

# Endogenous Generation of Goals and Homeostasis

Lev E. Tsitolovsky

Bar-Ilan University, Ramat Gan, Israel  
tsitolovsky@rambler.ru

**Abstract.** Behavior can be both unpredictable and goal-directed, as animals act in correspondence with their own motivation. Motivation arises when neurons in specific brain areas leave the state of homeostatic equilibrium and are injured. The basic goal of organisms and living cells is to maintain their integrity and life, and their functional state is optimal if it does not lead to physiological damage. This can somehow be sensed by neurons, and the occurrence of damage elicits homeostatic protection to recover excitability and the ability to produce spikes. It can be argued that the neuron's activity is guided on the scale of "damage-protection", and it behaves as an object possessing minimum awareness. We have no possibility of determining how the cell evaluates its own states, e.g., as "too little free energy", or in terms of "threat" to life. In any case, the approach of death increases cellular efforts to operate. For the outside observer, this is reminiscent of intentional action and a manifestation of will. Thus, homeostasis may evidently produce both maintenance of life and will.

**Keywords:** goal-directed action, adaptation, consciousness, neuron, damage, protection, regulation, homeostasis

## 1 Introduction

The main difference between living creatures and non-living things is generally considered to be the capacity to reproduce and give offspring. But understanding the laws of heredity has not clarified the mysteries of individual life, and properties of living systems sharply differ from those of non-living ones. Firstly, living beings actively counteract their degradation in a constantly changing environment. And secondly, in living systems the relationship between cause and effect is a paradoxical one: organisms are characterized by poorly predictable motility, which is supposedly managed by their internal motives. An element of subjectivity is attributed to any living being, while higher animals manifest consciousness – unless of course this is an epiphenomenon. Consciousness resists attempts to give it an exact definition, except a trivial one, such as stating it is non-material. However, the most accurate definition of life belonging to M.F.X. Bichat is also trivial: "those sets of functions which resist death" [1]. Both of these mysteries are based on individual life and can have a common cause.

## 2 The Brain as a Construct and as a Collective of Neurons

The brain is the most complex organ of the organism, the neuron is the most complicated cell, and the subjective world of the brain stores the complexity of the objective world. Therefore, the study of behavior, and conscious behavior in particular, has not yet achieved decisive progress. On the one hand, images of whole-brain activity are available for monitoring, as well as the activity of individual neurons in different conditions. Comprehensive maps of neural connections in the brain, connectomes, are intensively elaborating, and the diversity of chemical processes in nerve cells is also widely studied. There are now means available of local impact on the intracellular apparatus through the optogenetic method in behaving animals, as well as cell type-specific knockout strategies, and so on. However, the question how does the brain generate subjectivity – has remained a mystery.

In earlier times, the brain was considered to be a highly complex network consisting of simple neurons. Any long-term memory-trace was thought to be necessarily embodied in some steadfast changes in the brain. Correspondingly, memory could be considered as the establishment of new connectivity in the space of the brain, i.e., as the change of synaptic efficacy. This was suggested by I.P. Pavlov [2], who proposed that during conditional reflex acquisition, a path is formed (as if blazing a trail or a short circuit) between conditioned and unconditioned representations of cortical signals. Pavlov likened this process to the establishment of a link between subscribers of a telephone station – the most complex artificial system at the time. It was believed that during training, the

structure of the brain is being modified both through the formation of new connections between neurons and changes in their efficacy. D.O. Hebb suggested the probable mechanism of synaptic efficacy changes after training [3], and notions of such plasticity and memory have for a long time been synonymous with synaptic plasticity – with no consideration of other forms of plasticity, like the intrinsic excitability changes of neurons [4]. While this line of mainstream 20<sup>th</sup> century neuroscience explains features of behavior as a system of signals and reflexes, it is interesting to note that in a fundamental review of the past century's achievements in the neurosciences [5], among the 349 references there was no record of the work of Pavlov.

Certainly, as a first approximation, neurons can be seen as components and the brain as a construct. But the idea of synaptic plasticity meets difficulties in furthering a plausible explanation of the facts of memory recovery after brain injury. Although synaptic efficacy does depend on current behavior, chemical processes beginning in activated synapses can also interact within a neuron, and therefore the efficacy of a synapse depends on other simultaneously activated synapses. If a single neuron recognizes a synaptic pattern as a whole, memory does not exist at all on the synaptic level. In principle, a neuron could regulate its excitability through the tuning of potential-dependent membrane channels. Where else, except in the chemical substratum, could temporarily lost information be maintained? The only possible 'connectivity' of a single neuron is connectivity in the world of chemical reactions. Neurons possess a number of biochemical devices: multifarious chemoreceptors, ion channels, sensors, kinases, carriers, motors, contractile proteins, pumps, gap junctions, etc. Brain cells are the most complex cells in the body. It's also known that memory may stay intact while brain morphology is strongly reorganized in the course of individual development, as for instance during insect and amphibian metamorphosis. On the other hand, experimental substantiations of the idea of memory localization within neural network structure do not hold water (for a review see [6]). At present, viewing memory in terms of fixed changes in network structure after learning (i.e., memory as something akin to a whole picture-gallery written on a single art canvas) is mainly of historical interest. Besides, none of the "hard problems" (such as why aware performance is always integral and unified, why the principle of localization is not realized in the brain, or how neuronal activity is transformed into feeling) may be explained from the viewpoint of the brain as a construct.

Strictly speaking, there is no way to determine whether behavior consists of simply responding to signals, or if it's freely generated by the brain. However, if the reactions of the brain would be predetermined by its structure, and depended solely on ephemeral differences in initial conditions, it would lead not only to variability, but also to chaotic behavior and would impede goal-directed action. The brain is not a construct made up of neural and glial cells. It is a collective of primitive organisms – neurons. Networks of such neurons are capable of short-term reorganization after evaluation of current conditions in the environment. In this case, memory of individual neurons is a code in a chemical language, although this code is still not deciphered.

