21st century: what is life from the perspective of physics?

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<u>Abstract.</u> The evolution of the biophysical paradigm over 65 years since the publication in 1944 of Erwin Schrödinger's *What is Life? The Physical Aspects of the Living Cell* is reviewed. Based on the advances in molecular genetics, it is argued that all the features characteristic of living systems can also be found in nonliving ones. Ten paradoxes in logic and physics are analyzed that allow defining life in terms of a spatial-temporal hierarchy of structures and combinatory probabilistic logic. From the perspective of physics, life can be defined as resulting from a game involving interactions of matter one part of which acquires the ability to remember the success (or failure) probabilities from the previous rounds of the game, thereby increasing its chances for further survival in the next round. This part of matter is currently called living matter.

1. Introduction

Sixty five years ago, Erwin Schrödinger gave a lecture in which he broached the idea of studying life processes at the atomic and molecular levels. In 1944, he substantiated this approach in the book entitled *What is Life? The Physical Aspects of the Living Cell* [1]. The book was translated into Russian and published under a slightly modified title, *What is Life from the Viewpoint of Physics* in 1947 and 1972.

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Received 2 December 2009, revised 15 January 2010 Uspekhi Fizicheskikh Nauk **180** (4) 337–369 (2010) DOI: 10.3367/UFNr.0180.201004a.0337 Translated by Yu V Morozov; edited by A Radzig The year 2009 was an eventful one with plenty of significant dates in the context of the issue discussed in this communication. It marked the 200th birthday of Charles Darwin, the 150th anniversary of his *On the Origin of Species by Means of Natural Selection* [2], and the 200th anniversary of issuing *Philosophie Zoologique* by J B Lamarck [3]. Schrödinger's metaphor, 'Life is the existence of aperiodic crystals', influenced many researchers, including Francis Crick and Maurice Wilkins. The description of the DNA double helix in 1953 [4] laid the foundation of modern molecular genetics.

The first decade of the 21st century witnessed the development of nanotechnologies alongside the creation of formerly unknown materials and devices, such as nanobiocoatings, nanobiocontainers, nanobioplatforms, nanobiomotors, and neurocomputers. These processes are paralleled by the further extension of global information networks, the appearance of planar bioinformation fabrics (biochip technologies), and the transformation of classical medicine to biomedicine, opening up the prospect of restoring the functional abilities of every patient on an individual basis, taking into account the specific features of his/her genetic portrait. Taken together, these facts prompt a new definition of life, different from that given by Schrödinger 65 years ago. Since that time, Physics-Uspekhi has published over 20 reviews [5-26] pertinent to the issues addressed in the present work, designed to approach the question of the definition of life from the standpoint of modern biophysics.

2. Life. The problem of definition

2.1 The change in paradigm

One can speak about two lines of investigation, *bottom–up* and *top–down*, of life processes and biological evolution.

In April 2003, the mass media announced the completion of a large-scale international scientific project undertaken to determine the sequence of three billion chemical base pairs which make up DNA and store human genetic information. Concurrently, genomes of many microorganisms and multicellular animals were sequenced during the 12-year project. All these organisms were found to have a universal genetic code, even if differing in the number of genes. Overall, the distinctions proved not so large as expected.

Initially, there was no shortage of optimistic forecasts for the changes that human genome decoding could bring to evolutionary biology and modern medicine, even if they were greeted with skepticism in some circles. Human DNA proved to contain only 30,000 genes, or at least three times fewer than the expected 100,000. The mouse has almost as many. Moreover, murine and human genomes qualitatively differ in the structure of only 300 genes. Some 100 human genes are similar to those identified by which time in viruses and bacteria. Up to now, the nature of extended nucleotide sequences located between human genes and their role in the development of an organism remain obscure. Only a 10^{-4} fraction of nucleotides of the human genome are operational. Nevertheless, the bottom-up studies, from a molecular level to integral organisms, made it possible to follow up the evolution of nucleic acid and protein sequences.

Complete genomic sequence analysis permits studying the history of karyotype or the entire set of chromosomes in living organisms. Similar to genes in the DNA chain, the event here consists in the translocation of chromosomal 'texts', the fusion and breakage of chromosomes. Knowledge of these changes allowed phylogenetic trees to be built based on whole genomes. Events contributing to genome formation (duplications, horizontal transfers, etc.) proved to be of primary importance for the study of prokaryotes characterized by remarkable genomic plasticity. A 30% difference between genomic composition was revealed at this level for strains of a single species [27].

Finally, a new possibility has recently emerged for surveying the evolution of regulatory systems and the hierarchy of gene expression levels. It may be expected to bring an understanding of such processes as the evolution of the animal body structure, the irregular rate of morphological evolution, the saltatory evolution and so forth. The problem of transition from one-dimensional genetic code to threedimensional morphological structure of a living organism remains a matter of dispute. It provides a basis for debate between advocates of evolutionary theory and *creationism* [1].

Worthy of mention is the replacement of the molecular biophysics paradigm within the span of past 65 years. Astrophysics experienced a similar change over the same period, and high-energy physics even earlier. Molecular biophysics started to work with databases that have grown in size in geometric progression. The existence and availability of large volumes of genetic information enabled researchers to arrive at important conclusions based on comparison of decoded genomes of different living species.

2.2 The advent of new biophysical sciences (genomics, proteomics, metabolics)

Decoding complete nucleotide sequences in many genomes, including the human genome, and sequences of metagenic DNA fragments of organisms from different natural communities allowed their polymorphism to be investigated and yielded data on hierarchical gene transcription. In this way, *genomics* fused with *proteomics*, or the science of the origin of proteins and their biosynthesis. Today, the efforts of researchers in this field are organized as a series of complementary DNA \leftrightarrow RNA \leftrightarrow protein studies, giving cause to speak of a new science, *metabolics*, that is rooted in molecular genetics and studies how various biochemical reactions are brought together into synthetic pathways to new substances. In the end, the three sciences integrated into one, *genomics* \leftrightarrow *proteomics* \leftrightarrow *metabolics*.

The knowledge of many genomic sequences makes possible in a number of cases the detailed reconstruction of the history of structural reorganization in regulatory systems of certain bacteria and yeasts. Experimental studies of regulatory systems of multicellular eukaryotes give even more convincing results. For example, the replacement of the regulatory domain in the Prxl gene controlling the forelimb growth by the regulatory domain of the homologous bat gene (without altering the gene itself) resulted in the lengthening of the murine foreleg [27].

Comparison of those few regulatory systems of multicellular eukaryotes that were investigated at the molecular level showed that radical changes in body structure may even result from relatively small interchanges in the hierarchy of regulatory modules. However, comparison of gene sequences has thus far failed to shed light on the earliest stages of the evolution of biochemical systems [28].

2.3 The evolutionary history of living organisms at a molecular level

Construction of the *molecule-based* phylogenetic tree appears to be the sole reliable way to restore the history of the evolution of life, first and foremost of bacteria and viruses. There have been scores of studies designed to explain when and how various pathogenic bacteria, viruses, and their vectors came into being. For example, comparative genetic studies of numerous strains of the causative agents of human and bovine tuberculosis, *Mycobacterium tuberculosis* and *Mycobacterium bovis*, raise doubts about the hypothesis for the recent origin of *M. bovis from M. tuberculosis* [27]. Such examples amount to several tens, not only at the bacterium– virus level but also at the level of overall phylogenetic row of plants and animals.

Genomic research helps elucidate the origin of new genes. One DNA copy resulting from duplication retains its function, while the other may acquire a different function. Indeed, comparative genetic analysis revealed accelerated evolution soon after duplication event, which in many cases involved only one of the copies. Reproduction of individuals heightens the mutation effects, whereas their extinction caused by environmental changes leads to convergence among the survivors.

Convergence may be exemplified by the biosynthesis of cryoprotective proteins in fish inhabiting Arctic and Antarctic waters. Glycoproteins preventing formation of ice crystals that destroy cells are found in the Arctic cod (*Gadidae*) and Antarctic toothfish (*Nototheniidae*). They contain disaccharides bound to a large number of tripeptide repeats (threonine– alanine–alanine). However, comparison of exon-intron gene structure and analysis of synonymous codons point to an independent origin of these proteins in northern and southern species; specifically, they suggest that the cryoprotective glycoprotein of the purplehead evolved from trypsinogene, a precursor of the proteolytic enzyme [29].

Analysis of existing mitochondrial genomes and Y-chromosomes in humans (*Homo sapiens*) has shown that 'Eve' and 'Adam' population — the ancestry of all modern humans — inhabited Africa some 100-200 thousand years ago. Extensive studies demonstrated that South African tribes diverged genetically to give rise to another line of humans some 120 thousand years ago. Modern humans started to abandon Africa some 60-70 thousand years ago. In the glacial period, they migrated through Asia to reach the American continent via the frozen Bering Strait or a thenexisting isthmus. One more migration route brought humans to Oceania and Australia (the first people appeared in southeast Australia some 45,000 years ago). The DNA of modern humans bears traces of these ancient migrations [30], even if the above estimates are somewhat arbitrary due to the irregular rate of the molecular ('evolutionary') clock.

Sequencing (determination of the exact order of nucleotide bases and amino acids in individual DNA and protein chains) of the female-transmitted mitochondrial and nuclear DNA of extinct hominids is an extremely difficult task due to the small amount of the material available for analysis. However, every year is marked by significant advances in this interesting area (both for researchers and the lay public). It is now safe to assert that all modern races are historically *closely related*; their genomes differ only by 0.1% [30].

2.4 Identification of factors accelerating the evolution of living systems

Molecular genetics provides evidence of two factors accelerating evolution. Genomic sequencing demonstrated *complete genome duplications* in the history of many taxons; in other words, genetic information was transmitted as whole texts. For example, complete genome duplication in progenitors of the modern yeast from genus *Saccharomyces* was revealed by comparison with sequenation data for *Kluyveromyces waltii* genome. Similarly, complete genome duplications were identified in the history of fishes and premature vertebrates. Genetic analysis makes it possible not only to describe duplications and other events (chromosome fusion and breaks, major inversions, etc.), but also to reconstruct hypothetical ancestral karyotypes [31].

The second factor accelerating evolution is shown to be horizontal gene transfer; by this mechanism, organisms appear to have borrowed genes from one another. Extensive gene transfers are documented between bacteria and archeans and even eukaryotes. It was especially frequent among closely related species but very rare between taxonomically distant organisms [31].

Many of these discoveries were awarded the Nobel Prize long after the publication of Schrödinger's book [1]. Still, the difference between living and nonliving matter from the physics viewpoint remains to be elucidated.

2.5 Borderline between living and nonliving matter

It is difficult to offer a substantive definition of living matter. Many textbooks list a number of traits supposed to be characteristic of living organisms, but on closer examination they prove to be equally inherent in objects regarded as nonliving. Table 1 illustrates such a comparison. It exposes the

Characteristics of living matter Characteristics of nonliving matter No. 1 Living organisms are characterized by an ordered All nonliving objects satisfy the same condition and are arranged on the hierarchical hierarchical structure principle: elementary particles \rightarrow atoms \rightarrow molecules \rightarrow macromolecules, etc. 2 Whirlwinds, typhoons, wind, and lightning receive energy from the Sun, while Living organisms are open systems, acquire energy from the environment, and use it to maintain their volcanic eruptions, earthquakes, and continental drift are accounted for by the consumption of energy from the Earth's interior. Thus, openness is not unique to high structural order living systems 3 Ability to respond to external stimuli (receptivity) is Magnetization, electrization, luminescence, polarization, deformation, inertia, moa universal property of all living systems tion, disintegration, etc. are forms of response of nonliving objects to external actions 4 Responses of nonliving objects are usually directed to 'neutralize' external influences Ability of living organisms store information about their previous states and adapt to a changing and thereby to retain their initial states (Le Chatelier and Lenz principles, Newtonian environment inertia). Some nonliving objects exhibit elements of memory, e.g., magnetic hysteresis 5 Living organisms develop and become more compli-Astrophysical (formation of interstellar gas-dust clouds \rightarrow nebulae \rightarrow galaxies), cated geophysical (formation of a hot planetary core \rightarrow relatively cold mantle of a planet surface \rightarrow tectonic platforms \rightarrow continents and oceans), and chemical (substrate transformation into products) processes also experience evolutionary alternations and become more complicated Coacervate droplets of organic matter can grow and divide. Crystals grow from salt 6 All living things propagate solutions. A fragment of one broken crystal turns into a nucleus for a similar crystal Black smokers and white columns at the oceanic bottom also multiply 7 Stable eddies, tornadoes, Rayleigh-Bénard convection cells are self-regulating Living organisms are capable of self-regulation and regeneration of damaged structures systems. A broken icicle grows again. Crystals are able to repair defects (dislocations). Thus, neither self-regulation nor regeneration are unique to living organisms 8 Living organisms are capable of metabolism and This property is intrinsic in all oxidation reactions, e.g., burning. Energy conversion is a common property of nature at large rather than a specific feature of living systems exchange of matter and energy with the environment for reproduction and expansion Ferromagnetic particles in a magnetic field, ions in an electric field, Brownian particles 9 Living organisms exhibit taxis in a thermal field, and mass-carrying particles in a gravitational field possess this property 10 Departure from equilibrium is inherent in living Rains, snowfalls, avalanches, waterfalls, etc. exemplify nonequilibrium states things

Table 1. Characteristics of living and nonliving matter.



(the phage adsorption apparatus) $400 \times 200 \text{ nm}$



Figure 1. Bacteriophage T4: *is it a living or nonliving entity*? Threedimensional (3D) reconstruction of the bacteriophage (a), 3D-reconstruction of its extended (b) and contracted (c) tail. (From our work dating from the 1980s [36-38].)

futility of any attempt to define a single universal evidence of life. In other words, *living systems do not possess properties not found in various nonliving objects*.

Moreover, in the context of the aforementioned traits, such entities, for instance, as *viruses or bacteriophages cannot be regarded as living* in the proper sense of the word; rather, they constitute complex composite materials capable of performing such functions as searching, recognition, or multiplication by destroying cells or bacteria (Fig. 1).

We spent almost 15 years elucidating the three-dimensional structure of the bacteriophage and understanding the operating mechanism of this molecular machine [32-35]. It lacks most characteristics listed in Table 1, and does not maintain internal biochemical processes or consume or utilize energy (food). Moreover, the bacteriophage is unable to reproduce itself. Viruses are machines composed of protein and DNA (sometimes RNA) subunits. DNA, RNA, and protein are polymeric materials with a charge distributed along their

length. Any heterogeneous polymer material is characterized by a variety of states relating to its spatial configuration, each corresponding to the ambient temperature and anion/cation composition of the surrounding medium. Once an ion, cation, or any polar particle alters or neutralizes the charge in a certain polymer region, the polymer bends and assumes a new spatial configuration (conforming to the charge action) to match the energy minimum in the medium \leftrightarrow polymer system. The polymer gets back to the initial state after the charged particles are neutralized in one way or another [39].

Briefly, the interaction scenario involving a bacteriophage and a bacterial cell is as follows. The bacteriophage encounters the cell and spreads out its end fibrils to probe the chemical composition of the cell's outer membrane. If the cell is appropriate for a given species of bacteriophages, the phage attaches to the outside of it, contracts its tail sheath, and releases DNA (or RNA) packed in the head, which is 'swallowed' by the cell.

