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PHYSICS OF OUR DAYS

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Subject of study — the aging brain

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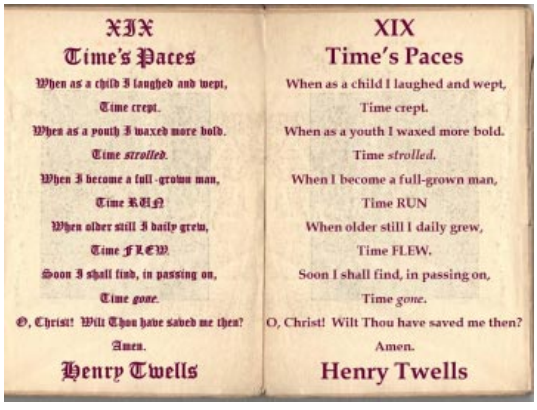
Contents

Abstract. Progress in research aimed at combating neurodegenerative diseases requires a systematic biophysical analysis. It has been shown that the efficiency of cleaning the brain of metabolic and informational 'toxins' depends on the thresholds of excitation of neural networks and waves of 'pollution and purification' propagating inside the brain. This process affects the increase in the characteristic time of the normal functioning of the brain and, consequently, in human life expectancy.

Keywords: neurodegenerative diseases, biological rhythms, sleep, mathematical modeling, wave processes, dynamic stability of life


XIX
Time's Paces
When as a child I laughed and wept,
Time crept.
When as a youth I waxed more bold.
Time *strolled*.
When I become a full-grown man,
Time RUN
When older still I daily grew,
Time FLEW.
Soon I shall find, in passing on,
Time *gone*.
O, Christ! Will Thou have saved me then?
Amen.
Henry Twells

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When as a child, I laughed and wept,
Time crept.
When as a youth, I dreamt and talked,
Time walked.
When I became a full-grown man,
Time ran.
Soon, as I journey on, I'll find
Time gone.

Loosely based on ''Time's Paces'',
a poem by Henry Twells

1. Introduction

1.1 Urgency of the issue and statement of the problem

Life expectancy in populations of economically developed countries is increasing, notwithstanding annual epidemics and occasional pandemics. As a result, neurodegenerative diseases, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease, are becoming a leading cause of disability and death. In medicine, they are collectively termed *senile dementia* (from Latin *senilis* — of, or pertaining to, old age and *dementia* — madness or out of one's mind). The management of these conditions places a heavy financial burden on the health care system. In 2018, the estimated annual per-patient cost of treating Alzheimer's disease or multiple sclerosis in the USA amounted to more than $30,000. Failure to stop further growth in the incidence of these pathologies will result in their occurrence in roughly 135 million people by 2050 and will probably cost the country more than USD 4 trillion per annum to treat affected patients [1].

However, it is more than a matter of huge expenditures. The tragedy is that brain function often becomes impaired up to complete amnesia, while most other organs remain

unaffected. Neurodegenerative diseases are not somatic disorders. They are first and foremost brain diseases characterized by the loss of the sense of self (depersonalization). This leads to a social tragedy: the patient's relatives are destined to suffer for years watching the gradual mental degradation of the one they love. The affected person shows indifference to surrounding people, does not recognize even close family members, tends to commit illogical acts, gradually loses the power of speech, and slowly approaches death. In other words, the illness of one person may have a strong psychological influence on other people and thereby endanger their health.

It is estimated that manufacturing a drug to slow the development of Alzheimer's disease will take approximately 13 years and require more than USD 5.5 billion (in prices as of the end of 2018). References [1, 2] cite 112 different studies that were ongoing in the beginning of 2018 and aimed at elucidating mechanisms behind the aforementioned neurodegenerative diseases. Were it possible to obtain by 2025 some means to hinder the increase in the rate of neurodegenerative diseases for at least 5 years, the number of patients with these conditions in 2050 would be half of what is expected [1]. Unfortunately, this is thus far an unattainable goal for the lack of knowledge about mechanisms underlying pathogenesis of neurodegenerative diseases, first and foremost Alzheimer's disease.

Resources available for relevant research are either experimental models or patients with a fully developed disease staying in clinical settings.

On the one hand, it remains unknown whether it is possible to elucidate *mechanisms of neurodegenerative diseases* in humans using rats and mice as models of human neurological disorders.

On the other hand, clinicians as a rule encounter an already irreversible pathological process in the human brain and have to retrospectively discern the cause of the disease based on its visible effects. In other words, an ill-posed inverse physical problem needs to be solved, i.e., the cause must be deduced from the consequence. Clearly, it is extremely difficult to unambiguously determine the true contribution of various causative agents to the formation of clinical signs and symptoms from the totality of pathological manifestations. The uncertainty is due to confusion of causes and effects. The assumed additivity of the causes of a disease accounts for the possibility of the same conclusion from the analysis of a set of different factors.

Increasingly complex challenges to modern biomedicine lead researchers to put great hopes on systemic approaches to the investigation of neurodegenerative conditions with due regard for the difference in concepts and methods adopted by clinicians, neurophysiologists, and biophysicists. A neurophysiologist usually seeks to find an answer to the question about the nature of the phenomenon of interest, while a clinician mainly focuses on the practical application of the results of neurophysiological studies.

A biophysicist is interested in the functional dynamics of a biological system at all hierarchical levels of its organization in time and space. When and why does it attain a functional limit?

As the tasks facing modern biomedicine become more and more complicated, an analysis based on a mathematical description of the relationship between phenomena and their computer simulation is gaining in importance. It provides a possible additional efficient way to achieve the goal allowing us, if successful, to simultaneously reveal the entire spectrum of applications important both for biomedicine and related high-tech fields, including biosafety and gerontology.

1.2 List of questions which the article answers

The present article is designed to combine answers to four questions currently relevant in the context of searching for methods to prevent or slow down the incidence of neurodegenerative diseases. The questions are listed in Table 1. Such a combination permits setting out strategies for further research aimed at combating neurodegenerative diseases.

Table 1. Four main questions whose answers could contribute to the understanding of mechanisms behind the development of neurodegenerative diseases.

Questions	Authors of references	Years of publication
1. What is the mechanism of brain purification from its own waste products?	M Nedergaard et al.	1994 [3], 2013 [4]
2. Why is it necessary to change the paradigm of approaches to the study of the impaired human brain function?	Result of 'round table discussion': (X Castillo, S Castro-Obregon, et al.)	2019 [5]
3. Is it possible to slow down brain aging and considerably prolong active human life?	Nongovernmental SENS Research Foundation (Strategies for Engineered Negligible Senescence)	2009 [6]
4. Why is it desirable to use the language of wave mechanics in a mathematical description of the brain for constructing models of its work (from a biophysical perspective)?	G R Ivanitskii, V I Krinskii, A G Bragin, A B Medvinskii, M A Tsyganov, E R Zemskov, et al.	The 1980s [7], 1994 [8], 2014 [9]

1.3 Organization of the article: from intuition to mathematical models

The human brain appears to be the most complex structure challenging modern science. The second half of the 20th century passed under the 'brain as a computing machine' slogan. However, disappointment came very soon. Neurodegenerative diseases of the brain have nothing in common with computer breakdown. When humans cogitate during normal conscious wakefulness, the entire body, including the brain, is involved in the process. Moreover, the sleep of a normal human being and the 'sleep' of an electrically-dead computer are not alike in any way.

To begin with, here are two common general considerations that form the basis of this article.

Starting from scratch, a series of books collectively entitled *The Book of General Ignorance* was published by S Fry in Great Britain in 2006 to popularize the QI science-oriented TV game show. The first book in the series was translated into Russian [10]. The books present a list of false hypotheses (formulated as questions) originating from the lack of knowledge that are believed by many to be correct, because they are still widely discussed in the mass media. Here is a quote from the book translated into Russian [10, p. 10]: "*Biologists claim that there are three primal drives for human beings as well as for animals*: *food, sex, and shelter*. *We add the*

forth one, curiosity, that is supposedly the most important because, unlike the other three drives, it is what makes us uniquely human.'' From an early age, humans pose thousands of questions in an attempt to understand how the world really works and obtain insight into their own surroundings and behavior.

However, *curiosity* is only the starting point of the fourth driving force that distinguishes humans from other animals. In fact, *curiosity* is just as well inherent in many mammals, e.g., rats, cats, dogs, and especially primates. But only in humans has it acted as a catalyst to give rise to a stepwise chain process intensified with time over successive generations in the following manner:

curiosity → (*knowledge* → *memory* → *intuition* → *criticism* → *experiment*) → (*knowledge* → *memory* → *intuition* → *criticism* → *experiment*), etc.

Second, this accelerating process is likely to continue as long as humanity exists. In the early 21st century, the use of Internet resources made it possible to formulate the EDGE project [11]. Its simple idea is based on the following premises:

• science progresses by making assumptions and forwarding hypotheses sometimes by analogy with the beauty of many outside world images. Thereafter, the hypotheses are verified in experiment. Hence, the beauty of science: it requires imagination. Science is the main driving force of human civilization;

• to reach the forefront of the global knowledge-based practices, it is necessary to join the efforts of original thinkers and unite them online to exchange questions that they usually ask themselves about things they believe but can not explain;

• great minds sometimes intuitively guess the truth much before facts or arguments in its favor become available. Denis Diderot called such ability 'the spirit of divination';

• means of communication markedly contribute to the development of human society.

These four ideas of the project are not new: they came long before the Internet era; really new were the means of communication, greatly facilitating and accelerating the exchange of ideas. For example, Internet and e-mail enabled the development of the 'university without borders' project, having an obvious analogy to brain work in an individual person. Our brain has no borders either, due to receptor systems for information perception and transfer. Brain cells (neurons and glia) also communicate with one another using a biochemical language.

This article briefly touches upon current views of the interaction between three cycles in the mammalian organism, namely the brain ↔ body, brain ↔ outside world, and body↔ outside world cycles. Taken together, these three mini-cycles make up a macrocycle. An analysis of the relationship among the mini-cycles gives an answer to the question: 'How does the organism cogitate?' Only humans have a noticeable extension over these cycles in the form of the frontal part of the neocortex with connections allowing the formulation of goals and questions for their achievement. For example: 'What is the aim we wish to have?', 'How can it be reached?', 'What is the forecast for the subsequent period?'

Here is a brief comment on the brain's sleep. Neurophysiology long ago gave rise to a self-contained branch of research known as *somnology* (the term coined from the Latin word somnus meaning sleep and the Greek word λόγος — *study*). Somnology deals with sleeping and its influence on human health. This research field has been extensively developing in the last 30–40 years to meet the requirements of medicine. A few dozen sleep disorders have been identified associated with jet lag, stress, depression, narcolepsy, hypersomnia, respiration disturbance, etc. [12]. The main questions in connection with these phenomena are 'What is sleep needed for?' and 'Can it be controlled, and if yes, how?'

To recall, the human organism is a unified whole, while scientific classification is always subjective. The brain as the main information-driven control system is subject to fatigue. However, its fatigue differs from a muscle fatigue failure. A *virtual model of the body* begins to form in the brain in early childhood and even before the birth. The formation of a *virtual model of the outside* world is underway in parallel as a set of patterns, i.e., organism behaviour programs in accordance with the environmental conditions. The brain operates these two models to solve various problems posed either by itself or by the environment and social milieu.

It was supposed in the first half of the 20th century that humans make use of only 10% of brain potential. Discussions were popular about what an individual could achieve if he or she were able to realize the remaining 90% of brain capacity. For example, it was proposed to use sleep in the study of foreign languages. The idea originated in the early 20th century (1927) from the American inventor Alois Benjamin Saliger (1880–1969) whose psychophone conveyed information to a sleeping person. Tape recorders that came later were used for the same purpose. However, it became clear by the end of the 20th century that all test subjects who managed to remember information transmitted while they were sleeping were in the state of transition from wake to sleep; also, the trainees experienced interrupted sleep and complained of tiredness upon waking up. In a word, this way of teaching proved inefficient. At the same time, it was shown that all brain neurons, not 10% of them, are active during waking, even if they are functioning successively rather than simultaneously. Thus, the assertion that we use only 10% of our brain neurons is false. Excited neurons collectively form the forefront of propagating and mutually interacting autowaves. Simultaneous excitation of a large number of neurons is a pathological condition, e.g., an epileptic attack.

Section 2 overviews evidence of success in the understanding of brain neurodegenerative diseases in the second half of the 20th century and attempts to answer question listed in Table 1. Section 3 focuses on problems and their solution in the last 20 years. The wave model of neurodegenerative diseases is considered in Section 4.

Hopefully, this article will be read not only by physicists familiar with modern methods of mathematical analysis but also by physiologists interested in neurodegenerative diseases, as well as by graduate and post-graduate students. Therefore, we tried to present the subject matter in a nontechnical, readily understandable language.

2. Biological wave rhythms and sleep

2.1 Beyond waking

What is sleep needed for? The aging brain experiences *informational fatigue* (memory overload) under the effect of information (both essential and nonessential) continuously delivered through receptor channels. The terms *essential* and *nonessential information* are arbitrary, since they are used depending on the character of problems an individual has to address in the course of a lifetime. Essential information helps

to reduce time needed to reach a specific goal; otherwise, information is nonessential [13].

Psychologists not infrequently argue that humans operate consciously in the state waking while subconsciousness dominates dreaming sleep. However, such opposition is wrong. Waking and sleep are two closely associated and indivisible processes involving consciousness and subconsciousness, i.e., neocortex and subcortical structures. They are indispensable for the maintenance of the human organism under variable environmental conditions.

A physically tired person falls asleep within 5–10 minutes, while an overexcited one ransacks memory for fragments of essential information to combine patterns to solve problems he or she had during the day. The painful feeling may persist throughout the night and sleep never comes. Also, one can forbid oneself to sleep if such a need arises.

