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Biomechanical and coherent phenomena in morphogenetic relaxation processes

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ABSTRACT

Biological forms can be studied independently of the principles of their actualization, which was demonstrated in the book of D'Arcy Thompson "On Growth and Form" (1917) and in the nomogenetic theories of evolution. However the principles of actualization of forms have to be established and they are not directly related to the genetic system, being the generic phenomena non-reducible to the formal language of the genome. It is suggested that for the description of morphogenesis the concept of conformational relaxation is just as important as for enzymatic catalysis. Long-term relaxation properties are provided by the cytoskeleton. Compared to a single protein molecule, the cytoskeletal structures allow conformational movements on longer distances and for longer duration that can generally lead to a hyper-restoration of the initial state with the increased tension triggering further morphogenetic events. During this prolonged relaxation, the cytoskeleton microtubules hold the coherent state characterized by ultraweak emission of photons. This allows non-local interactions and assembly similar to that demonstrated recently for self-coordinated operation of photosynthetic antennae. As a result, the spatiotemporal patterns are formed based on the optimality principles that are established via internal reflective activity of biological systems.

1. Introduction: Platonic and Aristotelian Approaches to Form

Relative independence of the biological form from underlying molecular processes that include genes regulation and expression can be considered as one of major biological principles. It allows studying morphology independently of its generation and considering only the basic principles of transformation of geometry. This approach, philosophically arising to Plato, was successfully applied by D'Arcy Wentworth Thompson in his famous book "On Growth and Form" (Thompson D'Arcy, 1917) where he showed that transformations of coordinate system correspond to generation of forms specific for concrete biological species. He, however, mentioned that "morphology is not only a study of material things and of the forms of material things, but has its dynamical aspect, under which we deal with the interpretation, in terms of force, of the operations of Energy".

The basic understanding of the space of biological forms comes from the observation that it is essentially curvilinear, being non-Euclidean and more diverse than any physical space–time of the general theory of relativity. The ideas of D'Arcy Thompson were developed in different works, and here we would like to note Van Valen (1982) who emphasized the informational continuity of repetitively homologous structures, which is neither genetic nor environmentally imposed, and Petukhov (1989) who described basic principles of biological transformations grounded in the non-Euclidean geometry. In the evolutionary theories, it was suggested by Berg (1922/1969) in his nomogenesis theory and further developed by many authors including Lima-de-Faria (1997), that the laws of evolution are based on objective rules of transformations of forms independent on adaptability and natural selection.

The concept that form is not "encoded" but it is unfolded within the whole organization was discussed in my earlier paper (Igamberdiev, 1986) in relation to the basic idea that the whole system cannot be reduced to its internal description, which can be viewed in biological systems primarily as the genetic structure of encoding patterns. Although this thesis can support the idea of analyzing a form (and its transformations) itself without relation it to molecular and submolecular processes, in fact, to understand a relation of morphogenesis to underlying phenomena, we need to go beyond the concept of genetic determination and analyze fundamental principles of biological organization based on percolation between different levels of physical reality from basic quantum phenomena to the upper levels (Conrad, 1996). It will correspond (philosophically) to actualization of *potentia* and represent the Aristotelian approach to understanding the biological form. Genes are, in fact, the subsets of metabolites in the autopoietic structure of biological system (Igamberdiev, 1999) stably reflecting proteins and their functions, but the form appears beyond this reflection. It is a projection into 3D of a whole structure consisting of metabolites, enzymes and genes bootstrapping each other. This means that morphology is not "encoded" in genes. Most papers in this special

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issue claim the irrelevance of the genetic approach when it is strictly applied to morphogenetic phenomena and aim to establish the concrete basic principles to explain the morphogenetic actualization grounded in definite physical mechanisms (Beloussov, 2012; Isaeva et al., 2012; Kučera and Havelka, 2012; Levin, 2012).

This approach turns us to original ideas of the founder of embryology K.E. von Baer and, in modern frames, suggests consideration of the genotype–phenotype interaction as not that of determination but as interpretation (von Baer, 1864; Kull, 1998). In these interpretation patterns, the same limits of iteration are formed in different generally non-equivalent biosystems (Igamberdiev, 2008). The closed loops of causation appear as objective and are mapped into a single coherent space–time frame (Rosen, 1993). Coordinate systems are set in the omnium of non-equivalent observers, and the fundamental parameters may correspond to a consistency of the spatiotemporal landscape formed through communication of these observers (Igamberdiev, 2008). A physically embodied reflective loop has certain parameters that make it objectively existing. These parameters include certain values that can be redundantly repeated in all loops if they co-exist, corresponding to a topological inevitability of certain developmental processes. These topological singularities inevitably emerge in biological morphogenesis, and are retained and transformed during pattern formation. It is the topological language that can provide strict and adequate description of various phenomena in biological morphogenesis (Isaeva et al., 2012).

