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## Self-Organization in Biological Systems

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**Abstract**—Biological systems are considered that are capable of dynamic self-organization, i.e., spontaneous emergence of spatio-temporal order with the formation of various spatio-temporal patterns. A cell is involved in the organization of ontogenesis of all stages. Embryonic cells exhibit coordinated social behavior and generate ordered morphological patterns displaying variability and equifinality of development. Physical and topological patterns are essential for biological systems as an imperative that restricts and directs biological morphogenesis. Biological self-organization is directed and fixed by natural selection during which selection of the most sustainable, flexible, modular systems capable of adaptive self-organization occurs.

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### SELF-ORGANIZATION IN NONLIVING AND LIVING SYSTEMS

Biological morphogenesis involves the process of self-organization, i.e., spontaneous emergence of spatio-temporal order, during which the global pattern of systems is formed by local interactions of its elements. The properties of systems called complex ones, including biological systems, do not possess the properties of their elements, and such systems display new arising, or emergent features. Kolmogorov, Rashevsky, and then Turing (Taboni, 2006) theoretically predicted spontaneous emergence of a dissimilar pattern in some chemical reactions in far-from-equilibrium initially homogeneous systems. Later, the possibility of dissipative structure formation was proved as spatially inhomogeneous states in open nonequilibrium systems (Nikolis, Prigogine, 1979; Prigogine, Stengers, 1986), that is, the ability of sets of homogeneous units of self-organization with the emergence of order in space and/or time (Haken, 1980). The Belousov–Zhabotinskii reaction, the formation of Benard cells and Liesegang rings, and similar phenomena became classical examples of self-organization in nonliving nature (Bird, 2003; Isaeva, 2005; Ball, 2009). The parallelism of morphogenetic rows and the similarity of nonliving and living natural forms were repeatedly emphasized by many researchers (D’Arcy Thompson, 1942; Camazine et al., 2001; Bird, 2003; Ball, 2009). Complex network systems with nonlinear dynamics are capable of self-organization characterized by feedback, stability, flexibility, modularity, and hierarchy. Such systems having a restricted finite number of discrete states and capable of collective order include artificial (computer) neural networks, cellular automata, Boolean networks, and connectivity graphs. Self-

organization is inevitable in complex biological networks systems, e.g., gene regulatory systems, systems of interacting gene products, and networks of morphogenetic interactions during development. In particular, both connectivity graphs and the systems of proteins with autocatalyzing properties gain collective order by self-organization (Kaufmann, 1986, 1993). Positive feedback containing internal mechanisms of self-organization is the most essential element of autocatalytic processes of various natures.

Living systems are open far-from-equilibrium systems maintained by continuous flows of matter, energy, and information with their environment. Biological systems are capable of dynamic self-organization with the formation of various spatio-temporal patterns. During self-organization, the global pattern of a system appears as epiphenomenon by numerous nonlinear interactions between the elements of the lower levels. Biological self-organization is directed and fixed by natural selection (Parrish, Edelstein-Keshet, 1999; Camazine et al., 2001; Parrish et al., 2002; Glass, 2005; Kirschner, Gerhart, 2005).

Thom (Thom, 1970a and 1970b, 2002), the author of catastrophe theory, was the first to show that biological concepts can be expressed in the terms of vector fields, attractors, and bifurcation. The curves of successive states of a system developed by a change in the position of a point in the phase space, or the phase trajectories, tend towards the attractor, which can be a point, limit-cycle, torus, or a so-called strange, or chaotic, attractor. Strange attractors are intrinsic to nonlinear dynamical systems, including biological ones. The complex unpredictable behavior of a deterministic nonlinear system—dynamic (deterministic) chaos—is characterized by nonlinear interactions

between the structural components, feedback, stability, and hierarchy (Arnold, 2000; Bird, 2003; Goldberger, 2006).