First doubts in the decisive role of brain structures in the organization of its functions actually appeared in the works of K. Lashley [7], the teacher of D.O. Hebb, although the idea of Hebb agrees more closely with the theory of I.P. Pavlov. On the other hand, at the time Hebb's idea of the synapse appeared, P.K. Anokhin had already formulated the theory of functional systems [8]. In Anokhin's theory, the brain was interpreted as a collective of neurons capable of individual behavior [9]. Indeed, it was discovered that neurons transiently reorganize their excitability in accordance with learning [10,11]. This understanding of the role of single neurons in behavior has begun to be recognized in scientific literature only 50 years later [6,12-20].

### **3 Systemic Approach to the Problem of Goal Generation**

Behavior, at least in its simple forms, directs efforts to satisfy metabolic needs associated with the deviation of vital functions from their physiological norms. Needs are at the heart of motivations, which is already not a purely physiological concept with measures and dimensions. Motivation is the subjective attitude of a living creature in relation to its current or future physiological state, and it gives rise to goal orientation: to achieve an optimum of some kind for vital functions. The main objective of an organism is the preservation of its own life.

A living being is an integrity (functional, structural, dynamic, etc.), the elements of which have properties that differ from the properties of the whole. Consciousness is not additive, but hierarchical, and has internally interdependent distinctive features – it is also an integrity, like life. This requires it to be analyzed within the theory of systems. By definition, a system united by a common function is called a functional system [8]. To achieve an adaptive result, the functional system of current adaptive behavior establishes a temporary association of particular machineries of the body. This association is directed to the satisfaction of needs, and the elimination of mismatch

between the target and actual conditions of the system. The directedness in the operation of a functional system may appear spontaneous because of its unpredictability and orientation to a goal. On the other hand, its autonomy is reflected in the maturational process within the functional system – it consists in the assumption that the need for an adaptive result, the purpose of obtaining this result, and the decision-making to undertake activity is a developmental process within the system, in the depth of its structure and at the heart of it lie metabolic and hormonal processes. Therefore the system is almost isolated from the outside world during its decision-making.

The properties of the functional system of behavior do not explain the nature of conscious states, but give hope of improving our understanding of them. The immanent traits of consciousness, such as the subjective nature of feeling, the emergence of a goal, and free will are so paradoxical that sometimes it appears to be incompatible with the laws of logic and the fundamental laws of physics. The existence of arbitrary actions means that the power of thought can control material objects (e.g., muscles). The alternative can only be the assumption that behavior is predetermined by initial conditions, i.e., described by reflexes.

In the framework of functional systems, a different approach is taken. In analyzing behavior, motivations and goals play a central role. The result that should be obtained at a given time, according to P.K. Anokhin, depends on the dominant motivation of the organism, its information about the current state of the environment, and the memory of the past results of behavior in similar conditions [8]. Motivation to achieve specific optimal conditions somehow modulates the generation of actions, until an optimal state will be obtained. In their primitive form, motivations occur in the system prior to the formation of memory, as becomes evident based on the existence of genetically predetermined characteristics of signals of inherent behavior [21]. Therefore, memory and motivation are different, independent entities. However, the phenomenon of motivation should be explained as a physiological phenomenon: transformation of an objective need into a subjective motivation. And above all, we must understand how does a living being determine what result is relevant for the system at present.

## **4 Useful Result as Homeostatic Recovery**

The cell's functioning is designed to maintain its integrity, and goal-directed behavior is intended for the preservation of the organism. If we consider only individual life, rather than the existence of species, it is homeostasis and not heredity which makes life alive, and the end of homeostasis leads to death within seconds. Indeed, the system is alive until homeostasis maintains the system's integrity in the presence of perturbing influences. The presence of homeostasis-based motivation turns an object into a subject with its own behavior. Thus, the mystery of arbitrary action may be disclosed by exploring homeostasis.

Under the homeostasis, we mean the ability of living organisms to maintain viability, i.e., stability of physiological functions in a changing external environment. Homeostatic regularities can be traced on the level of particular parameters of a cell, cells in general, physiological systems of an organism, an organism as a whole, populations, species, and ecological systems. Most important for present purposes is the homeostasis of the cell and the organism.

### **4.1 Homeostatic Control of Viability**

Living beings actively oppose their degradation in the continuously changing environment by means of homeostasis [22] that supports the body's intrinsic constants within acceptable limits. Maintenance of vital activity looks like a manifestation of the mystical "vital force", which prevents disorder and violates the laws of thermodynamics.

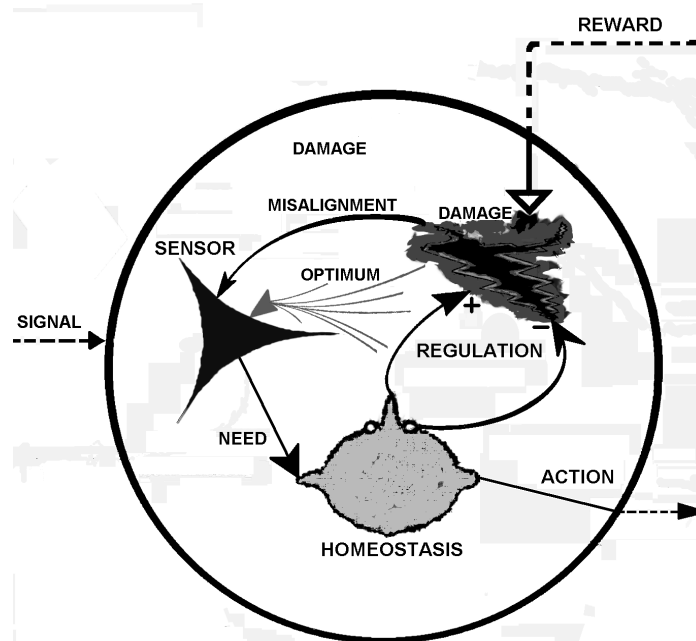
The status of the internal environment is not sustainable for all life. Homeostasis does not simply restore the original state, it adapts to external influences. In particular, there are different solutions for the same metabolic problems. Not all parameters of the internal environment are equivalent to cellular homeostasis. Living beings reconfigure their homeostasis in order to maintain some of the higher order criteria that distinguish the living from the non-living. If the value of a deviated parameter is not restored, the cell may be able to maintain itself by restructuring the optimum of other parameters. For example, stabilization of neuronal activity can be achieved by configuring both efficiency of synapses and excitability [23].