2. Spatiotemporal Pattern Formation in the Biological Morphogenesis

The existence of metrics, according to basic ideas of Riemann (1868/2004), can be explained by certain external physical forces of connection that are applied to individual objects. This is an example of imposing limitations on mathematical forms through application of physics, which is essentially the science about the limits of computation appearing to us as *physical laws* (Igamberdiev, 2007). These forces of connection, as suggested by Riemann, are related to the discreteness of space, and form its actual observed structure. There is no mathematical preference to any curvature. The basic question here is "how geometry is formed", i.e. what is the basis for the curvilinearity of space? The matter of introduction of physics is, in fact, the introduction of the action of observer. When there is no "active" observer concerned, the modeling of space–time results in the Newtonian geometry with the single unitary Euclidean coordinate system. When we consider the observer "actively" measuring space–time by signals with finite velocity, we come to Einstein's relational space–time but with the equality of all coordinate systems. And when the effect of measurement is concerned, we come to the choice (generation) of coordinate system and its transformation according to search of the stable (or homeostatic) state. This generates various structures which generation can be described by the non-Euclidean geometry. Already in physics we can expand the spacetime of general relativity to the conditions of inequality of transmission of signals corresponding to "anisotropy" of the spacetime, which in this case is called the kinematic spacetime (Pimenov, 1991). This follows from understanding of the local relation of causality introduced by the observer. For the biological system, it may be worth to introduce a virtual notion of the endo-observer realizing the internal measurement and establishing spacetime relations, which is analyzed in detail in works of Gunji (Gunji et al., 2008; Gunji and Ono, 2012).

When we consider an individual living system embedded in the physical space–time, we assume that the spatiotemporal structure of living system itself should have certain optimality parameters that allow coordination of processes inside this structure and their optimal fitness in system's embedding into the external space. This principle of optimality is an evident basis for understanding the spacetime generation by living organisms. Robert Rosen in his earlier book "*Optimality Principles in Biology*" (1967) and in the later paper (Rosen, 1980) showed how morphogenetic structures correspond to most optimal functional solutions. For example, the expected branching angles and radii of blood vessels can be calculated by minimizing resistance to flow or work done by heart. Similar ideas were developed earlier by Golenkin (1927) in relation to optimality of vessels in plants. Rosen considered some empirical relations that govern evolution, growth, and the transformation of biological forms. He analyzed feedback control principles to explain optimality in different, in particular related to morphogenesis, processes.

The optimality principle was developed by Liberman et al. (1998) to "*the principle of optimum prediction*" that claims the emergence of a basic inequality of different coordinate systems when living system is embedded into the physical space–time. This inequality is realized in determination of the direction of reduction in the potential field, which is casual (probabilistic) in non-living systems, while in living systems it is driven by the selection of optimal coordinate scales. The main problem of morphogenesis can be determined as a problem of deterministic actualization based on the optimality principle defined through the internal point of view of the endo-observer. The spacetime in which the coordinate system is actively generated and selected according to the principle of optimality is more diverse than any physical space–time of the general theory of relativity but the concrete form is context-dependent being realized as embedded into the particular environmental pattern.

While the notion of endo-observer, which remains a thought-design similar to Maxwell's Demon, is grounded in the fundamental role of quantum measurement as the basic actualization process, the stable realization of quantum measurements is possible via prolonged relaxation times (Braginsky et al., 1980; Igamberdiev, 1993). The quantum mechanical actualization pattern forms a kind of a field which is however not quite similar to classical physical fields because it is based not on the distribution of forces like in force fields but on the parametrization of parameters of movement of particles already charged with their forces. David Bohm called it *pre-space* and the movement of actualization he defined as *holomovement* (Bohm, 1980). The pre-space appears in biology as the ordering internal factor called by Gurwitsch (1922, 1923) *the biological field*. It represents an intrinsic ordering principle, itself not causally dependent on genes (Beloussov et al., 1997; Beloussov, 2011).

3. The Concepts of Morphogenetic Field and Epigenetic Landscape

How is the spatiotemporal structure formed if it is grounded in certain physical forces of connection as Riemann stated? For this we can turn to the notion of implicate order of David Bohm. According to Bohm (1980) and further to Stapp (2007), the overall implicate order determines a particular explicate order, i.e. a particular spatiotemporal structure, via holomovement. From the overall implicate order one may abstract a particular explicate order, which forms a relatively independent and autonomous context. The Bohmian implicate order (pre-space) is not a physical field in a strict sense of its definition. It is a potential field determining realization (holomovement) but not a field of forces of the classical and relativist mechanics. In other words it is a potential field for quantum reduction. In this way field is not a very relevant word, it is better to call it the actualization landscape or the landscape of reduction of potentialities.

In relation to biological systems, their "implicate order" is the dynamic integral field of all cells of the organism which is changed over time and has a property of a whole. It is rather a vectorial field, like a landscape. In the vectorial field, particles are directed by this field not because of the energy of the field but spending their own potential energy. This reminds the idea of Bauer (1935) that living systems work in expense of non-equilibrium, and the external energy is used not directly to perform work but to support the stable non-equilibrium state. Most of this energy is transformed into the kinetic energy. When the energy is spent and the molecule returns to its non-excited state, the effect of the field on it is no longer taking place. As a result, the actual ordered state is formed, in which non-equilibrium *molecular constellations* (Gurwitsch's definition) are formed which are characterized by the elevated energetic potential. In comparison, Prigogine's dissipative structures cannot be reproduced in this way. They are different in different repetitions and very sensitive to minimal changes of parameters of chemical reaction and to external influences. On the contrary, living systems cannot support their organization only due to the influx of external energy, i.e. the ordering internal factor is involved.

We return to the question what is the "morphogenetic field". We can define it as a potential field of all wave functions that directs actualizations during generation and transformation of a living system. In this sense, it has a similarity more to a potential landscape rather than to the field, and the concept of *epigenetic landscape* of Waddington (1968) may be relevant here. If we follow the consistent histories approach to understand the reduction of wave function in quantum mechanics (Albrecht, 1992), we can consider actualization as a refinement procedure in consistent histories, and in frames of this approach Gurwitsch's field as a *refinement landscape*. It contains its own attractors and directions of optimal transformations. According to Beloussov and Grabovsky (2007) the "information about a form" is distributed throughout three main components: the dynamic laws, the parameters, and the initial/boundary conditions. The invariant dynamic laws pertaining to the entire process of development correspond to the "whole" of the developing organism which is actualized through the physical limitations by the parameters and boundary conditions. General laws of morphogenesis are relevant to internal constraints explaining the entire process without reducing it into its individual parts. This corresponds to considerations of Gurwitsch (1922) in his concept of the biological field and of Spemann (1921, 1938) in his concept of field of organization, where the general law establishes causal links between parts of a whole in the course of its development.