Some principles have been formulated in biology, i.e., *omnis cellula e cellula* (every cell originates from another cell) by Virchow, *omnis vivo ex vivum* (all life is from life) by Pasteur, and *omnis molecula e molecula* (every molecule is from a molecule) by Kol'tsov (Inge-Vechtomov, 2003; Samoilov, Vasil'ev, 2009). Asymmetrically oriented embedding of membrane proteins into the membranes of the endoplasmic reticulum and the translocation of the secreted proteins are predetermined by the signal sequences of the preexisting membrane proteins that allowed developing a principle of *omnis membrana e membrana* (Blobel, 1983). The established order of biological matrix processes: DNA–RNA–protein also became an axiom. However, even in the canonical matrix processes on linear DNA and RNA templates, polyvariation, ambiguity, modularity, and interchangeability of components are exhibited (Inge-Vechtomov, 2003). The author postulates the existence of conformational matrix structures, e.g., prions. Conformational spatial matrices are represented by preexisting protein molecules which form a sort of prionization cascade in a cell.

Eukaryotic cells are known to contain self-reproducing organelles, i.e., mitochondria and chloroplasts. In addition to these membranous organelles, a centrosome exists in a cell, i.e., the center of microtubule organization, a cytoplasmic regulatory center that controls the dynamic morphology of a cell (Uzbekov, Alieva, 2008). Germinal granules or a more dispersed material of the germplasm are considered as the key organelles of the cells of a germ line. Germinal granules comprise molecular components controlling translation and transcription, and they function as a specific regulatory cytoplasmic center that presumably maintains pluripotency and potential immortality of gametogenic cells (Leatherman, Jongens, 2003; Isaeva, 2010; Ewen-Kampen et al., 2010).

Nonlinear interactions of elements can lead to complex behavior of a biological system with the formation of a pattern ordered in space and time based on the chaotic dynamics of individual elements of a system. We will outline the investigations of biological self-organization performed at various levels and with various approaches.

#### INVESTIGATION OF EXCITABLE MEDIA AND ASSOCIATIONS OF ORGANISMS

Interdisciplinary biophysical investigations of excitable active media, an example of which is chemical reactions similar to the Belousov–Zhabotinsky reaction, and of various biological systems interpret wave dynamics sufficiently correctly; such media are shown to be capable of spatio-temporal self-organization. The physiological systems of an organism, organs, and tissue and cell complexes that form a hier-

archical network with interdependence and subordination can be considered as active media with positive and negative feedback and an autowave mechanism of self-organization (Glass, 2005). A clear display of chaotic dynamics and self-organization was found during experiments with oscillating excitable systems such as heart tissue, where concentric and spiral waves arose spontaneously and distributed, and neural networks (Bub et al., 2005; Glass, 2005). Therefore, active media are capable of dynamical self-organization, i.e., spontaneous emergence of spatial and temporal order. However, biological systems considered to be excitable media consist of single cells that are capable of individual reactions and generation of various spatio-temporal patterns.

Heterogeneous patterns of spatial distribution of individuals are universal among living organisms, ranging from prokaryotic to higher multicellular ones. At the level of cell populations, self-organization of branched, vortex, and fractal spatial patterns was investigated for bacterial colonies, e.g., motile bacterial *Bacillus subtilis* colonies develop a vortex pattern due to correlated motion of cells parallel to one another with a tendency of cell stream twisting. The self-correlated organization of complex patterns lead to a publication about bacterial intelligence (Ben-Jacob, 1998).

Populations of eukaryotic unicellular organisms, e.g., chlamidomonada, are also capable of self-structuring, i.e., self-organization interpreted in terms of chaos, bifurcation, and catastrophe (Albrecht-Buehler, 1990). Aggregation of *Dictyostelium* myxomycete amoebas became a classical example of biological self-organization and an object for investigations of excitable media. The complex movement and morphogenesis of social *Dictyostelium* myxomycete amoebas is known to be governed by a simple mechanism of chemotaxis in response to the chemoattractant concentration, i.e., cAMP (Dormann et al., 2011). Aggregated cells move towards an increase in the concentration of cAMP with the formation of concentric or spiral waves of cells, i.e., the spatio-temporal order around the centers of aggregation (Thom, 1970b).