Homeostatic functioning depends on sensors (fig. 1), which register the deviation from the norm. The sensor is usually a protein molecule that contains the chemical group sensitive to the given quantity. There are known sensors

for temperature control, oxygen concentration, osmolality,  $\text{Na}^+$ ,  $\text{K}^+$ -exchange,  $\text{Cl}^-$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Fe}^{3+}$ , cAMP, NMDA, and others (See [6]).

The nature of the sensor for damage-recovery viability is not very clear, though there are options which are significant for survival of whole cells and even significant for the whole organism. These are energy (ATP level), excitability, intracellular pH, concentration of certain proteins (caspases, cytokines, antioxidants). These cannot be disregarded by highest sensors – this might threaten with death. For the functions of a neuron, the integrity of its spike-generating mechanism can be considered as the most important manifestation of its health.

Fig. 1. illustrates the role of homeostasis in the generation of goals and actions. Appearance of a metabolic flaw triggers the homeostatic device to compensate for shortage. Sensor of the cell's state tracks the difference between the normal and the current states (determining the goal of regulation), and sends the discrepancy to the unit of homeostasis. However, the resources of homeostasis may not be sufficient to restore disturbed functions. For example, shortage of metabolites for oxidative phosphorylation may aggravate the mismatch and will cause tissue damage. This could be prevented by the reception of necessary metabolites from the environment (e.g., replenishing the stockpiles of food, water or oxygen). To do this, the environment must be included in the interaction.



**Fig. 1.** Diagram of endogenous decision-making without the participation of memory. Dotted lines show the optional influences: external signals may or may not arrive, and the signal to act can be subliminal. The decision-making process, temporarily isolated from the environment, is limited by the bold circumference. “+” and “-” refer to the management of a variable in opposite directions.

The question is – how does homeostasis reach the optimum? If it is algorithmically pretuned by the genetic apparatus, the body needs to recognize the current situation and to select a genetically predetermined variant of protection. However, this would create enormous loading on the genome, since the number of possible optima can be as high as there are non-lethal states of the environment. In addition, homeostasis may be improved with experience [24], and genetic defects often have a limited impact on the relevant paths of functioning, since homeostasis is capable of compensating many such defects [25,26]. It is possible to assume spontaneous recovery to a sustained state. If so, homeostasis is the process of relaxation to minimize the damage to viability, and somehow, by means of a still unknown physical process, it turns an inanimate system into living one.

At first glance, the mechanism of homeostasis is not too complicated. In theoretical works, the problem is usually solved by the introduction of positive and negative feedback loops between the sensor and the metabolic flaw [e.g., 27,28]. To overcome the local minima, test signals are used in adaptive control systems. Instability of such systems makes them not quite predictable, like systems really observed in living nature. Known attempts to date at mathematical modeling of homeostatic regulation consider only direct homeostasis, and the optimum is set in advance: homeostasis for each variable is introduced through regulation of individual controllers. However, when

homeostasis starts working against a permanent factor of environment, the caloric cost of compensation may turn out too high. To avoid this, living systems themselves assign their optimal parameters, depending on the actual situation.

#### 4.2 Homeostatic Control of Behavior

Motivation stems from a shift of internal constants from their optimal values and is therefore related to transient injury or to the threat of injury. Thus, motivation is associated with the property of living tissue to heal itself, and in a broader sense, with its need to survive, i.e., with homeostasis. The final result of behavior is a recovery of homeostasis. Motivation has the same function for the organism that homeostasis has for the physiological constants of the organism. Dissatisfied motivation augments damage of specific neurons, while reward inhibits and protects them from damage (see [17]). Motivation arises when neurons in specific motivational areas leave homeostatic balance, are damaged, and need restoration. This is true at least for basic biological motivations, such as thirst (through osmoreceptors), hunger (through energy metabolism and glucose sensors), sex (via sensors that are configured on the deleterious effect of the steroid hormones), respiratory motivation (through CO<sub>2</sub> and pH sensors), and defensive motivation (with the direct participation of irritants, damaging not only the body, but specific brain neurons through their pathological activation via the receptor of excitatory amino acid, GABA, and potential-dependent Ca<sup>2+</sup> channels).

Deviations in metabolic equilibrium are normally compensated by homeostasis, but if the adaptive response cannot be generated internally (say, because of a shortage of energy, water or oxygen), it must be achieved via interaction with the environment. Temporary deviation from the norm (damage in Figure 1) and homeostatic compensation are integral components of a functional system of behavior. Deviation of internal parameters from optimum leads to damage, activation of specific neurons, and to an internal motive to act, while a useful result usually inhibits neurons in the motivational centers, protects them from damage, and causes an euphoric effect [17].

In the systemic approach, the cause of behavior lies in the endogenous activity of the nervous system, and is not a passive reaction to external signals [8,29]. It is likely that the occurrence of conscious action arises from the ability of a living system to counteract its degradation, and thus to turn its current status in a stationary one. Motivation looks like a generalized desire to live, and may turn into conscious decisions. Therefore, arbitrary actions can originate in the homeostatic compensation of damage.

Maintaining optimal conditions on a specific level, and not on another one, is formed in the system through autonomous tools for evaluating the necessary conditions for life. Living beings need to be able to evaluate their own state. A desired outcome of behavior represents the achievement of an optimal state of the system, with no violation of its integrity and stability. The organism reduces the deviation of its internal parameters from the optimal conditions and thus ensures the stability and integrity of the body. Accordingly, the best state of the system will be the state that presents the smallest load on homeostasis. However, the autonomous mechanism of need and goal evaluation remains unclear until we have not revealed the reasons and conditions of maintaining the optimum on a particular level, and not a different one.