4. Temporally Developing Stable Non-Equilibrium-Homeorhesis

To substantiate the optimality of biological structures, we need to define the basic physical state which underlies any living process. Living systems are essentially non-equilibrium systems, and their basic state can be defined as the *stable non-equilibrium* (Bauer, 1935). While in the non-equilibrium thermodynamics developed by Prigogine (1980) the non-equilibrium state is externally imposed, this state is maintained internally in biological systems. Prigogine's dissipative structures cannot be reproduced, since they are different in different repetitions and very sensitive to minimal changes of parameters of chemical reaction and to external influences. Living systems support their organization not only through the influx of external energy but by using this energy to maintain the stable non-equilibrium state which then performs the work internally (Bauer, 1935). The process of homeostatic maintenance of the stable non-equilibrium state was described as a homeostatic flux control by Fridlyand and Scheibe (1999) and developed in relation to the maintenance of metabolism via thermodynamic buffering in our previous works (Igamberdiev and Kleczkowski, 2003, 2009, 2011; Roussel and Igamberdiev, 2011; Igamberdiev and Roussel, 2012). By including buffering reactions, that aim to maintain stability of metabolic fluxes of load and consumption via dissipation of energy, the stable non-equilibrium state includes both equilibrium and non-equilibrium components from the enzyme function through the formation of metabolic cycles to the generation of form.

Instead of the trend towards thermodynamic equilibrium, in biological systems we observe the temporally framed trend towards the maintenance of stable non-equilibrium. The use of external energy to support stable non-equilibrium state can be reached, in particular, via a "fitting function" of special thermodynamic buffering enzymes that equilibrate fluxes of load and fluxes of consumption of major metabolic components, e.g., ATP and pyridine nucleotides (Igamberdiev and Kleczkowski, 2003, 2009). The commonly accepted idea that irreversible reactions in cycles limit their turnover has been shown to be generally incorrect (Fridlyand and Scheibe, 1999, 2000). There are strong theoretical arguments and experimental evidence against the idea that highly regulated enzymes catalyzing reactions far from equilibrium must be considered a priori rate limiting. Conversely, the actions close to equilibrium frequently limit flux when the amount of enzyme is reduced. Changes in provision of a substrate to biochemical cycle or pathway are controlled by thermodynamic buffering reactions that can reverse a product back to the substrate, dissipating energy. Also, when levels of a metabolite provided by the equilibrium enzyme are insufficient for maximum flux, the cycle flux could still be increased by involving separate depots of stored intermediates.

Thus, the stable non-equilibrium system, being fed by the external energy, uses this energy for the maintenance of stable non-equilibrium. Different mechanisms of such maintenance in relation to metabolism have been described and reviewed (Igamberdiev and Kleczkowski, 2009). However, the activity of the system is fully determined by the internal pattern of this non-equilibrium and any work performed by the biological system appears as *the work of its structural forces* (Bauer, 1935). Therefore the pattern of this work by system's forces is always consistent, which also results in development of a *stable morphology* (contrary to irregularity of morphology of Prigogine's dissipative structures). From the above concept, the fundamental principle follows that the biological movement is related always to a relaxation, i.e. to the movement towards local equilibrium placed within the surrounding non-equilibrium state. We will demonstrate how this is realized in morphogenesis process, which in fact appears as a projection from the multidimensional space of kinetic parameters to a three-dimensional space of structural forms. In brief, contrary to the metabolic non-equilibrium, morphogenesis is based on already existing matrices, i.e. it is more context-dependent. At any point in time, the local microenvironment is influenced by the macroscale tissue geometry, which sculpts long range signals by affecting gradients of morphogenes and mechanical stresses. The geometry of a tissue thus acts as both a template and instructive cue for further morphogenesis (Nelson, 2009). At cellular and supracellular levels, the morphogenetic relaxation is responsible for originating of visible shapes via normalization of orientation of cells with respect to surfaces that integrate cells into supracellular sheets (Beloussov et al., 1975).

The basic non-equilibrium process, maintained by the homeostatic flux control, corresponds to homeostasis. To understand morphogenesis, we need to analyze the temporally developing stable non-equilibrium state projecting itself into the 3D space and corresponding to the notion of *homeorhesis* (Waddington, 1968). While the basic stable non-equilibrium is supported by relaxation of the system to its previous state, to generate the form the temporally developing stable non-equilibrium should provide

not a simple relaxation as in the case of homeostatic flux control, but a kind of hyper-relaxation (leading not to the initial state but to a hyper-restoration) that provides a possibility of accumulation of additional energy and making an extra-work in the next cycle (Beloussov, 1998, 2011). This includes the positive feedback between active and passive shaping, similarly to the co-existence of non-equilibrium and equilibrium reactions in the metabolic non-equilibrium state (Igamberdiev and Kleczkowski, 2009). The process of hyper-restoration takes place until the organism develops to its adult state and its morphology is fully unfolded. After that, further developmental changes may occur mainly via removal of certain structures (apoptosis is an example) to provide further development, i.e. as a process occurring at the expense of the structural energy of other parts of the cell. In other words, morphogenetic phenomena occur when the system performs hyper-restoration after being disturbed and correspond to a build-up of patterns in the non-Euclidean space. Due to this, the stable non-equilibrium state attains the properties of temporality and geometrically the curvilinearity of shapes is developed. The relaxation dynamics in morphogenesis resulting in a hyper-restoration can be considered as a peculiar kind of relaxation that by itself is associated with the energy spending and can be reached with applying the additional force. This in turn results in an increased capacity of the work of system's forces (the principles of increased extrinsic work, according to Bauer, 1935). The advantage to move along the relaxatory pathway is that it provides vectorization of the morphogenetic movement to make it invariable. The relaxation time of a heterogeneously structured system generally depends not on its slowest component but rather on the spatial organization of the components with different characteristic times of change, which permits to consider the development of organisms as a long-term relaxation.