The synchronized collective behavior of animals with the appearance of various ordered spatial patterns, which has primarily been investigated for social insect colonies, shoals of fish, and flocks of birds, is considered as an example of self-organization (Parrish, Edelman-Keshet, 1999; Parrish et al., 2002). Animal populations function as a comprehensive whole and generate an ordered pattern taking collective decisions and performing a consistently collective response by nonlinear interactions of individual reactions. A simple and highly adaptive mechanism of collective intelligence with the activation of self-amplifying positive feedback is studied for social insects. Every ant exploring its environment leaves behind a signal pheromone trace, and the secretion of the pheromone is enhanced upon finding a source of food; other ants

following the same trace additionally enhance the signal (positive feedback) (Camazine et al., 2001; Kirschner, Gerhart, 2005). A simple mechanism of collective intelligence functions during termitarium construction as well. Termites first bring and randomly lay out pieces of earth that contain an attractant. The random closeness of arrangement of several such pieces determines the localization of the center for attraction of a large number of termites, and afterwards feedback, i.e., self-enhancement, starts to function (Prigogine, Stengers, 1986). One of the spectacular examples of self-organization is the synchronization of flashes of firefly males, which form a sort of collective light signal for attraction of females (Mirollo, Strogatz, 1990). Correlated synchronization is a cooperative phenomenon, and a temporal analogue of phase transition is also observed in other populations of biological oscillators, e.g., cricket's chirping in unison or heart cells and neural networks that synchronize electric impulses (Mirollo, Strogatz, 1990). The collective behavior of animal associations is not always adaptive; however, during evolution the features of organism assemblies or cell associations inevitably become an object of natural selection (Parrish, Edelstein-Keshet, 1999; Camazine et al., 2001; Parrish et al., 2002; Kirschner, Gerhart, 2005).

#### THE EUKARYOTIC CELL AS A UNIT OF SELECTION AND BIOLOGICAL ORGANIZATION

A living cell is an open system in which energy can flow in and out that creates conditions for considerable deviations from thermodynamic equilibrium that leads to the manifestation of self-organization, the parameters of which are established by genetic and epigenetic restrictions (Hess, Mikhailov, 1994). A cell of a multicellular organism is involved in the regulation of ontogenesis at all levels. An organism, a kingdom of cells, strictly controls self-renewal, differentiation, and apoptosis of cells, which are its components and building blocks, maintaining its integrity and suppressing cell individuality. However, competition between cells also occurs in an organism. A hierarchical multilevel concept of natural selection has recently been developed that considers competition and selection at the cellular level of a multicellular organism. It was postulated that during evolution selection occurs at various levels, which include not only organisms but also gene systems, cells, and groups of organisms (Buss, 1987; Gould, 2002; Kirschner, Gerhart, 2005). Natural selection directs and fixes biological systems capable of self-organization (Camazine et al., 2001; Glass, 2005; Kirschner, Gerhart, 2005; Johnson, Lam, 2010).

According to Beklemishev (1994), contract socialis is common in nature; all living things are collective: any living individual consists of other living individuals, an organism comprises subordinate organisms

representing semimutualistic, semiparasitic cohabitation, the life of which is based on competition and death of its parts. Cells serve as actual individualities of a lower order.

Most essential events during the early evolution of Metazoa are determined by evolutionary acquisitions at the cellular level, first of all, the symbiotic appearance of a eukaryotic cell and the emergence of multicellularity with a network of specialized intercellular contacts, intercellular communication, and cell differentiation. A cell in a multicellular organism retains the features of an individual that is capable of exploration, collective behavior, and collective self-organization. A cell is complex matter that possesses individual, very complex behavior (Samoilov, Vasil'ev, 2009). The social behavior of normal cells is displayed by the contact inhibition of movement at the cell contact. In particular, the social behavior of fibroblasts was experimentally shown for a monolayer culture as a wound healing response when cells crawl on a free surface and divide, providing the recovery of a confluent cell layer (Samoilov, Vasil'ev, 2009). Tumor cells are characterized by the absence of contact inhibition and the ability to metastasis development, i.e., asocial behavior (Vasil'iev, 1997).