In the early 20th century, Constantin Alexander Economo forwarded a hypothesis [14] that insomnia is due to lesions in the anterior part of the subcortical hypothalamic structure. Economo's hypothesis was based on clinical observations correlating destruction of the anterior hypothalamus with insomnia. On the contrary, the posterior hypothalamus was deemed to be responsible for the maintenance of long-lasting sleep occasionally interrupted for food intake or bowel emptying and micturition.

However, further studies failed to confirm the existence of a single sleep center. They revealed instead a system of interconnected nerve centers localized at different levels of the structural organization of living creatures (see Fig. 1). They interact to maintain one of the two states, sleep or waking, while the hypothalamus (its anterior and posterior parts) is only one of the components of this system.

In an awake person, changes inside the body occur at different hierarchical levels. What levels (molecular, organelle, cellular, tissue, organ, organism, or social) should be examined to elucidate brain functioning mechanisms? Obviously, a systemic approach to the choice of the proper level implies simulation of brain work mechanisms at all levels. However, researchers have failed to solve the problem by uniting all levels into an integral whole since the time of Ludwig von Bertalanffy, who was the first to propose the use of a systematic approach in investigations of living organisms [15] for the simple reason that the work at each level requires a special mathematical language to be described. Nor is there yet a common language for the description of the totality of levels. Possibly, the string theory with nodes [16] will provide such instrument.

Thus far, researchers confine themselves as in the 20th century to a combined analysis of two or three levels in the framework of wave mechanics [17] (see Section 4). At the same time, the brain searching for mechanisms to maintain stability of the organism successfully solves the unification problem as it works on all levels at a time. It can be concluded that the *brain and the body collectively control the stability of the whole organism by feedback mechanisms through functional restructuring of all hierarchical levels*.

Brain, body, and environment may be in a short-term nonequilibrium state, usually referred to as *stress*. This state is associated with changes in excitation and inhibition thresholds. The relaxation period following the achievement of the goal is used to recover stability [18].

Sleep during which harmful metabolites are removed from the brain and other organs facilitates the recovery. In fact, it does more than that, as will be shown in due course.

It was demonstrated in studies conducted during the 20th century that the state of waking is maintained by a continuous pulse flow coming from the reticular formation composed of subcortical structures to neurons across nonspecific thalamic nuclei. This flow causes depolarization of neuronal membranes in different parts of the cerebral cortex. The reticular formation receives signals from receptor regions of the cortex and sends activating or inhibitory pulses back to the cerebral cortex, thus giving rise to an interaction cycle [19].

Animal studies revealed a few groups of neurons involved in controlling sleep phases. It allowed a comparison of sleep mechanisms in different species. At the cellular level, the mechanism responsible for sleep induction involves mixed groups of wake (excitatory) and sleep (inhibitory) neurons. The neurons of these two groups are in a competitive relationship. They interact in an oscillatory regime, with one or the other group winning alternately. Neurons depolarized at the onset of sleep (inhibitory neurons) suppress the activity of neurons that are awake.

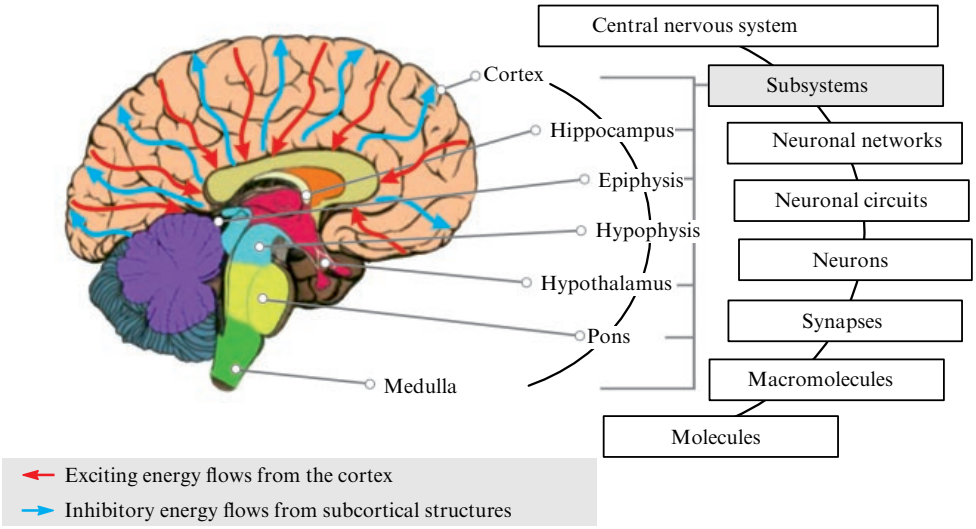


Figure 1. (Color online.) Subsystems of the human brain: direction of excitation (red lines) and inhibition (blue lines) flows.

The suppression is, in turn, stimulated by flows of body fatigue pulses passing through subcortical structures. This process is associated with an increase in cortex excitation thresholds, because both the entry of sodium ions into axons and the exit of potassium ions across axon membranes are hampered. The observed interaction paths give reason to think that sleep neurons are ancient products of natural selection that appeared at the early stages of the development of the nervous system in animals [20].

The algorithm of sleep and waking regulation in humans is associated with the body's internal biological clock, i.e., the 24 h circadian rhythm. At the molecular level, epiphysis produces during sleep one of the important hormones, melatonin, even if it is not the sole agent responsible for sleeping. Anatomic studies show that epiphysis is connected with the optic thalamus, meaning that vision and the brain region involved with vision can also play an important role in sleep mechanisms. One side of the epiphysis is turned toward the mesencephalon, while the other adjoins the third ventricle of the brain filled with the cerebrospinal fluid (CSF). At the molecular level, a *wake* → *sleep* transition is accompanied by a rise in concentrations of many hormones and neurotransmitters, viz., adenosine, cortisol, growth hormone, prolactin, thyrotropic hormone, testosterone, renin, insulin, leptin, ghrelin, tyrosine (a precursor of neuromediators), etc. [21].

In other words, *sleep eliminates the deficit of all products utilized during waking*.

2.2 Changes in wave rhythms — the language of organ-to-organ interaction

Each organ of the human body (brain, heart, lungs, stomach, etc.) functions according to its own rhythm. Today, the mathematical problem of interaction rhythm synchronization in application to neurodynamics can be regarded as partly solved. A general meeting of the Russian Academy of Sciences (RAS) was held in December 2007 to discuss brain research. It was preceded by a scientific session of the RAS Physical Sciences Division, "Methods of wave-based physics in neuroscience problems and applications" (November 31, 2007) [22]. In 2013, the journal *Physics–Uspekhi* published a review article on this topic [23]. In 2018, a thesis for the degree of doctor of physico-mathematical sciences was defended at the Institute of Theoretical and Experimental Biophysics (ITEB), RAS, Pushchino [24]. An essential part of this work was devoted to mathematical models for synchronization of excitations in oscillating neural networks. Since all these publications are readily available, we present here only their main results.

The mathematical description of synchronization of an ensemble of phase oscillators is based on the work of Kuramoto [25, 26], who derived an equation to evaluate the stability of phase-locked states in autogenerators that form interaction cycles during their joint operation:

$$\frac{\mathrm{d}\theta_i}{\mathrm{d}t} = \omega_i + \sum_{j=1}^{n} K_{ij} f(\theta_j - \theta_i)\,, \tag{1}$$

where θ_i is the phase of the ith oscillator, ω_i is the eigenfrequency of the ith oscillator, f is the odd nonperiodic function of interaction between oscillators, and K_{ij} is the coupling parameter determining the force of interaction between the jth and ith generators, where $i = 1, 2, \ldots, n$. In the absence of coupling, each oscillator works at its own frequency ω_i.

If the connection K_{ij} is given in the form of phase oscillations, i.e., trigonometric functions, the expression for model (1) takes the form of the Kuramoto–Sakaguchi model [27]:

$$\frac{\mathrm{d}\theta_i}{\mathrm{d}t} = \omega_i + \sum_{j=1}^{n} K_{ij} \sin(\theta_j - \theta_i - \alpha_{ij})\,. \tag{2}$$

Most authors consider the case of all-to-all pair-wise coupling. However, a real brain system contains central network nodes called *hubs*. At the cellular level, many neurons in neural networks are connected to hub nodes, thereby making clusters. Such a system may give rise to two types of synchronization: (1) coherent (i.e., complete synchronization), with all oscillators having similar frequencies and phases, and (2) partial, with only some of the oscillators operating at the hub frequency, while the remaining ones have their specific frequencies. Such a system, unlike the Kuramoto model, is capable of rearranging synchronization patterns depending on the eigenfrequency of the main hubs; it is described by a set of two equations:

$$\frac{\mathrm{d}\theta_0}{\mathrm{d}t} = \omega_0 + \frac{A}{n}\sum_{i=1}^{n} f(\theta_i - \theta_0 + \gamma)\,, \tag{3}$$

$$\frac{\mathrm{d}\theta_i}{\mathrm{d}t} = \omega_i + B\sin(\theta_0 - \theta_i + \delta)\,, \quad i = 1, 2, \ldots, n\,, \tag{4}$$

where A and B are the coupling parameters of interaction.

Equation (3) describes the dynamics of the main hub with satellite oscillators. Peripheral oscillators are described by expression (4). It can be assumed that $A > 0$, $B > 0$, $\delta = 0$, and the parameter γ can be both positive (phase advance) and negative (phase lag). Subtracting expression (4) from (3) yields the phase difference equation

$$\frac{\mathrm{d}\phi_i}{\mathrm{d}t} = \mu_i - B\sin(\phi_i + \delta) - \frac{A}{n}\sum_{j=1}^{n} \sin(\phi_j - \gamma)\,,$$
$$i = 1, 2, \ldots, n\,, \tag{5}$$

where $\mu_i = \omega_0 - \omega_i$, $\phi_i = \theta_0 - \theta_i$.

Because the number peripheral oscillating clusters in a brain neural ensemble, n, is large, it is possible to obtain, by means of limiting transition, an equation for a given frequency that describes either complete or partial synchronization as a function of (ω_0, A) and (ω_0, B). Solutions of these equations are uniformly distributed within the $(-1, 1)$ range [28, 29]. This result is not unexpected, but it needs to be made clear how stable synchronization regimes of oscillators with a central element are by analyzing stationary solutions of Eqn (5). There is no difficulty with this in the simplest case when the system is initially composed of phase oscillators with identical frequencies, i.e., $\omega_0 = \omega_i = \omega$. It is necessary to introduce more general functions of phase interaction with derivatives by setting the boundary conditions

$$\dot{f}(0) = a_1\,, \quad \dot{f}(\pi) = a_2\,,$$
$$\dot{g}(0) = b_1\,, \quad \dot{g}(\pi) = b_2\,, \tag{6}$$
$$A = \frac{1}{n}\,, \quad B = 1\,.$$

Phase points $\Phi = (\varphi_1, \varphi_2, \ldots, \varphi_n)$ with coordinates belonging to set $\varphi_i \in \langle 0, \pi\rangle$ at $i = 1, 2, \ldots, n$ will be the stable points of a system with the boundaries described by

expression (6). In this case, the set of phases $(\varphi_1, \varphi_2, \ldots, \varphi_n)$ in function Φ_k falls into two groups, with k being zero and $(n-k)$ equaling π. These two states are stable. The states of the phases between zero and π are unstable and do not represent a transition process. Extending the system described by Eqns (3), (4), and (6) with local couplings permits showing that, at large n, even a minor desynchronization impact extending from the central element to peripheral oscillators perturbs initial phase stability $\Phi_n = (0, 0, \ldots, 0)$. This means that even weak excitation can induce synchronization $\leftrightarrow$ desynchronization transitions. Local couplings between peripheral oscillators allow Φ_n phases to retain stability [29].

It can be concluded that the above *approach to the description of brain function may be useful but is oversimplified, because its application is based on the assumption that information processing in the brain is underlain by frequency-phase modulation of autowaves. Moreover, autowaves vary in intensity, i.e., mixed frequency-phase modulation parametrically controlled by hubs takes place.*

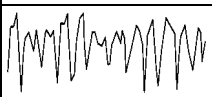
2.3 What brain rhythms say

As to experimental identification of the totality of macrocycles, the classification of electroencephalogram (EEG) rhythms was proposed as long ago as the first half of the 20th century, when the correlation between EEG rhythms and various waking and sleep stages was documented [30] (Table 2).

An analysis of EEG findings demonstrates cluster synchronization (work rhythm combination) and desynchronization (each cluster has its own work frequency and phase).

Normal sleep is characterized by reduced muscle activity with relatively constant heart and breathing rates. The brain retains selective responsiveness to environmental changes of which it becomes aware through acoustic and tactile receptor channels. When awake, the brain experiences an active interplay of simultaneously activated neuronal groups of receptors and increased connectivity between them. It was mentioned in a preceding paragraph that the sleeping brain iterates and combines patterns arising from enhanced connectivity. These patterns represent essential and nonessential images of the external environment that the brain perceived and stored earlier in the waking state. EEGs reflect the iteration rate. Dreams can happen during sleep.

Table 2. EEG frequency and rhythm shape in humans and their correlation to wake $\leftrightarrow$ sleep states.

Definition of biological rhythms in cerebral structures (oscillation frequency and amplitude)	Rhythm shape disregarding amplitude value	Brain condition reflected in the rhythm
Δ (delta)-waves 0.5–3.5 Hz 40–300 μV		Relaxed waking state especially with closed eyes (up to 15% of such rhythms)
Θ (theta)-waves 4–7 Hz 40–300 μV		Initial sleep stage
A (alpha)-waves 8–13 Hz 50–100 μV		Wakefulness at rest
B (beta)-waves 14–40 Hz 5–20 μV		Anxious wake state with active brain work and during fast-to-slow sleep transition: at Δ → B when dreams happen

Note. B is a beta-wave having a frequency 13–28 times that of a Δ (delta)-wave and an amplitude 8–15 times smaller due to accelerated low-energy memory pattern iteration during sleep in search of a solution to the problems encountered in the waking state.