From this point onwards, the biochemical apparatus of the bacterial cell functions for a span of 20 minutes under the control of phage DNA. In the beginning, it synthesizes special enzymes that arrest production of the cell's own proteins and DNA and stimulate synthesis of phage DNA and proteins. These newly synthesized proteins are assembled first into constituent structures (heads and tails), and then into whole bacteriophages (Fig. 2).



Figure 2. Successive stages of phage assembly [40]. Digits are serial numbers of genes whose products are used at respective stages. Solid arrows indicate stages reproducible by self-assembly *in vitro*. The phage head cannot be reconstituted by self-assembly and needs the involvement of regulatory genes.

After approximately 20 minutes, all the available energy of the victim cell is spent for reconstituting new bacteriophages. Rupture of the cell envelope releases 100-200 offspring phages ready to invade new bacterial cells.

Thus, viruses and bacteriophages partially possess properties that, on the one hand, are certainly inherent in living organisms, but, on the other hand, are so much reduced that these particles can be assigned to nonliving objects. However, virology is a biological science. Therefore, the classification proposed in Table 1 is inconsistent and leads to paradoxes.

Formalization of the question of the definition of life is a matter of course. There are many meaningful physical terms and two sets of objects, V (*vita*) and M (*mort*), with the region of overlap in the space of chosen features. Their combination should be used to separate V and M sets in the light of available scientific facts. In other words, it is necessary to transform the entangled set of traits, F(V, M), into two isolated sets:

 $F(V,M) \to F_1(V) + F_2(M) \,.$

In such a formulation, $F_1(V)$ provides the definition of life. Evidently, the separation procedure is the classical problem of image recognition making possible the construction of logic functions of initial features. The difficulty lies in the fact that it is impossible to predict the combination of features that may prove useful for the separation. The borderline between living and nonliving matter is changeable and the knowledge of it comes to us through our perception of the outside world.

3. Interplay between living and nonliving matter (ten paradoxes)

3.1 Plato-Socrates' paradox

At the turn of the 20th century, a series of public disputes were held in Moscow between upholders of Christian philosophy and advocates of a materialistic worldview. Contemporary records describe them as an important ecclesiastic and cultural event [41]. The dispute between idealism and materialism actually pertains to the philosophical question of the meaning of life. The clerics affirmed compatibility between religious faith and natural-science outlook. The materialists raised objections. Admission of the compatibility of scientific knowledge and religious experience was perhaps the central argument in the reformed apologetics of the church. The situation was complicated by the fact that some natural scientists appeared to share religious beliefs [42]. Memoirists described the event as a debate of intellectuals taking up a role of controversy, conflict and contradiction. It all came to nothing, the truth was not revealed in the dispute. The further course of events showed that once God is dethroned his 'position' does not remain vacant too long. The totalitarian regime that succeeded its predecessor created a new 'religion' and physically eliminated its opponents: some were exiled, and others were sent to labor camps or shot.

Such discussions seem to make no sense, because science and religion apply to different sides of the human conscience. Faith transmits uncertainties of knowledge into the sphere of subjective perception, while science puts them to objective experimental verification.

It may be thought that any attempt to find an adequate definition for the phenomenon of life is doomed to failure.



Plato says: "The next statement by Socrates will be false." Socrates responds: "What Plato said is true." These two statements create a vicious circle. If a third party interferes by arguing that Plato tells a lie more often than Socrates, it breaks the *symmetry* of the statements and the state of a closed stable contradic-

tion circle evolves into the movement pointed to statistical disentangle of contradictions. Let us now explore the probability of one interlocutor (Plato or Socrates) telling the truth or a lie more oftener than the other. If n of Plato's N statements are true, Socrates tells truth m times. In u cases, it is impossible to distinguish between the truth and the lie. At N = n + m + u, the probabilities that both Plato and Socrates are telling the truth are $p_{\rm P} = n/N$ and $p_{\rm S} = m/N$, respectively, while the probability of their speaking lies is defined as $q_{\rm P} = (N-n)/N = m/N \pm \varepsilon,$ $q_{\rm S} = (N-m)/N = n/N \pm \varepsilon,$ where $\hat{\varepsilon} = \pm u/N$. If $\varepsilon \to 0$, the probability P of coming back to the starting point of the vicious circle is 1 only in the symmetric case, when p = q = 1/2, because P = 1 - |p - q|. Otherwise, when $p \neq q$, such probability is less than unity, i.e., the starting point of the vicious circle is unattainable and the contradictions can little by little be resolved.

Such supposition ensues from two Gödel's incompleteness theorems [43, 44]. The question is whether the totality of the available facts and the language of genomics, proteomics, or metabolics are sufficient for the identification and description of traits distinguishing living and nonliving things under experimental conditions.

We shall attempt to give the definition of life in terms of ternary logic, bearing in mind the limitation imposed by Gödel at his time. The two notions, *truth and lie*, need to be supplemented by a third, *uncertainty*. Then, the definition of life can be given to the accuracy of its *uncertainty* at the open intersection boundary between the sets of living and nonliving things. This approach is based on the so-called *Plato–Socrates' paradox* (paradox 1). In the ternary logic, the scope of notions is extended.

When formulating the definition of life, humanity believes that it enriches life, but the consistency of this new and richer (as we thinks in our hearts) theory cannot be proved by its own ways and means (second Gödel's theorem); it again leads to a vicious circle. As the definition is extended, it becomes more complicated, giving rise to the tautology 'life is everything alive'. In the light of the above paradox, if this assertion is true, it is at the same time false, and vice versa. In other words, it is internally inconsistent. Such assertions can neither be proved nor refuted in the framework of *binary logic* [45].

3.2 Zeno's paradox

The operation method provides a sure way of creating a knowledge base. In this method, *any postulate and hidden parameter whose corollaries cannot be tested in experiment should be regarded as unscientific.* Disregarding the operation method leads to paradoxes. Let us consider the simplest among them, Zeno's paradox (paradox 2).

Given there is a limit of measurement accuracy, ε , the distance s_A run by Achilles by the time he has passed the tortoise is described by the relation $q_{n_{\text{max}}} = 1/m^{n_{\text{max}}} = \varepsilon$ at $n = n_{\text{max}}$, as shown in Fig. 3. Thus, the paradox is actually a fallacy.

Very small intervals cannot be measured in physics, even less so in biology. If wavelength $\lambda = 10^{-50}$ cm is used as a ruler, the energy (in the CGS system) needed to generate such

Paradox 1



Paradox 2

It is known as Achilles and the tortoise paradox. A fleetof-foot Achilles is unable to catch a plodding tortoise which has been given a head start, since during the time it takes Achilles to catch up to a given position, the tortoise

has moved forward some distance. As Achilles travels an infinite number of steps, the distance between him and the tortoise will never be zero in length. Solution: Let Achilles run *m* times as fast as the tortoise. When Achilles runs distance *l*, the tortoise runs l/m; when Achilles runs distance l/m, the tortoise runs l/m^2 , and so on up to infinity. The distance between them will always be nonzero. Summation of path segments run by Achilles and covered by the tortoise gives two geometric sequences. The path traversed by Achilles is $s_A = l + l/m + l/m^2 + \ldots + l/m^n + \ldots = l + l\sum_{n=1}^{\infty} 1/m^n$, and that covered by the tortoise is $s_{iq} = l/m + l/m^2 + \ldots + l/m^n + \ldots = l \sum_{n=1}^{\infty} 1/m^n$. As a result, according to Zeno, Achilles can run forever, but will never be able to catch the tortoise. The paradox arises from the assumption that space and time *can be infinitely divided into any small intervals*.



Figure 3. Normalized curve corresponding to expression $q = 1/m^n$. The intersection point between the curve and the straight line ε corresponds to the instant of time n_{max} at which Achilles overtakes the tortoise.

a wave should be on the order of

$$E = hv = h \frac{c}{\lambda} \approx \frac{2 \times 10^{-16}}{10^{-50}} = 2 \times 10^{34} \text{ erg},$$

where *h* is the Planck constant, *v* is the frequency, and *c* is the speed of light. High energies would kill a living system long before the measurement is completed, suggesting a measurement limit ε that creates *uncertainty*. These instrumental limitations were explored in a number of earlier studies (see, for instance, Brillouin's book [46]). The quantity ε will always be left between cognizable and unknown matters.

Moreover, let us consider reverse motion of Achilles and the tortoise, mentally causing them to turn and run back by the signal. Will they simultaneously reach the starting point after *n* steps? The binary logic says 'yes'. However, this is not true because the burden of uncertainty will bring the two runners to an uncertainty region of $\pm 0.5\varepsilon$ in size. If the procedure for changing the direction of their motion is repeated *N* times, the size of this region will grow as $\pm 0.5\varepsilon\sqrt{N}$. Accumulation of measurement errors is a major imperfection of all experiments, including numerical computer experiments, where they accumulate due to quantization of the process and summation of errors resulting from rounding values. These considerations can be supplemented by numerous examples using other mathematical models, viz. Lorentz 2D gas [47], Sinai's billiards [48, 49], strange attractors [50], etc. They all lead to the same conclusion: namely, *the world we live in is not totally determinate and contains uncertainties*.

3.3 Maxwell's demon paradox

Corti [51] was the first to describe the directed motion of microparticles in living cell protoplasm streams 225 years ago. Since then, this phenomenon has been the subject of extensive studies. It can be observed in fungi and giant plant cells of *Acetabularia, Nitella*, etc. with an optical microscope, and in *Physarum polycephalum* with the naked eye [52, 53].

Thermal motion of nonliving microparticles was noticed by J Ingenhausz back in 1785, i.e., 150 years after the invention of the microscope by Antoni van Leeuwenhoek. Leeuwenhoek observed the motion of bacteria, spermatozoa, and protozoa that was very similar to that of nonliving things, ground charcoal particles, on the surface of alcohol as described by Ingenhausz. The phenomenon of thermal motion was named after the botanist R Brown, who published the results of his observations of the motion of small particles (flower pollen, dust, and soot) on the water surface in 1828 [54]. In the early 1970s, H Berg of Harvard University used a scanning microscope in the Lagrangian reference frame to detect the trajectory of motion of individual bacteria under experimental conditions and demonstrated its random nature in an attractant isotropic volume [55-58]. It was shown that periods of steady unidirectional floating randomly alternate with changes in the direction of motion. In other words, both living and nonliving microparticles obey common laws of motion.

Schrödinger tried to deduce the definition of life by passing from the general to the specific as follows [1, the next to last chapter]: "How would we express in terms of the statistical theory the marvelous faculty of a living organism, by which it delays the decay into thermodynamic equilibrium (death)? We said before: 'it feeds upon negative entropy', attracting, as it were, a stream of negative entropy upon itself, to compensate the entropy increase it produces by living and thus to maintain itself on a stationary and fairly low entropy level."

This definition reflected the opinion of many eminent biologists and physicists who studied the mechanisms of Brownian motion 65 years ago, and was therefore readily accepted by the scientific community. Today, it looks unconstructive. Entropy is too broad a characteristic to be suitable for the description of motion and the development of living systems. It does not allow reliably discriminating between living and nonliving systems. Why? Let us consider Maxwell demon (paradox 3) to receive the answer.

Particles of order $10^{-8} - 10^{-6}$ m in size, e.g., soot or dust in a liquid, show stochastic motion under the action of liquid molecule impacts or mutual collisions (billiard model). Albert Einstein and Marian Smoluchowski were the first to theoretically describe Brownian mobility in 1905 [68–70]. In 1908, Paul Langevin [71] supplemented the theory by postulating two components of the force governing microparticle movements. One is the impact force with which molecules of the medium act on the particles with high frequency and change their directions, which vanishes upon averaging over a certain time interval. The other component is a viscosity-dependent force undergoing low-frequency fluctuations. Paradox 3

Maxwell demon sorting out Brownian microparticles, i.e., separating rapidly-moving particles from slowly-moving ones, has attracted the attention of researchers for

almost 140 years (since 1871). A few generations of physicists did their best to drive it out of science. They considered limitations precluding a microparticle, regardless of its structure, to vectorize a random trajectory without inflow of additional energy; an increase of entropy in a 'demon \leftrightarrow microparticles' system [59–61]; the influence of the uncertainty principle [62–64]; the impossibility of recording the direction of strikes under thermal equilibrium, etc. [65–67]. For all that, the problem remains a key focus among researchers. In the light of modern knowledge, it is formulated as follows: 'How does the formation of particle motion kinetics refute Maxwell's demon paradox'?

These two forces act independently, which accounts for their additive effect. This, however, is true only in the first approximation. Varying the medium parameters causes changes in the shape of the particles that may undergo 'loosening', 'rounding', or pulsation, and thereby influence both the viscosity of the medium and the dynamics of their own motion [72–74]. In other words, feedback appears and a motion cycle develops in which the particles and the medium mutually affect each other. Since that time, the theory of Brownian motion has been continuously modified to cover a variety of its (motion) manifestations in living and nonliving matter [75]. In all such issues, *the thermodynamics of the process is not so important as the kinetics of relative changes in the rate of motion* of the particles influenced by the medium.

The notion of thermodynamic probability makes sense only for quasiequilibrium states. L Onsager's nonequilibrium thermodynamics [76, 77] and its extension by Kasimir [78] and Meixner and Prigogine [79–83] do not provide material for the elucidation of differences between living and nonliving matter. These approaches are unsuitable even for the description of nonliving dissipative nonequilibrium or farfrom-equilibrium structures (such as Bénard's cells [84] or structures in the Belousov–Zhabotinsky oscillating reaction [85–92]). A description of open systems is possible based on *a kinetic approach* that allows for the comparison of individual rates of the processes in living and nonliving matter.

Solving the energy problem has become the first outstanding achievement in moving from a description of nonliving matter to that of living matter. Emergence of irreversibility in macrosystems is possible without the permanent transfer or extraction of energy from an external source, and may arise from *the kinetics of processes in heterogeneous systems maintained by the previously accumulated energy and due to their nonequilibrium nature* [93]. The greatest event in the course of living matter evolution was the appearance of a number of proteins capable of exchanging one sunlight quantum frequency for another and the use of the released energy for the needs of living things. Chlorophyll and rhodopsins became accumulators of energy (a sort of energy bank) continuously releasing it to maintain the growth and development of living organisms.