#### SELECTION AT THE CELLULAR LEVEL IN THE SYSTEM OF AN ORGANISM

Regulatory development, which is typical for chordates and the majority of Deuterostomia, correlates with the redundancy of cell material, the possibility of selection at the cellular level within an organism (which was shown for immune cells and neurons) and a relatively high level of cell death (apoptosis). These features are exhibited well and investigated in chordates, especially in higher representatives of the type. The multiplication of a number of cells during ontogenesis and evolution of chordates and humans is likely to have been a key condition for essential evolutionary transformations.

During the development of the spinal cord and brain from the neural tube of chordates, a considerably larger number of neurons emerges than is necessary for the establishment of connections between the target cells; facts are found of overreproduction and competition of neurons and their projections and synapses in the developing nerve system of chordates (Edelman, 1993; Savel'iev, 2001; Kirschner, Gerhart, 2005). Additional neuroblasts and other derivatives originate from the cells of the nerve crest, i.e., pluripotent cells with exploratory behavior that migrate and are capable of homing, which search the environment and find the target (Kirschner, Gerhart, 2005). Hall (Hall, 2000) considers the nerve crest as the fourth germ layer and chordates as four-layer organisms. The redundancy of neuroblasts which survive upon establishing a connection with the innervating target testifies to the competition and selection at the level of neuron groups

(Edelman, 1993). Competition at the cellular level inevitably provokes elements of chaos (randomness, variability) detected in the organization of neural networks, which is related to the ability of circuits and networks of neurons of self-organization (Goldberger, 2006). Nerve cells display a high ability of self-organization with the development of various spatio-temporal patterns. In particular, self-organization was revealed in a neural cell culture as synchronization of the activities of two or more numbers of interacting neurons (Tononi, Edelman, 1998). The striking diversity and complexity of brain organization, polymorphism and the variability of neural organization, and neural network self-organization, as well as chaos manifestation in their morphology and functioning, provide adaptation of an organism to the variety and unpredictability of a chaotically changing environment (Tononi, Edelman, 1998).

### CYTOSKELETON SYSTEM SELF-ORGANIZATION

At the subcellular level, self-organization can be defined as the ability of a macromolecular complex or a cell organelle to determine its own structure based on the functional relations of the components (Misteli, 2001). Macromolecular complex formation during the construction of cytoskeletal structures is traditionally considered as self-organization, which has been investigated and documented sufficiently (Albrecht-Buehler, 1985, 1990; Hess, Mikhailov, 1994; Misteli, 2001; Kirschner, Gerhart, 2005; Vøntegodt et al., 2006; Pinot et al., 2009). Cytoskeleton reorganization is the leading mechanism of morphogenetic processes (Vasil'ev, 2007); the cytoskeleton is the generator of morphogenesis.

Actin and tubulin were shown to polymerize forming actin filaments and cytoskeleton microtubules that define the shape of a cell, its migration and polarity, intracellular transport, and the mitotic spindle during division. Every cell function requires different architecture that is generated by a limited set of components. Noninterrupted dynamic exchange of actin and tubulin subunits and their interaction with associated proteins are essential for polymerization of various structures of the cytoskeleton. Self-organization was repeatedly demonstrated for the cytoskeleton microtubule system with the formation of various structural patterns (Hess, Mikhailov, 1994; Taboni, 2006; Pinot et al., 2009). Particularly, in the very simple system that included solely tubulin and GTP, a complex, diverse, and dynamic pattern of microtubule self-organization occurred, and a correlation was observed in the pattern on weak external exposures, such as gravitation and magnetic field (Taboni, 2006). Depending on the concentration of tubulin and the motor proteins of microtubules, structurally diverse patterns developed (Misteli, 2001; Pinot et al., 2009).