#### 4.3 Neuron as a Living System

Primitive sentience and goal-directed behavior could possibly be present in a single cell, judging by its attractive taxis, avoidance behavior, predator-prey behavior, and even learning [30,31]. Probably, cells forming the body do not become its components and do not cease to be individual organisms. Particularly, the capacity to perceive, remember, and behave certainly occurs already on the level of a neuron [9].

In special experiments, learning may be artificially directed to a restricted population of neurons, even to a single cell, and hence a neuron may be seen as a full-fledged system [6]. Certainly, in natural conditions, many neurons participate in the same function. However, in exceptional cases, a single neuron has power over an entire behavior. Moreover, not only a single neuron, but a single action potential in a single neuron may be responsible for the action of an entire animal [6]. Sometimes brain robustly controls goal-directed behavior using signals so small they're at the boundary of molecular processes.

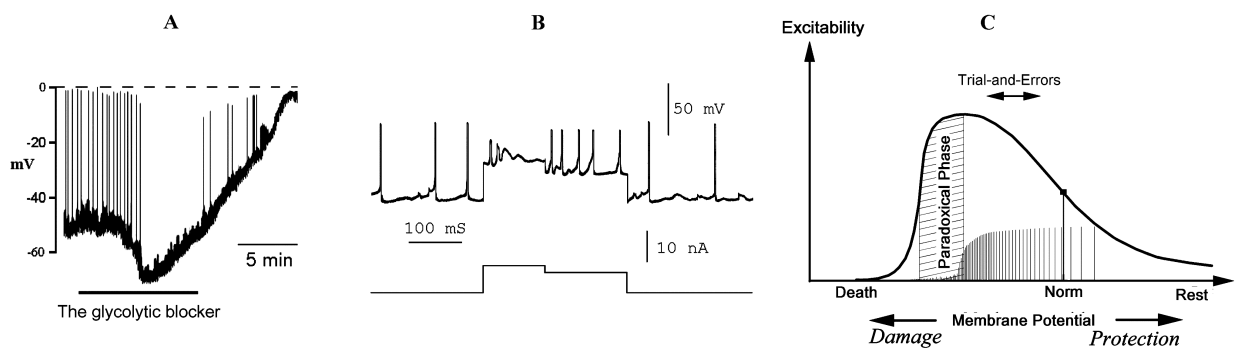
We have ascertained [10,11] that after learning, neurons appear to evaluate the significance of the input signal (not only its strength), transiently change their own excitability, and only later compare the magnitude of the impact and threshold. This means that neurons decide whether or not to participate in a given behavior. Thus, neurons can

be selectively activated or inhibited for one stimulus, but not for another one. A neuron generates a more powerful spike if a stimulus with greater biological significance acts on it, and in this case evokes a stronger postsynaptic potential in the target neurons. This extends the possibilities of an individual cell to participate in various types of activity during different situations. In addition to the ability to learn, an individual neuron tends to avoid damage and shows features of purposeful behavior. Further analysis has revealed that a single neuron can even display drug-dependence to heroin [32]. Recently it was established that neurons exhibit selective excitability not only as a result of learning. Excitable membrane plasticity is a reason for neuronal reaction selectivity during visual image recognition and during selective responses to the preferred orientation of whisker angular deflection [33].

Artificial incongruity of homeostasis leads to injury, causes increased activity, and this in turn leads to the aggravation of damage (fig. 2A). Usually the reaction of nervous tissue is proportional to incoming excitation. On the other hand, superfluous excitation and neuronal damage are closely connected (excitotoxicity) [34]. Thus, the activity of damaged tissue generates action potentials, which, however, by their nature are non-specific (apart, of course, for the locus of damage), and are not directed to getting an adequate result. However, this kind of activity could generate trial-and-errors (§ 5).

Excessive excitation damages the nervous tissue, violates its function, and reduces activity (Fig. 2B). There is an area of paradoxical status for excitable tissues, where excitation is reduced due to damage, but irreversible deterioration of the state has not yet occurred. In this case, inhibition (or decrease of excitation) counteracts the injury, paradoxically recovers excitability, and promotes the emergence of action (Fig. 2C, parabiosis according to N.E. Wedensky [35]). Properties of homeostatic compensation make it tempting to consider homeostasis as a driving force, which induces actions directed against actual or anticipated damage: protection against damage partly improves output characteristics of neurons, and helps to ensure health-giving results from the environment. Thus, a single neuron can live, learn, want, suffer, delight, and tries to survive [6]. Exertion of neuronal metabolism, leading to damage compensation and goal-directed behavior, is rather appropriate for the description of conscious actions.

However, the separate regulation of individual constants (temperature, oxygen consumption, osmolarity, intracellular calcium level, etc.) does not explain the general control of cellular activity during aware decisions. Homeostasis somehow regulates a certain general quality of the neural cell, such as the extent of damage to itself. A neuron somehow regulates its major demand, the avoidance of injury and the aspiration to life, as it shifts towards death or towards life.



**Fig. 2.** Generation of action potentials by a neuron as a result of homeostatic recovery after damage. **A.** Metabolic disturbance changes electrical activity in an inspiratory neuron in the brainstem-spinal cord preparation of rat. The glycolytic blocker iodoacetate irreversibly abolishes respiratory rhythm and elicits a hyperpolarization, followed by a prominent depolarization. Dotted line indicates zero level of membrane potential, when the cell is near its death. Spike amplitude decreases irreversibly. Calibration in the figure. **B.** Paradoxical effect of decrease in excitatory current on intracellular activity of a neuron of the parietal ganglion of *Helix*. The neuron was hyperdepolarized by the direct excitatory current and failed to generate spikes. Decrease in the degree of hyperdepolarization improved the neuron's state and recovered its ability to generate spikes. At the top: spontaneous neuronal activity and response to the direct current injection; at the bottom: value of depolarizing current. Calibrations in the figure. **C.** A schematic illustration of the dependence of neuronal excitability on excitotoxic influences. Abscissa: shifts towards damage or protection (or, in the first approximation, a membrane potential). Ordinate: the change in excitability. A paradoxical phase borders the interval in which hyperpolarization or decrease in the level of damage leads to reaction augmentation. The changes in amplitude and frequency of spikes are shown along the abscissa axes. (Source: [6]).