Another very important advancement in the passage from nonliving matter to living matter was *structurization* of the latter, which considerably prolonged its *existence*. Here is a simple example from nonliving nature. As known, a highdensity gas cluster, for instance, in the form of a ball of radius R, is dispersed in the air at the speed of sound c_s :

$$c_{\rm s} = \sqrt{\frac{\gamma T}{m}},$$

where γ is the adiabatic index, T is the temperature, and m is the mass of the molecules. The motion inside the cluster is reversible. The number of molecules decreases as the cluster disperses, but remains for some time τ_1 higher than in the surrounding air. The mean free path of gas molecules at the cluster border is greater than inside it. At a given density, the cluster's radius decreases with time as $r_s = R - c_s t$. The cluster disappears after time $t = \tau_1 = R/c_s$, when its molecular density becomes identical with that of the surrounding region. Evidently, the bigger the cluster, the longer its lifetime τ_1 . It can be prolonged by enclosing the cluster inside an envelope, e.g., a soap bubble. In this case, the characteristic lifetime τ of the cluster will increase depending not only on its initial size and internal pressure but also the elasticity and penetrability of the envelope. These are two additive processes. The lifetime of such a system increases to $\tau \approx \tau_1 + \tau_2$, where τ_2 is the lifetime of the envelope (soap bubble). The lifetime of the cluster can be further increased by introducing a water droplet (or, better, a droplet of perfluorocarbon) into the envelope. Up to 50% of the gas will dissolve in perfluorocarbon, and only 2% in water. Then, after the removal or disappearance of the envelope, the cluster will persist as long as the gas diffuses from the droplet to the surrounding medium. Overall, its lifetime will increase and become $\tau \approx \tau_1 + \tau_2 + \tau_3$, where τ_3 is the characteristic time of gas diffusion from the droplet. Structural heterogeneity contributes to the enhancement of the system's lifetime. As this takes place, the combination of the reversible and irreversible parts of the system comes into being. In other words, correlation between initial intermolecular interactions breaks down at the cluster's front, and the classical mechanical system with the reversible trajectory localizes behind the advancing front. Correlation in molecular motion continues to be destroyed with a different characteristic time at the front of the next phase, while the classical mechanical system with the reversible trajectory still remains behind the front, and so on. As long as the last structure exists, its internal entropy is lower than in the surrounding medium. The values of entropy inside the cluster and around it are immaterial for further consideration. Much more important are kinetic characteristics, such as lifetime $\tau \approx \tau_1 + \tau_2 + \tau_3$, or the time of existence of the system. Existence is the key word in this context.

The problem of entropy-based assessments was considered by Blumenfeld [94]. Here is an example from his book [94, p. 6]. The body of an adult man contains about 7 kg of protein and 150 g of DNA (3×10^{25} amino acid residues and 3×10^{23} nucleotide bases, respectively). A single sequence of the $20^{3 \times 10^{25}}$ variants possible for protein requires roughly 1.3×10^{26} bits of information to be built (6 $\times 10^{23}$ bits for DNA). These figures correspond to 300 and approximately 1.4 entropy units (e.u.) for protein and DNA, respectively, which means that the ordering of the biological organization of the human body does not exceed 301.5 e.u., with the overwhelming contribution introduced by the regular distribution of amino acid residues in protein molecules. Such a fall in entropy in the formation of an extremely complicated biological structure, the human body, is readily compensated for by ordinary physical and chemical processes. For example, the evaporation of 170 cm^3 of water or the oxidation of 900 g of glucose increases entropy by 300 e.u.

These estimates indicate that evolvement and complication of biological organization occur thermodynamically on a zero-cost basis, due to the alternation of reversible and irreversible processes inside a system. The entropy of a totality of 10^{13} different unicellular organisms is practically identical with that of the human body consisting of 10^{13} cells. All speculation with respect to 'anti-entropic trends' in biological evolution arise from misconceptions. Under thermodynamic criteria, any biological system is no more ordered than a piece of rock of equivalent weight. *The difference between them is in the kinetics and ability to remember favorable structurization scenarios* (the latter characteristic will be considered in Section 3.9).

In 1990, Max Perutz wrote in his article "Physics and the riddle of life" [95]: "The apparent contradictions between life and the statistical laws of physics can be resolved by invoking a science largely ignored by Schrödinger. That science is chemistry. When Schrödinger wrote, "The regular course of events, governed by the laws of physics, is never the consequence of one well-ordered configuration of atoms, not unless that configuration repeats itself many times," he failed to realize that this is exactly how chemical catalysts work. Given a source of free energy, a well-ordered configuration of atoms in a single molecule of an enzyme catalyst can direct the formation of an ordered stereospecific component at a rate of $10^3 - 10^5$ molecules per second, thus creating order from disorder at the ultimate expense of the solar energy."

Although correct, this line of argument is only of historical interest. In the first half of the 20th century, classical biology gave rise to two branches of science: biochemistry and biophysics. They sought a common goal-to sound the depths of life-but used different languages for description. Nature operates as a whole, and the breakdown of science into branches is always arbitrary. In view of the pre-Lamarkian concept, physics studies nature at large (both living and nonliving matter) while the language of biochemistry is a form of physical language [75], which in a number of cases is more suitable for the description of events and phenomena in living nature. This language is currently developing at a fast pace for the quantitative description of metabolic processes. The first results of this progress are expounded in our book [96]. Thus far, however, this language lacks the generality needed to unambiguously formulate the difference between living and nonliving matter.

A few attempts have recently been made to apply one more language, *the language of information theory*, to the description of living systems [97]. It is not an easy task because the quality of information, i.e., its value, is more important than its quantity as far as biological systems are concerned. The value of information cannot be assessed unless the mission and vision of life are defined. When the target for life is known, the notion of the 'value of information' is readily characterized in probabilistic terms because the probability of attaining a goal increases when information is available.

The assessment can be made in different ways, e.g., as proposed by M M Bongard [98], A A Kharkevich [99], or V I Korogodin [100]. The use of information theory for the description of living systems depends on the definition of the *life goal*. What is it, if any? What other point in life may grass or a tree have but *to exist*, i.e., to come into the world, feed, grow, propagate, and die? The assumption of a reason for being as regards living nature inevitably suggests that it originated from nothing or was born from above. Such an assumption leads to *creationism* (the belief that the goal was set by a willful act on the part of a supernatural agent) or to the thesis that *it arose from nothing, which means that disorder is a source of order, i.e., it has the properties of organizing origin.* In the latter case, it is necessary to understand how random events bring an ordered pattern (the mechanism of this phenomenon will be discussed in Sections 3.9 and 3.10). At the same time, the information-based approach is successfully applied to the solution of many specific problems in biology (analysis of reception, replication, and mutations; interpretation of biomolecules as nanomachines; designing neurocomputers) [97].

3.4 Schrödinger's cat paradox

Because life has its roots in atomic and molecular processes, the distinction between living and nonliving matter has been sought at the quantum level. Quantum physics, like classical physics, is irreversible, even though the Schrödinger quantum-mechanical equation is reversible.

The fact is that measurements in quantum mechanics are based on two postulates [97]. One is the Schrödinger equation itself, $i\hbar \partial \Psi / \partial t = H\Psi$, where \hbar is the Planck constant, H is a Hamilton operator, and Ψ is the wave function of the system. The other is the dependence of the probability density $\rho(x)$ of detecting a particle at a given point x (or points $x_1, x_2, ..., x_n$, ...) on Ψ :

$$\rho(x) = \Psi^*(x) \,\Psi(x) \,,$$

where $\Psi^*(x)$ is a complex-conjugate function for $\Psi(x)$. Detection of a particle suggests a collapse of the wave function that shrinks into a point; in other words, probability density takes the form of delta-function $\delta(x)$:

$$|\Psi(x)|^2 = \rho(x) \to \delta(x)$$
.

As known, reduction cannot be described by Schrödinger's equation, even if the entire system together with the measuring device is incorporated into the Hamiltonian. These postulates are incompatible in the framework of quantum mechanics. The crux of the matter is that reduction of a wave packet is irreversible in time. Consequently, entropy should grow during this process. This is, however, impossible in accordance with the von Neumann theorem [101] because the Schrödinger quantum-mechanical equation is reversible in time. According to Wigner's theorem [102], the integral measure of early deviations in quantum-mechanical systems remains constant and does not grow with time (sign of reversibility); hence, a thought experiment known as *Schrödinger's cat paradox* [17] (paradox 4).

Schrödinger used this paradox to show that quantum mechanics is incomplete without certain rules specifying conditions in which the wave function collapses and the cat either survives or dies, but ceases to be a superposition of both states. Schrödinger argued that quantum mechanics does not comprehensively describe reality. His original article [103] was published in the German journal *Naturwissenschaften*. The author discussed the Einstein–Podolsky–Rosen paradox [104] published earlier in the same year, by which the atomic nucleus resides in the *binary* situation like the cat that is *both alive and dead*. It must be either fissioned or unfissioned; there is no in-between. After the parent nucleus disintegrates into particles A and B, they are the quantum superposition of



Paradox 4 In 1935, Erwin Schrödinger set himself the task of demonstrating the incompleteness of the transition from subatomic to macroscopic systems [103].

In Schrödinger's gedanken experiment, the cat, along with a flask containing a poison, is placed in a sealed box. If the internal counter detects a quantum particle, the flask is shattered, releasing the poison that kills the cat. The quantum-mechanical interpretation implies that, in the closed box, the equally probable states are in superposition and mixed — that is, *the cat is simultaneously alive and dead*. Yet, when the experimentalist looks in the opened box, he sees the cat either dead (the counter detected radiation) or alive (no poison released), not both alive and dead. The question is: *when does the system cease to exist as a mixture of two states, and only one of them is selected, i.e., the system becomes irreversible*?

many entangled states differing in particle momenta. In binary logic, this introduces uncertainty into the prediction of their localization when detecting.

There are several explanations for *the irreversibility of quantum-mechanical systems*. Schrödinger's equation can be used when considering wave motion, but it does not describe a particle-recording device (photographic plate or any other detector). It may be argued that the projection operator of the macrodevice acts on the wave function during registering by shrinking the wave function smeared over space into a point. It is the operator that makes the system irreversible. Then, the question arises: Shall we use the projection operator as a makeweight to the Schrödinger equation, and where do probabilities in the Schrödinger wave equation come from?

Adepts of Bohr's (Copenhagen) school [105] proclaim the occurrence of the principle of complementarity, implying that elements of physical reality (momenta or coordinates) are not objective characteristics of the microworld, but directly depend on the choice of detectors used for their registering. In this interpretation, quantum mechanics needs no hidden parameters to be introduced. Quantum mechanics can be understood assuming that the wave function $\Psi(x)$ has a different sense-that being none other than the distribution of probabilities. In quantum mechanics, the wave function can have any name, e.g., information function. In other words, it is different from all other wave fields of classical mechanics obeying conservation laws, such as laws of conservation of energy or charge. These laws are inapplicable to the quantum wave function. The collapses of wave functions result in erasing quantum information by their factorization. Nature develops through a sequence of stages: at each new stage of system development the memory of the preceding one is *partially cancelled*, which makes the two independent [106]. Moreover, an essentially nonlocal quantum particle is made local by the registration process. When speaking of probabilities, we are not embarrassed by the fact that each concrete realization of a random process eliminates all other possibilities. It is not so with wave functions. Everything new first seems impossible, but we finally get accustomed to it.

Bell's theorem [107] postulates the possibility of statistically testing the existence of hidden parameters influencing any physical characteristic. Such experiments carried out in 1976 in the context of the quantum-mechanical theory showed that Schrödinger's wave equation does not require the introduction of hidden parameters [108]. This and a few later experiments were discussed in one of the last lectures delivered by B B Kadomtsev and published recently in *Physics – Uspekhi* [106]. In 1985, Aspect and Grangier [109] reported an experiment that also confirmed that the Schrödinger quantum-mechanical equation is sufficient for the description of quantum effects and does not require the introduction of hidden parameters. The quantum world proved to be probabilistic in nature and totally unlike the world of classical mechanics. There remained nothing else to do but either to recognize that they are two different worlds or to renew the search for hidden parameters.

Of interest in this context is Everett's hypothesis for the multiple universes [110]. Everett argued that the assumption of entangled combined state for quantum and classical systems makes no sense so far as a compound quantum-classical system, such as a particle interacting with a measuring device, is concerned. He arrived at a conclusion about the *relative* nature of the state of one of the systems with respect to the other.

DeWitt [111] modified Everett's many-worlds interpretation of quantum mechanics and proposed considering the superposition of wave functions as a set of states of identical but noninteracting parallel worlds, each having an 'alternative history' of decay of the parent particle and a characteristic momentum. It is impossible to say in which of these worlds the experiment is performed until the necessary measurement is made. During the measurement, irreversible 'splitting of the worlds' takes place, and the history of both particles, A and B, becomes definite and irreversible from the instant of time of splitting. As soon as particle A is recorded, its influence on the state of B is no longer apparent. Any theory needs experimental verification. However, the manyworlds concept suggests that 'parallel worlds' do not interact and their existence cannot be verified in principle. This hypothesis can be neither proved nor refuted in experiment.

Nevertheless, certain researchers recognize that this hypothesis has the right to existence [112]. For example, M B Menskii published a few papers in *Physics–Uspekhi* [5, 113–117] in an attempt to explain the phenomena of life and conscience based on a modified version of Everett's many-worlds concept [5, 117]. The author argues that *conscience* evokes the feeling of irreversibility because the experimentalist subjectively finds himself placed in one of Everett's worlds where the measurement is being made. Seeing only one world, he cannot see the others that none-theless continue to exist, even if unseen by the experimentalist. On this ground, Menskii concludes: "Life is the choice and consciousness of alternatives."

This hypothesis cannot be tested in experiment. I think it would be more productive to entertain the notion of structural stability of a recording device rather than the term 'conscience', which makes little sense in this context. True, part of the above definition appears acceptable ("the choice of alternatives"), but it ensues from a different line of reasoning, as will be shown in Section 3.9.

3.5 Stochastic ratchet paradox

Stochastic Feynman's ratchet is properly the same Maxwell's demon. This device rotates only in one direction, giving rise to irreversibility of a sense of rotation. In the clock mechanism, the ratchet serves as *a memory device* that preserves information about the rotation angle reached during rotation of the gear. In a mechanical clock, for example, rotation is driven by the wound spring, and the ratchet secures unidirectional rotary motion. The mode of feeding energy into the system

is immaterial: it may be thermal, mechanical, or electrical. The idea of *a ratchet* in biophysics is transformed to the search for logically similar devices in living systems, providing a simple explanation for their directional development. Based on this idea, Feynman tried to prove at the molecular level that the operation of such a mechanical system with *memory* does not contradict the second law of thermodynamics; in other words, it cannot do work without a temperature drop. Feynman formulated the *stochastic ratchet paradox* in his lectures [118] (paradox 5).



Paradox 5 Consider a device consisting of two thermal baths filled with a gas at temperatures T_1 and T_2 , respectively. One of them contains a gear known as a ratchet that is prevented from rotating in the opposite direction by a pawl.

The ratchet is connected by a rod to a paddle wheel in the other bath. It is assumed that $T_1 = T_2 = T$. The device is designed such that individual collisions of the molecules with the paddle cause it to be jiggled. The net effect of many collisions is for the paddle to turn in only one direction allowed by the pawl. The ratchet's motion can be used to lift a small weight suspended from a thread attached to the axle. *Can such a system put out some work*? The answer is it cannot actually do this if the system is at thermal equilibrium.

R Feynman suggested the following explanation. As gas molecules collide with a paddle, they impart an impulse required to move the gear to the next tooth, which lifts the pawl against the clamping spring. After the gear advances further, the spring pulls the pawl down, and its tip strikes the gear and begins bouncing up and down. If there is a new thermal fluctuation, the gear may slip backward when the pawl is just above one of its teeth. Thus, a mechanism is needed to make the gear's rotation irreversible by damping pawl jumps forward and backward. The pawl gives up its energy in the form of heat to the entire system, the temperature of which grows as the gear continues to rotate. Both the ratchet and the gas are heated. The motion of both the pawl and the spring is also subject to random temperature fluctuations, due to which the pawl from time to time goes up, letting the gear pass when the same fluctuation tends to turn it backward. The higher the temperature, the more frequently this happens. Feynman demonstrated that if the entire device is at thermal equilibrium, the ratchet does not rotate continuously in one direction, but moves randomly back and forth, so that during one cycle the axle retains its initial angular position.