5. Relaxation Concept and the Role of Cytoskeleton in Morphogenesis

Biological morphogenesis consists of an apparently complex set of movements. The most important and best of all investigated kind of collective cell movements is cell intercalation (Beloussov, 2012). This kind of cell movements, as well as all the others, is connected with the cytoskeleton activity. The idea of the role of cytoskeleton in morphogenesis arises to N.K. Koltsov who proposed in 1900s that the shape of cells is determined by a network of tubules and first introduced the term "cytoskeleton" (Koltzoff, 1906). Here we develop the idea that during the prolonged relaxation the elements of a cytoskeleton are in the coherent state allowing non-local interaction permitting to create and maintain macroscopic shapes of a curvilinear geometry. The term "coherence" is used here beyond its classical physical definition of an ideal property of waves that enables stationary interference. We rather consider the quantum coherence where the quantum waves represent a potential reality that can be hold in superposition for a prolonged time. Large-scale (macroscopic) quantum coherence leads to the macroscopic quantum phenomena which may arise in the biological morphogenesis in the relaxation processes.

The relaxation concept at the level of protein molecule was developed in detail by McClare (1971) and Blumenfeld (1983) and discussed in my previous papers (Igamberdiev, 1993, 1999, 2004). In brief, it postulates the conformational relaxation of macromolecular systems acting as macroscopic oscillators to be an elementary action of the bioenergetic process. In this action, the fast quantum effect (e.g. the capture of electron) is followed by a slow conformational transition during which the energy is not dissipated and remains stored for a total lifetime long enough for the work to be performed. The conformational motion of biomacromolecules is many orders of time slower than the initial quantum effect, and the rate of a bioenergetic process is, therefore, determined by the rate of the conformational relaxation. The latter takes place only after the action of a force converting the system into a new conformational state, i.e. after the generation of a non-equilibrium state resulting from fast initial interaction. From this point of view, the specificity of enzymes is connected with the recognition of specific configurations of electron clouds (distributions of electron wave functions) in certain compounds and should, therefore, be described by using the quantum mechanical formalism.

The energy released when a substrate is recognized by the enzyme molecule (which corresponds to a new coordinate scale emerged) turns the latter into a different alternate conformation which results in the realization of the actual work of the substrate conversion into the product (Blumenfeld, 1983). This conformational movement passes slowly, providing for the transition to a macroscopic time scale. In this theoretical model of enzymatic reaction, the modulation of the reaction coordinates by low-frequency conformational motions of the enzyme molecule causes the lowering of the activation energy barriers until they completely disappear. The process of protein folding and conformational change during catalysis (morphogenesis at the level of protein molecule) proceeds autocatalytically (Veeraraghavan et al., 1996). The conformational relaxation is essentially the elementary act of enzymatic reactions, and the rate of substrate-product transformation is determined by the rate of this conformational change. As Conrad (1979) mentioned, an enzyme can be considered as a macromolecule which makes a cyclic reaction possible, involving energy loan which is used for barrier removal and which arises from transient pairing. Similar ideas were developed by McClare (1971, 1972) who suggested that the enzymatic catalysis can be described as liberating internal energy stored in a single molecule so that the resonant transfer of this energy can approach 100% efficiency (see also a recent review of Kamerlin and Warshel, 2010).

While the conformational relaxation of enzymes occurs at a microscopic level, the scale of relaxation can be expanded to a macroscopic size by arranging protein monomers into cytoskeletal fibrils. This is what we observe in muscle contraction, in nerve tissue, and during morphogenesis. Mechanical movements are shown to be a central component to the differentiation and development of embryos (Gordon, 2006). We observe mechanical movement at the level of single biological molecules, such as in the mechanism of ATP synthase which performs the rotational movement for 120° during conformational relaxation (Stock et al., 2000). This movement allows binding the substrates of phosphorylation, forming ATP (without energy expense), followed by the energy-consuming release of ATP into the surrounding solution. The operation of cytoskeleton is related to ATP hydrolysis (viewed as the work of myosin ATPase) and can span to the macroscopic distances and times (Becker, 2000).

