by the function $\boldsymbol{a}(\xi)$.[11] It is convenient to present ξ in the form $\xi(t) = \xi(t)\boldsymbol{n}(t)$, where $\xi(t)$ and $\boldsymbol{n}(t)$ are the scalar and vector functions, respectively, with $|\boldsymbol{n}| \equiv 1$. Then Eq. (23) takes the form

$$\dot{\xi} = -\gamma_c n_i \Omega_{ij}\ a_j, \tag{24a}$$

$$\dot{n}_i = -\frac{\gamma_c}{\xi}\left(\Omega_{ij}\ a_j - n_i(n_k\Omega_{kj}a_j)\right). \tag{24b}$$

If $\boldsymbol{a} = \varphi(\xi)\xi$, where $\varphi(\xi)$ is a scalar function, these equations are simplified:

$$\dot{\xi} = 0, \tag{25a}$$

$$\dot{n}_i = -\frac{\gamma_c\varphi}{\xi}\Omega_{ij}\ n_j. \tag{25b}$$

Therefore, in this case, $\xi = \xi_0 = \text{const}$..

In the case of two *R*-variables, we can write ξ as

$$\xi = \xi_0\begin{bmatrix}\cos\varphi\\ \sin\varphi\end{bmatrix}, \tag{26}$$

which implies that $\varphi = \varphi(\cos\phi,\ \sin\phi)$, and Eq. (25b) takes the form

$$\frac{d\phi}{dt} = -\frac{\gamma_c\varphi}{\xi_0}\left(\cos\phi\frac{\partial\varphi}{\partial\sin\phi} - \sin\phi\frac{\partial\varphi}{\partial\cos\phi}\right)^{-1}. \tag{27}$$

Therefore,

[11] Note that because matrix Ω_{ij} is antisymmetric, *R*-variables exist only if there are at least two *R*-variables.

$$\xi_1 = \xi_0 \cos(\phi(t)), \tag{28a}$$

$$\xi_2 = \xi_0 \sin(\phi(t)). \tag{28b}$$

where function $\phi(t)$ should be obtained from Eq. (27).

3.3. Simulation results

For easy visualization of the typical behavior of systems with homeostasis, we consider a system with two *C*-variables and two *R*-variables: $\boldsymbol{x} = \{\boldsymbol{x}_1, \boldsymbol{x}_2\}$, $\xi = \{\xi_1, \xi_2\}$ and $m_{ij} = m_i \delta_{ij}$ with constant $m_1 \ll m_2$, making $\boldsymbol{x}_1$ fast and $\boldsymbol{x}_2$ slow variables. In order to clarify the influence of *C*-variables and *S*-index upon the homeostatic behavior, we choice also $W = W(\boldsymbol{x}, S)$ and a simplest form of $\boldsymbol{a}$

$$a = \begin{bmatrix} a_{01} & 0 \\ 0 & a_{02} \end{bmatrix} \begin{bmatrix} \xi_1 \\ \xi_2 \end{bmatrix}, \tag{29}$$

with constant a_{01}, a_{02}. In this case, Eqs. (11a), (11b) and (11c) are simplified and we have[12]

$$m_i \ddot{\boldsymbol{x}}_i - \frac{\partial W}{\partial S}\, m_i \dot{\boldsymbol{x}}_i = -\frac{\partial W}{\partial \boldsymbol{x}_i} \tag{30a}$$

$$\dot{\xi}_i = \frac{\partial W}{\partial S} \Omega_{ij} a_j, \tag{30b}$$

$$\frac{dS}{dt} = -\frac{1}{2} m_i \dot{\boldsymbol{x}}_i^2 + W(\boldsymbol{x}, S). \tag{30c}$$