Fibroblast migration occurs through continuous rearrangement of the actin cytoskeleton (Samoilov, Vasil'ev, 2009). Cytoskeleton structures are organized by the trial-and-error method as the result of the exploratory behavior, which is similar to the behavior of ants, e.g., such as microtubule stabilization upon finding a target (Kirschner, Gerhart, 2005).

Self-organization, which is intrinsic to the cytoskeleton system, upon a localized binding of receptors with ligands, determines the integral reaction of polarization of the entire cell with disruption of symmetry. During ooplasmic egg segregation, which is a key process for establishing axis polarity of a new organism, the cytoskeleton of an egg cell functions as the global morphogenetic determinant, which directs and fixes the anisotropy of molecular information distribution in the ooplasm (Isaeva, 1994; Isaeva et al., 2008).

An egg is a unicellular canal of the relation between the generations; in addition to the genome, an egg carries the map and clock of the early stages of development (Raven, 1964), and this vital information for the future development of an organism is localized outside the genome, i.e., in the cortical layer of the ooplasm. The genome functions in the cellular environment, and it is not able to perform the program of development outside the ooplasm. Animal cloning is only achieved by placing the cell nucleus (not the naked genome) into an enucleated egg. It is the extragenome information that activates the program of development after gamete contact or parthenogenetic activation.

### SELF-ORGANIZATION OF CELLULAR SYSTEMS IN VITRO AND EMBRYONIC CELL REAGGREGATES

Experiments with cultivated in vitro dissociated cells of an organism uncover the remarkable potential cell organization in the absence of controlling influences from an organism (Isaeva et al., 2008; Samoilov, Vasil'ev, 2009). Cells in vitro spontaneously form assemblies with coordinated social behavior and generation of ordered morphological patterns. An alteration in the collective behavior is observed as a sudden spontaneous transition from chaos (irregular movement of single cells) to order (correlated movement or self-organization of cellular aggregates) similar to a phase transition in physical systems (Isaeva, 2005; Isaeva et al., 2008; Deisboeck, Couzin, 2009). Such collective behavior of cells decreases the energy expenses per cell optimizing the energy expenses of the population (Deisboeck, Couzin, 2009). Searching the behavior of cells (Kirschner, Gerhart, 2005; Vasil'ev, Gel'fand, 2006), contact orientation of cells (Weiss, 1958), and contact inhibition of cell movement (Abercrombie, 1980) are obviously displayed in cell cultures. In a unilayer culture of miogenic cells of a chicken embryo, enlarged myoblasts self-organize into parallel rows by contact orientation (Isaeva, 1994;

Isaeva et al., 2008). The radial pattern of cell migration from cell aggregates is determined by the contact inhibition of cell movement that prevents crossing of cell migration pathways (Abercrombie, 1980). A further step in self-organization is the emergence of an integrated reticular pattern by the formation of cell bridges that connect aggregates and form a polygonal system. Along the bridges formed by the cells, migration of other cells occurs and this positive feedback provides maintenance and enhancement of the emerging pattern (Isaeva, 1994; Isaeva et al., 2008).

Experiments with dissociation and reaggregation of cells testify to the huge regulatory potential of multicellular organism cells. The concept of self-organization is fully valid for reaggregation of cells that spontaneously generate ordered morphological patterns of cell assemblies by collective social behavior. When investigating aggregating cells in vitro of various organisms, a common scenario for fractal self-organization was revealed as the transition from chaos to order, the phase transition of the cell system state. Blood and hemolymph cells are a system of a quick response characterized by chaotic dynamics and rapidness of transition from one state into another, and the finite state is preceded by intermediate chaos of a fractal nature, which is subjected to fractal geometry rules (Isaeva, 1994, 2005, 2009; Isaeva et al., 2008).