The actomyosin molecular structures are primary mechanochemical devices in the cytoskeleton. Via ATP hydrolysis the energization takes a very minor fraction of the entire turnover time in which the mechanical work is produced in the course of prolonged relaxation. The relaxation model of actomyosin contraction developed by Masuda (2008, 2009a,b) involves the mechanochemical "driven by detachment" mechanism, which assumes that the energy of power strokes originates from the potential energy generated by the attractive force between the static protein (actin) and the dynamic protein (myosin or kinetin). The role of ATP in this mechanism is not to directly supply energy for contraction, but to temporarily reduce the attractive force and to increase the potential energy. The efficiency of converting the potential energy into intramolecular elastic energy determines the number of power strokes per each ATP hydrolysis. A critical requirement for this mechanism is that ATP must preferentially

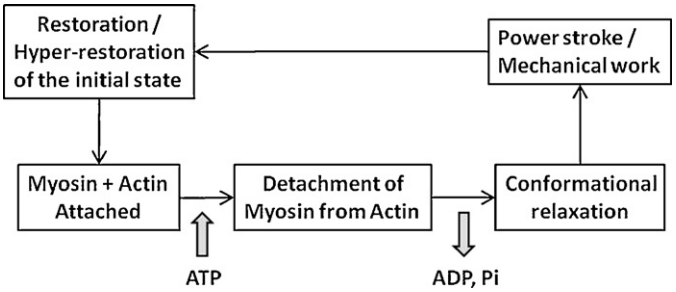

Fig. 1. The general scheme of operation of cytoskeleton during muscle contraction. The energy of ATP is used for detachment of myosin from actin and not directly for power stroke.

facilitate the detachment of myosins that have completed their power strokes, which is fulfilled by ATP hydrolysis tightly depending on the conformation of a myosin molecule. This mechanism underlies the directionality of myosin motors (Masuda, 2008), which is simply determined by the direction of the neck with respect to the head in the dissociated configuration. This mechanism is also applied to kinesins which constitute another type of molecular motors (Masuda, 2009b). The ideas of Masuda are in line with the conformational concept of biological movement (including morphogenesis) and support the view that the movement takes place due to the structural energy of the system, and the role of ATP consists in releasing this energy by reducing attractive force between filaments and providing condition for the conformational relaxation (Fig. 1).

According to Beloussov (2011), at the cellular level, we observe a fast generation of mechanical stresses (essentially the non-equilibrium process) and their prolonged discharge (quasi-relaxation, related to a slow equilibration), in which the cytoskeleton may play a crucial role. Beloussov regards developing embryos as self-organized systems transpierced by feedbacks among which those linked with mechanical stresses are most important. He formulates a concept of the mechanical stress hyper-restoration as a basis for the developmentally important feedback loops. In relation to muscle contraction, the idea of hyper-restoration was introduced by Arshavsky (1972) who formulated the *energy rule of skeletal muscles* claiming that any muscular motility activity, which is based on the energy used for realization of a certain work, is later restored with a surplus, and this "surplus anabolism" supports further growth and development of an organism. This is the case showing that due to the fulfillment of its own work, the biological system gets more than it spends. It increases its general pool of energy and living mass, making it more structurized and morphologically developed. The level of this surplus energy can be regulated: more futile recyclings, faster are living cycles and lower are biomass accumulations, leading to simpler morphology and smaller size (McNulty et al., 1988).

In agreement with the concept of hyper-restoration, the relaxation of an embryonic part tends not only to restore its initial tension value but even to increase it ("*irrepressibility of development*", according to Gurwitsch). Such a hyper-restoration can be a basis for the complication of the morphological structure of developing organisms indicating the universal role of relaxatory pathways in shapes formation. In this process, the causal chain of morphogenesis is closed at the macroscopic level by the nonlinear feedbacks interlinking successive spatiotemporal structures (each next form being derived from a preceded one, "form out of a form") without addressing each moment to the molecular level events. This makes possible to study the geometry of forms and their transformations without an ultimate necessity of addressing their generation at the molecular level. The relaxation and hyper-restoration processes lead to a symmetrization of elementary cells and a dissymmetrization of the entire body (symmetry exchange between different levels) (Beloussov, 2011). A rapid phase of stress generation corresponds to the creation of morphogenetic information which is translated into visible shapes during the relaxation period. A feedback loop linking relaxatory pathway with the opposite trend is directed toward accumulation of energy. The initial passive deformation caused by external force triggers active energy-consuming mechanochemical response which reinforces its own deformation and at the same time stresses the neighboring parts, triggering the latter's similar responses, and so on. The active (energy requiring) response to a change in its mechanical stress caused by an external force is directed toward restoring this part initial stress value, but as a rule overshoots this value to another side (hyper-restoration). If an embryonic part is relaxed, it tends not only to restore its initial tension value but even to increase it to a certain extent actively increasing the imposed curvatures. Thus morphogenesis proceeds from simple to complicated forms. The model described above expands the mechanochemical conformational model of function of biomacromolecules to the macroscopic levels of biological organization.

In respect to a striking similarity of muscle contraction and the dynamics of morphogenesis, we can mention a very precise kinematic similarity of actomyosin interactions and the behavior of hydroid polyp cells during pulsatorial growth (Beloussov, 1998, p. 138). In hydroid polyps the role of actin fibers as a substrate for crawling is played by the inner surface of an exoskeleton, the perisarc. Similarly to myosin molecules, at the beginning of each new cycle the cells become detached from the inner perisarc surface, then rapidly send the protrusions in the distal direction (toward a stem tip), changing thus their fixation points on the perisarc, take highly oblique shape and pull distalwards a huge bulk of the proximally located part of cell layer (Beloussov et al., 1989). It is this latter phase which corresponds to the power stroke and is at the same time a kind of an energy spending relaxation, the latter comes from the increase of a symmetry order of the individual cells (due to their swelling). Thus, the latter phase precisely corresponds to the power stroke during muscle contraction. The dimensional orders of the both events differ in no less than 4 orders of scale (from nanometers to dozens of micrometers) supporting the idea of astonishing invariability of main biomechanical devices.