Conditions (i)–(iii) on page 8 allow us to choose the functions $I(\boldsymbol{x}, S)$ and $A(\boldsymbol{x}, S)$ in the form[13]

$$I(\boldsymbol{x}, S) = \Phi_1(S) J(\boldsymbol{x}), \tag{31a}$$

$$A(\boldsymbol{x}, S) = S \Phi_2(S) \Gamma(\boldsymbol{x}), \tag{31b}$$

where $\Phi_1(S)$ and $\Phi_2(S)$ are monotonically increasing and decreasing functions of S, respectively, with $\{\Phi_1(0), \Phi_2(0)\} > 0$ and $J(\boldsymbol{x}) \geq 0, \Gamma(\boldsymbol{x}_c) > 0$.[14]

Results of the simulation are shown in **Figures 1** and **2** for the different initial conditions.

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[12] There is no summation on i.

[13] Generally speaking, both $I(\boldsymbol{x}, S, \xi)$ and $A(\boldsymbol{x}, S, \xi)$ may depend on *R*-variables far from the stable states, but here we have neglected this opportunity.

[14] Simulation shows that the qualitative behavior of $\boldsymbol{x}(t)$, $S(t)$, and $\xi(t)$ weakly depends upon the concrete choice of the functions $\Phi_1(S), \Phi_2(S)$ and $J(\boldsymbol{x})$, $\Gamma(\boldsymbol{x})$ if they satisfy conditions (i)–(iii). For results are shown below we have used $\Phi_1(S) = (1 + bS^k)$, $\Phi_2(S) = (1 + cS^n)^{-1}$, with $b = c = 1$ and $k = n = 2$.

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In **Figure 1A**, light injuring of the system causes the main ground state to be slightly disturbed. We see that the fast and slow *C*-variables[15] quickly find their stable points. Injure (**Figure 1A**, row 4) and *S-index* (**Figure 1A**, row 5) approach zero, while the *R*-variables (**Figure 1A**, rows 6 and 4) remain running. Therefore, in this case, homeostasis cares for the injury, fully reduces the stress (*S*-index becomes zero), and returns the system to its main ground state. Interestingly,[16] in spite of the fact that injury and protection can quickly oscillate, *S-index* approaches zero much more smoothly and does not "feel" the quick alteration of the injure parameter (**Figure 1A**, row 4).

In **Figure 1B**, the initial perturbation was somewhat stronger, resulting in the system being unable to return to the main ground state. However, after further trials, homeostasis finds another non-distressing (zero *S-index*) ground state (**Figure 1B**, rows 1 and 2), where injury and distress are vanished, as well (**Figure 1B**, rows 4 and 5).

In **Figure 1C**, the initial perturbation was more stronger, so protection (**Figure 1C**, row 3) cannot fully reduce injury and distress. Nevertheless, homeostasis finds the region of *C*-variables where the system is stable (**Figure 1C**, rows 1 and 2), because protection was able to compensate the injury, but, unlike the previous case, the protection mechanisms should be permanently running. So the system remains damaged and distressed (**Figure 1C**, rows 4 and 5).

Figure 2 shows a situation where the system was heavily injured. We see that protection (**Figure 2A**, row 3) failed to compensate for the injury (**Figure 2A**, row 4) and after short-time damage and stress drastically increasing (**Figure 2A**, rows 4 and 5), *C*-variables leave the life-compatible region (**Figure 2A**, rows 1 and 2) and the system inevitably moves toward death or destruction. We see that crossover to this way can be very sharp. Moreover, in this situation, the behavior of *R*-variables differs considerably from the behavior near the stable states. The system appears to be "crying" in response to the dangerous situation (**Figure 2A**, row 6). Interestingly, a similar situation occurs in the case of an initially strongly stressed system, although the initial injury was small (**Figure 2B**).

It should be emphasized that the decreased protection observed in **Figures 1A** and **B** and **Figure 2** is different. In **Figure 1**, the protection mechanism has done the work and the system returns to its ground state with zero stress and injury, unlike the situation observed in **Figure 2** where protection fails to compensate for the injury and slows down due to the stress level becoming too high.