It was noticed long ago by patriarchs of medicine (Hippocrates, Avicenna, and the like) that days seem to last long in childhood, while years seem short as we get older. We chose to include a quotation from Twells as the epigraph at the beginning of the article. It is a liberal translation of his Time's Paces poem engraved in the 19th century on the clock case in the North Transept of the ancient Chester Cathedral, England.

In certain cases it is convenient to describe the model representation of brain work in terms of inverse function values, i.e., characteristic times, rather than in terms of functions. In an active brain, the characteristic internal subjective time scale is reduced in comparison with subjective perception of time in the absence of events. This suggests that external time t runs fast. In sleep, the characteristic internal time scale is smaller than during waking. When sleeping, we actually do not notice the flight of time.

In childhood, the number of patterns is large, because neuronal domains are still small and only begin to form clusters, which accounts for the low density of couplings. Therefore, information processing and uptake rates $v(t)$ in this lifetime period rapidly increase. Memorization of new information plays an important role, which explains why the famous maxim "memorizing in childhood is like engraving on stone" is so popular in many cultures.

For a child, thoughts prance through their mind; the child easily gets distracted from the task at hand but readily assimilates new information. The age-dependent function of the information processing rate $v(t)$ is a bell-shaped, saw-like asymmetric function that first grows but thereafter collapses. There is a bending point at the lifetime axis corresponding to point τ_i. The speed of information processing $v(t)$ takes the maximum value. Cognitive training facilitates control over the position of this point on the lifetime axis by its shifting.

The speed of information processing in the brain is a function of four variables, viz., current external time t, acceleration/deceleration $\pm a$ of information treatment, characteristic internal time τ, and lifetime T. The duration of T limits the growth of t. In the case of a smoothed trajectory, the acceleration vector $\mathbf{a}_i$ has a '+' (plus) sign in the time interval $\langle 0, (1/2)T\rangle$ and a '−' (minus) sign in the $\langle (1/2)T, T\rangle$ range. Therefore, the expression for the speed of information processing in the brain can be written in the form

$$\begin{aligned} v(\tau_i) &= +a_1(T-\tau_i) \quad \text{at} \quad 0 \leqslant (\tau_i = t) \leqslant \frac{1}{2}\,T, \\ v(\tau_i) &= v_{\max} - a_2(T-\tau_i) \quad \text{at} \quad \frac{1}{2}\,T \leqslant (\tau_i = t) \leqslant T, \end{aligned} \tag{7}$$

where

$$v_{\max}(\tau_i) = \frac{1}{2}\,aT \quad \text{at} \quad \tau_i = \frac{1}{2}\,T.$$

Accelerations $\mathbf{a}$ and quantization period τ_i depend on the frequency and intensity of energy biorhythms of the body.

The rhythm frequency in all organs first increases with advancing age but thereafter lowers. For example, the heart rate, i.e., energy supply to the brain, during the first month of life ranges from 110 to 170 beats per minute. It gradually decreases later to 55–95 beats per minute at the age of 12–15 years. Naturally, it influences the information processing rate in the body, including the brain. At the beginning and end of life,

$$v(0) = at = 0\,, \quad \text{because} \quad \tau_i = t = 0\,,$$
$$v(T) = a(T - \tau_i) = 0\,, \quad \text{because} \quad \tau_i = T\,.$$

Exploration of the external environment and adaptation of one's internal time τ to external time t start with the baby's first cry. The speed of information processing grows very fast. The dimension of $v(t)$ is a unit of information (bit, byte) per unit time. Lifetime T and modulus of acceleration vector **a** are determined first and foremost by genetic factors, while a delay of neurodegenerative disorders in the brain depends not only on genetic characteristics but also on the degree of brain training, i.e., the position of the saddle point of the function at the time axis. The saddle point τ_i corresponding to the maximum value of the information processing rate belongs to set $\langle 0, T \rangle$ and can be displaced within this interval during the lifetime. On the time axis, τ_i corresponds to expressions

$$\tau_i = \frac{i}{i+1}\,T\,.$$

Hence, we have a series of values for the saddle point τ_i as the function of lifetime duration T where $i = 1, 2, 3 \ldots$. We have

$$\tau_1 = \frac{1}{2}\,T\,, \quad \tau_2 = \frac{2}{3}\,T\,, \quad \tau_3 = \frac{3}{4}\,T\,, \ldots\,,$$

etc. However, a person's individual energy opportunities are always restricted. Nevertheless, it is desirable that the saddle point τ_i be located as close as possible to the lifetime point $t = T$ on the time axis. A trivial conclusion is it is *necessary to begin mental activity at an earlier age and continue it throughout the lifespan. Other things being equal, it allows preventing or postponing the development of neurodegenerative brain disorders in old age*.

2.4 Sleep phases

Not all subcortical structures of the human brain 'sleep' throughout one's time asleep, as exemplified by the hippocampus, which 'sleeps' for only a short period of the total sleeping period but remains dormant for the rest of the time to continue functioning as a 'sentinel', ready to awake when an occasion requires. The hippocampus is capable of responding to new information even in sleep. Reduced muscle activity during sleep contributes to a decrease in energy consumption for body movement, leading to energy redistribution in favor of the brain [31, 32].

Changes in EEG rhythms indicate that sleep occurs as the alternation of two phases, fast and slow.

What is the difference between them? In a healthy human, the sleep cycle begins from the first stage of slow sleep (non-REM sleep), i.e., dreamless sleep. The succession of sleep stages and their duration are usually illustrated graphically on *hypnograms*[1] (Fig. 2).

The first cycle of slow and fast sleep is 1–3 hours long. Then, the two-phase cycles repeat, with the duration of the slow phase gradually increasing and that of the fast phase (REM sleep), i.e., dreaming sleep, decreasing. Usually, at least 2–5 two-phase cycles follow each other during normal healthy sleep.

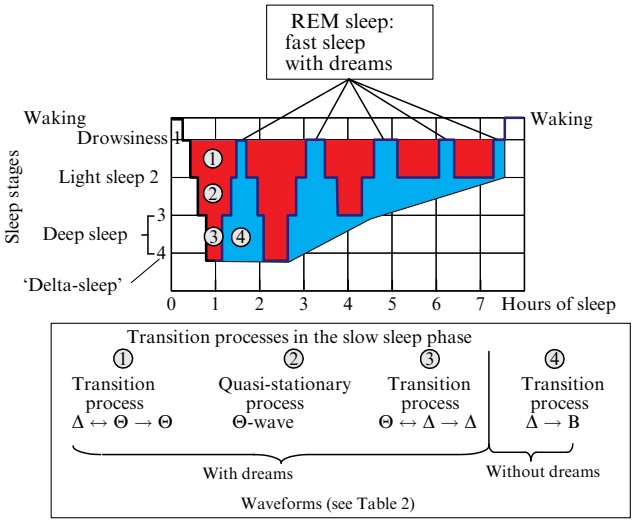


Figure 2. (Color online.) An example of an averaged hypnogram of repeating sleep phase cycles in a human: slow (red) and fast (blue) sleep. Fast sleep is sleep with dreaming. EEG patterns during fast sleep resemble those of waking (EEG beta waves) because the brain remains active [31].

How many hours should an average person sleep every day? The total sleep time of an adult is 7–8 hours, meaning that one sleeps during a third of one's life and is awake for the remaining two thirds. In 2004, Professor Daniel Kripke of the University of California reported results of a 10-year study designed to assess sleep duration and its influence on mortality that involved 1.1 mln volunteers [33]. Many of these subjects died in those 10 years. Among the survivors were both men and women who slept less than 8 hours but more than 4 hours a day. Based on these statistics, the author concluded that long sleep is unhealthy. We shall continue to consider statistical data in Section 3 below.

Kripke's conclusion that one should sleep less than 8 hours is incorrect. Both sleep structure and total duration differ among individuals. They vary both from childhood to old age and from one population to another. Moreover, sleep duration depends on the person's habits, diet, environmental conditions (temperature, pressure, humidity, oxygen concentration in the air, the length of darkness), and the physical and intellectual burden during waking. Sleep duration also depends on the person's occupation. Creative people (politicians, writers, researchers, etc.) and those working under jet lag conditions, i.e., experiencing the strong influence of environmental factors on biological rhythms (pilots, flight attendants, workers doing shiftwork), have trouble falling asleep and suffer from loss of sleep (insomnia). Many creative personalities, e.g., Leonardo da Vinci and Albert Einstein, preferred broken sleep schedules, i.e., sleep interrupted every 4 hours, while other celebrities are used to working at night and sleeping till midday. Nonetheless, many of them lived beyond the average lifespan in their generation.

Neurons of the human brain remain active during fast (REM) sleep. The eyeballs continue to move under closed eyelids. The neuron-to-neuron interaction remains almost as active as during waking even though many receptors recording signals from the outside are inhibited, visual receptors

[1] *Hypnogram* is a diagram containing information about the sleep structure and the number and quality of phases and stages.

behind the closed eyelids are isolated from external influences, and muscle systems of the body are practically motionless.

2.5 Why is fast sleep needed?

As was mentioned in a preceding section, the brain experiences informational fatigue because it is incessantly engaged in problem-solving and communication activities during waking. It has been thought since long ago that neural connections between synchronously activated clusters strengthen during waking; some of them weaken during sleep, while others formed during waking continue functioning effectively [34]. *The principal cause of the altered relative importance of various couplings is changes in excitation thresholds in neuronal networks. Sometimes, a sleeping person finds a solution to a problem that concerned them during the day.*

Animal experiments confirm this inference. For example, if a rat is placed in a maze to evaluate its orientation skills, concrete hippocampal neurons are activated in a uniquely determined sequence. A statistical analysis confirms that the animal reproduces this sequence right after sleep better than before [35]. It brings to mind the proverb "Take counsel of your pillow." It can be concluded that the *brain works actively in the fast phase of sleep*.

However, the function of sleep extends further than that. Variations in EEG patterns of the cortical network (delta waves) arise from the enhanced inflow of lymphatic fluid (LF) and cerebrospinal fluid (CSF) to brain parenchyma and the outflow of waste products referred to as toxins below [36–38].

Delta waves in naturally sleeping animals are indicators of the search for equilibrium between neurochemical activities inside and outside of neurons [39] that facilitates scaling, i.e., scale invariance [40]. To recall, scale invariance in mathematical modeling is understood as invariance of individual functions with respect to similarity transformations being used. In other words, some sets of quantities are rigidly connected, i.e., remain unaltered (invariant), while others change. The changing quantities are responsible for the search for system stability. An invariant variable in the brain is biochemical stability of intercellular fluid (lymph) or, to be precise, stability of physical fields present in the interneuronal medium. Supporting this invariance is a condition for normal brain functioning. In this respect, the human brain resembles the atom to which formulas for isolated systems are inapplicable. For an isolated system, both its total energy E equaling the sum of subsystem energies and their full pulse $\mathbf{P}$ are preserved. This suggests that the system's total mass $M^2 = E^2 - \mathbf{P}^2$, where E is the total energy and $\mathbf{P}$ is the full pulse, because the space between subsystems is never empty: on the contrary, it is filled with a material milieu (physical fields). The interatomic space is likewise filled with an electromagnetic field, whereas a denser and stronger field fills nuclei. The presence of the field energy implies that it must be included in the expression for the total mass in two closely interacting subsystems of the cerebral cortex (visual and acoustic analyzers). As a result, $M < m_1 + m_2$. Quantity ε ($\varepsilon = m_1 + m_2 - M$) is the coupling energy. To break the system down into subsystems, an energy equivalent to or exceeding the coupling energy is needed.

The maximum coupling energy is inherent in subsystems formed at the early stages of evolution (in phylogenesis), such as subcortical lower-level structures. Small energy connections are present in the cerebral cortex, which explains the release of large amounts of kinetic energy during transitions in subcortical structures. This energy serves to strengthen cortical fields and thereby contributes to the lowering of neural excitation thresholds. In other words, cortical fields are controlled by subcortical ones.

A much lower energy is released in chemical reactions involved in information transfer in cortical networks. The source of the kinetic energy produced in chemical reactions is the difference between initial and final masses of particles (molecules, ions, electrons) in each cortical subsystem. As the subsystems are nonrelativistic, the notion of potential energy is applicable to their description. The mass difference can be calculated from the amount of energy released and attributed to the conversion of potential energy into kinetic energy.

An active recovery of brain stability is impossible during waking, when the brain has to memorize a large amount of essential and nonessential information coming from the outer world through all receptor channels. This process encompasses all systems of the nervous system, including the brain.

It follows from the above that the *brain gets rid of external impacts on its core during sleep. Simultaneously, the relative intensity of the work of subcortical structures that stimulate activity of the interneuronal space increases. This enables the cortex to iterate, combine, and inhibit nonessential patterns formed during the elapsed period, i.e., to operate memory*.

2.6 "Sleep clean!"

In 2013, a group of neurophysiologists headed by Nedergaard published an article in *Science* [4]. The authors argued that *sleep promotes removal of metabolic products* through a network of lymphatic channels. They called the system of channels for the flow of lymphatic fluid the glymphatic system, taking into account that its capacity is controlled by brain glial cells, *astrocytes*,[2] functioning as vents. This publication was preceded by many other articles by Nedergaard giving evidence of the important role played by astrocytes in the mechanisms of regulation of fluid movements in the brain [3, 4, 41–46].

One of them, published in 2013, became most widely known by 2020 due to advertising in the mass media. In early 2014, the American newspaper *The New York Times* published material from this study under the heading "Goodnight. Sleep Clean" [47].