As the well-known experiments by Wilson show, dissociated cells of the sponge formed aggregates developing into small sponges (Wilson, 1907). Similar experiments using sea urchin embryonic cells showed that cell reaggregates formed embryoids (Giudice, 1962; Spiegel E., Spiegel M., 1986). Such embryoids were able to develop into larva (Giudice, 1962), and following metamorphosis, into fertile urchins (Hinegardner, 1975). Blastulation, gastrulation, and mesoderm formation (Millonig, 1975; Tamura et al., 1998; Isaeva et al., 2008; Presnov et al., 2010) during the development of the whole organism from dissociated blastomeres of echinoderms occur in a different way than during the embryogenesis of intact embryos, leading to the development of a normal organism. In particular, mesoderm formation in the embryos of starfishes developed from reaggregates of dissociated embryonic cells can be formed through both the normal enterocoelic-like pathway and the schizocoelic-like pathway, which is unusual for echinoderms and Deuterostomes (Tamura et al., 1998). Large chimeric aggregates formed after the dissociation of a number of urchin embryos into cells are able to separate out blastula- and gastrula-like formations from the total mass (Isaeva, 1994, 2010). Therefore, a change in the conditions of morphogenesis in vitro leads to an altered morphogenesis of the system of embryonic cells (Isaeva et al., 2008; Isaeva, 2010). The developing self-organizing system is able to achieve the finite state (attractor) through various pathways demonstrating the equifinality of development.

## PHYSICAL IMPERATIVE

In addition to the biological rules that determine the directions and restrictions of morphogenesis, physical and topological restrictions are inevitable. Biological systems are complex systems that cannot be understood solely by the basic rules of physics and chemistry; nevertheless, these rules direct and restrict the biological morphogenesis. For example, gravitation vectors and the direction of photon flow determine the axes of terrestrial plant morphogenesis, and this dependence of the orientation of basic axis of an organism on the physical gradients of the environment is obvious. One of the simplest physical restrictions of biological morphogenesis is sufficiently obvious in a monolayer culture where an artificial substrate for cell attachment determines two-dimensional morphogenesis.

The mechanical tension that is able to activate gene expression is inherent to morphogenetic fields of an embryo and other cell systems (Belousov, 2005; Ingber, 2005; Desprat et al., 2008). Mechanodependent modulation of gene expression was experimentally shown, particularly, in the *twist* gene under mechanical deformation during gastrulation in *Drosophila* (Farge, 2003; Desprat et al., 2008). The morphogenetic role of mechanical stress was revealed during myogenesis (Dartsch, Hämmerle, 1986). The absence of a surface for cell attachment turns out to be a physical restriction of morphogenesis and cytodifferentiation of some types of cells. An attachment to a solid substrate is necessary for differentiation of the myotube sarcomeres in the myogenic culture, which creates mechanical tension as a necessary prerequisite for completion of in vitro myogenesis; in a suspension culture, myogenesis is considerably modified with the formation of atypical myosimplasts (Isaeva, 1994; Isaeva et al., 2008). Mechanical tension is essential not only for the organization of the cytoskeleton, but also for cell vitality, its fate, i.e., without attachment to a substrate cells quickly undergo apoptosis and die (Vasil'ev, 2007).

Under certain critical conditions, the activity of physical factors can become a limiting factor. Under nonequilibrium conditions near the bifurcation point, a system is very sensitive to external exposure. This is the role of gravitation in the formation of dorsal-ventral polarity after amphibian egg fertilization, and the influence of the light gradient on zygote polarization of furoid algae (Isaeva, 1994, 2005). The orientation of axial polarity of a developing egg depending on the vector of the external physical field, gravitation, or light displays imprinting of physical gradients of the environment by a biological system according to the P. Curie principle: the symmetry elements of the causes is contained in the generated effects.