A sense of the quality of its own state, that is, the ability to distinguish between approaching death (negative sense) and moving away from it (positive sense), can be regarded as the distinctive feature of all life. A neuron can hardly appreciate its condition in a more complex manner than in the category of “closer to death” (worse) and “farther away from death” (better), or in terms of physiological concepts like “excitation” and “inhibition”, or in the language of physical parameters, such as “not enough free energy” and “sufficient free energy”, for example. Probably only such primitives may represent “qualia” at the cellular level. Subjective feeling within these material limits can be considered as the value of a common parameter associated with its shift in the directions of death or survival.

Thus, a neural cell is a primitive organism, living, behaving, suffering, and dying in the brain. One way or another, it feels injury, strains its metabolism, improves its state, and restores the function of spike generation. 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’s self-maintenance are inseparable, and the grouping together of sentient neurons may underlie complex behavior on the higher level.

#### **4.4 Functional Neuronal Ensembles**

Only in exceptional cases does a single neuron control holistic actions, and these can hardly be evident at the level of the organism. During the transition from unconscious to conscious actions, the number of cells involved usually dramatically increases [36]. In natural conditions, their coordination is enhanced when neurons are combined in a joint task, for example, when responding to biologically meaningful signals [37], generating motor activity [38], and during the performance of goal-directed behavioral acts [39].

Neurons in the brain remain confined to one skull, receive the same kinds of rewards and punishments during their life, learn similar skills, and therefore react uniformly, even without any agreement. However, nearby neurons respond more in concert than distant ones, because of direct electrical links (gap junctions) between the protoplasm of neighboring cells [40]. In fact, the blockers of direct contacts cause psychosis and hallucinations [41].

However, neurons recover coordinated decision-making even after brain injury, when their coherence is artificially disturbed. It is especially surprising that the organism does not make use of such unique stability in daily life. Although (days or even months) after brain injury, behavior can be partially or fully restored, in the wild the injured animal will likely not be able to survive that long without artificial nursing. It is possible that the stability of functions in conditions of brain damage stems from the need to assemble a whole functional system from the many components of the consciousness-associated neurons. Naturally, carrying out this assemblage requires additional time. Indeed, conscious actions run more slowly than unconscious ones, and the latency of the first spike in aware responses is usually increased [42,43].

Activity of neurons in the brain is reminiscent of collective activities in a pack of animals, which depend weakly on the efforts of single members and qualitatively surpass them in accuracy and complexity with respect to their individual activities [44]. Synchronization of activities in the nervous tissue is much more accurate than the dispersion of time propagation of nerve impulse transmissions in the brain. Although each neuron generates processes which have an element of chance, instability is not averaged in large populations of neurons and in behavior [10,11,45]. Collective behavior of a group as is well known is qualitatively different from the behavior of each of its members. For example, collective behavior may contradict the interests of its each member. However, the collective behavior of neurons still awaits to be explored from this perspective.

## **5 Instability, Search for Optimum, and Free Will**

Unlike artificial computing systems, the human brain does not need external programming for effective management of the body in complex environments. Before the final decision is made, we are at liberty to freely make a choice, or at least so it seems. The resulting behavior is unsteady and poorly predictable if one proceeds from the initial conditions and, therefore, there is an assumption that it depends on the subject's free will. Similar instability is demonstrated during modeling after introduction of the specimen steps that allows searching of the optimum value. However the adaptive nature of behavior means that free choice cannot be explained only by

fortuitousness. For example, trials and errors can serve as an example of purposeful behavior only if this consists of deliberate actions, and not pure coincidence.

The variability of neuronal activity actually exists as a relevant category. Instability is observed at the very primitive levels of life and can have beneficial meaning. It is not necessarily noise, which impedes the brain in its functioning. The unsteadiness of behavior could be based on chaotic activity of a complex system of the brain, thermodynamic instability, or even quantum uncertainty. Instability is higher in higher animals, in higher nerve centers, during wakefulness and deliberate behavior [17,46], and in difficult situations instability grows [47]. Damaging factors increase the instability of neuronal activity, while factors that prevent damage reduce instability, and this applies to molecular processes, neuronal activity, behavior, and psyche [48-51]. In this way, transient damage possibly participates in brain function.

One of the sources of instability may be the counter-regulation of homeostatic variables (+ and – in the Fig. 1). Usually several independent factors control the balance required for the maintenance of an intracellular parameter [see 6]. So, many chemoreceptors and potential-dependent channels manage each neurotransmitter. Several proteins control the metabolism of cAMP. During translation, synthesis and decay are regulated separately, transcription is controlled by co-receptors and co-activators,  $\text{Na}^+/\text{K}^+$ -ATPase is controlled by external and internal gates, two regulatory proteins regulate metabotropic glutamate receptors and intracellular iron level, etc. In particular, cell chemotaxis is regulated by switching the direction of rotation of the molecular motor of flagella (via methylation and demethylation), and the higher the variability, the stronger the chemotaxis [52]. When *Drosophila* larvae search for the attractant, the length of the sequential steps agrees with the change of the attractant intensity, and twists are directed accidentally [53]. An example of a similar process in inanimate nature is the selective diffusion of Brownian particles to the cold pole [54]. Counter-control of each variable creates the possibility of molecular trial-and-error, paradoxically accelerating the regulatory process.

The degree of variability is probably connected with alteration in the state of damage-protection of cells. Modeling has shown that reaching the optimum can be achieved if the fluctuations of instability increase together with growing deviations of the quality criterion from the optimal state of a system [45]. The problem is solved by a simple rule: if you feel bad, do at least something. Optimal value, i.e., the goal, serves as the value of the criterion in which fluctuations are zero. The goal is thus a quasi-stationary status, and the sequence of steps as a whole is the goal-directed action. Search in such a system is far more effective than a random quest, and directed at a goal; though the latter is not predetermined beforehand, and if there are a quantity of targets, the system can reach any of them.