Further studies by Nedergaard and other authors showed that the protein aquaporin-4 plays an important role in the regulation of LF flow between the *perivascular space*[3] and the brain *interstitium*.[4] It turns out that slowing this flow impairs functional recovery of inflamed brain regions after a traumatic injury and promotes accumulation of toxins, such as beta-amyloids. It was concluded that disturbances of the LF flow can suppress the immune system of the brain and cause neurodegenerative diseases [48].

[2] The term *astrocyte* derives from the Latin word astrocytus, which is a combination of Greek *αστερι* (star) and Latin cytus (cell). Astrocytes are large star-shaped neuroglial cells with many processes. These cells perform a variety of functions. In the context of this article, the most important of them is the maintenance of stability of brain systems by forming a lymphatic flow and removing glutamate and potassium ions from synaptic clefts after signal transmission among neurons.

[3] *Perivascular space* is the space between vessel walls and white matter filled with glial cells and axons. These structures are also called kriblyurs or Virchow-Robin spaces. See https://fb.ru/article/412408/perivaskulyarnyie-prostranstva-rasshirenyi—chto-eto-takoe-prichinyi-i-lechenie for details.

[4] *The Interstitium* is the space inside tissues filled with cerebrospinal fluid (CSF).

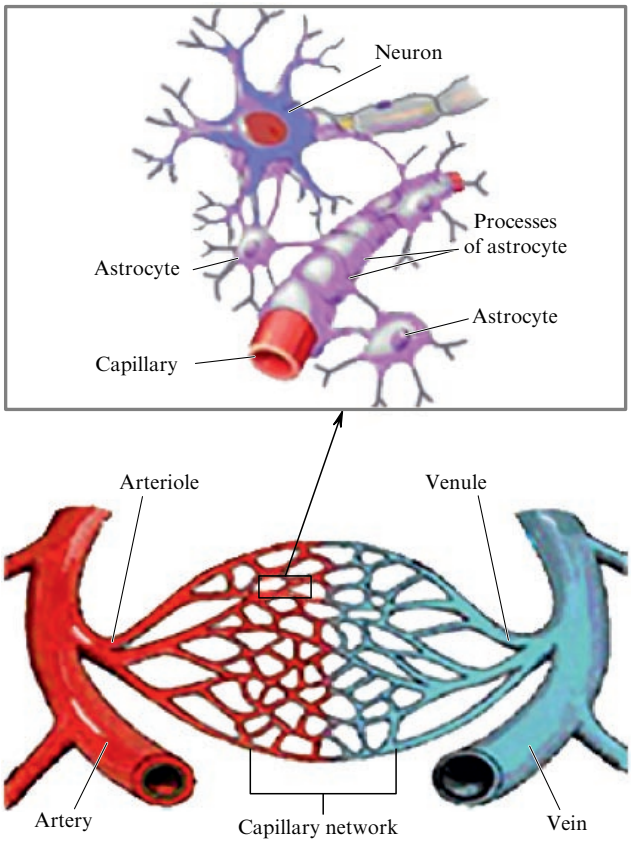


Figure 3. (Color online.) Schematic of *neuron → astrocyte → capillary* interaction (top). Blood supply to the brain as arterial blood passes to the venous part of vasculature (bottom). There are three mass-transition macrosystems: blood movement in capillaries, LF movement in lymph vessels, and CSF movement in the brain.

By wave of purification is meant cleansing the brain of metabolic and informational toxins by the lymphatic fluid that flushes them out and sends them via venous blood to the liver, kidneys, and finally the environment. There are three types of pathways in the brain performing different functions. One is the capillary system of arterial blood flow plus astrocytes, which serves to deliver basic food components (sugars including glucose, amino acids, and oxygen) to the brain. Another is the system of lymph ducts + astrocytes draining toxins to venous blood. The third pathway is the cerebrospinal fluid. The role of this pathway will be considered at greater length in Section 2.7.

The first pathway, intended to bring in nutrients, is shown in Fig. 3.

The self-contained system of lymph-filled output channels supplements the system of input channels of the blood circulatory system. These channels are connected in the venous part of the blood circulatory system into a cyclic formation. Lymph moves more slowly than blood, but also accumulates toxins slowly due to the high efficiency of the brain. In the waking state, lymph is driven by the contraction of all muscle systems of the body. The main driving force in a person who sleeps in a prone position is diaphragm vibrations caused by breathing movements and heart ventricle contractions. LF is regulated by the vent switching wave via astrocytes, i.e., by altering physical fields in the interneuronal space.

Almost two liters of lymph is produced daily in the human body. This amount is equivalent to $\sim 10\%$ of the total fluid volume in the body. Lymph analysis showed that it consists of plasma and blood cells. The liquid plasma contains unutilized proteins, salts, sugars, cholesterol, and other substances. The protein content in lymph is 8–10 times lower than in blood. Up to 80% of the blood cells present in the lymph are specialized leukocytes (lymphocytes), while erythrocytes are normally absent. Lymphocytes and phagocytes are cells of the immune system that protect the body from toxic extraneous agents. Lymph removes destroyed cellular building material, including unutilized proteins, lipids in the form of oxidized lipoproteins, and other products, such as small and large protein molecules and toxic waste [49].

Vascular valves are operated at the molecular level by the protein aquaporin-4 (AQP4) located in large amounts at the ends of astrocyte processes in contact with vascular canals [50–53].

Brain purification from toxins in animals and humans occurs more actively during sleep than during waking [54]. It was shown that electrical oscillations in cortical neuronal networks (13–40 Hz EEG beta waves) may be indicators of waste diffusion into the lymph fluid.

It can be concluded that the *lymphatic system of the brain functions as a route of drainage and simultaneously purifies the brain from metabolites and toxic waste by draining them to the environment, thereby maintaining constant physical fields in the interneuronal space. An equally important role in supporting the stability of the interneuronal milieu is played by electronic interaction between neural networks and neuronal activity of the glial system* (see the model in Section 4.2).

2.7 Informational 'toxins'

Informational toxins are present in the brain together with metabolic ones. Informational toxins result from the generation of physical field oscillations in the interneuronal space, i.e., the formation of electrolyte balance in the interneuronal milieu, which can lead to a change in neuron excitation thresholds. A constant ion composition needs to be maintained to avoid errors. Lymph is present in the brain together with the rapidly renewable *cerebrospinal fluid* (Latin — *liquor cerebrospinalis*). CSF pulsates in brain ventricles at the heart rate frequency and circulates through paravascular pathways between the pia mater and network shells of the brain and the spinal cord [55].

The total CSF volume in an adult subject is less than the LF volume. It is estimated at 140–270 ml, or $\leqslant 2\%$ of the total brain volume, whereas the LF volume amounts to 10% of the total. However, CSF is renewed at a higher rate than LF. Around 600–700 ml of CSF is produced daily, which means that CSF is renewed roughly 4 times a day. In other words, the brain is a very 'neat' organ subject to 'general wet cleaning' 4 times a day with simultaneous removal of informational toxins and the maintenance of constant electrolyte composition of the cerebral milieu.

To compare, the volumetric blood flow rate in the cardiovascular system is 4–6 l min^{-1} (an average adult person has $\sim$ 4–6 l of blood). This means that blood completes its motion cycle and returns to the heart for 1 minute. Saturation of blood with oxygen, blood renewal, and the removal of CO_2 merge into one continuous process. Evidently, the continuity of blood flow ensures continuous delivery of nutrients to the brain and continuous elimination of metabolic toxins from blood by the liver. In other words, *the brain is a 'voracious' organ 'eating' each second or more often. Consequently, it should be self-purified at approximately the same rate* ($\sim$ 1 Hz).

CSF and LF support exchange processes between blood and the brain and thereby ensure stability of the water-electrolyte composition (the ion ratio, Na^+, K^+, Ca^{2+}, Cl^-, and glutamate levels) in the latter organ. In this way, a closed loop for nutrient supply and toxin elimination is formed composed of arteries, arterioles, capillaries, the brain, LF + CSF, veins, the liver, and kidneys.

Classics of biology and biogeochemistry, e.g., V I Vernadskii, argued long before researchers of the 21st century that constancy of the *internal medium* is an indispensable condition for the long-lasting existence of a living organism, its organs, and the *biosphere at large*. Not a single part of a living system can exist in its faecal waste. This assertion is equally relevant for material and informational systems as well as for the ionosphere as a whole.

To sum up, the *main function of CSF is not only to serve as a 'safety bag' for protecting the brain and the spinal cord from mechanical injuries and maintaining stable intracranial pressure but also to clean the brain and keep its internal milieu constant*.

2.8 Toxic waste suppresses brain's informational activity

The inhibitory action of toxins on the system of connections is easy to explain in the context of the theory of information transfer over communication channels. In terms of the information theory, toxins are noise. The amount of information I is defined according to Shannon as

$$I = N \log_n m\,, \tag{8}$$

where N is the number of neuronal clusters containing information, and n is the logarithm exponent determining units (bits, bytes, etc.) in which information is measured. If bits are chosen for the purpose, $n = 2$, and m is the indicator of the number of levels distinguishable in each cluster:

$$m = \left(1 + \frac{kA_s^2}{A_n^2}\right)^{1/2}, \tag{9}$$

where A_s/A_n is the ratio of signal/noise amplitudes and k is the safety factor depending on noise statistics ($1 > k$). If the noise distribution over amplitudes obeys the normal law, k lies in the range from 0.15 to 0.26 with an error below 5%. Noise intensity A_n^2 increases in proportion to the viscosity coefficient of the medium.

As a result, the information processing rate at each point of the cerebral cortex $c(\tau, A_s^2, A_n^2)$ has the form

$$c(\tau, A_s^2, A_n^2) = \frac{N}{\tau} \log_n \left(1 + \frac{kA_s^2}{A_n^2}\right)^{1/2}. \tag{10}$$

At $A_n^2 \gg A_s^2$, expression (10) tends to zero. The growth of the noise amplitude is equivalent to the increase in the neuron excitation threshold in a local cluster zone. While expression (7) describes a change in the information processing by the entire brain at large times in ontogenesis, expression (10) describes the local speed of information processing by the cortex.

Within certain limits, exchange operations between entities filling the internal milieu of the brain (anions, cations, water, sugars, oxygen, proteins, and lipids) take place. This gave rise to the term *homeostasis* defining the ability or tendency to maintain internal stability in a system [56]. The term *homeostasis is synonymous with stability* [18].

In conclusion, to preserve the adaptive capacities of the cerebral cortex and increase its longevity, it is necessary to keep the number of toxins in its internal milieu, i.e., the magnitude of noise, at a low level.

3. 21st century: combating neurodegenerative diseases

3.1 Systematic approach to the problem

There has been an exponential growth in publications on neurodegenerative diseases since the 2000s. An analysis of papers published in leading journals for the last 20 years showed that the authors could be divided into two groups.

One comprises clinicians whose observations show that neurodegenerative diseases occur mostly among subjects aged 50 years or older. They affect not only the activity of the nervous system but also that of other systems (cardiovascular, hematopoietic, etc.). They cause inflammation of various organs and impair clearance [5] of toxic metabolites responsible for these effects and cell death.

The other group consists of neurophysiologists dealing largely with animal models of neurodegenerative diseases. They maintain based on the results of rat and mouse experiments that clinical symptoms observed in patients represent consequences rather than causes of the disease. The first disorders that eventually lead to neurodegeneration manifest themselves at least 20–30 years before pathological signs and symptoms become clinically apparent. For this reason, treatment is usually started only at the late stages of a disease and is actually aimed at managing its symptoms but not causes, accounting for the low therapeutic effectiveness. In a best case scenario, the pathology is suppressed but not cured [57, 58].

A German–Mexican round table conference with the participation of a few researchers from the USA was held in October 2018 to consider systemic analysis of neurodegenerative diseases. The results of discussions were summarized in a paper published by 19 authors under the title "Rethinking the Etiological Framework of Neurodegeneration" in the journal *Frontiers in Neuroscience* (2019) [5].

The discussions actually boiled down to the statement that the paradigm of the approach to the study of neurodegenerative diseases needs to be changed. Four main reasons for these conditions were identified.

First, weakening of the cardiovascular system, i.e., vascular pathology responsible for insufficient blood supply to the brain and the resulting deterioration of its energy metabolism. A combination of these events may cause a stroke.

Second, cell aging manifested as slowed replacement of old and dead astrocytes by new ones.

Third, impaired quality of brain purification from toxins.

Fourth, changes in the gastrointestinal biota as a causative factor responsible for a neurodegenerative disease. The composition of gastric and gut biota is also affected by enhanced acidity. Toxic metabolites can be transported from the bowel to blood, across the blood-brain barrier, causing intoxication and/or inflammation of brain structures.

All these reasons are presented schematically in Fig. 4a.

[5] *Clearance* (in medicine) is an indicator of the speed of tissue cleansing of harmful toxins.

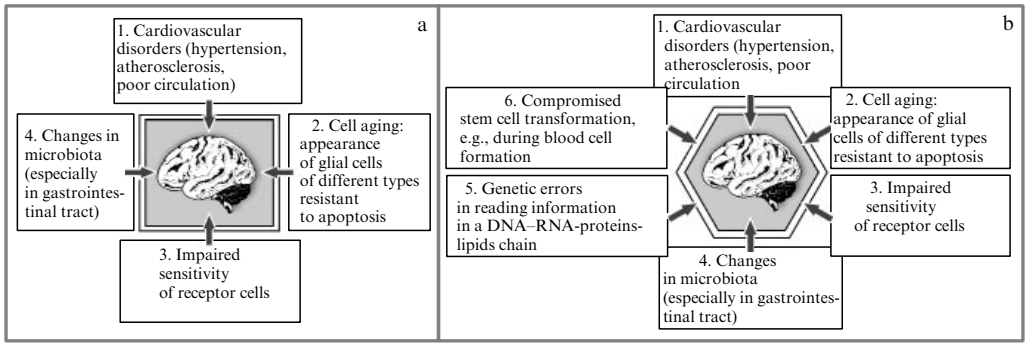


Figure 4. Causes of neurodegenerative diseases: (a) causes identified in [5]; (b) extension of the scheme by adding two more risk factors.