The axle rotates in one direction only if the temperatures of the paddle wheel, T_2 , and the ratchet, T_1 , are such that $T_1 < T_2$. In other words, the temperature gradient $\Delta T = T_2 - T_1$ can deliver work on the condition that it is sufficient to compensate for friction in the system. This trivial explanation agrees with the Carnot cycle: $Q_1/Q_2 = T_1/T_2$, where Q_1 , T_1 and Q_2 , T_2 are the thermal energy and temperature of the paddle and the ratchet, respectively. This means that the above paradox is fallacious. The result is in excellent agreement with the laws of thermodynamics.

The kinetics of the process in the ratchet at $T_2 = T_1$ becomes more interesting after additional energy is introduced by changing the mass of the suspended load. Too heavy a load may cause plenty of problems. The pawl may slip, the spring may break, etc. If the load is small, an analysis of the probabilities of the gear turning forward or backward at equal temperatures gives the following result. At any change in temperature, the axle turns through the angle θ , so that the angular velocity is θ multiplied by the probability of fluctuations per unit time. The ratchet gear turns forward with the probability $p_1 = (1/\tau) \exp[-(\varepsilon + L)/kT]$, and backward with the probability $p_2 = (1/\tau) \exp(-\varepsilon/kT)$. Here, τ is the characteristic time corresponding to the period between fluctuations, $\varepsilon + L\theta$ is the energy generated by the paddle wheel due to fluctuations, L is the weight's moment of inertia, θ is the rotation angle of the axle, k is the Boltzmann constant, T is the temperature, and the ratchet angular velocity is given by

$$\omega = \frac{\theta}{\tau} \left[\exp\left(-\frac{\varepsilon + L\theta}{kT}\right) - \exp\left(-\frac{\varepsilon}{kT}\right) \right]$$
$$= \frac{\theta}{\tau} \exp\left(-\frac{\varepsilon}{kT}\right) \left[\exp\left(-\frac{L\theta}{kT}\right) - 1 \right].$$

The plot of ω vs. L presented in Fig. 4 shows different results at positive and negative values of L. The plot is asymmetric. If positive L grows (when we want to turn the gear backward), the angular velocity of backward rotation is virtually unaltered (right-hand side of the plot). At negative L, the exponent sharply increases (left-hand side of the plot). Moving in one direction (from right to left), we obtain a high angular velocity from a weak force. For reverse motion, the axle rotates only insignificantly, despite a stronger force. The result is asymmetry.

A similar asymmetry develops, for instance, in an electrical rectifier whose operation is based on the principle of asymmetric resistance. In this device, mechanical force is substituted by electric current, and angular velocity by current strength. The above analysis is equally applicable to a mechanical system and an electrical rectifier.

Let us turn to the Feynman mechanism described in the preceding paragraphs. Had T_2 been higher than T_1 , the ratchet would have rotated forward. In the opposite case $(T_1 > T_2)$, the ratchet would have rotated backward. The backward rotation of the ratchet with excess internal heat is due to the bouncing of the pawl. When the pawl is on an



Figure 4. The plot of ratchet angular velocity ω vs. weight's moment of inertia L.

inclined plane, it pushes the plane up but only during *a limited time*; otherwise it would go too high and find itself on another inclined plane. In other words, the hot ratchet is ideally designed to rotate in the direction opposite to that initially meant for gear rotation.

Interestingly, if the mass of the suspended object moving downward changes in time, e.g., as $\cos \Omega t$, the above expression for the frequency assumes the form

$$\omega = \frac{\theta}{\tau} \exp\left(-\frac{\varepsilon}{kT}\right) \left[\exp\left(-\frac{\theta L_0 \cos \Omega t}{kT}\right) - 1\right]$$
$$\approx \frac{\theta^2}{\tau kT} L_0 \cos \Omega t \left(\frac{\varepsilon}{kT} - 1\right).$$

Then, mass oscillations play the role of temperature fluctuations and for $\varepsilon/(kT) \ge 1$ can turn the gear either forward or backward. In such a system, the nature of the oscillations becomes inessential. Whether the temperature fluctuates and the mass of the suspended object or ratchet elasticity vary, the net result will be the same.

Biological systems are perfectly adapted to using different modes of energy exchange to maintain themselves in a varying environment. Nevertheless, even the most intricate 'asymmetric' mechanism would not rotate in one direction more frequently than in another or vice versa under the effect of symmetric forces. It may alternately turn one way or another but on the average it remains in the same position no matter how long it operates. 'On the average' is the key word in this context. However, the fluctuation dispersion increases as the spectrum of fluctuations narrows. The growth in fluctuations within a limited observation time may result in an appreciable rotation of the gear both forward and backward, but its direction is impossible to predict: it is a matter of chance. A similar mechanism is realized in biological structures [119, 120]. The current boom in nanobiomotor technology gave rise to an avalanche of publications demonstrating the operation of molecular chaotic ratchets in chemical and biological systems [121-140]. Examples of biological prototypes of such devices will be given below (see Section 3.10).

The main physical laws are reversible; irreversibility arises from transformation of *order into disorder*. However, this assertion remains unclear until we know whence *order*, i.e., vectorization of motion, comes. The fact is that situations we routinely observe are nonequilibrium. In biology, the term 'memory of past states' is usually used instead of Feynman's term 'ratchet'. In this context, the words *ratchet* and *memory* are synonymous (see Sections 3.9 and 3.10).

3.6 Paradox of time deficit

In 1981, F Hoyle and N C Wickramasinghe, two astrophysicists, published the book, *Evolution from Space* [141]. The main idea of the book was formulated by the latter author in an article under the title "An astronomer reflects: was Darwin wrong" (UNESCO Courier, June 1982) as follows: "My own philosophical preference is for an essentially eternal, boundless Universe, wherein a creator of life, an intelligence considerably higher than ours, somehow emerged in a natural way. Just as the earth was proved not to be the physical centre of the Universe, it seems to me equally obvious that the highest intelligence in the world cannot be centred on the Earth. It is ridiculous to suppose that the information provided by one single primitive bacterium can be upgraded by copying to produce a man, and all other living things that inhabit our planet. This conventional wisdom, as it is called, is similar to the proposition that the first page of Genesis copied billions upon billions of times would eventually accumulate enough copying errors and hence enough variety to produce not merely the entire Bible but all the holdings of all the major libraries of the world.... The number of alternative permutations needed for a continual addition of information for life is many orders of magnitude greater than the number of atoms in the visible Universe. A tornado blowing through an aircraft scrap-heap has a better chance of assembling a brand new jumbo jet from bits of junk than life being assembled from its components by random processes."

The authors of the book and their proponents [142, 143] alluded inter alia to the work of the DNA molecule in the living cell. Its replication is regulated by a specific enzyme that propagates along the DNA strands reading out their nucleotide sequences and producing copies. If it encounters a wrong nucleotide, the 'repair mechanism' induces a different enzyme that 'cuts out' the wrong base and corrects the defect. The central question put by the authors is whether such a repair mechanism could develop in the course of random natural events. On the one hand, it would have been of no use whatever if it had formed prior to DNA. On the other hand, if DNA was the first to appear, how could it 'know' that it would need repairing? It means that both the DNA molecule and the mechanism of its repair had to arise spontaneously in the same place at the same time. DNA is unstable and rapidly decays by chemical oxidation and other processes without regular repair. How, then, could DNA exist millions of years waiting for the repair mechanism to evolve? It would have had to disintegrate into nucleotides before billions of random mutations created the repair mechanism.

This uncertainty gave rise to *the paradox of the lack of time* necessary for the development of living matter (paradox 6).

This paradox is easily refuted by the following consideration. Evidently, the assembly of a whole from constituent elements is possible by means of the *bottom-up* strategy passing successively from small to larger blocks, i.e., from atoms and molecules to the integral organism. It is in this way that the development and complication of living systems proceeded. The entire process consisted of separate levels at which the building blocks necessary for further assembly were selected. It is the so-called block-hierarchical selection (BHS) rule [144] that gives significant gain in assembly time (Fig. 5).

It is easy to estimate how much time can be gained with this strategy. Let us introduce the following notations: N is the number of bottom-level fragments contained in the complete top-level assembly; k_i is the number of assemblies at the *i*-th level selected for the i + 1-th level; n_i is the length of assembly of the *i*-th level fragments; k_1 is the initial number of assemblies at the first level; *m* is the number of hierarchical levels; *i* is the serial number of the level, i = 1, 2, ..., m; W_i is the number of exhaustions for proper assembly at the *i*-th level; τ is the time necessary to assemble one variant at any of the *i*-th levels, and T_i is the time necessary to select correct variants at the *i*-th level. Let us further assume that correct assemblies are selected at each level, while wrong ones are discarded, and accept the postulate of Darwin's theory about environmentally-driven selection. Correct assemblies are allowed to pass to the second level. Then, the time of assembly of the entire sequence is $T_0 = \sum_{i=1}^{m} \tau_i W_i$. Here, W_i is the number of exhaustions at each *i*-th hierarchical level and the value of W_i depends on variables m, N, k (there may be msuch different k_i), and n_i (similarly, there may be *m* different



Paradox 6

The paradox arises from consideration of a complete exhaustion (CE) at a single hierarchical level (see the figure). Given all variants are permissible, the number of variants of complete exhaustion for the assembly of a desired whole is $W_{CE} = P_N = A_N^N = N!$, where P_N are permutations out of N elements differing only in the sequence of constituent fragments. For example, permutations out of three elements a, b, and c are: adc, abc, cab, cba, bac, acb; A_N^N are permutations out of N identical elements taken N at a time and differing only in their arrangement. Once the mean time needed for the formation and selection of one assembly variant is τ , the time needed for the formation and selection of all variants is $T_0 = \tau W_{CE}$. Calculation by Stirling's formula yields $W_{CE} = N! \approx N^N \exp(-N)\sqrt{2\pi N} (1 + 1/(12N) + 1/(288N^2) + ...)$. According to this formula, the logarithm of the factorial, ln N!, can be simplified and approximately expressed in the form $\ln N! \approx N(\ln N - 1)$. This expression gives a good approximation for N > 100. The time needed for the selection of one variant of the whole assembly is $\tau W \approx \tau N^N \exp(-N)$. It is an incredibly large value, even at relatively small N; suffice it to say that for $N \ge 100$ such problems cannot be resolved by exhaustion. A whole cannot be assembled from a large number of fragments within a reasonable time. In this sense, Hoyle and Wickramasinghe were right. The time needed to complete the assembly shown in the above figure would be on the order of $(10^{18} - 10^{21}) \tau$. The assembly would be unfeasible even at $\tau = 1$ s. To recall, the age of our Universe is estimated at 1017 s; hence, the paradox of a deficit of time for living matter to evolve. The question to be answered is whether living systems actually developed from nonliving matter under such a scenario.

 n_i). Naturally, all values of m, k_i , and n_i are lower than N. W_i may change depending on these variables. On the whole, however, despite a significant spread of W_i values, this variable tends to decrease when passing from level to level in the bottom-to-top direction because N is higher than each of the values of m, k_i , and n_i . For certainty, here are numerical examples at N = 16.

The first variant shown in the left part of Table 2 corresponds to the selection process depicted in Fig. 5. Clearly, we shall have to sort out 240 variants for selecting required eight assembles for the second level by assembling at first two-element blocks from the initial 16 fragments. The choice of four variants needed for the third level will require exhaustion of 1960 variants: hence, a total of 2,213 variants. However, the same result can be achieved by starting from the selection of four-element blocks at the first level (exhaustion of 43,705 variants). This means that assembly beginning from

the selection of small blocks saves time. Let us see now how the time of assembly depends on the number *m* of levels. In the case of four levels, this time varies (depending on the applied strategy of assembling) from 2213τ to $43,705\tau$; for three levels (Table 3), it increases to $1.6 \times 10^9\tau$, and for two levels (complete exhaustion), it becomes unbelievably large: $1.2 \times 10^{21}\tau$.

Despite the random spread in W_i values, the number of exhaustions usually decreases when moving to each next level, i.e., $W_1 > W_2 > W_3 > ... > W_m$, because this chain contains the following sequence of transitions:

$$W_{1} = A_{N}^{n_{1}} = \frac{N!}{(N-n_{1})!} \to W_{2} = A_{k_{1}}^{n_{2}}$$
$$= \frac{k_{1}!}{(k_{1}-n_{2})!} \to W_{3} = A_{k_{2}}^{n_{3}} = \frac{k_{2}!}{(k_{2}-n_{3})!} \to \dots$$
$$W_{m} = A_{k_{m-1}}^{n_{m}} = \frac{k_{m-1}!}{(k_{m-1}-n_{m})!}.$$

If, in this sequence, $N > k_1 > k_2 > ... > k_{m-1}$ and $n_1 > n_2 > n_3 > ... > n_m$, while $N \ge n_1$, $k_1 \ge n_2$, $k_2 \ge n_3$, ..., $k_{m-1} \ge n_m$, each next exhaustion is, as a rule, smaller than the preceding one.

From these $k_{i-1}^{n_i} \exp(-n_i)$ blocks, k_i variants assembled at a previous level are selected for the next level, and the remaining ones are discarded. These k_i variants are randomly combined into blocks of the next hierarchically higher *i*-th level. That part of them that has passed the test for adequacy of the fragment sequence goes up to the next level, and so on. As a result, using Stirling's formula, one finds

$$W_{\text{BHS}} = \sum_{i}^{m} W_{i} = \sum_{i}^{m} \frac{k_{i}!}{(k_{i} - n_{i})!}$$
$$= \sum_{i}^{m} \frac{k_{i}^{k_{i}}}{(k_{i} - n_{i})^{(k_{i} - n_{i})}} \exp(-n_{i}).$$

Assume now that the time of assembly and selection of a single variant is roughly the same at all levels, i.e., $\tau_1 \approx \tau_2 \approx \ldots \approx \tau_i \approx \ldots \approx \tau_m$. Then, the gain α in time in the case of replacement of complete exhaustion (CE) by BHS exhaustion takes the form

$$\alpha = \frac{W_{\text{CE}}}{W_{\text{BHS}}} = \frac{N^N}{\exp N} \left[\sum_{i}^m \frac{k_i^{k_i}}{(k_i - n_i)^{(k_i - n_i)}} \exp\left(-n_i\right) \right]^{-1},$$

or

$$\ln \alpha = N(\ln N - 1) - \ln \sum_{i}^{m} \frac{k_{i}^{k_{i}}}{(k_{i} - n_{i})^{(k_{i} - n_{i})}} \exp(-n_{i})$$

The second term in the latter expression is always much smaller than the first one; therefore, $\ln \alpha \approx N(\ln N - 1)$. This is easy to see, turning back to the numerical examples given in Tables 2 and 3. At N = 16, the simplified form of Stirling's formula gives $N(\ln N - 1) = 28.36$ (see Table 3, variant 2). Determination of the second term at m = 4, $n_1 = 2$, $n_2 = 4$, $n_3 = 2$, $n_4 = 1$, N = 16, $k_1 = 8$, $k_2 = 4$, $k_3 = 1$ (see Table 2, variant 1) by the same Stirling formula yields

$$\sum_{i}^{m} \frac{k_{i}^{k_{i}}}{(k_{i} - n_{i})^{(k_{i} - n_{i})}} \exp(-n_{i}) = \frac{16^{16}}{14^{14}} \exp(-2)$$
$$+ \frac{8^{8}}{4^{4}} \exp(-4) + \frac{4^{4}}{2^{2}} \exp(-2) + \frac{1^{1}}{1^{0}} \exp(-0)$$
$$= 223.7 + 1200 + 8.66 + 1 = 1433.36.$$