If a system has a "latent time" between consequent actions ("time of decision making"), differential equations (11a)–(11c) should be replaced by finite-difference equations. Although Eqs. (11a) and (11c) are deterministic equations, the system imitates random *trial-and-error* behavior if the latent time is not very small (**Figure 3**). It should be noted that such a pseudo-chaotic behavior of finite-difference equations' solution is quite typical for many nonlinear

[15] **Figure 1A**, rows 1 and 2 correspondingly.
[16] This is quite typical for the considered situation.

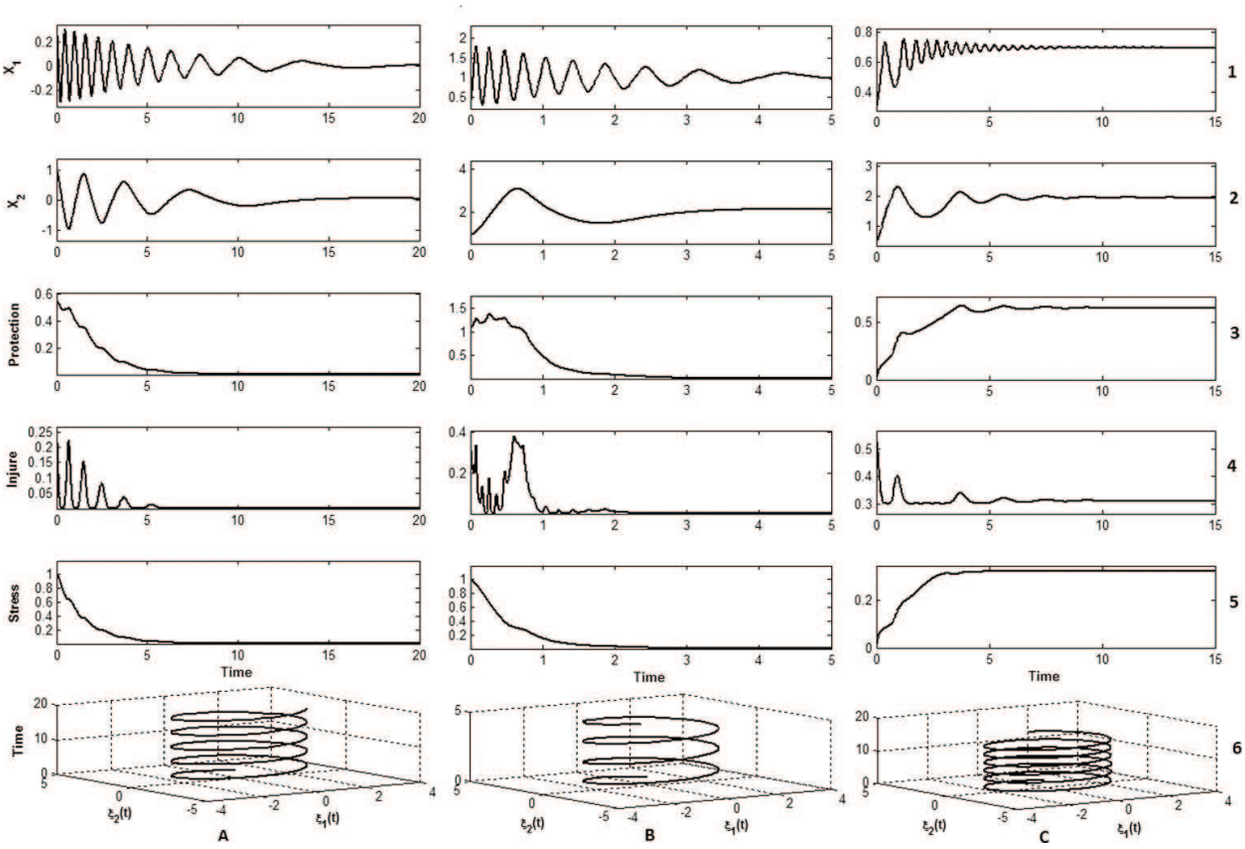

Figure 1. Homeostasis for different initial conditions. Here, x_1 and x_2 are *C*-variables and ξ_1 and ξ_2 are *R*-variables. (**A**) Light injury. (**B**) The system cannot return to the main ground state, but finds another comfortable state without damage and distress. (**C**) Homeostasis cannot fully compensate for injury and distress, but some discomforting stable state exists.