## TOPOLOGICAL IMPERATIVE

At the subcellular, cellular, and supracellular levels of biological organization, heterogeneous distribution of structural components, ion flows and electric fields, the fields of mechanical tensions, of directed cell movement, etc., generated by them, are exhibited as scalar, vector, and directional fields; e.g., transcellular ion flows generate electric fields at the cellular and tissue levels. The axis polarity of an oocyte and an egg is displayed by transcellular ion flow that generates an extracellular electric field (Nuccitelli, 1984). The spatial organization of morphogenetic fields is analyzed by topological terms, and the topological language can provide a strict and adequate description of biological morphogenesis. A topological interpretation was given of some events of early development based on the known concepts of mathematics and the Poincaré–Hopf, Brauer, and Gauss–Bonnet theorems (Presnov et al., 2010). The inevitability of egg cell polarization as the emergence of the topological feature (singularity) of the vector field on spheres follows from the Poincaré–Hopf formula. The presence of a fixed point on the cortical sphere of an egg cell is inevitable for ooplasmic segregation according to Brouwer’s theorem. Zygote division creates pattern of contacts on the surface of an embryo, i.e., a discrete morphogenetic field with inevitable topological singularities. The positional information of a discrete morphogenetic field is described by the Gauss–Bonnet theorems as the relationship between the local and integral order. According to the theorem, cells with a negative or positive curvature inevitably emerge on the surface of an embryo, and the negative curvature determines the location of invagination during gastrulation (Presnov et al., 2010). Gastrulation is an inevitable topological transition from the sphere with heterogeneity and singularity of the field to a torus with a homogeneous field. A toroid embryo or a larva is a topologically stable object.

In a monolayer cell culture, self-organization of planar directional fields is observed with a certain set of topological singularities (Isaeva et al., 2008; Presnov et al., 2010). The limited number of topological singularities of directional planar fields (Penrose, 1979) determines the corresponding topological constraints of planar morphogenesis in monolayer cultures during the formation of biological two-dimensional patterns (Elsdale, 1973; Isaeva, 1994; Isaeva et al., 2008). The spatial patterns in the cultures of myogenic cells and fibroblasts are the result of intercellular interactions: contact orientation cell–cell and contact inhibition of cell movement. By the contact orientation cell–cell and cell–substrate, a transition occurs of the local order of cell interactions into the global order of cell fields (Isaeva et al., 2008).

Minimization of energy expenses for construction and maintenance of biological structures determines the functional design of some biological forms, e.g.,

branching structures; such forms represent topological attractors (Isaeva et al., 2008). The topological imperative, being a certain set of topological rules, constrains and directs morphogenesis of biological systems (Isaeva et al., 2008; Johnson, Lam, 2010; Presnov et al., 2010).

## GENE REGULATORY NETWORKS AND NONLINEARITY OF THE GENOTYPE–PHENOTYPE RELATIONSHIP

Investigations concerning the molecular mechanisms of development reveal the modular hierarchical architecture of developing systems and networks of their gene regulation (Davidson, 2006; Ben-Tabou de-Leon, Davidson, 2007; Peter, Davidson, 2011). Gene regulatory networks include a large number of genes that code for transcription factors, ligands and receptors of intercellular signaling, and the sequences that control the expression of each of these genes. These elements of coding and noncoding sequences of DNA altogether comprise the regulatory genome. Interacting regulatory genes form the regulatory network, i.e., the gene program of development (Ben-Tabou de-Leon, Davidson, 2007; Erwin, Davidson, 2009; Peter, Davidson, 2011). The regulatory genome includes many thousands of units of information processing in the form of *cis*-regulatory modules, each of which performs a certain function in the control of gene expression. The program of development is encoded in the form of a huge network of functionally interrelated *cis*-regulatory DNA modules; various subcircuits are active in various embryo domains and in various periods (Davidson, 2006; Erwin, Davidson, 2009; Peter, Davidson, 2011).