Figure 5. Schematic of block-hierarchical selection of variants for assembling fragments. Hierarchical level 1 contains elementary fragments. They pass to level 2 after self-assembly. The environment selects second-level fragments meeting its conditions and discards the remaining ones (crossed out in the scheme). This process repeats at the next levels. The scheme shows four levels of self-assembly and five selection levels.

m = 4							m = 4					
16	n_1	2	W_1	240	Ν	16	<i>n</i> ₁	4	W_1	43,680		
8	n_2	4	W_2	1960	k_1	4	n_2	4	W_2	24		
4	n_3	2	W_3	12	k_2	4	n_2	4	W_2	24		
1	n_4	1	W_4	1	k_3	1	n_4	1	W_4	1		
				2213	Total					43,705		
	16 8 4 1	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$m = 4$ 16 n_1 2 W_1 8 n_2 4 W_2 4 n_3 2 W_3 1 n_4 1 W_4	$m = 4$ 16 n_1 2 W_1 240 8 n_2 4 W_2 1960 4 n_3 2 W_3 12 1 n_4 1 W_4 1 2213 2 W_3 1	$m = 4$ W_1 240 N 16 n_1 2 W_1 240 N 8 n_2 4 W_2 1960 k_1 4 n_3 2 W_3 12 k_2 1 n_4 1 W_4 1 k_3 2213	$m = 4$ W_1 240 N 16 8 n_2 4 W_2 1960 k_1 4 4 n_3 2 W_3 12 k_2 4 1 n_4 1 W_4 1 k_3 1 2213	$m = 4$ $m = 16$ n_1 2 W_1 240 N 16 n_1 8 n_2 4 W_2 1960 k_1 4 n_2 4 n_3 2 W_3 12 k_2 4 n_2 1 n_4 1 W_4 1 k_3 1 n_4	$m = 4$ $m = 4$ 16 n_1 2 W_1 240 N 16 n_1 4 8 n_2 4 W_2 1960 k_1 4 n_2 4 4 n_3 2 W_3 12 k_2 4 n_2 4 1 n_4 1 W_4 1 k_3 1 n_4 1 2213 Total	$m = 4$ $m = 4$ 16 n_1 2 W_1 240 N 16 n_1 4 W_1 8 n_2 4 W_2 1960 k_1 4 n_2 4 W_2 4 n_3 2 W_3 12 k_2 4 n_2 4 W_2 1 n_4 1 W_4 1 k_3 1 n_4 1 W_4 Z213 Total		

Table 2. Dependence of W_i on the length of assembly of n_i fragments at the *i*-th level.

Table 3. Depen	dence of	W_i on t	he num	ber <i>m</i> of	hierarchical	levels.
----------------	----------	------------	--------	-----------------	--------------	---------

m = 3						m = 2					
N	16	n_1	8	W_1	1.6×10^{9}	Ν	16	n_1	16	W_1	1.2×10^{21}
k_1	2	n_2	1	W_2	2	k_1	1	n_2	1	W_2	1
k_2	1	n_2	1	W_2	1						
Total					1.6×10^{9}	Total					1.2×10^{21}

Paradox 7

The logarithm of this number equals 7.26. It is, however, an underestimation because $n_i < 10$ for all n_i , and the simplified form of Stirling's formula gives an error. Combinatorial formulas $A_N^{n_1} = N!/(N - n_1)!$, $A_{k_1}^{n_2} = k_1!/(k_1 - n_2)!$ allow this sum to be calculated more accurately as 2213 (see Table 2, variant 1). Thus, whatever method is used to calculate $\sum_{i=i}^{m} W_i$ and its logarithm, the result is the same: $N(\ln N - 1) \ge \ln \sum_{i=i}^{m} W_i$. For the numerical example under consideration, one has 28.3 > 7 - 10, meaning that the gain in time amounts to 18 - 20 orders of magnitude. It may be even higher given the number of blocks increases. The gain in time in the case of assembly under the BHS scenario amounts to $\ln \alpha \approx N(\ln N - 1)$ compared with CE assembly. Here, α is the gain in time, and *N* is the initial number of primary fragments. It follows from the above that the assertion of Hoyle and Wickramasinghe about time deficit is fallacious.

3.7 Paradox of homochiral structure

Chirality is the notion characterizing handedness of an asymmetric molecule. A chemical or biological object is called chiral (from the Greek word for hand, $\chi \epsilon \iota \rho$) if it differs from its mirror image. It has been known since the time of L Pasteur [145, 146] that many organic compounds having an identical set of atoms but different mirror symmetry smell and taste different and show different biological activity. Living nature is built up of substances of definite form and does not use their artificially synthesized mirror-image replicas as building material.

The functional proteins of all organisms contain only L-amino acids (from Latin *laevus* meaning left). Any such protein is a polymer chain of L-amino acids. There are short polypeptides with D-amino acids (*dexter*—right), such as neuropeptides, but they are signal, not structural, proteins. Certain familiar enzymes are composed of more than 100 amino acids, all of which are in the L-form, i.e., rotate the plane of light polarization in one direction. Living organisms use D-amino acids for information transfer. Figure 6 and 7 present two examples of chiral compounds.



Figure 6. Amino acid tetrahedral molecules in which the carbon atom is bound to four groups of different symmetry: L- and D-forms [9]. Asterisks label the carbon atoms in the center of mirror symmetry.



Figure 7. L- and D-isomers of a biologically important molecule, ribose, of which the sugar backbone of RNA and DNA macromolecules is made.

It is remarkable that RNA and DNA backbones contain only D-sugars. Certainly, the definitions 'left' and 'right' are arbitrary. They imply that each of these forms has a mirror image (optical antipode). Had a single D-amino acid been incorporated in the active center of an enzyme built from L-amino acids, it would have been inactivated. Hence, the paradox of homochiral structure (paradox 7).



Simultaneous assembly of polymers from a mixture of L- and D-molecules is impossible. The figure illustrates schematically the cause of arrest of assembly from a mixture of L- and D-isomers (a). The assembly of the long linear polymer in such a mixture stops because the L-isomer binds only to another

L-isomer, and the D-isomer to another D-isomer. Left-handed and right-handed configurations do not match (b). Only L- (or D-) molecules form polymer chains of any length (c). Homochirality may be regarded as a life invariant complementary to the genetic code common to all organisms on Earth. *How could homochirality develop in the world of symmetric processes*?

It can be thought that in the course of some random events asymmetric living entities somehow emerged, and this asymmetry was maintained and upgraded by replication of the code and reproduction. In this way, the chirality of all living things has formed. Reasoning along this line raises the question: What was the primary mechanism of mirror symmetry breaking in the course of natural pre-biological processes? It was known before Pasteur that crystals with left and right angularities have different optical polarization signs, left and right. Had chemical transformations of minerals that supplied energy for reaction cycles at the dawn of evolution produced a single isomeric form of matter, AL, another product of this transformation, substance B_L, and all other products would have acquired the same configuration. The type of configuration becomes important when small optically active molecules begin to link together giving rise to linear or cyclic polymers.

Spontaneous decomposition of the symmetric mixture resulting from the formation of L- and D-crystals that are initially present in equal amounts does not by itself break symmetry. If a crystallization experiment is repeated N times, the average number of homochiral L- and D-crystals will be the same; in other words, chirality restores in a large sample. This means that homochirality in living systems is a stochastic phenomenon related to the initial conditions of natural selection. Such experiments have been carried out many times with thousands of crystals and demonstrated equiprobable distribution of crystals of either form (a discrete spontaneous but equiprobable manifestation of different types of chirality throughout a long period of time). In other words, homochiral structures of either form spontaneously and with equal probability arose in a given small volume.

Consideration of this process not only in time but also in space reveals spontaneous formation and evolution of homochiral structures in different parts of a chemical mother medium. This process is akin to the formation of spiral selfsustained dissipative structures observed in the Belousov– Zhabotinsky reaction. These autowaves break up as they encounter an obstacle, giving rise to pairs of L- and D-helical structures. Globally, symmetry remains unaffected within the boundaries of this area even if local breakage occurs within a small distinguishable region inside the areal.

Can this analogy be helpful in explaining the origin of homochirality in sufficiently complicated structures, thus forming homochiral sequences in DNA and RNA, and homochiral polymer chains within a given time and in a given place?

It seems that self-organization should allow building up rather long chains that might coil into DNA and RNA type structures. However, it turned out that a length of 30 units is critical in a random process. It is insufficient for biological evolution because such fragments cannot transfer the necessary amount of information. The longer the chain, the more errors occur, and its assembly stops.

The cause of the error appearance is very simple. In order to assemble a given sequence of, for example, left-handed molecules alone from a very large number of possible sequences of L- and D-molecules spontaneously formed in the mother solution, it is necessary to select a single variant, L or D. When this number becomes too large, the probability of an error increases (by analogy with tossing a coin N times, when the probability of getting tails only on each successive flip rapidly decreases with N). Therefore, selection accuracy must grow steadily to ensure that only one of the species, either L or D, survives. Otherwise, the error conditions will arrest further assembly (in the literature, this phenomenon is frequently referred to as Levinthal's error catastrophe).

To assure accuracy of selection, the process needs to be adjusted with the help of specific structures, e.g., enzyme proteins, as in present-day living systems. In the absence of enzymes, the only option is to have a pure medium containing practically one isomer needed for self-assembly, for instance, L, and as few D-isomers as possible to make the probability of appearing erroneous chain with their involvement negligible.

In other words, an exchange operation takes place by which the enzyme-driven process (improvement in selection accuracy) is replaced by an improvement in medium purity (elimination of unwanted enantiomers). The question is if a 'pure' medium of homochiral fragments could exist at the first stage of evolution and be used at the second stage for enzymeindependent assembly of long chains. Had a certain initial mechanism acted instead of enzymatic regulation, it would have been of no consequence in which medium, symmetric or asymmetric, the assembly occurred.

In the end, it was generally accepted that nonlinear reactions in strongly nonequilibrium systems with critical behavior may result in almost spontaneous loss of stability of the sustained symmetric state. Wherever instability prevails, a *weak* effect turns into a *strong* one. Then, even a minor impact may throw the system out of balance. Small causes may have large effects [9], inducing off-beat phase transition at a critical point. It was necessary to show what force and time are needed for this to occur (see the Saint Petersburg paradox in Section 3.9). Many systems and processes were found to meet these conditions, viz. meteorites, changes in magnetic field rotation, or temperature fluctuations, i.e., disrupted behavior of the Earth's atmosphere and hydrosphere.

The problem of chirality and spontaneous separation has not only theoretical but also applied implications, such as preparation of chirally pure nanocompounds. The modern pharmaceutical industry is oriented toward production of chirally pure medicines. This trend was initiated by a scandal that broke in the 1970s when a few hundred infants were born with so-called phocomelia, a congenital malformation characterized by agenesis of the long bones of the arms or legs and resulting in limbs that look like the flippers of a seal. The pathology was caused by the use of a sedative/hypnotic drug, thalidomide, containing a mixture of enantiomers of a synthetic derivative of glutamic acid (alpha-phthalimidoglutarimide). Separate testing of their activities showed that the D-isomer was safe, whereas the L-isomer provoked malformation. This case clearly demonstrated the importance of homochirality for biological systems.

3.8 Paradox of the part and the whole

The Selfish Gene [147] published by Richard Dawkins in 1976 immediately became a bestseller and was translated into 13 languages. Dawkins coined the term 'selfish gene' as a way of expressing the gene-centered view of evolution, which holds that evolution is best viewed as acting on genes, and that selection at the level of organisms or populations almost never overrides selection based on genes. Although detrimental to their host, genes nonetheless propagate themselves at its expense. Is it possible, based on the bottom-up approach, to regard each hierarchical level of organismal evolution as a receptacle for the preceding one? Evidently, the problem reduces to regulation of the mutual influence of one hierarchical level on the other (paradox 8).



Paradox 8

At first site, arguments in favor of the primacy of the genetic code appear quite reasonable, bearing in mind that many species of organisms came to life and became extinct, while the code once brought into existence remained conserved, despite 'errors'. This conflict constitutes *the paradox of the part and the whole*. Genetic code periodically replicates itself in cells (in DNA or RNA chains, chromosomes of somatic cells, mitochondria) and its operation is manifest in the formation of tissues and organs; indeed, in the habitus of the whole organism. Genetic code is the common language of Earth's biosphere. It is an invariant. What is then more important for the development of life: *the preceding or the next hierarchical level, the code or the organism*?

Errors (mutations) during replication of the genetic code are a frequent cause of the faulty operation of a cell or an organism as a whole, leading to the death of both. In this way, cells with the defective code, e.g., cancer cells, are eliminated. At the other hierarchical level, it is distinctly 'selfish' of a parasite (the part) to modify the behavior of the host (the whole), so as to make a ruminant vulnerable to the attack of a carnivore doomed to become its secondary carrier. Certain parasites influence the behavior of the intermediate host after they penetrate its central nervous system. By way of example, *avertin*, a ruminant, e.g., an ovine, disease makes the affected animals walk with a staggering gait or in circles and eventually break from the nerd. Avertin is caused by a canine tapeworm *Taenia multiceps* located in the brain or spinal cord of a sheep, which finally falls prey to wolves or wild dogs hunting the stray animal. In fact, parasites do not induce a new type of behavior, but just cause the host to behave so as to reduce its chance of survival [148].

Despite a relatively short lifespan, all living organisms are active participants in the evolutionary process. Had a generation of organisms at the very outset of evolution been able to ideally (without errors) reproduce the genetic code (i.e., had the code existed by itself), further evolution would have stopped. Pra-organisms precisely reproducing and transferring genetic information would have been the sole inhabitants of our planet. However, they would have simultaneously died as soon as environmental conditions changed.

This means that the genetic code and its modifications selected at lower hierarchical levels are integrated into higher ones to become their constituent elements and evolve further. Propagation enables an organism to conserve the lowest hierarchical level, even if with some errors, and reproduce it in the progeny. In other words, biological evolution proceeds in two distinct modes: as the existence of short-living organisms, and via mutations in the long-lived genetic code.

Mathematically, this situation can be described in a variety of ways, for instance, by the Heaviside step function [149] or Kronecker δ -functions [150, 151]. The totality of different means for the description of interactions between hierarchical levels and their critical states in biological systems can be tentatively termed the science of cooperative hierarchical self-organization. H Haken called it *synergetics* [152]. Cooperation at the bottom level creates the topmost one. Flexible connections at the level of cooperation increase rather than decrease the stability of the organism as a whole, enabling it to adapt to changing environmental conditions. On the other hand, the lack of rigidity accounts for the occasional loss of control on the part of a higher level over the lower one, and may lead to the death of all the system.

3.9 Saint Petersburg paradox

According to Darwin [2], heredity, variation, and natural selection are the driving forces behind evolution. However, selection cannot be a driving force. It can only select from the existing traits, and cannot create new characters, thus reducing variation. Selection implies *reduction*. Reduction of some properties of living organisms occurs in the framework of the existing system comprising them as its constituent elements. Darwin's term 'variation' is poorly defined and should be substituted by the term 'self-complication'. But how is the mechanism of self-complication realized?