Search for the optimum can be organized even without the use of a memory device. However, homeostasis would operate more effectively if it could be improved as a result of experience. Indeed, homeostasis supports the steady state of a neuron under conditions of adaptation to the external environment, when acquired memory has irreversibly changed the cell's internal state. Besides, moderate damaging impacts enhance the effect of homeostatic compensation of a stronger damage caused after the first [55].

There is no guarantee that the described mechanism of choice really takes place in the nervous system. However, the principled possibility of explaining goal-directed choice through free search that depends on disagreement indicates that the existence of free will is not inconsistent with the laws of nature, and thus, the task is solvable.

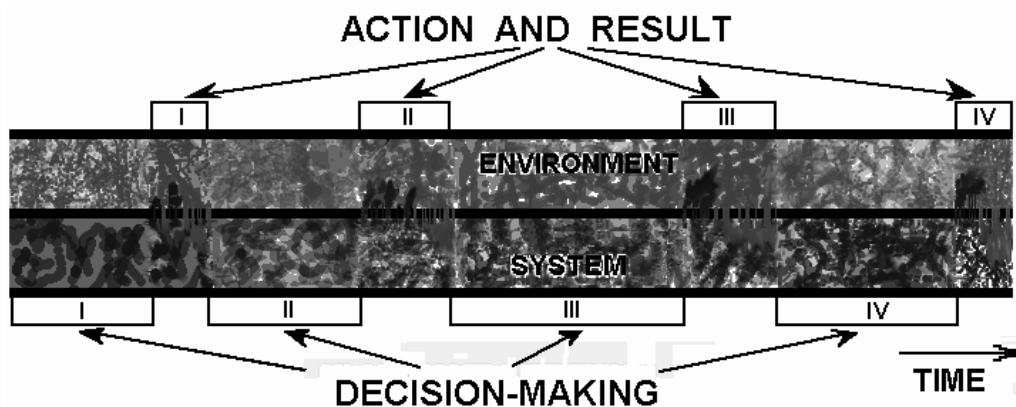
## **6 Stability of Physiological Functions and Conservation Laws of Physics**

Homeostatic compensation occurs spontaneously, the cell spends on recovery the lion's share of its stored energy and, of course, although counter-intuitive, entropy is increased after recovery. So, in the waking state, consumption of ATP is three times higher than at the rest [56]. Cerebral metabolism increases before and at the time of decision-making, as demonstrated by the increase in brain temperature of warm-blooded animals (usually stable parameter) during that period of time [57]. It should be expected that the sustainability of living systems is based on processes that determine the integrity and self-organization of inanimate nature. Simple (or direct) homeostasis may be organized in accordance with Le Chatelier's principle, i.e., on the basis of conservation of energy. Counteraction to small rebalancing can be provided by molecular complementarity, while interaction of adjacent elements should engender cooperativity in their behavior [58], and instability will ensure transition from a local minimum to a global one. However, homeostasis is not reduced to recovery of the norm. Displacement on the scale of "damage-protection" is not one-digit, specific decisions are not predetermined beforehand. Therefore, a functional system of



behavior cannot possess Lyapunov's stability, and its equilibrium does not correspond to the free energy minimum [59]. Possibly, stability of living systems is maintained by diverse conservation laws (conservation of linear momentum, angular momentum, electric charge, and even quantum conservation laws).

These laws are realized only in isolated systems and we may suggest that living systems are temporarily thermodynamically isolated from the environment during homeostatic recovery and decision-making. Living systems are open systems, for example, when they accept energy or substances from the environment or during output action generation. Nevertheless, it can be assumed that the control system of the organism is isolated and separated from the environment while making a decision (Fig. 3), during which the living system practically does not share any energy, matter or information with the environment. This time interval is sufficiently short compared to the period when the system interacts with the environment (these intervals are exaggerated for clarity in Fig. 3), though the relaxation periods of spontaneous molecular fluctuations that subserve decision making are even faster.



**Fig. 3.** A functional system isolated from the environment makes decisions, operates, and receives results, as shown (schematically) in four consecutive goal-directed actions. Solid boundaries between the system and the environment designate isolation periods, while gaps in the bold line denote interactions. The isolation interval begins after the impact of the system on the environment and reception of the metabolic effect of external signals; the same interval ends after decision-making. Intense patterns show the temporal developmental status of the biological system (below) and the state of the environment (top).

The extent of communication between the system and the environment has an influence upon the implementation of conservation laws in this system. As is known, consciousness is subjective, detached, isolated from the outside world, and the main distinguishing feature of conscious behavior is the autonomy of its occurrence. Through that, the system is not necessarily separated from the environment by a physical barrier. Rather, it simply acts independently and, from time to time, does not reply to the environment (Fig. 3). During the time of transient isolation, neurons recover their metabolic mismatch, while the brain at this time continues to generate spikes, but does not generate an output action. Probably, this temporary isolation creates a detachment of consciousness from the environment, and the signs of consciousness arise in the living system at the time intervals when the functional system of behavior becomes temporarily isolated. The conservation laws of physics that are not relevant for the open biological system can be effective when the system autonomously decides to get a useful result for sustaining its vital functions.

## 7 Relationship of Life and Consciousness

The nature of subjective feelings, goals, and arbitrary actions is still the greatest of mysteries. Development of the theory of homeostatic systems regulating optimal parameters of their own state gives hope to solve the problem of senses, as homeostasis is the key mechanism that keeps the system alive. Most likely, the emergence of consciousness as an isolated state separated from the environment is a consequence of the unique vitality of biological systems. Individual life probably by necessity has to evaluate its own integrity, and the process of maintaining its optimality is indistinguishable from goal-directed actions. Perhaps life awakens as the capacity to sense one's own state and its health, and the process of homeostatic compensation is a manifestation of the will to live.

Arbitrary actions may be generated as the result of effort by the homeostatic device during compensation of damage. Augmented compensatory metabolism is a driving force against damage. Homeostasis improves the functional condition of damaged neurons and restores their excitability. However, in cases where the damage cannot be completely compensated by available resources, metabolic problems may be solved through actions directed at the environment. The resulting goal-directed behavior will for outside observers look like a manifestation of motivation, the desire to live, and is consistent with conscious decision-making.