However, it is hard to agree with those who state that the development of neurodegenerative diseases is underlain only be the above four causes. There are at least two more leading to them [59] (Fig. 4b).

To be fair, it should be recognized that the authors of Ref. [5] understand that their list of causes is far from complete. They write: *We do not consider here genetic components as risk factors of neurodegenerative diseases since their comprehensive analysis can be found elsewhere*. They refer to [60].

The list of causes underlying neurodegenerative diseases is actually endless. It might include, inter alia,

• compromised gas metabolism (respiratory disturbances);

• locomotor problems (muscular dystrophy);

• impaired functioning of the endocrine system (reduced hormonal activity);

• disturbances in the energy-producing systems (mitochondrial dysfunction);

• the influence of environmental factors (too emotional a perception of environmental events leading to constant stress);

• poor condition of organs and systems (liver, kidneys, etc.) responsible for toxin elimination.

The resulting conclusion can be formulated as the saying 'where it is thin, there it breaks.'

The problem of combatting neurodegenerative diseases is not reduced to extending the list of their causes. What is actually needed is a dynamic study, from a biophysical perspective, of the mechanisms controlling the stability of living systems composed of a large number of interrelated subsystems, including the brain. It is equally desirable to reduce such study to examining a minimal number of interaction cycles, as shown in Fig. 5.

In what follows, attention will be focused on the transition presented in Fig. 5 and the related problem of brain purification from toxins.

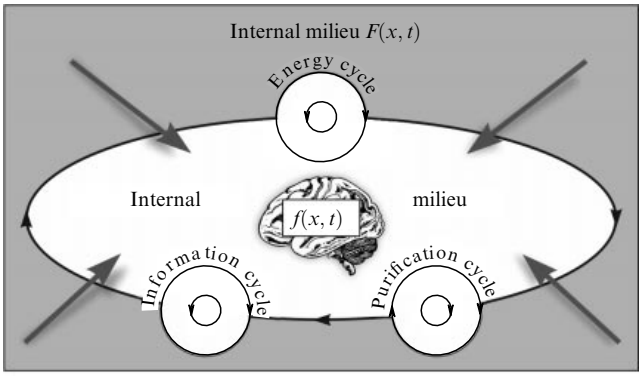


Figure 5. Three oscillatory interaction cycles in mapping information received from the external environment, $F(x, t)$, onto the brain's virtual model, $f(x, t)$. The three cycles form a unified 24-h cycle. Oscillations of each constituent cycle are phase shifted and partially overlap within the total daily period, then decay then again increase in amplitude and frequency.

3.2 From animal models to computer simulation technologies

Seemingly, a detailed study of pathophysiological processes leading to neurodegenerative diseases is possible only with the use of rats, mice, and other laboratory animals, because keeping them does not require great expenses.

In the end, everything depends on the correct problem setting. The murine genome is not significantly different from the human one, but the neocortices of mice and humans are totally different. Today, dozens of lines of genetically engineered mice are available for modeling neurodegenerative diseases in humans. For example, FUS-TGF19 mice can be used to model motor neuron disease by virtue of an FUS gene mutation, whereas 5xFAD mice having a triple mutation in the gene that encodes the APP protein and double mutation in the gene of the transmembrane protein presenilin are used to model a hereditary form of Alzheimer's disease. The list of such transgenic animals includes scores of variants [60, 61].

The pathological condition of affected mice is characterized by the presence of amyloid deposits, substitution of dead neurons by glial cells (brain gliosis usually associated with disturbances of blood supply), neurodegeneration, loss of memory, accumulation of intracellular amyloid protein Aβ, development of amyloid plaques, and massive neuron death.

It is, however, extremely difficult to line up the entire transition path through numerous hierarchical levels, from 'genetic' information obtained using transgenic mice to the systems controlling the stability of the human body. Experiments with knockout mice lacking a gene of interest allow the observation of a fragmentary mosaic of the causes of the disease. Assembling a whole picture from such a mosaic is fraught with uncertainties due to the fact that each element of the mosaic makes its own nonlinear contribution to the change in the general picture of the disease.

Great care is needed in investigations of neurodegenerative processes in humans and mice, because models do not guarantee clinical success.

The aforementioned differences are readily apparent in studies using the old method of inducing a stroke by surgical ligation of certain blood vessels in healthy animals [62, 63]. Marked plasticity of the rodent brain tends to distort the results [64]. The brain itself finds a new state of stability for the organism, thus giving the researcher the illusion that a drug of interest helps the rodent to recover.

It would seem possible to use a different approach to the investigation into mechanisms behind neurodegenerative diseases and their treatment as exemplified by the use of a culture of nerve cells growing in a petri dish. Recent studies using this strategy opened up additional opportunities for modeling early stages of neurodegenerative diseases. In vitro observations of neuronal networks permit studying the birth and death of nerve cells, as well as coupling formation and disappearance [65, 66]. In vitro experiments based on cell culture models have a long history [67]. The application of this technique in studies on Alzheimer's disease is described in Ref. [68].

What are the results? Competing processes in the cell control protein shape, transport, and degradation inside and outside it. These processes support the stability of normally functioning neurons. Disequilibrium is the main cause of diseases associated with improper folding of proteins that results in their dysfunction. They must be evacuated from the brain to avoid inflammation.

A group of Japanese researchers [69] elucidated mechanisms of this self-purification process at its earlier stages. They used a fluorescence analysis and genome-based screening of proteins; also, the pathway of their degradation was traced. It turned out that improperly folded extracellular proteins are selectively captured by a set of cell chaperones.[6] The capture is mediated through heparan sulfate receptors located on the cell surface. The cell takes up improperly folded proteins and digests them by lysozyme. A biochemical analysis showed that positively charged residues on the heterodimeric protein clusterin-HS synthesized by the cell itself originate from the splitting of improperly folded proteins and their conversion into low molecular weight wastes. This protein material electrostatically interacts with negatively charged HS groups. Its capture by the cell facilitates decomposition of amyloid β-peptide and other adhered proteins in the extracellular space. It can be concluded briefly that each cell keeps clean its nearest outer space by means of self-purification. It acts as a vacuum cleaner 'swallowing' improperly folded proteins and breaks them down into amino acids by lysosomes; thereafter, it 'spits out' the unwanted material.

However, all the above models simulate only components of real processes in the human brain. This mosaic has to be integrated into a whole picture. The mosaic hampers the use of the data obtained in practical applications. The paper by Ransohoff in the *Journal of Experimental Medicine* published in 2018 was entitled "All (Animal) Models (of Neurodegeneration) are Wrong. Are They Also Useful?" [70].

Ransohoff starts as follows: *The thesis proposed in this article is that it's not helpful for neurodegeneration drug development to perform preclinical efficacy experiments in animal models. George Box's epigram quoted above is commonly projected at the beginning of discussions of this topic, suggesting a 'don't let the perfect be the enemy of the good' stance. It isn't perhaps widely known among audience members, and possibly speakers as well, that Box was addressing participants at a statistical workshop and that the example he offered was Boyle's Ideal Gas Law, which is useful but not true for any real gas.*

In what follows, we shall try to demonstrate, reaffirming Box's thesis, that physico-mathematical models can be useful for obtaining a systemic picture of the underlying causes behind brain neurodegeneration even if the majority of the currently available models do not yet allow the neurodegenerative process as a whole to be described.

The creation of digital databases, including genotype and phenotype information, in combination with rapidly developing computational methods promotes the construction of new models. Databases are needed for the successful solution to the mathematical modeling problem. The main efforts to create such databases are concentrated in a small number of organizations. To the best of our knowledge, there are so far only four such institutions: the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL), the Parkinson's Progression Markers Initiative (PPMI), and the UK Biobank.

Systematization of information obtained in studies of heterogeneous groups of patients presenting with neurodegenerative diseases improves the efficiency of statistical approaches. However, the potential of approaches based solely on the analysis of large amounts of heterogeneous data is limited by their nature. A statistical analysis always caused a wary attitude, sometimes expressed in such sarcastic sayings as "lies, blatant lies, and statistics" or "average normal temperature in the hospital ward — two deceased and two patients with fever" or "the puddle can be bypassed to the right or to the left; we average ...."

Evidently, not only and not so much mean values and variances but also the form of distributions, i.e., signs of second derivatives, are of importance for the purpose of a statistical analysis. Finding correlations cannot serve as evidence of causation. On the basis of statistics, one can only put forward hypotheses, but their reliability must be verified in experiment [71].

The first attempt to construct a mathematical model was based on the results of investigations into the kinetics of toxin accumulation in the form of tau-proteins in patients presenting with Alzheimer's disease [72]. Computer modeling was also used to build up a model of the causes of aging due to DNA damage, insulin gene transcription factors TOR and Fox03a, oxidative stress reactions, dysregulation in mitochondria, and mitophagy [73]. A review of mathematical models of neurodegenerative diseases in [74] focuses on some of them, simulating energy metabolism and its influence on synaptic plasticity. Moreover, a multivariate Bayesian probabilistic biomarker assessment model was elaborated that provides a basis for modeling the earlier stages of Alzheimer's disease [75]. However, Bayesian models need to be treated with great care. In Bayes's formula

$$p(A|X) = \frac{p(A)\,p(X|A)}{p(X)} \tag{11}$$

the hypothetical probability $p(A)$ is originally based on the belief that event A is the main cause of the disease. Such fiducial (from Latin fides — faith, trust) probability based solely on the subjective faith of the researcher may be wrong.

[6] *Chaperones* make up a class of proteins contributing to the restoration of protein ternary and quaternary structure, formation, and dissociation of protein complexes.

For example, more than 40 years ago, J G Pederson wrote [76] that "fiducial probability" has limited success and is often error prone. Probability $p(X)$ is the probability of new information that can change the a priori belief that event A is the main cause.

The conventional probability $p(A|X)$ in the Bayes formula measures the extent to which our preliminary conviction was correct that the value of probability $p(A)$ corresponds to the main cause of the disease. The popularity of Bayes's formula [77] seems to be due to the fact that it gives an opportunity to apply the method of successive approximations and thereby accurately calculate the probability $p(A|X)$ which characterizes the true cause of a disease based on new information X obtained with the use of animal models. This provides a basis for the concept of the so-called *ideal Bayesian observer* [78].

However, one can prove the correctness of any probability $p(A)$ without examining the hierarchy of $p(A|X)$ and $p(X)$ probability weights. In other words, it is not enough to merely collect statistics of events: it is equally important to be confident in their reliability (i.e., stability of the result obtained), because any hypothesis can be proved by collecting all the 'pros' and increasing their weight, while lowering the weight of 'cons'. The researcher's thinking process tends to ignore general information about the frequency of events and concentrate on specific information about a concrete event of interest to them alone, thus distorting the real situation described by probabilities.

Finally, some researchers have tried to find the causes of neurodegenerative diseases by comparing changes in the morphology of brain structures in good health vs the presence of disease. A multidimensional model of morphological images of normal and pathological brain tissues was developed in order to clarify the relationship between morphological abnormalities that could be responsible for the development of Alzheimer's disease [79]. However, such models only ascertain the presence of the disease and the amount of harm it inflicts on the patient but do not answer the question about causes of the accompanying morphological changes, because their determination is hampered by the incorrectness of the inverse problems of physics, as was mentioned in a preceding paragraph.

All the aforementioned models disregard the fact that the main function of the brain is the treatment of information received from the outside world.

To summarize, *it is highly likely that a disturbance of information processing and storage in the cerebral cortex, with all other organs being unaffected, is not only an important indicator of neurodegenerative conditions but also their main cause. This inference follows from the fact that the brain regulates and supports its own stability and that of other organs by the feedback mechanism.*

3.3 Is it possible to slow aging in humans?

The authors of some publications that appear in the press from time to time inform readers that, because Alzheimer's disease is associated with the accumulation of beta-amyloid plaques, i.e., neurofibrillary tangles (Aβ), and hyperphosphorilated tau proteins in the brain, the treatment of this condition must be first of all directed at reducing these pathological depositions having a common cause that relates these two improperly folded proteins and suggests positive feedback between them. This may be a source of misconception and mislead researchers. Clinical trials of different pharmaceutical products proposed for the treatment of neurodegeneration in recent years have failed to demonstrate their ability to break this pathological cycle and proved their low efficiency. This leads to the conclusion formulated in a preceding section: brain pollution is a consequence, not the cause.

The authors of a recent study [80] proposed a combined vaccine capable of breaking the said feedback and preventing subsequent neurodegeneration. The vaccine aims to simultaneously reduce both Aβ and tau protein levels. However, its high efficiency in animals does not guarantee the success of its human testing. The vaccine is likely to prevent consequences of pathology but will not eliminate its cause. Hopefully, it may slow down the progression of Alzheimer's disease.

Natural selection over millions of years appears to have gone through a diversity of options and chosen a single possible one for the continuation of the eternal youth of humankind by fixing it at the genetic level. Children repeat the age cycle of the parents and renew their youth in each subsequent generation. As to the informational content of the brain, it is not completely determined by genetics. This has been shown more than once by those who study the behavior of identical twins separated in early childhood and trapped in socially different families. Brain content depends in the first place on teaching by the example of parents, teaching at school, and using other sources of information, including the Internet and self-education by the trial and error method.