A specific driving force is needed to direct the process of complication of living things and thereby promote biological diversity. This inference brings us to the central issue of this review, i.e., the complication and expansion of living matter. In other words, it is necessary to show how a random symmetric chaotic process builds up into a directed one. As mentioned above, the kinetics of individual elements are more important in this context than the thermodynamics of the system as a whole (in its integral characteristics).

Let us assume a certain process, e.g., spatial displacement, of a group of particles x, and construct a plot of probability distribution P(x) of different mean free paths for a certain time. Integration results in a loss of information about the motion of individual particles, and averaging over integrated plots makes it difficult to describe the situation covered by this distribution.

In the beginning, the problem of individualization was considered in terms of the theory of probability in relation to games of chance, which gives a demonstrative example of many important aspects of time scales and fractality in biosystems (homochirality, self-complication) and also describes mechanisms of the evolution of life. A few remarks are in order.

Tossing a coin N times and taking N to be large give a sequence of heads (gains) and tails (losses) (Fig. 8).

The pattern of gains and losses suggests their random distribution over time along with the formation of clustered strips of different widths dominated by either gains or losses. Let us break down the coin tossing interval into larger parts, e.g., containing sequences of flips of 20, 40, etc., and mark the



Figure 8. Gain–loss (heads–tails) sequence in the coin toss game. Light strips are gains, and dark strips are losses. The number of flips (time) is plotted on the abscissa; here, N = 10,000.



Figure 9. Fractal-like pattern of combined time events in a random process within the range of 1 to 7 iterations. Light and dark intervals correspond, in the average, to dominated gains and losses, respectively. Distribution of gains and losses is, on the average, symmetric.

clusters dominated by gains as light, and those dominated by losses as black (Fig. 9).

Mean probabilities of gain, p, and loss, q, for an infinitely long time period are equal: the process is symmetric and p = q = 0.5. The question is whether the player can somehow break the symmetry of distribution for his own benefit. If yes, why could living nature not use the same strategy in the course of evolution?

In the mid-1920s, P Levy tried to clear up under which conditions the distribution P(x) for the sum of N steps $X = X_1 + X_2 + \ldots + X_N$ is the same as individual distributions P(x) on an N-step scale. This problem is directly related to the splitting of processes into fractal-like streams when the whole picture looks like its separate portions but on a different scale. The standard answer is self-evident: the sum of N Gaussian distributions will also be the Gaussian distribution. However, Levy showed that there is another answer [153]: namely, the second moment of the probability P(x) must tend to infinity, i.e., $\langle x^2 \rangle \to \infty$.

Long before Levy, a similar phenomenon was considered by D Bernoulli in the Commentaries of the Imperial Academy of Sciences of Saint Petersburg (early 18th century). It became famous as the Saint Petersburg paradox of gambler's ruin [154, 155]. The paradox arises from the appearance of a set of time scales in a random process when it begins to be influenced by previous history. In this case, the number of gains and losses depends on the gambler's whereabouts, i.e., the light or dark strip (paradox 9).

Every time the coin is tossed, all previous results of the game are seemingly forgotten, and it begins anew. The probabilities of each new game do not depend on the results of the preceding one. This means that there is no strategy that guarantees a gain to one player, and ruins to another. According to the von Neumann *minimax theorem*, the optimal strategy for each player in a finite zero-sum game brings equal gains [156, 157]. In other words, if the random guessing strategy is set against the chance of getting heads or tails on the tossed coin, the player neither wins nor loses. In reality, however, there is always a winner or a loser. Why?



Paradox 9 A probabilistic binary game is a discrete process in which the gain distribution function grows (decreases) in discrete steps only in a countable set of round termination points but remains constant in the intervals between them, corresponding to round duration τ . Additional information about the preceding round is inessential for the prediction of the outcome of the next one, because *the*

correlation time or *memory* is determined by round length, for instance, the rotation time of the tossed coin. The player cannot influence the course of the game during interval τ . However, 'memory' of at least one round may provide a strategy leading to a gain due to an increase in *correlation time*. Is it really so?

In terms of biological evolution, the stickman functions in the capacity of the environment, and the player himself is living matter. Let us turn back to coin tossing. The coin is flipped by the stickman, and the player cannot influence the outcome. Nevertheless, he can govern the win-loss process in each game comprising N flips by changing the stakes before each new flip depending on the result of the preceding round. If he has a memory of the outcome (win or loss) of at least one round, he can choose a stake-changing strategy for the next one, which will be different from the previous one in terms of the stakes. Independent probabilities will become dependent. The aim of the strategy is to introduce asymmetry (a change in the stakes) into the initial symmetric distribution of wins and losses. If the gambler wins the first round (e.g., gets heads), he may consider himself in a run of good luck and raise the stake to get heads again, e.g., linearly (in an arithmetic progression) or in the form of the Fibonacci number series. If the gambler loses, he reduces the stakes in the third round and does not change them till the next win. Thus, in each game gains may grow regardless of the round in which the gambler wins. Table 4 illustrates the asymmetry of wins and losses achieved with two strategies (linear and as a Fibonacci number series).

Clearly, raising the stakes according to arithmetic progression in a run of good luck gives two sums, one negative:

 $s_1 = -\sum_{i=0}^{1} p_i \Delta_i = -\frac{1}{2} \ 0.5 - \frac{1}{4} \ 1 = -0.5 \ ,$

and the other positive:

$$s_{2} = \sum_{i=2}^{\infty} p_{i} \varDelta_{i} = \frac{1}{8} \ 0 + \frac{1}{16} \ 2 + \frac{1}{32} \ 5 + \frac{1}{64} \ 9 + \frac{1}{128} \ 14$$
$$+ \frac{1}{256} \ 20 + \frac{1}{512} \ 27 + \frac{1}{1024} \ 35 + \frac{1}{2048} \ 44 = 0.717 \ .$$

Adding the two sums, and taking account of their relative frequency of occurrence w, gives $S = (1 - w)s_1 + ws_2$. At w = const = 1/2, one finds S = 0.109 > 0 (see Table 4). The distribution of wins and losses becomes slightly asymmetric in favor of the gambler. In fact, it is the question of multiplying the number of win clusters in which one and the same side of the coins appears several times in succession. Figures 10 and 11 give the results of a computer experiment using the linear stake-raising strategy according to arithmetic progression.

The key issue is the game bankroll. Evidently, if the player plans to participate in 8 rounds at doubled stakes, he must

No n_i	Probability of cluster	Raising the (in a	e stake in a run of good luch rithmetic progression)	k	Raising the stake in a run of good luck (as a Fibonacci number series)				
	p_i	Change in stakes in a run of good luck, +b	Change in stakes in a run of losses, $-b$	Total gain, $+b - b = \Delta_i$	Change in stakes in a run of good luck, $+b$	Change in stakes in a run of losses, $-b$	Total gain, + $b - b = \Delta_i$		
0	1/2	1 or 1	-2 or -1	-1 - 0	1 or 1	-2 or -1	-1 - 0		
1	1/4	1 + 2 = 3	-3 - 1 = -4	-1	1 + 2 = 3	-3 - 1 = -4	-1		
2	1/8	1 + 2 + 3 = 6	-4 - 1 - 1 = -6	0	1 + 2 + 3 = 6	-4 - 1 - 1 = -6	0		
3	1/16	1 + 2 + 3 + 4 = 10	-5 - 1 - 1 - 1 = -8	2	1 + 2 + 3 + 5 = 11	-8 - 1 - 1 - 1 = -11	0		
4	1/32	1 + 2 + 3 + 4 + 5 = 15	-6 - 1 - 1 - 1 - 1 = -10	5	1 + 2 + 3 + 5 + 8 = 19	$ \begin{array}{r} -13 - 1 - 1 - 1 - 1 \\ = -17 \end{array} $	2		
5	1/64	1 + 2 + 3 + 4 + 5 + 6 = 21	-7 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 = -12	9	$ 1 + 2 + 3 + 5 + 8 \\ +13 = 32 $	-21 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1	6		
6	1/128	1 + 2 + 3 + 4 + 5 + 6 + 7 = 28	$ \begin{array}{r} -8 - 1 - 1 - 1 - 1 \\ -1 - 1 = -14 \end{array} $	14	1 + 2 + 3 + 5 + 8 +13 + 21 = 53	-34 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -	13		
7	1/256	1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 = 36	$\begin{array}{c} -9 - 1 - 1 - 1 - 1 \\ -1 - 1 - 1 - 1 = -16 \end{array}$	20	1 + 2 + 3 + 5 + 8 + 13 + 21 + 34 = 87	-55 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1	25		
8	1/512	1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 = 45	-10 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1	27	$\begin{array}{c} 1+2+3+5+8+13\\+21+34+55=142 \end{array}$	-89 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -	45		
9	1/1024	1 + 2 + 3 + 4 + 5 +6 + 7 + 8 + 9 +10 = 45	-11 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1	35	1 + 2 + 3 + 5 + 8 +13 + 21 + 34 + 55 +89 = 231	-144 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1	78		
10	1/2048	1 + 2 + 3 + 4 + 5 +6 + 7 + 8 + 9 + 10 +11 = 66	$\begin{array}{c} -12 - 1 - 1 - 1 - 1 \\ -1 - 1 - 1 - 1 - 1 \\ -1 = -22 \end{array}$	44	1 + 2 + 3 + 5 + 8 +13 + 21 + 34 + 55 +89 + 144 = 375	$\begin{array}{c} -233 - 1 - 1 - 1 - 1 \\ -1 - 1 - 1 - 1 - 1 \\ -1 = -243 \end{array}$	132		

Table 4.

have as many as $2^8 - 1 = 255$ chips. To reduce the risk, he must raise his stakes during a lucky streak in arithmetic, rather than geometric, progression, although it reduces the total gain. This scheme implies a cycle with varying feedback factors. The player (living object) changes the stakes in the course of the game and thereby introduces asymmetry into the symmetric distribution of randomness created by the environment (coin tossing). This is the simplest example of the formation of a cycle with a varying feedback factor in a random process. As known, a similar approach is widely used to simulate Bernoulli particle walk [155]. Asymmetry results from the change in stakes in the run of good and bad luck, but not from coin tossing, i.e., from a change in gain/loss probabilities in kinetics of the process.

Long-term computer simulation confirms the validity of the above consideration of the game process. Figure 11 presents the results of a computer experiment comprising six 10-round games with 100, 1000, 10,000, and 100,000 coin flips, respectively. Our computer experiment consisted of 10⁷ trials ('coin flips').

It can be concluded that the greatest event in the course of natural evolution was the appearance of *primitive memory* for at least one cycle of environmental changes. *This godsend immediately divided nature into living and nonliving*. One part (living matter) acquired the ability to predict (albeit not quite accurately) the conditions of its existence. What was that primitive memory? The genetic code is a memory intended to scale up the game, but it is not the sole option. Any successive chemical reaction also possesses memory:

$$A + B \xleftarrow{k_1}{k_2} AB, AB + AB \xleftarrow{k_3}{k_4} ABAB,$$

$$ABAB + ABAB \xleftarrow{k_5}{k_6} ABABABAB \dots,$$

where A and B are the substrates, and AB is the product formed in the first cycle. For the next cycle, AB and AB are the substrates, ABAB is its product, etc., and $k_1, k_2, ...$ are the chemical constants of forward and reverse chemical reactions. Under real conditions, the value of k_i may vary with changes in the physical parameters of the environment (temperature, acidity, electric and magnetic fields) and cause departure from equilibrium between the forward and reverse reactions. The lengthier the chemical cycle (i.e., the more new products are formed under favorable conditions), the lower the probability of reverse reaction toward the starting substrates A and B. Such is *the memory* of the cycle of chemical reactions *about the past*.

The strategy designed to win reliably required very much (ideally infinite) time and a very large bankroll (energy) or its inflow during the game. It consisted in scaling the game by $n\tau$, where *n* is the number of rounds in a game. Living systems evolved exactly under these conditions. They had both 4.5 billion years to develop and a steady inflow of solar energy.

A living particle that assimilated the solar energy could change, for instance, its Stokes (hydrodynamic) radius [158] and thereby control the probability of motion in both time and space in the search for favorable conditions. For p > q, the probability of losing, i.e., of vanishing, tended to zero. In other words, once on a lucky streak, the particle (a primitive living system) could stay there for a very long time [155].

Another mathematical paradox, very much like paradox 9, was formulated by Juan Parrondo in 1999 [159, 160]. In 2009, M McDonnell and D Abbott used it to design a winning strategy for the two-envelope game [161].

The player is given two indistinguishable envelopes, each containing a positive sum of money (no weighing, touching, or illuminating was allowed). It is only known that one envelope contains twice as much sum as the other but it is



Figure 10. (a) Linear increase in the stakes in a run of good luck; they are minimal or unaltered in a run of bad luck. (b) Sums of losses (columns extending down the ordinate axis) and gains (columns going up the ordinate axis). The number of flips (time $n\tau$) is plotted on the abscissa. Total number of flips N = 150.

unknown in which envelope and what sum of money may be found. The player may select one envelope to open. After that he can either take this envelope for himself or exchange it for the other. There is the option of swapping envelopes either at random or following a certain rule. The puzzle is to find the erroneous step in the swapping procedure and thereby win the maximum sum in N rounds.

The strategy leading to the maximum gain consists in exchanging envelopes in each round with a probability depending on the sum of money contained in the chosen envelope. The smaller the sum, the more likely it is that the player should swap the envelope, and vice versa. The paradox lies in the fact that the sum of money seen by the player does not tell him anything about the intentions of the stickman who filled the envelopes and the proportion in which money was distributed between them. The paradox is resolved in the same manner as the Saint Petersburg paradox, i.e., by breaking symmetry of the game in favor of the player [161].

At first sight, application of the Saint Petersburg paradox to real processes is in conflict with the laws of conservation of force and energy momenta. But this is not the case. The energy comes from the exterior, and directional motion is created by asymmetry introduced by the player. The mechanism of this phenomenon can be explained based on a mechanical model called *a linear oscillating conveyor with the ratchets* shown in Fig. 12. A weight with mass *m* is placed on the conveyor belt driven by the swings of a massive harmonic pendulum (Fig. 12a). This oscillation force moves the conveyor equally in both directions. Pendulum mass M is much greater than weight mass m. In this model, the pendulum functions as the environment, and the weight plays the role of a living system.

The belt of the conveyor has *symmetric* teeth, while the teeth at the bottom side of the weight are *asymmetric* (Fig. 12b; see inset). The conveyor moves with speed v and periodically changes direction of motion under the action of the pendulum. Due to teeth asymmetry, the weight undergoes different strains as the belt moves right and left. According to the Hooke law, force **F** pushing the weight causes elastic deformation of the teeth:

$$F = \gamma \, \frac{\Delta L}{L} \, ,$$

where L is the weight length, ΔL is its contraction, γ is the coefficient, $\gamma = ES$, where E is Young's modulus, and S is the teeth cross section. The teeth of the conveyor lock into the weight's teeth and thereby move the weight. The expression for Hooke's law can be converted to

$$F = \gamma \left(1 - \frac{a}{L} \right),$$

because $\Delta L = L - a$, where a is the chord length (Fig. 13a).



Figure 11. Win and loss histograms. Dark columns—losses, and white columns—wins. Win/loss ratio is shown under the histogram of each test series. Wins prevail in most of them (at least in three of the four), although losses are just as well possible.