The development of morphology starts from a direct action of the mechanical force on elementary cells (small body particles) reducing symmetry order. For example, in plants, morphogenesis can be initiated by generation of internal pressure (Harrison et al., 2012), which is followed by the formation of non-chaotic macroscopic shapes. Mechanics of morphogenesis in plants is related to close relationship between cytoskeleton and cellulose microfibrils, in other words, how cytoskeletal systems and cell wall biosynthetic activities are integrated during morphogenesis (Mathur, 2004). The precise nature of the cytoskeletal–cellulose relationship remains uncertain but it is shown that cortical microtubules orient the direction of cell expansion primarily via their influence on the deposition of cellulose into the wall (Smith and Oppenheimer, 2005). This influence may be considered as a case of determination of the movement of plasma membrane and of the shape of the cell via action of actin filaments that are most abundant near the cell surface (Lange, 2000, 2011). The filaments of cytoskeleton expand to form microvillar F-actin bundles shielded by a lipid membrane. They play major role in provision and regulation of ionic fluxes and also appear to function like electronic integration devices for signal-to-noise enhancement. In this process, the influence of coherent signals on cation transduction is amplified, whereas that of random noise is reduced (Gartzke and Lange, 2002). Thus the intimate connection between the orientation of microtubules and that of mechanical stresses is now firmly established in plants both at the cellular and supracellular levels.

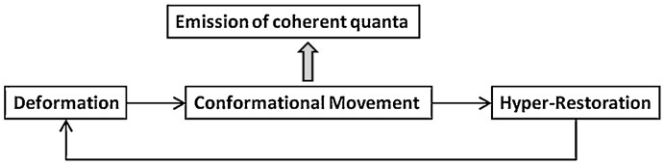

Fig. 2. The basic simplified scheme of the relaxational model of morphogenesis. Fast deformation is followed by the slow conformational relaxation which moves not to the initial state but to a hyper-restored condition that causes further deformation. This sequence of events is accompanied by emission of coherent quanta that can bear the morphogenetic information.

6. Percolation Networks in Morphogenesis

The relaxation concept of enzymatic catalysis allows the explanation of very high precision of enzyme operation based on the concept of quantum non-demolition measurements (Igamberdiev, 1993, see also Braginsky et al., 1980; Igamberdiev, 1999, 2004). The recognition of specific signals by enzymes and precise transformation of these signals are based on a very low dissipation of energy during catalysis in accordance with the Heisenberg's uncertainty ratio "energy-time". As we discussed earlier, in morphogenesis, due to the operation of cytoskeleton (in coordination with membranes and boundary water), the conformational relaxation is expanded to macroscopic scales (in space and time) corresponding to multicellular units of relaxation in most eukaryotic organisms. The striking precision of morphogenetic events gets the same explanation as the precision of operation of enzymes, with one major difference. While the enzyme molecule specifically recognizes the substrate (also based on its relational spatial coordinates relative to coordinates of enzyme molecule), in morphogenetic phenomena the recognition of a previous form triggers conformational relaxation that leads to formation of a new form. The instrument for this recognition is the whole organization, while the phenomenon of recognition, similarly to the enzymatic catalysis, is based on coherence between the recognized state and the whole structure of recognizing instrument (body). This is the crucial point that unites the mechanical approach to morphogenesis and the field approach exploiting low-energy electromagnetic fields operating for accomplishment of morphogenetic events. These approaches can successfully work together being complementary and supporting each other. Fig. 2 schematically illustrates the mechanism of conformational relaxation in relation to morphogenesis.

An important problem of morphogenesis and spatiotemporal development is a coexistence of both long-lived coherent states and high energy dissipative processes. As we showed earlier, the basic principle of the maintenance of highly ordered coherent states can be found in the concept of quantum non-demolition measurements that provide "time retardation" in macromolecular processes related to enzymatic catalysis and other events involving conformational relaxation (Blumenfeld, 1983). The relaxation time can exceed the excitation time by 9–10 orders of magnitude in operation of biomacromolecular machines, and during this relaxation time the coherent state is supported. This state is connected with coherent photon storage and emission. These coherent photons may be used for cell communication (Cifra et al., 2011). The coherent state represents a percolation milieu for exhibiting quantum phenomena at the macroscopic level of organization (Conrad, 1996). The motion and coherence appear as a unitary process accompanied by a cycle involving the annihilation and creation of superpositions (Conrad, 2001). Following Conrad (1996), we can present the hierarchically interleaved dynamics in biological systems in relation to conformational dynamics and relaxation phenomena in morphogenesis as a percolation network uniting

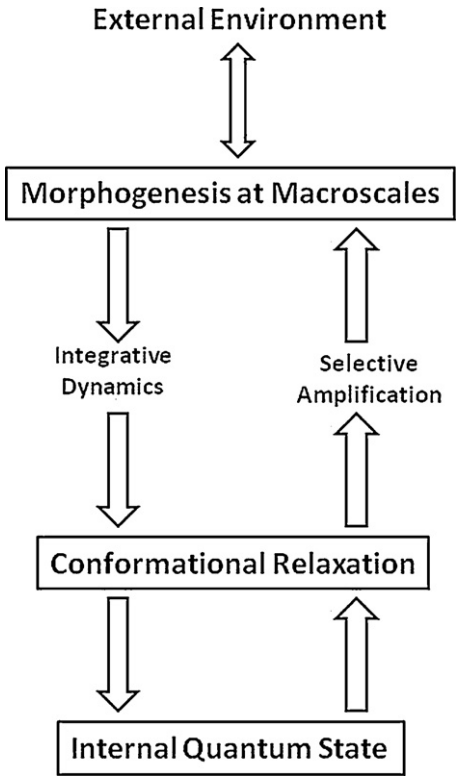

Fig. 3. Mesoscopic dynamics of morphogenesis (following Conrad, 1996). The percolation network includes the coupling of coherent and mechanical degrees of freedom at the microscopic level during conformational relaxation of biomacromolecules that maintains their internal quantum state. The relaxation events are amplified at meso- and macrolevel to macroscopic morphogenetic events that in turn control molecular events (via integrative dynamics) and affect the external environment providing its input in the process of morphogenesis.

coherent (unmanifest) and mechanical (manifest) dynamics in the whole mesoscopic phenomenon (Fig. 3).