There are currently two universally accepted methods for the struggle to prolong human life. The traditional approach, called "Healthy aging" — maintaining good health and activity until a ripe old age — is promoted by the World Health Organization (WHO). The essence of it is very simple: it is necessary just to change the shape of the human survival probability curve characteristic of the 19th–20th centuries and the early 21st century (Fig. 6a) by turning its trailing, obliquely falling front into a sharp decline in the area close to one hundred years (Fig. 6b). This task was declared long ago [81], but there is still no efficient approach to its solution.

In the struggle for funding research, the above WHO-supported approach was supplemented by another method. In 2009, a group of American experts in so-called *regen-*

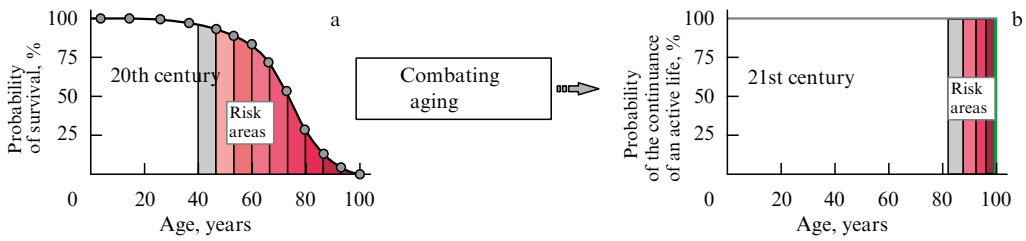


Figure 6. (Color online.) Life expectancy probability (excluding death cases — transport and industrial accidents): (a) in the 20th century; (b) the projected probability of human survival in the 21st century. Areas of risk of developing neurodegenerative diseases are marked in color.

erative medicine aimed at the development of a strategy to achieve negligibly slow aging set up the noncommercial SENS Research Foundation (Strategies for Engineered Negligible Senescence Research Foundation). Both its name and program were proposed by the gerontologist Aubry de Grey, one of the founders of SENS. The bioengineering techniques to be used in the work of the foundation include both currently available methods and those to be developed to correct damage and harm caused to the human body by age-related changes in cells, organs, and systems. The prime goal of the proposed combined therapies is to ensure slow aging by delaying the formation of age-related disorders. To this effect, a series of periodic therapeutic interventions is planned, directed to restoration, prevention, and elimination of all types of molecular cell damage responsible for the development of senile pathologies and degeneration. Seven sections of the SENS program encompass almost all topical problems facing modern medicine [6]:

- elimination of cancer mutations;
- preventing damage due to mutations in mitochondria;
- cleansing cells of accumulated toxins;
- removing intercellular toxins;
- replacement of dead cells;
- removal of malfunctioning cells;
- breaking intercellular polymer bonds.

The addition of one more item (prevention of age-related shortening of telomers) to this list is likely to create the illusion to philanthropists and officials who are far from science that it is possible to extend the lifespan of humans beyond 100 years of age in a short time. Some people believed in the possibility of reaching such a goal. As of 2013, the annual budget of the SENS Research Foundation was USD 4 million. In 2017, receipts amounted to $7.8 mln, including grants (25.5%) and additional donations from sponsors. Two million was allocated to research.

What can be said about this project? A systematic approach to solving a problem is always useful if a project has a worthy goal. The main thing is how realistic the solution is to given problems today.

In November 2005, the EMBO Journal published a report by 28 biologists under the title "Science fact and the SENS agenda. What can we reasonably expect from ageing research?" [82]. The authors stated that many concrete proposals of the SENS program are impracticable at the current stage of biomedical knowledge. It will take decades of hard work to push aside human diseases on the age scale. The experts concluded that the 'purpose-oriented' approach of SENS in gerontology is still going nowhere.

At present, there are no universal technologies for extending the human lifespan. The surest sign of failure to keep the promise to do this is the ease with which it was pitched to patrons by the organizers of the SENS project. The cause of failure of hasty promises is known from olden times: one cannot build the Tower of Babel without knowing the resistance of materials.

The key thesis in human longevity depends on the overall stability of the organism supported by normal brain functioning. The brain is known to operate information by its processing, storage, and prognostication, but we do not yet know how it does so.

In short, *the brain is an energetically and informationally open dissipative and far-from equilibrium self-sustaining organ. The latter characteristic is of paramount importance, because the brain's death kills the organism; everything else can be reparable to one degree or another. SENS organizers lost sight of this main aspect of the longevity problem in their program.*

4. Mathematical model of brain pollution and purification

4.1 Fundamentals of a mathematical description of the brain's work

A summary of the above facts is presented in Table 3.

It can be concluded based on the foregoing that the *slow sleep stage is necessary for removing toxic metabolites, whereas fast sleep is needed to get rid of toxins as by-products of information processing in the brain during dreams.*

Table 3. Kinetic characteristics of the brain's toxin purification system during sleep.

Slow sleep phase		Rapid sleep phase	
Removal of metabolic waste		*Removal of informational waste* (maintenance of constant ion balance in the interneuronal milieu)	
Factors involved		Factors involved	
Name	Characteristics	Name	Characteristics
Carrier — *Lymphatic fluid* (LF)	1) Driving force — *oscillatory movements of lung diaphragm + heart contraction + astrocyte-generated brain purification wave* 2) Fluid volume $\approx 2-4$ l 3) Renewal rate ≈ 2 l day^{-1} 4) Speed ≈ 4 mm s^{-1} 5) Mass-transfer pressure $\Delta p \approx 5$ mm Hg	Carrier — *Cerebrospinal fluid* (CSF)	1) Driving force — *heart contraction + oscillatory movements+astrocyte-generated brain purification wave* 2) Fluid volume $\approx 140-270$ ml 3) Renewal rate $\approx 2.4-2.8$ l day^{-1} 4) Electrolyte speed range $10-10^4$ mm s^{-1}: for sugars 16 mm s^{-1}, for urea 1200 mm s^{-1}, for water 6800 mm s^{-1}, for caffeine 4320 mm s^{-1}, etc.
Wave rhythm in organs maintaining fluid movements during sleep			
Lungs	Diaphragm movement rate at rest ≈ 2 Hz	*Lungs*	Diaphragm movement rate at rest $\geqslant 2$ Hz
Heart	Ventricle contraction rate at rest ≈ 1 Hz	*Heart*	Ventricle contraction rate at rest $\geqslant 1$ Hz
Brain	EEG frequency — delta waves (frequency 0.5–3.5 Hz)	*Brain*	EEG frequency — beta waves (frequency 13.5–40 Hz)

Summing up results of recent research on neurodegenerative diseases, it is possible to formulate the following five fundamental theses for a mathematical description of the brain's self-purification process:

1. The body's struggle against neurodegenerative diseases by cleansing the intercellular space of toxins is not confined to fluid (LF and CSF) movements alone, because the milieu between cortical subsystems is occupied by physical fields generated by ion-ion interactions between glial cells and neurons. This implies the necessity to take into consideration the energy determined by the relationship between these structures.

2. A bioengineering-based approach to solving the brain aging problem must be designed to identify generalizing functions in the form of the cycles shown in Fig. 5. It is necessary to write out at least two coupled reaction-diffusion equations to describe transitions in active media, the brain being one of them. Active media are defined as media possessed of the following two properties. On the one hand, they are open for an energy flux from the outside. On the other hand, they accumulate in themselves the energy coming from external sources. Waves can be generated and propagate in such systems, which means that the best mathematical language for describing brain work models is provided by wave mechanics [7, 8]. In active media in which two waves (e.g., W_1 and W_2) interact, the relationship between time t and space coordinates (x, y, z) is described in partial derivatives via the Laplace operator Δ:

$$\frac{\partial}{\partial t} = D\Delta\,, \quad \text{where} \quad \Delta = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}\,, \tag{12}$$

where D is the diffusion coefficient. In an elementary case of one simple wave $W(x, t)$ and unidimensional space (in the absence of drift), the relationship between time t and space x is described by the Fokker–Plank equation:

$$\frac{\partial W(x,t)}{\partial t} = D\,\frac{\partial^2 W(x,t)}{\partial x^2}\,, \tag{13}$$

where the diffusion coefficient $D = \text{const}$. The nonlinear interaction between two waves is described by the set of two reaction-diffusion FitzHugh–Nagumo equations [84–86] (at a point, it is a Van der Pol-type model [86]). Systems of reaction-diffusion equations began to be used to describe biosystems as long ago as the mid-20th century [7, 8, 87]. A collision of identical autowaves results in their annihilation [88]:

$$\begin{aligned} \frac{\partial u}{\partial t} &= f(u,v) + D_u\Delta u\,,\\ \frac{\partial v}{\partial t} &= g(u,v) + D_v\Delta v\,, \end{aligned} \tag{14}$$

where $D_{u,v}$ are diffusion coefficients, and Δ is the Laplace operator. System of expressions (14) corresponds at a point to

$$\begin{aligned} \dot{u} &= f(u,v)\,,\\ \dot{v} &= g(u,v)\,. \end{aligned} \tag{15}$$

3. The brain is an energetically open system having a set of stable and unstable states. Is it possible to maintain the stability of such a system by external control? Let us turn to the history of investigations into nonlinear processes. F Dyson wrote in his article [89]: "John von Neumann said that the computer will enable us to break down the atmosphere at each moment into stable and unstable regions. We can predict the behavior of the stable regions and know how to control the unstable ones." Von Neumann believed that an unstable area can be pushed by applying precisely measured small impacts in a certain phase to shift it in a desirable direction.

It would seem that Earth's atmosphere resembles the brain in the sense that it is a nonlinear system of alternating stable and unstable states. However, it is just an imaginary similarity. Von Neumann was overly optimistic as regards our ability to control atmospheric phenomena, because he ignored chaos properties. We now know that movements in the atmosphere are not merely locally unstable, they are chaotic. In chaotic movements, trajectories in the phase space move away from one another over time, which means that von Neumann's strategy of weather management is unpractical and can not be implemented. Nevertheless, his idea is suitable for describing quasi-chaotic biological systems on the order/chaos border. Any organism is such a system while alive [18]. The brain functions just as well at the edge of order and chaos, but its work has some peculiar features. Indeed, although closely spaced trajectories diverge with time, they do not move too far away from one another for a rather long time by virtue of the boundaries that hold them back. The brain itself blocks the move away from equilibrium in the phase space by its systems, e.g., the glial system. As a result, chaotic movements in time become suppressed, and the system can exist as a whole.

Laplace's view on the determined system as a perfect clockwork is not too different from the truth. The comparison of the brain to a clock shows that the mechanism continues to work, although its gears wear out and accumulate debris; the system remains stable for a long time balancing between order and chaos, meaning that such processes can be described at a certain time interval by the Newton equations and are reversible in time up to the amount of system contamination, i.e., the increase in viscosity of the internal medium to a critical level. Figuratively speaking, the brain slowly 'rusts' (membrane phospholipids are oxidized), but does not wear out abruptly. As a far-from-equilibrium biosystem characterized by self-organizing stability, the brain wears out sooner without constant training. Hence, the well known saying 'an idle brain does not live long'.

4. During sleep, the brain changes connections, puts things in order in memory, ranks the memorized information, and separates essential patterns from nonessential ones by changing excitation thresholds in different groups of neurons. This interaction regime is gradually broken due to energy dissipation and incomplete removal of metabolic waste in the course of water flow control by astrocytes. However, the low speed of this process with a large characteristic time enables certain people to live to 100–130 years.

5. The body's internal subjective time, τ [90, 91], and its work rhythm are determined by a variety of connections inside the brain. If an organ composed of excitable tissues, e.g., the heart, is isolated from other organs and the brain, it shows a relatively stable work frequency within a short time till it dies from an energy deficit or critical overfilling with toxic metabolites. This suggests that each organ has a pacemaker ('mini-brain') of its own. Each such pacemaker is

connected to the central nervous system (brain). The brain acts on all internal organs based on the results of information processing and changes their work rhythms to preserve the stability of the organism.

A key point in modeling neurodegenerative diseases is the disturbance of connections, because any living organism at all its hierarchical levels is a network of connections between wave interaction cycles.

4.2 Wave model of waste concentration prior to complete elimination of waste

When a neuron is excited, a pulse of K^+ ions generated by the entry of Na^+ ions through the axonal membrane propagates along the axon. Because the atomic weight of potassium is 1.7 times that of sodium, the substitution of Na^+ by an equal number of K^+ ions in the external medium close to the axon increases its density by 70%. The original density needs to be restored to ensure normal functioning of the neuronal network, since a deficit of sodium ions in the medium and its increased density are equivalent to a rise in the neuron excitation threshold, which can be detrimental to its work.

A pulsating CSF flow washes and mixes the exterior medium, thereby restoring electrolyte and density balance. This process can be regarded as the interaction between K^+ and CSF waves. It leads to a paradox: if neurons operate at a frequency of 100 Hz and the cleansing of the interneuronal space occurs at best with a frequency equivalent to the heart rate (1 Hz), the physical field (the ion level) inside the neuronal network is not constant and information transfer from one neuron to another is disturbed. This suggests the existence of one more wave mechanism responsible for the concentration of toxins before their fluid-mediated evacuation to the outside of the brain. A candidate for such a wave mechanism has already been found in the form of wave neuron-astroglia interactions. In what follows, these waves are designated $v(t)$ and $u(t)$. Let us consider the mechanism of these interactions.

In the framework of wave mechanics, wave-to-wave collisions have different outcomes, viz., annihilation, oscillation [92], and reflection [84, 93, 94]. The respective systems of equations can be used to describe, for example, an oscillating Belousov–Zhabotinsky chemical reaction [95]. O A Mornev, affiliated with ITEB, RAS, proposed new solutions in the Hodgkin–Huxley [96] and MacAllister–Noble–Tsien models [97].

Colliding waves flowing around an object are subject to bifurcation [98–100]. Moreover, wavefronts can repel each other at large distances and attract at small ones, depending on their chirality. In the case of bifurcation above the critical value, a pair of counter-propagating fronts can transform into a stationary front, and its shape becomes stable, forming symmetric patterns.