The chord length *a* may be expressed through the radius of curvature *R* and central angle β : $a = 2R \sin \beta/2$. Given a sufficiently elastic weight, its deformation is insignificant and $\sin \beta/2$ may be substituted by the angle $\beta/2$. As a result, one arrives at

$$F = \gamma \left(1 - \frac{R\beta}{L} \right).$$

Let us assume that the conveyer is made very stiff to prevent its bending, and friction in its bearings is infinitely small. An important characteristic of the experimental setup is the inequality of the radii of curvature of the weight, $R_1 \neq R_2$, as the direction of its motion alters (Fig. 13b, c). The last expression for the force implies that the weight largely moves in the direction of the force vector at which the weight bending is greater and the radius R is smaller. When the conveyor moves to the right after its teeth lock between the teeth of the weight, the latter's bend increases ($R_1 < R_2$). Hence it follows that

$$\vec{F} = \gamma \left(1 - \frac{R_1 \beta_1}{L} \right), \quad \vec{F} = m \frac{d\vec{v_1}}{dt},$$
$$\vec{F} = \gamma \left(1 - \frac{R_2 \beta_2}{L} \right), \quad \vec{F} = m \frac{d\vec{v_2}}{dt}.$$

Integration of these expressions permits estimating weight displacements to the right and left, respectively, as

$$\vec{x}_1 = \frac{\gamma}{m} t^2 \left(1 - \frac{R_1 \beta_1}{L} \right), \quad \vec{x}_2 = \frac{\gamma}{m} t^2 \left(1 - \frac{R_2 \beta_2}{L} \right).$$

Figure 13d presents a plot of weight displacement in time in relation to the change in speed vector direction. It is evident from the figure that the process of increasing the weight's displacement length is asymmetric in time.

Macrosystems with alternating friction depending on the direction of motion were known long ago. Some northern peoples are known to have for centuries attached pieces of animal skin to the bottom surface of skis to allow the ski to slide forward but resist sliding backwards, thereby facilitating faster movement of the skier. Today, these ideas are used at the molecular level in designing nanoconveyors.

The fixation of weight displacement during each pendulum period represents actually *memory*. Each next step of the weight movement in a new pendulum cycle starts from the one reached in the preceding cycle. It is easy to see that *a clock with a linear dial operates as an oscillating conveyor with ratchets* because the distance travelled by the weight depends on the number of pendulum oscillation cycles. There are many living natural systems operating in analogy with the oscillating conveyor carrying a weight. For example, a fibrillar protein or DNA chain is a conveyor along which an enzyme (weight)



Figure 12. Schematic of a pendulum-driven oscillating linear conveyor with ratchets. Inset: magnified view of a portion of the system showing the interlocking teeth of the weight and conveyor belt. Gripping forces (analog of living matter) between the weight and conveyor belt differ during movement to right and left. As a result, the weight moves only to the right. The driving force here is pendulum energy, acting as the environment. Eventually, the pendulum stops after the energy is spent on friction. However, the weight continues to move if the pendulum receives energy from an external source.

skims. Such systems show periodicity and spatial asymmetry conditioned by the genetic nature of their structure (see Section 3.10 for details).

With regard to biological systems, this phenomenon can be described in a different way, for example, as [162, 163]

$$\begin{aligned} \frac{\partial u}{\partial t} &= f(u,v) + D_1 \frac{\partial^2 u}{\partial x^2} + h_1 \frac{\partial}{\partial x} \left(Q_1(u,v) \frac{\partial v}{\partial x} \right), \\ \frac{\partial v}{\partial t} &= g(u,v) + D_2 \frac{\partial^2 v}{\partial x^2} + h_2 \frac{\partial}{\partial x} \left(Q_2(u,v) \frac{\partial u}{\partial x} \right). \end{aligned}$$

Here, u is the displacement of a living system (weight), and v is the displacement of the medium (conveyor) itself. At

 $h_1 = h_2 = 0$, the mathematical model is a reaction-diffusion type system with diffusion coefficients $D_1 \ge 0$, $D_2 \ge 0$ (at least one $D_i \neq 0$). The system becomes cross-diffusional when at least one of the coefficients $h_i \neq 0$ (regardless of sign). In linear cross diffusion $Q_i(u, v) = \text{const for } i = 1, 2$, while in nonlinear cross diffusion $Q_i(u, v) \neq \text{const}$ for at least one *i*. The third term in the first equation in the case of biological objects describes their oldest property: time-dependent variations of taxis, i.e., reactions to environmental gradients. Evidently, the recognition of a gradient implies *memory* of at least a single step of motion. The above system of equations differs from the example of an oscillating conveyor with the ratchets, considered in the preceding paragraph, in that the conveyor properties (environment) also vary. Such a system is able to spontaneously create and develop a variety of ordered dynamic structures. Interestingly, such systems exhibit a peculiar phenomenon, reminiscent of negative friction, called negative refractoriness in physiology [163].

It should be emphasized that a particle can change its hydrodynamic radius in a temperature or ion gradient even if it lacks metabolism; due to this, collisions with neighboring molecules convert its chaotic motion into the one directed along a gradient [168]. Figure 14 illustrates two such examples.

3.10 Buridan's ass paradox

What prevails in biosystems: determinacy or randomness? The discussion of this question has a long history and can be illustrated by the well-known Buridan's ass paradox, the last one considered in this review (paradox 10).

Today, this paradox elicits nothing but a smile. It arises from the wrong assertion that living systems are 'deterministic finite automata' containing no chaotic component that breaks down indeterminacy of choice at equal probabilities. The paradox is based on the assumption that p = q = 1/2, where p is the probability of choosing one stack, and q is the probability of choosing the other. However, any random fluctuation ε destroys this equilibrium, making $p = 1/2 - \varepsilon$, $q = 1/2 + \varepsilon$, thereby saving the ass.

In 2002, we happened to review a paper under the title "Can an organism select new information?" submitted for publication in *Biofizika* (Biophysics), which read as follows: "the experience with construction of artificial intellectual systems indicates that it is impossible to teach them; they can only be programmed (prepared). A machine cannot write a program for itself." The author concluded that all living



Figure 13. Schematic representation of weight bending as weight's teeth lock between the teeth of the moving conveyor (a); weight bending as the conveyor moves to the right (b) and to the left (c); weight displacement x in time t in relation to the change in conveyor speed direction \mathbf{v} (d) (see text for explanation).



Figure 14. Models of particles changing configuration in a gradient field, which enables them to move toward the gradient source: (a) changes in bacteriophage geometry; long end-fibrils spread out as temperature grows or when interacting with metabolic products of bacteria, thus changing the hydrodynamic profile of the phage as a whole; (b) hydrodynamic profiles of the bacteriophage (shown in black); (c) simulated changes in the geometry of a globular polymer (virus or protein). A change in the radius in the gradient field triggers directed motion [75].



make any rational decision to choose one over the other. In other words, the logic of *absolute determinism* does not allow choosing between two equally plausible courses of action. In a figurative sense, it is the choice between equally compelling options.

systems are somehow programmed. The paper was published [164]. We had to remind the author in the same issue [165] about self-learning neurocomputers [7, 167].

Buridan's ass paradox is resolved in terms of competition between determinacy and randomness of the processes both in the central nervous system of currently extant organisms and in the natural selection of organisms during evolution. *The modes of realization of such competition or of human thinking* were considered in a few reviews published in *Physics*- Uspekhi [7, 166, 167].

We shall try here to answer the question of how the variety of past and present living organisms could evolve. In the first approximation, all living systems can be divided into two large sets. One comprises primitive unpretentious organisms that rapidly reproduce, have short lifespans, and fairly well adaptability to external conditions due to mutations that are selected by the environment if beneficial for the species. These organisms (viruses, bacteria, insects, etc.) have no intellect and are incapable of adaptation through learning. The other set includes complex organisms that reproduce at a slow rate, live longer, and show signs of intellect that enables them to learn how to adapt to the environment. What strategy is more beneficial for sustainable existence? In a word, both are good



Figure 15. Initial distribution of subjects along axes X (learning ability) and n_X (number of subjects capable of learning in set N). Any number of gradations along the X-axis and arbitrary initial distribution of amplitudes corresponding to the number of subjects in these gradations are possible. This figure shows the uniform distribution (almost white noise) at $N = 1,000, X_{\min} = 0$, and $X_{\max} = 24$.

insofar as the two sets simultaneously exist on our planet. But no one can tell which will prevail in the future; it is a matter of chance, as appears from the model considered below [168].

This mathematical model is formulated as follows. A set of subjects N is divided into X groups of n_X subjects each. Each group is referred to as a gradation of distribution, and the number of subjects in each group as its amplitude (Fig. 15).

Subjects in each gradation of set X show a degree of learning ability realized either via mutations or intellect. Gradations are distributed over the range from X_{\min} to X_{\max} , while the number of subjects with property X is equal to amplitude n_X . Expression $N = \sum_{X_{\min}}^{X_{\max}} n_X = \text{const}$ holds true for this model. Reproduction of the subjects is not considered below because it does not change the results obtained with the model. Only the exchange of information between its carriers (elements of *memory*) is of importance for the case in question. In *pairwise random interactions*, the subjects can randomly pass from one gradation to another, upgrading or downgrading their property on the basis of a given feature X. The interaction rules for the subject features are formulated depending on the goal of simulation. For the purpose of the present discussion, two simple interactions are utilized:

(1) In certain cases of the pairwise random encounter of subjects, their features are assigned the *highest rank* of the features common to both of them.

(2) In other cases of the pairwise random encounter of subjects, indications of their features are assigned the *lowest* rank of the features common to both of them.

(3) Rules 1 and 2 operate alternately within a certain time interval.

The alternation pattern is determined by environmental changes (a pendulum) with period χ .

The feature of learning ability may be characterized by the indication of time needed to be educated. In other words, each subject has a feature, for example, a clock indicating the time of individual life either increasing or decreasing as a result of



Figure 16. Diagram showing kinetics of the learning process. The choice of the features is determined by a pair of objects randomly selected from any gradation *X*. Gradations are depicted as sets of subjects with identical features. Having met each other and acquired a new rank of feature, the subjects continue to encounter each other. The model implies a change in the rules for transferring subjects between the sets depending on the acquired feature rank. The rule operating at a given instant of time is determined by the position of the pendulum, either 0 (simplification) or 1 (complication).

learning in a range from 0 to 24 hours (or 0 to 24 million years, which makes no difference). It may be any other features, such as the set of chemical elements, their complexes, or complex macromolecules (nucleotides, amino acids, compounds). The pendulum motion stands for environmental changes and the subjects are individual organisms learning from each other during interactions. In the simplest case, learning occurs through horizontal gene transfer or by any other mode of information transfer from one subject to another (Fig. 16).

Organisms upgrade their feature X when interacting in accordance with rule 1, and downgrade it (lose the useful features acquired through learning but increase the reproduction rate) in interactions under rule 2. The total number P of possible transfers of subjects in set N equals N!. Interactions between subjects in each gradation n_X do not influence the feature distribution in the system as a whole because subjects in one group (one gradation in the distribution histogram) have similar properties. The number of different groups/ gradations is $X_{\text{max}} - X_{\text{min}}$; hence, the expression for the number of wasteful encounters A that do not change the features of the population at large. Expression A = $\sum_{X_{\min}}^{X_{\max}} (n_X!)$ holds true for any initial distribution. Given a uniform white noise type distribution at which amplitudes of all n_X gradations are practically equal, this expression is simplified and takes the form $A = (X_{\text{max}} - X_{\text{min}}) n!$. Let us denote $\Delta X = X_{max} - X_{min}$. The useful or efficacious exhaustion assuring property upgrade (rule 1) or downgrade (rule 2) in set N is the exhaustion of objects belonging to different groups. Therefore, the number of useful encounters B changing the property of the system is given by

$$B = P - A = N! - \sum_{X_{\min}}^{X_{\max}} (n_X!) ,$$

or

$$B = P - A = (N!) - \Delta X(n!).$$

This expression can be rearranged to $B = P - A = (\Delta X n)! - \Delta X(n!)$. The probability of occurring *useful encounters* p_{useful} for the uniform white noise type distribution has the form

$$p_{\text{useful}} = 1 - \frac{\Delta X(n!)}{(\Delta Xn)!} ,$$

and that of useless encounters $p_{useless}$ is expressed as

$$p_{\text{useless}} = \frac{\Delta X(n!)}{(\Delta Xn)!}$$

It can be seen that at $\Delta X = 1$, the probabilities take the following values: $p_{useful} = 0$, and $p_{useless} = 1$. When only two gradations with an equal number of subjects ($n_1 = n_2 = N/2$) remain in the distribution, the situation becomes analogous to the previous one because

$$p_{\text{useful}} = 1 - \frac{\Delta X(n!)}{(\Delta Xn)!} = 1 - \frac{2(N/2)!}{(2N/2)!} = 0,$$

 $p_{\text{useless}} = 1,$

i.e., the system enters a long-lasting steady oscillation regime or, in other words, two sets of living organisms are formed: primitive and complex ones. Only random fluctuations can disturb the oscillating equilibrium in such a system. However, such a calculation gives only probabilistic estimates of the stationary state of the process and says nothing about its kinetics. The character of transition process can be deduced from computer simulation.

Three time-related parameters are of importance here, viz. *T*, the time interval necessary for a system to acquire a single feature, i.e., single gradation (by rule 1 or 2); χ , the period of pendulum swing, and $r = \tau_1/\tau_2$, the period filling factor, i.e., the ratio of time intervals τ_1 and τ_2 within period χ , necessary to realize rule 1 or 2 (in this case, $\chi = \tau_1 + \tau_2$). Situations in which $\chi \ge T$ or $\tau_1 \ge \tau_2$ or $\tau_2 \ge \tau_1$, i.e., $r \to \infty$ or $r \to 0$, are of little interest. In these cases, pendulum swings do not appreciably influence trends in the organisms' features. The system has managed to reach complete synchronization within a single period (as a last resort, within three periods); in other words, the sole gradation with an amplitude equaling *N* will be retained.

An interesting case is when $\chi < T$, illustrating competition in the choice of a common feature for two gradations. When $\chi \leq T$ and $\tau_1 = \tau_2$, i.e., r = 1, where χ is the oscillation period of the control pendulum, simulation shows that the system actually passes into a long-lasting oscillation regime giving rise to competition between two equipotant distribution gradations, the amplitudes of which change in synchronism with the pendulum frequency (Fig. 17). When the pendulum is in position 0, the right amplitude decreases and the left one increases identically; the situation reverses when the pendulum resides in position 1.

Such an oscillation regime may last very long, but random encounters of two subjects sooner or later introduce asymmetry between competing gradations. In the end, only one of them remains, either right 6 or left 23 (Fig. 17), even if the outcome is a matter of chance and impossible to predict.



Figure 17. Mechanism of the formation of a relatively stable regime in a system with the appearance of two equal amplitudes of competing gradations that transform the transition process to the prolonged oscillation regime.

The character of the transition process can be illustrated in a compact form (using polar coordinates) by plots showing changes in root-mean-square deviation over the entire ensemble of subjects for time t. In this case, radius vector ρ is a function of time t and has the form

$$\rho = \frac{1}{(X_{\max} - X_{\min})(vt)} \left[\sum_{X_{\min}}^{X_{\max}} \sum_{0}^{t} (n_{ij} - \bar{n})^2 \right]^{1/2}$$

and angle φ changes as vt, where $\bar{n}(t)$ is the mean value of gradations, and v is the frequency of encounters, in the model v = const. In other words, the value of vector ρ decreases with time in the oscillation regime. As $t \to \infty$, the quantity $\rho \to 0$ and the rotation angle φ varies continuously with time from 0 to 2π , i.e., vector ρ alternately has an opposite sense of rotation within this range (Fig. 18).