In the spatiotemporal structure generation in biosystems, the percolation of quantum phenomena to the macroscopic level is realized in particular through the cytoskeleton. For the actomyosin molecular structures, which are primarily mechanochemical devices, and serve as a basis of cytoskeleton, the energization via ATP hydrolysis takes a minor fraction of the entire turnover time in which the mechanical work is produced during a prolonged relaxation time. During fast generation of mechanical stresses and their prolonged discharge, in relaxation processes, low energy coherent states and high energy dissipative processes coexist at different levels of organization of biosystems. While the operation of biological systems occurs at ambient temperatures of ~300 K, the supercold internal quantum state supported during conformational relaxation of biomacromolecules has its temperature of 10^{-3} K or lower (Matsuno and Paton, 2000; Igamberdiev, 2004, 2007) and can maintain long-range coherence through Bose–Einstein condensation as predicted by Fröhlich (1968, 1975) who viewed biological activity as a result of coherent collective vibrations of electric dipoles in biomacromolecules. Fröhlich suggested that the energy influx to the biological system can be transformed into coherent modes of longitudinal vibrations via a nonlinear interaction between elastic and polarization fields. This supports the idea that the external energy becomes the structural energy of the system that maintains non-equilibrium and is used by the system for its work by structural forces.

The water-membrane interface can be a substrate for a proton superflow based on the pairing of mobile hydrogen bonds by propagating electronic oscillations in polar side groups of the

membrane. It was also proposed that the region of water surrounding the cell is a dynamically ordered non-linear coherent optical device (Jibu et al., 1997) which provides that cells can receive electromagnetic signals consisting of evanescent photons tunneling through the dynamically ordered region of water. Saha et al. (2012) consider the possibility of stochastic resonance in tubulin dimers. The frequency-dependent expression for this resonance shows that the response of the electron-tubulin dimer system is enhanced by ambient dipolar oscillations in specific frequency regimes.

The coherent long-living quantum states in biological systems may explicit themselves in a phenomenon of ultraweak photon emission described by Alexander Gurwitsch in early XX century (Gurwitsch, 1922, 1923; Gurwitsch and Gurwitsch, 1959). In relation to this, the emission of quanta during actomyosin contraction allows calculation of effective temperature of its internal coherent state (Matsuno, 1995; Matsuno and Paton, 2000). Its millikelvin (10^{-3} K) temperature corresponds to de Broglie length of ~5 nm. This corresponds to the quanta of a very high energy that can make it possible to form mesoscopic quantum coherence over adjacent actin monomers, since the diameter of an actin monomer (2.5 nm) is less than the de Broglie length. Slight changes of parameters (e.g. length of microfibrils, rate of sliding of subunits, etc.) will result in increased wavelengths, closer to the UV light. The local coherence in cytoskeleton fibrils generates semi-local (mesoscopic) coherence involved in the interaction (co-measurement) of protein molecules. The calculated de Broglie wavelength makes it possible to form more mesoscopic or macroscopic quantum coherence over adjacent actin monomers along the actin filament through the quantum entanglement (Matsuno and Paton, 2000). A coherent coupling of quantum oscillators to electromagnetic modes of a cavity is postulated by Verhagen et al. (2012) and may have direct relevance to relaxation phenomena in biological systems.

The phenomenon of ultraweak photon emission was observed by several authors following original Gurwitsch's works and later confirmed by Popp et al. (2002). Popp, following original pioneering works of A.G. Gurwitsch, proposed physically oriented models for ultraweak photon emission interactions based on the coherence properties of delocalized cellular electromagnetic fields and their interference (Popp et al., 1989). According to his views, every biological system displays a complex species-specific wave pattern. The ultraweak photon emission correlation dynamics was more cooperative in highly organized samples (developing embryos, confluent fibroblasts cultures) as compared to poorly organized (non-fertilized eggs, non-confluent, poorly spread cell cultures). The emitted quanta can be of a high frequency corresponding to low UV range (190–330 nm) but very weak (only few quanta s^{-1} cm^{-2}) (Gurwitsch, 1922; Popp et al., 2002). Beloussov (2003) detected regular changes of the ultraweak photon emission (Fourier spectra) during embryonic development and physiological reactions of cell cultures. These changes involved broad spectral areas showing greater instability and the presence of a short-range order only at earlier developmental stages, while at the advanced developmental stages a long-range order has emerged within the spectra. The bursts of photon emission and the appearance of strong oscillations took place immediately after administration of the cytoskeletal inhibitors or other damaging agents. In this respect, these strong oscillations can be considered as "alarm signals" of disturbance of homeostasis, when the relaxation pattern is affected. These bursts may not necessarily exhibit long-range coherence patterns but be related to the processes of higher dissipation of energy than original relaxation phenomena. On the other hand, the hyper-restoration phenomenon by itself generates instabilities that can be linked to generation of electromagnetic oscillations that can bear morphogenetic information.

In recent papers (Havelka et al., 2011; Kučera and Havelka, 2012), the electromagnetic radiation and electric field of the whole cellular network consisting of 100 microtubules have been calculated from microtubule oscillations in the frequency region from 10^3 Hz to 10^{11} GHz, the total radiated power of the single cell for the lossless medium being highest (10^{-20} W) for the highest frequency (10^{11} Hz) calculated and lowest (10^{-52} W) for the lowest frequency (10^3 Hz) calculated. These calculations allow estimation of ultraweak fields occurring in living cells that can be used for their coherent interaction and communication.