Elastic collisions are associated with a more intricate behavior [101, 102] and the repulsive interaction results in wave reflection.

Usually, when interacting waves seem to pass through one another in reaction-diffusion systems, it is difficult to say whether it is a real (soliton-like) interpenetration or reflection. A similar uncertainty is intrinsic in other systems, e.g., cross-diffusion ones [103–106].

Our study [9] using a variant of the Rinsel–Keller model [107] showed that it is the reflection that takes place and that this effect accompanies changes in the wave propagation regime. In this case, there is a parameter area in which the set wave propagation regime depends on the initial conditions. We also observed wave phenomena exhibiting a complex behavior: first, the reflection of waves with increasing distance (distant reflection); second, periodic wave transformation with a jump from one propagation mode to another (trigger interaction). Oscillatory and bistable regimes of wave collisions were found analytically and numerically [9]. The latter variant of wave interaction in the form of a sigmoidal model with the functions of the Tonnelier–Gerstner reaction [108] can be used to describe not only the neuron work but also brain self-purification from toxins. Their interaction in the form of null isoclines is shown in Fig. 7a. This model has multivalued solutions, both stable and unstable. In fact, this model in the language of wave mechanics is an extended version of the model with Rinsel–Keller excitation [107] (Fig. 7b).

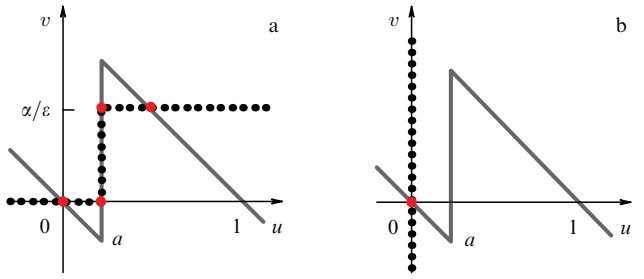


Figure 7. Sigmoidal models: bistable Tonnelier–Gerstner model [108] (a) and Rinsel–Keller model with a single excitable regime [107] (b).

The Tonnelier–Gerstner model is described by the equations

$$\frac{\partial u}{\partial t} = -u - v + H(u-a) + D_u \frac{\partial^2 u}{\partial x^2}\,, \tag{16}$$

$$\frac{\partial v}{\partial t} = -\varepsilon v + \alpha H(u-a) + D_v \frac{\partial^2 v}{\partial x^2}\,, \tag{17}$$

where ε, α, D_u, and D_v are positive constants, H is the Heaviside function, nonzero and having any sign (the use of the Heaviside function allows creating visual images of wave motion in the physical interneuron field), a is the excitation threshold, $u(t)$ is the CSF motion wave (cleansing wave), and $v(t)$ is the electrolyte pollution wave. (Note: designation a should not be confused with acceleration in expression (7); in this case, the letter a denotes the excitation threshold. We did not change this letter here, because it was used in our study [9] to denote the excitation threshold).

Waves $v(t)$ and $u(t)$ pulsate with similar frequencies (about 100 Hz) during the entire period of active brain work. In the general writing of wave interactions between two waves (16), (17), the function of reaction $f(u,v)$ in the first equation contains a cubic function, $f(u,v)=u-u^3+a-v$ or $f(u,v)=u(1-u)(u-a)-v$, whereas the second function shows the linear dependence $g(u,v)=\varepsilon(u-v-b)$ [9]. Wave annihilation in such reaction-diffusion models occurs when the solution to the respective system at a point (without diffusion terms) describes a stable oscillation of the limit cycle. For some parameter values, there is only one solution: a uniform stationary state. When both solutions coexist in the diffusion model, two propagating waves do not annihilate upon collision and realize the mutual wave reflection mode after a finite time. Since our paper [9] is readily available on the

Internet, we will not repeat all the mathematical calculations here, but briefly summarize only the final results. To recall, the excitation threshold a is

$$a = [(\alpha/\varepsilon) - 1]\,\frac{\lambda_2}{\lambda_1 - \lambda_2} - \frac{\alpha/\varepsilon}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_4)} \times \left[\frac{\lambda_4}{\mu_3}(\lambda_1 - \lambda_3) - \frac{\lambda_3}{\mu_4}(\lambda_2 - \lambda_4)\right], \quad (18)$$

with the following expressions for λ and μ:

$$\lambda_{1,2} = \frac{1}{2D_u}\left(-c \pm \sqrt{c^2 + 4D_u}\right), \quad (19)$$

$$\lambda_{3,2} = \frac{1}{2D_v}\left(-c \pm \sqrt{c^2 + 4D_v\varepsilon}\right). \quad (20)$$

The value of μ is given by the expression

$$\mu_{3,4} = c\left(1 - \frac{D_u}{D_v}\right)\lambda_{3,4} - \left(1 - \varepsilon\frac{D_u}{D_v}\right). \quad (21)$$

Equation (18) describes the excitation threshold a as a function of velocity c. The speed of pulse propagation along the axon ~ 25 m s^{-1}. The constant velocity of CSF movements in the intercellular space is low, $\sim 10^{-4}$ m s^{-1}. When a pressure jump occurs, the speed of a CSF pulse can increase by many orders of magnitude for a short time and approach the pulse speed along the axon. Parameter a is the threshold for switching from a stable upper state to a lower one.

The above basic provisions of wave interaction, (19)–(21), make it possible to observe by the *on-line* calculation method the mechanism of interaction between waves of purification W_2 (i.e., toxin concentration) and pollution W_1 (active work of neurons).

M A Tsyganov used numerical methods to consider some variants of wave interaction in the general case. We show here that some of them correspond to the mechanisms of purification of an electrolyte that ensures the restoration of the ionic and density balance after excitation (Fig. 8).

The first option (Fig. 8a) corresponds to the purification from K^+ ions during cyclic interactions between neurons and astrocytes. The second variant shown in Fig. 8b corresponds to the cleansing of the synaptic cleft after transfer of neuromediators from the excited neuron to an excitable one. In both cases, purification restores the original (pre-excitable) balance of the medium.

We shall confine ourselves to three examples. One is the cyclic cleansing of the interneuronal space in neuron-astrocyte wave interactions. The other two demonstrate purification of the synaptic cleft. The model algorithm is as follows: initial and boundary conditions are specified and the implicit Euler method is used [111]. The steps along the Δx and Δt axes are chosen to be of a certain size, e.g., $\Delta x = 0.01$ in space and $\Delta t = 2 \times 10^{-4}$ in time at fixed values of ε, a, and D_v. As a result, it is possible to observe the transition of the system from one stable state (0,0) to another $(1 - \alpha/\varepsilon, \alpha/\varepsilon)$. In this case, the threshold value corresponds to the value of α in the range $\alpha \in (0-0.05)$ at fixed ε, a and the following initial conditions:

$$\left.\frac{\partial u}{\partial x}\right|_{x=0,\,x=L} = 0\,, \qquad \left.\frac{\partial v}{\partial x}\right|_{x=0,\,x=L} = 0\,. \quad (22)$$

The initial conditions are set as follows: the system at $t = 0$ is localized in one of the two stable states. The limited area

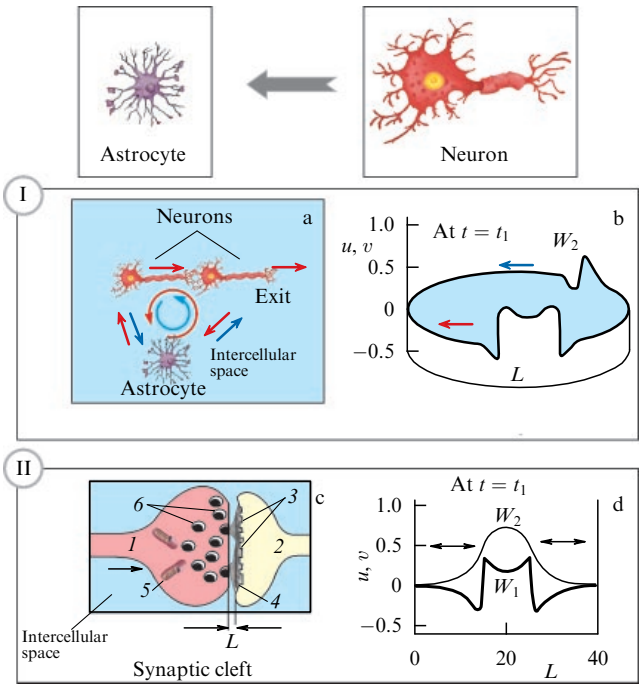


Figure 8. (Color online.) Two varieties of autowaves arising from neuron-astrocyte interactions, i.e., pollution and purification: I — cycle-forming interactions, (a) where W_1 (potassium wave) and W_2 (wave of the liquid from a pulsating astrocyte) move towards each other; (b) cyclic interaction with circular motion (L — circumference) with multiple collisions. II — interactions with alternating reflection of two waves from the walls of the synaptic cleft. (c) L — cleft width (~ 3–4 nm) where *1* — axon of the excited neuron, *2* — dendrite of the excitable neuron, *3* — neuromediator receptors, *4* — dendrite membrane, *5* — mitochondrion, *6* — depot of neuromediators in the form of vesicles; (d) remnants of neuromediators are washed out from the synaptic cleft by a pulsating astrocyte wave. W_2 — neuromediator wave after neuron excitation; W_1 — cerebrospinal fluid (CSF) wave generated by astrocyte pulsation.

$x \in [x_0; (x_0 + \Delta_0)]$ is excited. Two types of initial conditions were considered:

$$(\Omega_1)\colon u(x,0) = 0.05 \ \text{ and } \ v(x,0) = 0.95 \ \text{ for } x \in \left[x_0; (x_0 + \Delta_0)\right] \text{ and } u(x,0) = 0 \ \text{ and } \ v(x,0) = 0 \quad (23)$$

for other x values;

$$(\Omega_2)\colon u(x,0) = 0 \ \text{ and } \ v(x,0) = 0 \ \text{ for } x \in [x_0; (x_0 + \Delta_0)] \text{ and } u(x,0) = 0.005 \ \text{ and } \ v(x,0) = 0.095 \quad (24)$$

for other x values.

Wave interaction kinetics in multiple counter-rotations around a circle is exemplified by Fig. 9 with the following wave parameters: $\Delta_{0(1)} = 3$ and $\Delta_{0(2)} = 20$ in positions $x_{(1)} = 11$ and $x_{(2)} = 17$, $D_u = 0.1$, and $a = 0.01$.

Figures 10 and 11 illustrate two variants of cleft purification, i.e., the behavior of waves in collisions with boundaries. Evolution of wave interaction leads to a regime in which waves annihilate after collision. The W_2 wave formed at $\Delta_0 = 0.5$ moves to the right (Fig. 10).

Then, the velocity of wave W_2 decreases and its shape turns into that of W_1 propagating to the left. The processes are repeated after reflection at the boundary. When $\Delta_0 = 5$ and the initial conditions (Ω_2), the wave W_1 moves to the left,

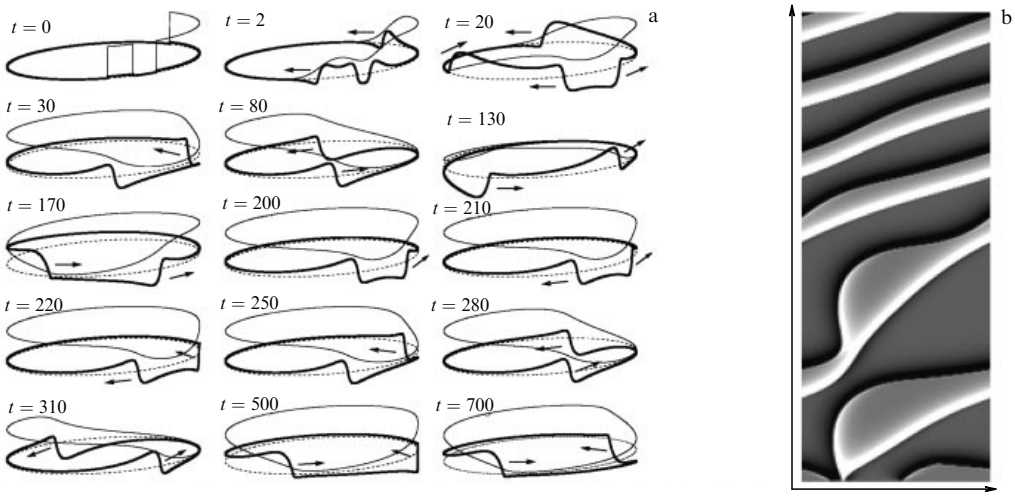


Figure 9. (a) Periodic transformations of W_1 and W_2. Wave interaction after initial perturbation of two regions occurs on a circle of circumference $L = 70$. Wave profiles u (thick line — cleansing) and v (thin line — pollution). (b) Spatio-temporal graph for the grey field $u(x, t)$, cleansing fields over time interval $t_{\max} = 700$ arb. units [9].

is reflected at the boundary, and takes the form of wave W_2 propagating to the right. The processes repeat until the velocity drops to zero. When reflected, the waves undergo mirror transformation of their shape. W_1 turns into W_2, and the former W_2 waveform becomes reshaped into W_1. This mirror transformation results in the pollution–cleansing process 'breathing' (Fig. 10a) and toxins being expelled from the cleft.

The following parameters are adopted in this example: cleft size $L = 40$ conv. units, $\Delta_0 = 5$, $D_u = 0.077$, $a = 0.01$. Wave oscillations gradually damp in the absence of energy inflow. In this case, there is no constant fluid flow through the cleft, and the initial movement of waves originates from the perturbation of a small central region of the medium due to neuron pulsation that causes the pulsation of astrocytes at moment $t = 0$. The source of these oscillations is a periodic change in the direction of propagation due to wave reflection from the boundaries.