finite-difference equations and it was widely discussed in the literature. A particular example of such a behavior was considered in Ref. [17] and a general explanation of this phenomenon can be found in Ref. [19].

4. Discussion

Feeling of stress or proximity to death is a basic feature of the living organisms and this feature exists already at a single cell [1]. The discovery of homeostasis W. Cannon [3] assumed that homeostasis results from tendency of the organisms to decrease the stress and avoid death. This point is a biological basis for our theory.

It has been shown in Ref. [17] that if system evolution complies with the causality principle and a system state space displays trivial local topology, system dynamics inevitably satisfy generalized Lagrangian equations (2a) and (2b) with an additional "*S-variable*." Since the above conditions are quite general, we believe that they are applicable to the living organisms. In the chapter, we identified *S-variable* with a level of feeling of stress (called *S-index*). It should be emphasized that the feeling of stress or discomfort is not metaphor for biological systems, but real feature of the living organisms (see Sections 1 and [1]). Note that *S-index* is a

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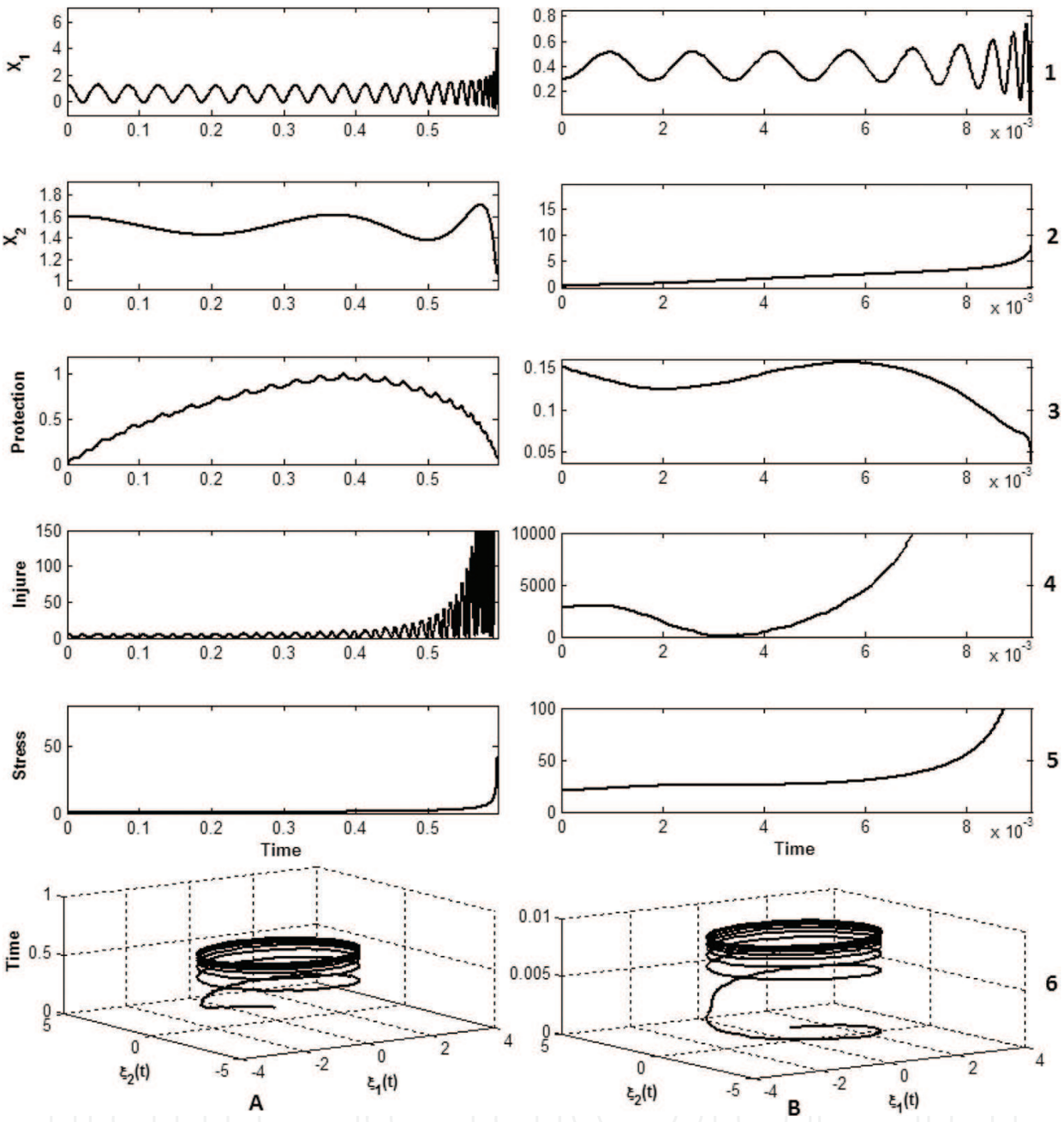