Optimal status will correspond to conditions that are not life-threatening and do not involve attempts to reorganize structure and function. Minimum homeostatic load could serve as a criterion for this state. Collective behavior of a quantity of such systems gives rise to more complex forms of consciousness. The brain concentrates in itself the capacity of all living objects to evaluate its own state and make an effort to survive.

## References

1. Canguilhem, G: Marie-FranGois-Xavier Bichat. In: Dictionary of Scientific Biography (Ed. Gillespie CC), pp. 122-123. New York Charles Scribner's Sons (1973)
2. Pavlov, I. P.: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex. Translated and Edited by G. V. Anrep. 142p London: Oxford University Press (1927)
3. Hebb, D.O.: The Organization of Behaviour. Science Editions. New York: John Wiley & Son (1949)
4. Sehgal, M., Song, C., Ehlers, V.L., Moyer, JR.: Learning to Learn – Intrinsic Plasticity as a Metaplasticity Mechanism for Memory Formation. *Neurobiology of Learning and Memory*, 105, 186-199 (2013)
5. Albright, T.D. Jessell, T.M., Kandel, E.R., Posner, M.I.: Neural Science: A Century of Progress and the Mysteries that Remain. *Cell*, 100 (Supplement), p.1-55 (2000)
6. Sandler, U., Tsitolovsky, L.E.: *Neural Cell Behavior and Fuzzy Logic*. 478p, Springer, USA (2008)
7. Lashley, K.S.: «Studies of Cerebral Function in Learning», *Journal of Comparative Neurology* 79, (1943)
8. Anokhin, P.K.: The Reflex and Functional System as Factor of Physiological Integration. *Fiziol. Zh. USSR, Moskow*, 35, 491-503 (1949)
9. Anokhin, P K: Systems Analysis of the Integrative Activity of the Neuron. *The Pavlovian Journal of Biological Science*, 19, 43-101 (1984)
10. Tsitolovsky, L.E., Guselnicov, V.I.: Non-Classic Neuron State. *Biol. Nauki* 10, 36-47 (in Russian) (1974)
11. Tsitolovsky, L.E.: Integrative Activity of Neural Cells during Memory Recording. *Usp. Physiol. Sci.* 17, 83-103 (in Russian) (1986)
12. Ratushnyak, A.S., Zapara, T.A.: Principles of Cellular-Molecular Mechanisms underlying Neuron Functions. *J. Int. Neurosci.* 8, 453–469 (2009)
13. Tsitolovsky, L.E., Babkina, N.V.: Neurons Evaluate both the Amplitude and the Meaning of Signals. *Brain Res.* 946, 104-118 (2002)
14. Arshavsky, Y.I.: Cellular and Network Properties in the Functioning of the Nervous System: from Central Pattern Generators to Cognition. *Brain Res. Rev.* 41, 229-267 (2003)
15. Steven, S.: Single-Neuron Theory of Consciousness. *J. Theor. Biol.* 238, 704-725 (2006)
16. Cook, N.D.: The Neuron-Level Phenomena Underlying Cognition and Consciousness: Synaptic Activity and the Action Potential. *Neuroscience.* 153, 556-570 (2008)
17. Tsitolovsky, L.E.: Protection from Neuronal Damage Evoked by a Motivational Excitation is a Driving Force of Intentional Actions. *Brain Res. Rev.* 49, 566-594 (2005)
18. Wester, J.C., Contreras, D.: Biophysical Mechanism of Spike Threshold Dependence on the Rate of Rise of the Membrane Potential by Sodium Channel. *Journal of Computational Neuroscience*, 35, 1-17 (2013)
19. Papoutsi, A., Kastellakis, G., Psarrou, M., Anastasakis, S. Poirazi, P.: Coding and Decoding with Dendrites. *Journal of Physiology-Paris*, In Press, Corrected Proof, (2013)
20. Bekisz, M., Garkun, Y., Wabno, J., Hess, G., Wrobel, A., Kossut, M.: Increased Excitability of Cortical Neurons Induced by Associative Learning: an *ex vivo* Study. *The European Journal of Neuroscience.* 32, 1715-1725 (2010)
21. Bolhuis, J.J., Honey, R.C.: Imprinting, Learning and Development: from Behavior to Brain and Back. *TRENDS Neurosci.* 21, 306-311 (1998)
22. Cannon, W.B.: Stresses and Strains of Homeostasis. *Am. J. Med. Sci.* 189, 13-14 (1935)