Positive and negative feedbacks are typical for gene regulatory networks. Recurrent use of the regulatory genes is possible (Ben-Tabou de-Leon, Davidson, 2007), e.g., the program of sketogenesis in embryos and adult urchins (Peter, Davidson, 2011). Recurrent events of morphogenesis are based on recurrent activation of genes. During morphogenesis of the respiratory system of mammals and *Drosophila*, a manifold recurrent expression was found of genes that code for fibroblast growth factor and its receptor at each stage of branching (Metzger, Krasnov, 1999; Warburton et al., 2000). Morphogenesis of biological fractal structures is determined by compact genetic encoding since the same mechanism of branching is repeated many times (Isaeva, 2009, 2010). The chordate immune system is an example of a biological system that is able to generate a virtually infinite number of specific responses by combined use of several hundred genes (Claverie, 2001).

During evolution, a tendency appeared for an increase in the number of regulatory genes; selection for the rate of adaptation to new conditions favors the maintenance of duplications in the genome in the genes that control morphogenesis (Berdnikov, 2003).

The number of regulatory genes was shown to be considerably higher in the human genome as compared with the mouse genome (Venter et al., 2001). The relation between the genotype and phenotype is not strictly determined, e.g., in polyphenism, the same genotype can be fulfilled through alternative pathways of development in the form of various phenotypes (Kirschner, Gerhart, 2005). It is supposed that the network of genes functions as a whole and should be studied using the concepts of current interdisciplinary science (Claverie, 2001). There is no simple relation between the number of genes and the complexity of an organism; nonlinearity and the complexity of gene networks should be taken into consideration (Venter et al., 2001).

Self-organization is an efficient way for constructing complex systems that is determined by the internal features of their components. During evolution, selection occurs of the most stable, flexible, modular systems capable of self-organization. Physical and topological rules are essential for biological systems as an imperative that restricts and directs biological morphogenesis.

Networks and trajectories of development are continually changing during ontogenesis and phylogenesis. Beklemishev defined an organism (1964) as a morphoprocess, an indefinitely lasting form amid a flow of stochastic changes. Beklemishev relates his definition of an organism with Cuvier's conception of life as a vortex. According to Beklemishev (1994), the object of biological investigation is not only individual organisms but also individual morphoprocesses. Thom (2002) considered a continuous spatio-temporal configuration that relates the parent individual with the offspring as the major object of biological investigation, but not a single individual. According to Thom (2002), a chicken and an egg are merely temporal sections of such a continuous global configuration.

Networks of development provide its regulation, repair, and regeneration, as well as asexual reproduction involvement into onthogenesis along with sexual reproduction; i.e., the equifinal state serves as an attractor of dynamics of the entire system during onthogenesis providing multivariance, ambiguity, modularity, and interchangeability of components.

The ability of self-organization is fixed genetically by natural selection, which controls the mechanisms of self-organization (Camazine et al., 2001; Johnson, Lam, 2010). Exploratory behavior continuously was selected throughout evolution, and competition and selection were used at the subcellular and cellular levels.

Efficient evolutionary findings—modules of gene networks, trajectories, and developmental networks—were duplicated and used for evolution, as a result of which repeats of genes and gene clusters emerged. In development, iteration appeared of cleavage, blastulation, gastrulation, and blastogenesis stages (in polyembryony and other types of asexual reproduction), morphogenesis stages, e.g., segmentation, branching

of respiratory system, glands etc. Symmetry, self-similarity (fractality), metamerism, polymerization, and other variants of morphofunctional repeats with a multiple activation of similar genes or gene network circuits represent an efficient means of morphogenesis based on a relatively minor genetic program.

The selection of self-organizing systems and self-unfolding modules of development lead to an increase in sustainability, reliability, and flexibility, i.e., adaptability and the ability to evolve. The selection of systems able to evolve leads to acceleration of evolutionary transformations (Berdnikov, 2003). Evolution itself is a self-developing, self-organizing, and accelerating process.

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