Figure 2. "Death-pathway" of the system. (**A**) System was heavily injured. (**B**) System was strongly distressed (initial *S-index* was high; graph **B5** begins from **20**), although initial injury was small.

phenomenological quantity and cannot be directly measured.[17] It should be noted that such a kind of the phenomenological variables (which cannot be directly measured) is widely used in physics (e.g., "mechanical action" of the physical systems, order parameter in superfluid phase transition, etc.).

Supposing that dynamics of the stress is determined by competition between damage and the protection mechanisms, we have obtained an *S-Lagrangian* and *dynamical equations of*

[17]Note, however, that in medical practice level of stress often is subjectively defined by the patients.

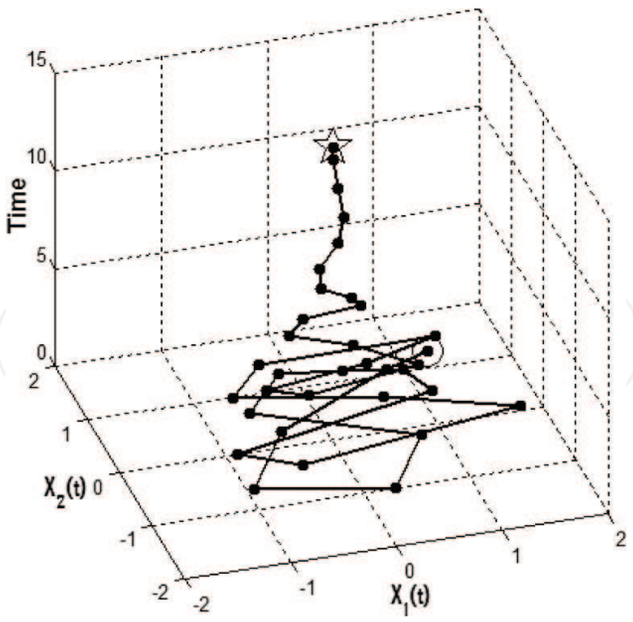

Figure 3. Pseudo-random behavior of the system with latent time of "decision making". *Circle* designates an initial state and *Star* designates the finish state.

homeostasis given in Eqs. (11a), (11b) and (11c). Moreover, since other systems, such as social systems, may also possess distress or discomfort, they may also undergo homeostasis.