23. Maffei, A., Bucher, D., Fontanini, A.: Homeostatic Plasticity in the Nervous System. *Neural plasticity*. pp. 1-2. Hindawi Publishing Corporation, (2012)
24. Selzner, N., Boehnert, M., Selzner, M.: Preconditioning, Postconditioning, and Remote Conditioning in Solid Organ Transplantation: Basic Mechanisms and Translational Applications. *Transpl. Rev.* 26, 115-124 (2012)
25. Sohl, G., Maxeiner, S., Willecke, K.: Expression and Functions of Neuronal Gap Junctions. *Nat. Rev. Neurosci.* 6, 191-200 (2005)
26. Wang, H., Hu, Y., Tsien, J.Z.: Molecular and Systems Mechanisms of Memory Consolidation and Storage. *Prog. Neurobiol.* 79 123-135 (2006)
27. Bergquist, S., Dickman, D.K., Davis, G.W.: A Hierarchy of Cell Intrinsic and Target-Derived Homeostatic Signaling Neuron. *Neuron.* 66, 220-234 (2010)
28. Thompson, J.W., Bruick, R.K.: Protein Degradation and Iron Homeostasis. *BBA – Mol. Cell Res.* 1823, 1484-1490 (2012)
29. Bernstein, N.A.: *The Co-ordination and Regulation of Movements.* 176p, Oxford: Pergamon Press. (1967)
30. Kőhidai, L., Lajkó, E., Pállinger, E., Csaba, G.: Verification of Epigenetic Inheritance in a Unicellular Model System: Multigenerational Effects of Hormonal Imprinting. *Cell Biol. Int.* 36, 951-959 (2001)
31. Houten, J.V.: Chemosensory Transduction in Eukaryotic Microorganisms: Trends for Neuroscience? *Trends in Neurosci.* 17, 62-75 (1994)
32. Kiyatkin, E.A., Rebec, G.V.: Impulse activity of ventral tegmental area neurons during heroin self-administration in rats. *Neuroscience* 102, 565-580 (2001)
33. Wilent, W.B., Contreras, D.: Stimulus-Dependent Changes in Spike Threshold Enhance Feature Selectivity in Rat Barrel Cortex Neurons. *J. Neurosci.* 25, 2983-2991 (2005)
34. Mehta, A., Prabhakar, M., Kumar, P., Deshmukh, R., Sharma, P.L.: Excitotoxicity: Bridge to Various Triggers in Neurodegenerative Disorders. *Eur. J. Pharmacol.* 698, 6-18 (2013)
35. Wedesny, N. E.: *Stimulation, Inhibition and Narcosis, (In Russian)* 315p. St. Petersburg, 315p. (1901)
36. Romo, R., Salinas, E.: Touch and Go: Decision-Making Mechanisms in Somatosensation. *Annu. Rev. Neurosci.* 24, 107-137 (2001)
37. Priebe, N.J., Lampl, I., Ferster, D.: Mechanisms of Direction Selectivity in Cat Primary Visual Cortex as Revealed by Visual Adaptation. *J. Neurophysiol.* 104, 2615-2623 (2001)
38. Tolkunov, B.F., Shnitko, T.A., Orlov, A.A.: Encoding of Conditioned Reflex Activity in Different Directions by Neurons in the Monkey Striatum. *Neurosci. Behav. Physiol.* 39, 281-287 (2009)
39. Lee, C.-C., Middlebrooks, J.C.: Auditory Cortex Spatial Sensitivity Sharpens During Task Performance. *Nat. Neurosci.* 14, 108-116 (2011)
40. Connors, B.W., Long, M.A.: Electrical Synapses in the Mammalian Brain. *Annu. Rev. Neurosci.* 27, 393-418 (2004)
41. Juszczak, G.R., Swiergiel, A.H.: Properties of Gap Junction Blockers and their Behavioral, Cognitive and Electrophysiological Effects: Animal and Human. *Prog. Neuropsychopharmacol. Biol. Psych.* 33, 181-198 (2009)
42. Lee, A.K., Epsztein, J., Brecht, M.: Head-Anchored Whole-Cell Recordings in Freely Moving Rats. *Nat. Prot.* 4, 385-392 (2009)
43. Guggisberg A.G., Dalal S.S., Schnider A., Nagarajan, S.S.: The Neural Basis of Event-Time Introspection. *Consc. Cogn.* 20, 1899-1915 (2011)
44. Ashley, J.W., Ward, J.E., Herbert-Read, D.J.T., Krause, J.: Fast and Accurate Decisions through Collective Vigilance in Fish Shoals. *Proc. Natl. Acad. Sci. USA.* 108, 2312-2315 (2011)
45. Tsitolovsky, L.E.: A Model of Motivation with Chaotic Neuronal Dynamics. *J. Biol. Syst.* 197, 301-323 (1997)
46. Bland, A.R., Mushtaq, F., Smith, D.V. Exploiting Trial-to-Trial Variability in Multimodal Experiments. *Front. Hum. Neurosci.* 5, 80-83 (2011)
47. Eagleman D.M. *Neuroscience. The where and when of Intention.* Science. 303, 1144-1146 (2004)
48. Corredor, R.G., Jeffrey, J.L.: Electrical Activity Enhances Neuronal Survival and Regeneration. *J. Neural Engineering.* 6, 055001 1-11 (2009)
49. Mehta, A., Prabhakar, M., Kumar, P.: Excitotoxicity: Bridge to Various Triggers in Neurodegenerative Disorders. *Eur. J. Pharmacol.* 698, 6-18 (2013)
50. Benvenuto, A., Battan, B., Porfirio, M.C.: Pharmacotherapy of Autism Spectrum Disorders. *Brain Devel.* 35, 119-127 (2013)

51. Tewelde, S.Z., Winters, M.E.: Cooling the Fire: Resuscitated Sudden Death. *Cardiol. Clinics*. 30, 639-650 (2012)
52. Park H., Pontius W., Guet C.C.: Interdependence of Behavioral Variability and Response to Small Stimuli in Bacteria. *Nature*. 468, 819–823 (2010)
53. Louis, M., Huber, T., Benton, R., Sakmar, T.P., Vosshall, L.B: Bilateral Olfactory Sensory Input Enhances Chemotaxis Behavior. *Nat. Neurosci*. 11, 187-199 (2008)
54. Liang, Z., Lixiao, R.: Relevance Search via Bipolar Label Diffusion on Bipartite Graphs. *Global J. Comp. Sci. Techn.. Neural Art. Intell*. 12, 18-24 (2012)
55. Lagace, D.C.: Does the Endogenous Neurogenic Response Alter Behavioral Recovery Following Stroke? *Behav. Brain Res*. 227, 426-432 (2012)
56. Fei, D., Xiao-Hong, Z., Yi, Z., Zhang, N., Ugurbil, K., Chen, W.: Tightly Coupled Brain Activity and Cerebral ATP Metabolic Rate. *Proc Natl. Acad. Sci. USA*. 105, 6409–6414 (2008)
57. Smirnov, M.S., Kiyatkin, E.A.: Phasic and Tonic Fluctuations in Brain, Muscle, and Skin Temperatures during Motivated Drinking Behavior in Rats: Physiological Correlates of Motivation and Reward. *Brain Res*. 1310, 87-102 (2010)
58. Root-Bernstein, R.: Molecular Complementarity III. Peptide Complementarity as a Basis for Peptide Receptor Evolution: a Bioinformatic Case Study of Insulin, Glucagon and Gastrin. *J. Theor. Biol*. 218, P. 71-84 (2002)
59. Kalman, R.E.: "Lyapunov Functions for the Problem of Lurie in Automatic Control", *Proc Nat Acad.Sci USA*, 49, 201-205 (1963)