Investigation of the transition process revealed the following six peculiarities:

(1) A system with an initially uniform distribution of features has less time to establish a single feature (i.e., to converge to one gradation). The time interval necessary for the single feature to be established with the initial Gaussian distribution is 35-40% longer than with the initial uniform distribution due to the decreased probability of useless encounters in case of a large number of gradations in the initial distribution X. In relation to evolutionary processes, this means that uniform accumulation of mutations in all organisms has a favorable effect on the rate of selection.

(2) The time of establishment of a single feature depends not only on the starting root-mean-square deviation and symmetry of the initial distribution curve, but also on local spreads in the gradation amplitude n_X and the frequency of the motion of the control pendulum. The probability of occurring a process with a prolonged transition regime increases in the absence of asymmetry and local spreads in gradation amplitudes. The higher the variety, the longer the system exists.

(3) Larger gradation amplitudes during the change of rules may successively give up their contents to small-amplitude gradations. The last remaining gradation n_X does not always correspond to the maximum gradation amplitude in the initial distribution because 'survival' of the gradation also depends on the local environment. Not infrequently, the process results in a gradation with small initial amplitude n_X if it falls between gradations with large amplitudes.

(4) Changes in ring density arrangement on plots of rootmean-square deviation in polar coordinates suggest nonuniform



Figure 18. Typical changes in time-related root-mean-square deviation in the polar coordinates in a transition process: (a) for *bell-shaped* (Gaussian) distribution; (b, c) for *uniform* white noise type distribution. N — number of subjects, χ — period of pendulum swing, r — period filling factor, i.e., ratio of time intervals within the period χ under rules 1 and 2.



Figure 19. A molecule of globular protein (myoglobin) with a flexible spatial atomic package. The size of the molecule is about 50 Å. The atomic 'cloud' encloses a group of atoms forming heme (light disk) which binds oxygen. Variations of the cloud shape resulting from the motion of atoms surrounding the heme either hamper or promote oxygen binding and detachment.

convergence to final results of synchronization under the transition regime (see Fig. 18). Changes in ring density are random and depend on the probability of encounters between the subjects and the second derivative of amplitude distribution of gradations X arising during the transition process.

(5) The time of arrival of *a pendulum-control system* at a final result (gradation) increases by a few orders of magnitude. At N = 10,000, for example, it increases (in arbitrary units) from 63×10^3 (without a pendulum control) to 144×10^6 (with a pendulum control).

(6) Periodic change of rules enables a system at multiple ratios T/χ and r = 1 to pass into the oscillating amplitude variation regime for the two remaining gradations, and thereby creates long-term competitive relationships between them.

This process is inherent not only in evolutionary selection; it also occurs at all hierarchical levels of real biosystems, from macromolecules to biocenoses, i.e., in all oscillating regimes with a significant chaotic component. Such controlled transitions from a higher hierarchical level, underlain by modulation of chaotic motion at a lower level, take place in practically all biological systems. The higher hierarchical level (pendulum) modulates high-frequency chaotic processes at the lower one. For example, a macromolecule of globular protein contains some 5,000 atoms that can be considered on this scale (around 0.1-50 Å) as randomly oscillating non-isochronic micropendula or randomly interacting objects with specified features (Fig. 19). They are randomly deflected from the direction of covalent bonds in the polypeptide backbone by $20^{\circ}-60^{\circ}$. Their oscillations are chaotic and not coordinated among themselves, but can be synchronized under the effect of periodic cleavage of adenosine triphosphate (ATP) or pH variation. The low-frequency dynamics of diluted solutions of linear polymers are known equally well [169].

The amplitude of atomic fluctuations inside globular proteins does not exceed 0.5 Å, compared with more than 2 Å on a surface with characteristic times $10^{-9}-10^{-3}$ s. Synchronization of fluctuations, e.g., in a myoglobin molecule (Fig. 19), lowers the energy barriers inhibiting penetration of oxygen molecules by almost 20 times. It enables myoglobin to perform its function of binding oxygen molecules in the dynamic regime with an energy expenditure of only 8.5 kcal mol⁻¹ [150–152]. The protein converts to a binary (open–closed) system.

Figure 20 illustrates natural prototypes of future nanodevices — Brownian biomotors [123, 127, 133, 136] — operating on the same principle. The principle of modulated chaotic mobility controlled by periodic fields underlies biological processes involving a variety of fibrillar proteins. A fibril along which the enzyme 'motor' skims exhibits periodicity and spatial asymmetry determined by the genetic nature of its structure. Spatial macroperiodicity of a fibrillar lattice determines the step of displacement of chaotically vibrating enzyme.

By way of example, the lattice spacing of the fibrillar protein tubulin is about 8 nm. In this case, the reading speed in experiment reaches 10^{-4} m s⁻¹. It may be thought that ATP hydrolysis is also a source of low-frequency (periodic) signal modulating (and thereby governing) high-frequency thermal white noise at the bottom level [119, 122] that translocates a system's element on fixed spatial potentials, while it is in two or more different states.

Intracellular molecular micron-sized machines built up of fibrillar proteins, such as kinesin, actin, or myosin, can transport vesicle- or chromosome-like microparticles under the action of modulating fields at a higher hierarchical level [130, 133]. The dynamics of these processes remain to be



Figure 20. Prototype living systems for the design of artificial nanomotors transforming chaotic motion into directional motion: (a) flagellar rotation motor driving bacterial motion; (b) ATP synthase enzyme, and (c) muscular motor.

described in quantitative terms because X-ray structural analysis provides data only on crystallized fibrillar structures. For example, muscular myosin filaments exist in this case in the artificially induced crystal-like stable state, and *in vivo* investigation of its structural rearrangements in time necessitates an insight into the dynamics of the transition process far from the equilibrium crystallized state with at least a 10^{-8} s time resolution.

To conclude this section, it should be noted that environmental changes are frequently characterized by a high periodic stability of solar and terrestrial cycles and the alternation of day and night, the seasons, and lunar phases. The periodicity of these processes modulates the internal programs governing the major functions of the organism. There are numerous amazing examples of periodic programs controlling behavior, metabolism, and reproduction in relation to circadian, lunar, seasonal, and multiannual rhythms [173]. However, the organization of adaptive mechanisms based on a biological clock remains a matter of debate. What type of biological clocks is preferable: an hourglass measuring time intervals by successive counting [174] or a nonisochronic oscillator [175] adjusting its phase and frequency to environmental conditions? Evidently, storage counters with successive counting must have large amounts of memory, the lack of which markedly reduces both the accuracy and the reliability of measurement. Operation of these devices is highly susceptible to temperature fluctuations and other internal factors. Oscillators are more sophisticated instruments compared to storage counters and are more reliable, too, because they can work at a fixed frequency throughout many cycles unaffected by external impacts. Experimental studies confirm the practicability of using nonisochronic oscillators [176]. The mechanism of deterministic chaoticity combines the advantages of the storage hourglass type counter and the oscillator with intrinsic periodicity. Its nonisochronic internal governor ensures adjustment to periodic environmental factors. It appears that this mechanism is used in various systems of evolutionary selection and regulation of the organism's internal conditions. Nature is wise and frugal when it comes to utilizing its resources: it uses each of its fortunate findings for a variety of purposes.

4. Discussion

The main point is that variations in the random process of environmental changes enabled living organisms to develop a memory strategy for the selection of advantageous mutations and modifications at different hierarchical levels from macromolecules to the biosphere as a whole; simultaneously, they learned how to survive in the course of evolution. In other words, the mechanism of selection consists in a gradual alteration of living matter responsiveness in time and space using memory of preceding results. This mechanism was realized in different modes at different stages of evolution by changing the pitch and the length of the genetic code, a set of biochemical reactions, inner links, exchange operation of learning for reproduction rate, etc. Selection gave advantages to the best forms of living matter and enabled them to build up new hierarchical levels of regulation by combining simultaneously arising elements, which promoted the transformation of both chaotic and deterministic environmental processes into the symbiotic deterministic-chaotic process inside the living organism.

Oscillatory processes in nonliving matter have continuously subjected that part of nature which we now call living to tests through such instruments as droughts and cold snaps, volcanic eruptions and earthquakes, typhoons and tsunamis. As a result, living nature has existed in only two forms, *adapted and deleted* species. The evolution of *living matter* is a history of gains and losses.

Living nature viewed at the macrolevel is an integrated system—the biosphere. The key words here are 'integrated system'. There is nothing new in this thought. It can be traced to the 18th and 19th centuries [the work of J B Lamarck and the Austrian geologist E Suess (1875)]. In the early 20th century, V I Vernadsky assigned to living organisms the role of major actors in the transformation of our planet in the past and present [177]. The notion of a biosphere as a whole is paramount for the definition of life. Vernadsky defined living matter as a totality of all living things inhabiting Earth, regardless of the species they belong to, meaning that viruses and bacteriophages with their strongly reduced features may be regarded as constituent elements of the biosphere possessing properties of living organisms, e.g., the ability to reproduce. Outside the biosphere, they are a mere polymeric nanomaterial of a nonliving nature [178]. The main features of living organisms that allow them to be integrated into a unitary system are as follows:

(1) All living things are essentially made of *carbon and* water.

(2) All biologically important macromolecules are composed of smaller molecules sharing *one type of spatial symmetry* (*homochirality*): L (amino acids), and D (sugars).

(3) All living organisms on Earth use *a universal genetic code*.

(4) The property of life is inherited through *a common mechanism of macromolecular replication*.

(5) All living forms on the Earth maintain *a common metabolic process* in which the products of one organism are used as substrates by another, and vice versa.

How and why these common features developed remains to be elucidated. The following sets of possible scenarios can be deduced from the paradoxes considered in this review:

(1) *Life as a result of fluctuation*. If life originated as a result of a local fluctuation in our Galaxy, there is little hope that order intrinsic in living matter can be found anywhere else. This means that life in other galaxies is highly improbable.

(2) Life as a result of starting conditions. Living matter appeared because immediately after the Big Bang the entire Universe was in the ordered, i.e., low-entropic, state. However, scientifically sound verification and exhaustive comprehension of this hypothesis will be possible only with the further advancement of astrophysics.

(3) Life as a result of initial conditions in the remote past, recent local fluctuations, and the appearance of a set of memory units in molecular machines at present. This variant is a combination of the first two and might represent the transition of chaotic processes in part of matter into deterministic-chaotic ones. Like a ratchet, memory is a unidirectional process because the system is in close contact with the past. Directionality arises from the fact that any structure, once it appears, gives rise to a sequence of future events; in other words, each new step determines the next one. This process develops from the bottom up and appears to be the main driving force of evolution that eventually gave rise to living matter, including humans. The past and the memory of it laid the foundation for the future. For example, the appearance of water on Earth predetermined the further choice of carbon compounds as the building material for living things instead of silicon, hydrogen instead of fluorine, and so forth [179]. It seems that the primordial Universe was not intended for life. Living matter arose as part of total matter that learnt how to win and ousted nonliving matter when the chances of surviving were equal for both. The 'whereto' and 'how' processes in living matter started to develop in parallel.

It is worth noting that the mass of living matter on our planet is still rather small $(2.4-3.6 \times 10^{12} \text{ metric tons}, dry weight)$, or less than 10^{-6} of Earth's mass. But the load it exerts on the planet is determined by *kinetics*, not mass, of living matter, i.e., by the energy being exhausted as it is consumed. According to different but close estimates, a few billion species have disappeared from Earth during the 4.5 billion years of organic evolution [31]. All these organisms had to let the entire matter contained in the envelope of Earth (the atmosphere, hydrosphere, lithosphere) pass many times through their organs, tissues, and cells. Thereby, they not only reproduced themselves, but also transformed atmospheric air, oceanic waters, and a huge mass of mineral substance into the products of their vital functions.

Today, we have a wealth of data about living matter, but the early period in the history of life remains hypothetical. Mathematical simulation takes us nowhere. The deduction of cause from effects is *an incorrect inverse problem*. Even if complete simulation of the process of the origin of life is ever achieved under laboratory conditions, it will give only a probabilistic answer; we shall never be absolutely sure that it is such a scenario that was realized on Earth. It will be necessary to prove that it is the sole, or at least most probable, scenario among the many other conceivable ones.

Much of what is written in this review seems to have been said before. In 1973, the German researchers M Eigen and R Winkler wrote *Ludus Vitalis* (The Game of Life) [180]. However, this book is focused on the game inside living matter, whereas we considered here the game involving all the matter on the planet, living and nonliving.

Living matter faces two threats: proper determinancy and proper chaoticity. The trajectory of life runs between two extremes, as between Scylla and Charybdis. Were all life processes absolutely deterministic, living matter could not withstand environmental changes. Conversely, were they chaotic, it would lead to permanent conflict between the parts and the whole at both the organismic and biospheric levels; living matter would not have developed in this situation. A deterministic process with a significant chaotic component or a chaotic process with a significant deterministic component forms the mainstay of living matter kinetics. To conclude, there is one more example.

All organs of living things operate in a periodic regime. For example, the human heart rate is 60-70 beats per min, that of a dog and a rat is 90-100 and 350 per min, respectively. The stomach of a human, a dog, and a cat contracts at a rate of 3, 4-5, and 6-7 cycles per min, etc. However, these are average figures, while each of the above cycles contains a hidden chaotic component. For example, a typical electrocardiogram is not the realization of a regular process but appears to be a manifestation of deterministic chaos.

The exploration of the chaotic dynamics of cardiac rhythm by measuring its regularity allows for early prediction of human diseases. Spectral analysis of heart cycles reveals a number of harmonics reflecting the state of subcortical respiratory nerve centers $(2 \times 10^{-2} - 2.5 \times 10^{-2} \text{ Hz})$ and the activity of the autonomous cardiac rhythm regulatory circuit $(3.3 \times 10^{-2} \text{ Hz})$. The chaotic component is known to decrease and the deterministic component to increase (reduction of the attractor region) 13 hours before cardiac arrest. Eight days before sudden cardiac arrest, the heart rhythm is stably periodic, while the chaotic component becomes markedly reduced (attractor transforms into the limiting cycle). The contraction kinetics become deterministic. Thus, sudden cardiac death is a result of the system's withdrawal from determinate chaos and entrance into the deterministic regime; these events rapidly lead to heart arrest and a fatal outcome. On the other hand, tachycardia and especially atrial flutter turn the work of the heart into a chaotic process and cause an even faster death [168].

5. Conclusion

Thus, we suggest the following expanded definition of life based on the enumeration of traits intrinsic in living (and not only living, as shown above) systems.

Life constitutes an integrated system (biosphere) having memory and capable of directional motion, self-propagation, metabolism, regulated energy flux, and reproduction.

Life from the point of view of physics can be briefly described as a result of a game process, an interplay between part of the system and its environment. During the game, this part acquired an ability to remember the probabilities of gains and losses in previous rounds, which gave it a chance to exist in the following ones.

The following epitaph on the tombstone of certain deleted species would be appropriate: '*They were impenetrable to new ideas and could not withstand changes in their environment*'. The epitaph on another tombstone would read: '*They did not learn to remember nor did they strive for integration because they behaved chaotically*'.

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