Solutions of the dynamical equations of homeostasis show that there are four types of system behavior. In the first, the system generates activity that quickly takes it to the main ground state with zero damage and stress (**Figure 1A**). In the second, the main ground state cannot be achieved; however, the system finds another ground state without damage and stress as well (**Figure 1B**). In the third, homeostasis cannot find the state with zero damage and stress and the system arrives at the damaged and distressed, but stable stationary states (**Figure 1C**). In the last type of behavior, the system cannot achieve any stable state, level of stress dramatically increases, system variables leave the life-compatible region, and the system moves toward death (**Figure 2**). It should be noted that there is a critical value of injure, which leads to fatal instability of a system by violation of the condition (21). Apparently, there is a critical value of the stress as well, so if *S-index* exceeds this value, an organism inevitably moves toward death. Note that near the injured stable states, where $I(\boldsymbol{x}_c,S_c) > 0$, the critical value of the stress may be lower than near uninjured states,[18] that is, injured organism is more sensitive to the stress than the healthy one.

All types of behavior are described by the same system of Eqs. (11b) and (11c) and *S*-Lagrangian, but differ by initial and/or environmental conditions (which are described by parameters of the Lagrangian). It was found that systems exhibiting homeostasis may have at least two types of variables. The first type is *C-variables*, which have stationary values in the stable states of the system. Injury disturbs these values and excites protection mechanisms. The other types

[18]For $I(\boldsymbol{x},S)$ and $A(\boldsymbol{x},S)$ from Eqs. (29a) and (29b), the critical value of *S-index* is obtained from $\frac{\partial\Phi_1}{\partial S_*}J-(\Phi_2(S_*)+S_*\frac{\partial\Phi_2}{\partial S_*})\Gamma=0$.

http://dx.doi.org/10.5772/66473

of variables are *R-variables*, which can run in a stable state without disturbing system comfort. This finding agrees with the experimental data. Examples of the *C-variables* are ATP level, intracellular pH level, intracellular and blood concentration of Na^+, K^+, Ca^+, and intracellular levels of certain proteins (caspases, cytokines, and antioxidants), and so on. Examples of the *R-variables* are blood flow, α-rhythm of brain, heart contraction, brain pacemakers, and so on.

Interestingly, if a system has a "latent time" between consequent actions ("decision-making time"), it imitates random *trial-and-error* behavior. This corresponds to a real situation in a brain. Although the physical parameters of the brain are continuously changing, time intervals that are shorter than the nerve impulse duration (milliseconds) do not have physiological sense. Moreover, decisions in the brain take tens of milliseconds. Therefore, psychological time is more discrete. Consequently, the chaotic behavior of nerve processes inevitably arises in nerve tissue and can serve as the basis of free decision-making target. This creates an opportunity for trial-and-error behavior. A random search will be targeted if instability fluctuations increase with increasing deviation from the optimum. For example, on/off switching of voltage-dependent channels in neurons can occur more than 100 times/s, which is an adequate speed for searching for the homeostatic optimum. This mechanism ensures that obstacles can be overcome [20]. Therefore, chaotic behavior, illustrated in **Figure 3**, can play a crucial role in homeostasis. It should be emphasized that this chaotic behavior is not determined by some stochastic process, but rather is governed by deterministic equations.

The simulation results displayed satisfactory agreement between the biological properties of homeostasis and theory. **Figure 1** demonstrated direct homeostasis for a weak injury and indirect homeostasis with the restructuring of some parameters for more severe damage. Damage aggravation caused the model to transfer to a working state, although the discomfort was not completely removed. Modeling was also amenable to the process of system destruction (**Figure 2**), with the behavior of the model depending not only on damage severity but also on "subjective" assessment (i.e., death threats).

The theory predicts that increasing of the stress itself (even without internal injure) leads to disturbing of the physiological parameters, that is, to physiological damage of the organism. This prediction is supported by the recent experimental data, which show that both in human and in animal models, the expression of many genes changed in response to early and to late stresses [21].

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