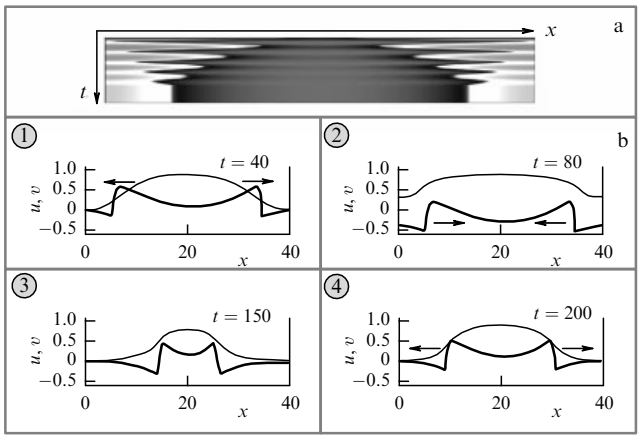


Figure 10. Wave interaction inside a cleft with boundaries: (a) space-time graph showing the halftone cleansing field $u(x, t)$. Time is plotted from top to bottom: from $t = 40$ to $t_{\max} = 200$ arb. units. (b) Specular reflection of the wave profile: u (thick line) and v (thin line). The change in the direction of motion of the cleansing wave $u(x, t)$ is indicated by the arrow.

Of special interest is the case of an obstacle in the cleft that splits a wave into two. The two cleansing waves interact with two pollution waves inside the cleft. Figure 11 illustrates such behavior during interaction of two pairs of coupled wavefronts in a medium with boundaries in the absence of a flow.

After a series of reflections (in the repulsive mode) and wave transformations, stationary structures are formed at the boundaries (Fig. 11a). It should be noted that these two pairs of flows do not merge. The picture remains stable. Each cleansing wave interacts with the respective pollution wave. Each of the two parts 'breathes', but their 'breathing' is synchronous.

This model has the following parameters: cleft size $L = 80$, additional flow is absent, initial perturbation of two regions of size $\Delta_{0(1)} = 5$ and $\Delta_{0(2)} = 10$ in positions $x_{(1)} = 15$ and $x_{(2)} = 45$, respectively, at $D_u = 0.077$ and $a = 0.01$.

The introduction of an additional low-speed wave with the threshold $a = 0.025$ slows the propagation of all waves and makes them stop. The third wave W_0 with a vanishing velocity corresponds to a high-viscosity medium. Other examples of various arising wave interaction patterns are presented in Fig. 12.

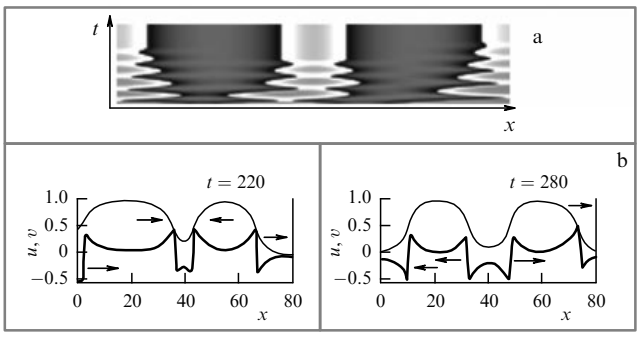


Figure 11. Interaction between two pairs of waves and the formation of a stationary pattern in a finite medium: (a) space–time graph for the grey field $u(x, t)$ (at $t_{\max} = 1200$); (b) profiles of u (bold line — cleansing) and v (thin line — pollution) [9].

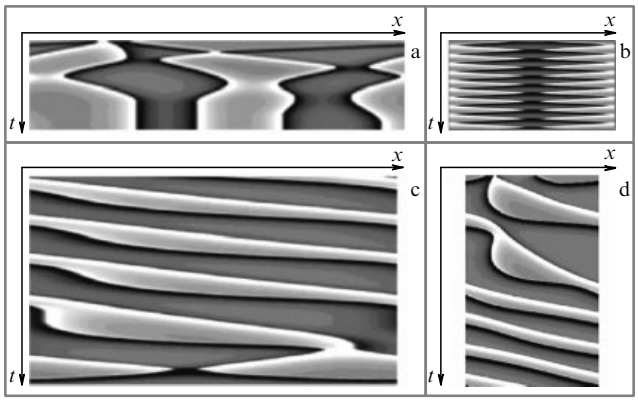


Figure 12. Diversity of stable wave patterns arising from interaction between cleansing and pollution waves [9].

Finally, the last question: "Why is the normal brain functioning limited?" The limitation is due to three causes:

1. Age-specific decrease in fluid reserves of the body resulting from density enhancement of all its structures in old age.

2. Reduced energy potential of all systems of the body as a whole.

3. Increased viscosity of all fluids (blood, LF, CSF) related to a decrease in the amount of water.

The body of an adult is 65–70% water. The total percentage reduction of body water is illustrated in Fig. 13a.

To conclude, mathematical models of complex processes can be divided into two large classes, so-called phenomenological and conceptual models.

The phenomenological models are formed on the basis of already discovered experimental facts about the behavior of the system. Such models are used to obtain a numerical description of dynamic phenomena inherent in an object of interest. Their construction implies transition from experiment to model.

On the contrary, the conceptual models are applied to consider a set of assertions in order to obtain a basis for a hypothesis about the possible mechanisms of the phenomenon of interest. Such models serve to confirm a hypothesis and present evidence in its favor in a visual form. In this case, the movement is from model to experiment.

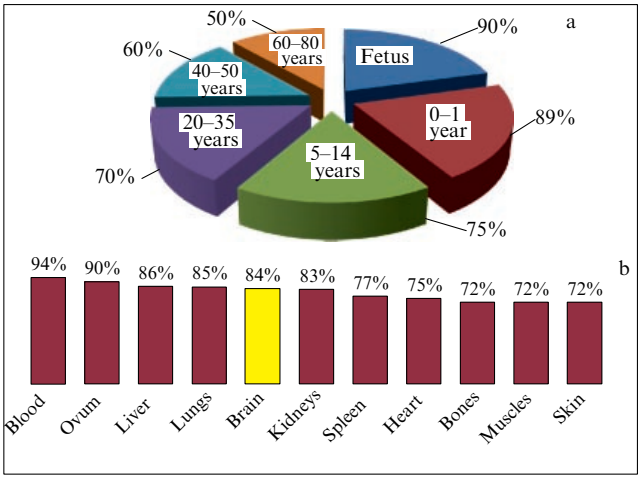


Figure 13. (Color online.) (a) Age-related variation of total body water percentage. (b) Percentage water content in human organs in adulthood (~25–35 years).

The models described in the foregoing are intermediate between conceptual and phenomenological. Many details of real processes are omitted in them, but they are illustrative. They are designed to elucidate variations in the dynamics of pollution and purification waves in response to a change in the wave interaction rules with the use of simple computer-assisted methods. To learn how to control these wave processes in the human brain, it is necessary to go from conceptual to phenomenological models. This requires an additional amount of quantitative data on brain functioning during both sleep and waking. So far, such data are scare.

The description of brain aging processes in terms of wave mechanics with the use of computational simulation models is more convenient than in the languages of other branches of mathematics, because it unifies the languages of topology, calculus of variations, complex analysis, etc. [109, 110]. As a result, visual metamorphoses of images appear that are easy to compare with the images observed in experiment.

To conclude the consideration of wave interactions in brain tissues, it should be noted that this process resembles washing everyday fabrics, the difference being 'washing' in the brain occurs on a nanometer scale.

To free fabrics from dirt, our great-great-grandmothers washed them using a paddle and a washboard. Wet clothes were first beaten with the paddle, then rubbed on a washboard, and finally rinsed in water. These procedures were repeated many times in succession. We can reproduce and observe a similar sequence of operations by changing wave images. First, there is a jump in speed (shock), then a decaying sinusoid (friction) and diffusion movement (rinsing).

The sequential interaction of two cycles, neuron ↔ astroglia ↔ heart and brain ↔ heart ↔ lung diaphragm, cleanses the brain of toxins in two steps. The first cycle concentrates the toxin suspension, the second (mediated through muscular systems) removes waste. The pulsating mobility of the heart and lungs moves lymphatic and cerebrospinal fluids most actively during sleep.

Some questions arise. "Is it possible to promote the self-cleansing process in the cerebral cortex from the outside, e.g., by creating, figuratively speaking, 'washing powders' to optimize the removal of toxins?" "Is it possible to make power systems capable of remotely pushing the emerging self-purification waves in the brain during certain phases of rapid sleep in an aging organism?" Finally, "Is it possible to create stimulants that would accelerate the movement of cerebral fluids?"

So far, these questions remain unanswered. With age, the amount of water decreases in all organs, including the brain, while their density increases. By the age of 70–80, the amount of fluid in the brain drops by almost 1.5- to 2-fold. Accordingly, the viscosity of the neurons, surrounding environment increases, which hampers toxin elimination.

5. Conclusion

Ten conclusions following from the above outline further approaches to slowing down brain aging and managing neurodegenerative diseases.

1. Mathematical simulation models provide an important addition to animal experiments. An advantage of mathematical modeling is it makes possible the identification of

uncertainties and thereby the choice of the shortest path to the goal.

2. The results of mathematical modeling presented in the foregoing suggest that the brain making up the middle component of the external environment → brain → body organs mapping triad at the subsystem level is the structure controlling the stability of wave interactions in the organism.

3. The cerebral cortex in cyclic interaction with the body controls via subcortical structures the heart rate, respiration rate, and functioning of other organs, which ensures the formation of a set of wave patterns for a compromise in the search for stability among changes in the external environment, body, and brain. The neocortex makes humans different from other species; therefore, animal experiments do not always lead to successful attempts to obtain an effective way to combat neurodegenerative diseases in humans.

4. The neocortex of each person is unique because, unlike other structures, it is not genetically determined. The core stores information about life experience and information processing skills. The neocortex not only distinguishes us from animals but also make individuals different. Memory operates via a set of controllable connections between patterns formed by neuron clusters.

5. An intervention in the body and the work of the cerebral cortex from the outside to promote the brain's self-purification activity occurs blindly and can be successful only with probability $p = 1/n$, where n is the number of different situations. If $n \to \infty$, the probability $p \to 0$. It is necessary to observe on-line exchange dynamics of all patterns of different shapes, i.e., to have a method for their registration and recognition in time and space in the same brain at the time of its medical treatment.

6. Processes at the cellular level in neuronal networks and in the intercellular space proceed on the millisecond scale in time and on the nanometer scale in space. Unfortunately, a repertoire of experimental methods for observing and recognizing their waveforms in space and time is still lacking.

7. Positron emission tomography (PET) has a low temporal resolution (≈ 10 s) insufficient for studying and distinguishing pattern shapes and dynamics. The temporal resolution of electroencephalography (EEG) is much higher (up to 2 μs), but its spatial resolution is rather low. Therefore, these techniques permit us to observe interactions of neuronal groups only as a whole. The wave pattern is smeared over space, and its borders and transitions are practically unobservable. The implantation of microelectrodes would increase the spatial resolution, but this invasive method can not be used in people. Finally, functional magnetic resonance imaging (fMRI) allows recording changes in oxygen consumption and therefore evaluating the rate of metabolic processes. The spatial and temporal resolution of this technique is of the order of 1 mm and 2 s, respectively, which makes it equally inapplicable in the studies in question [111–113]. Great hopes are placed on the development of neurophotonics. Formally, the temporal resolution of its methods is unlimited, and the spatial resolution is determined by the wavelength of the light used in the study. However, neurophotonic methods are also invasive, with the resulting disadvantages and uncertainty of results.

8. The algorithm of the brain purification process can be arbitrarily represented in the form of four successive stages:

(1) *reduction in waste particle size* at the cellular level (breakdown of large improperly folded proteins and their aggregates);

(2) *waste transfer into containers* (removal of small waste particles from cells into the intercellular space and from the intercellular space into zones where they do not disrupt the work of neural networks);

(3) *waste evacuation into a mobile fluid* (first into LF, then into venous blood);

(4) *removal of toxic waste into the external environment* (after processing and detoxification in the liver and kidneys).

Some amino acids resulting from protein breakdown are reused by brain cells for their own needs.

9. Were it possible to increase the space-time resolution of fMRI by two orders of magnitude, von Neumann's dream could be realized of managing unstable regimes by directing purification waves in concrete phases of the cerebral cortex to the steady state by precisely measured weak magnetic pulses. [7] This would help to speed up the removal of toxins and thereby optimize the treatment of Alzheimer's disease.

10. There is a lung lavage procedure in which a washing solution is inoculated into the airways and then collected to measure the toxin content in the sputum. The question arises: "Is it possible to wash the brain using a special mixture with a moderate lipophobic-hydrophobic index?" Such liquid could be, for example, a perfluorocarbon emulsion containing surfactant-coated particles. Preliminary studies to this effect were carried out in the early 1990s at the Dnepropetrovsk Medical Institute and Kiev Research Institute of Neurosurgery [117–119]. They demonstrated the effectiveness of such emulsions in animal experiments and some clinical cases. The future will show whether it is possible to create an efficient emulsion for brain lavage and techniques for managing unstable processes in the brain.

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[7] In the 21st century, certain companies have started producing devices to stimulate brain work by external magnetic fields [114]. To recall, Jacques Arsene d'Arsonval used an alternating magnetic field to stimulate neural structures in the 19th century [115]. Excitation of the visual areas of the cortex leads to the appearance of phantoms in the form of images. Synesthesia, such as fusion of sensations of color and sound or letters and color, represents analogous situations arising and fixed in memory [116]. Will it be possible to safely stimulate brain cleansing in this way? There is no answer yet.

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