This communication can trigger the processes with a higher dissipation of energy, e.g. connected with assembly and disassembly of cytoskeletal tubes. As the cytoskeleton is an important milieu for providing coherent events, it can be also the basis for acoustic: phononic transmission and quasiparticle processes. Liberman et al. (2008) suggested that nerve cells can solve problems using an intraneuronal medium based on the cytoskeleton. When a new situation arises, this structure has to be disassembled and then assembled again by the neuronal molecular computer. This corresponds to the search of optimal system of coordinates for living system and for its spatiotemporal structure. The latter can be formed based on the "multidimensional information" (Liberman et al., 1998) that includes "spatial" encoding and decoding of signals of a higher dimensionality than common one-dimensional transmission. The idea may be relevant to the claim of Hameroff and Penrose on long-living coherence in microtubules (Penrose, 1996; Hagan et al., 2002; Hameroff et al., 2002). It was developed by Craddock et al. (2010) who suggested that ions, condensed around the surface of the major filaments of the cytoskeleton, flow along and through microtubules in the presence of potential differences, thus acting as transmission lines propagating intracellular signals in a given cell. For muscle contraction, the mechanical aspect of cytoskeletal operation is most important, for nervous system the coherent events are of a major significance, while in morphogenetic events both the mechanical and the coherent phenomena provide a high precision of form generation.

The examples in biological systems where the quantum coherence was unambiguously established refer to photosynthesis in bacteria and algae, where the light-induced excited state of electrons in light-gathering proteins is instantaneously transferred to nearby reaction centers in the phospholipid membrane. This instantaneous transfer of the excited state is accomplished by quantum entanglement in a way that the two different particles separated in space have a link, in the sense that an alteration in one of the particles will immediately affect the other particle (Lee et al., 2007). It is claimed that correlated protein environments preserve electronic coherence in photosynthetic complexes and allow the excitation to move coherently in space, enabling highly efficient energy harvesting and trapping in photosynthesis. This work was successfully continued by Panitchayangkoon et al. (2010) who showed that near-perfect quantum efficiency of photosynthetic antennae is based on the coherent wave-like transfer mechanism. The authors are presenting evidence that quantum coherence survives at a physiological temperature for at least 300 fs, long enough to impact biological energy transport. Microscopically, they attribute this long coherence lifetime to correlated motions within the protein matrix encapsulating the chromophores. They show that proteins shape the energy landscape and mediate an efficient energy transfer despite thermal fluctuations. Similar phenomena should exist in all biological processes and be particularly important for morphogenetic events.

In connection to this, it is essential that while the coherent state itself is associated with a very weak emission of quanta of shorter wavelengths (~5 nm), it can trigger secondary emission of quanta with longer wavelengths (Gurwitsch's range of 190–330 nm), and then to acoustic wavelengths postulated by Liberman (1983), corresponding to hypersound frequencies of 10^8–10^{11} Hz. The extremely weak emission of quanta of ~5 nm wavelength predicted

by Matsuno and Paton (2000) corresponds to conformational relaxation of actomyosin complexes itself, while the photons of ultra-weak intensity of 190–330 nm wavelength discovered by Gurwitsch (1922) may be connected, in particular, with free radical reactions. This emission can be easily transmitted to long distances and transformed into other forms of energy. Longer wavelengths of the infrared part of electromagnetic spectrum correspond to rotations and vibrations of parts of many-atomic molecules. The longest wavelengths up to hypersound scales can accompany enzyme reactions with low catalytic constants (Shnoll, 1979) and rearrangements of cytoskeleton microfibrils (Liberman, 1983; Liberman et al., 2008). While the emission of short-wavelength quanta of the cold coherent state harmonizes interaction of protein molecules, the importance of UV-scale emission provides conditions for electromagnetic resonance in morphogenesis (Pietak, 2012), and higher wavelength emissions can be used for integration of the parts of developed biosystem into the whole entity.

7. Fundamental Parameters of Development

The development of morphogenetic patterns, as it was shown earlier, can be viewed as a sequence of unfolding patterns originating from previous states. We can study the unfolding pattern without reference to underlying phenomena. Nevertheless there should be something in the pattern of unfolding that refers to the system's internal activity and reflects its hyper-restoration dynamics. This dynamics by itself is generic as it generates novel patterns that generally cannot be derived from previous states via simple recursive rules. We can distinguish an internally developing generic process from an external non-generic phenomenon through certain proportions in the generated structure, which represent limits of iteration exhibiting an internal process. Some examples were provided already in Gurwitsch's works, e.g. the inflorescence outlines reach the parabolic envelope during growth, the cones of mushrooms during growth reach certain mathematical shapes, and this can be interpreted via the concept of attractor. In this part we will try to explain the unfolding patterns via introduction of certain parameters specifically characterizing the internal activity. Any internal choice exhibits a structure of the mixing the notion of indicating an element with the act of indicating a set consisting of elements (Igamberdiev, 2004). As it was mentioned, Rosen (1993) noted that physically embodied reflective loops have certain objective parameters that include the values that can be redundantly repeated. This leads to a topological inevitability of certain developmental processes so that the topological singularities inevitably emerge in biological morphogenesis, and are retained and transformed during pattern formation (Isaeva et al., 2012).

In the approach developed by Gunji, a certain transition rule is used recursively along time and the *fixed point* (the point of coincidence of the image and its reflection) is identified with a domain equation resulting in generation of a reflective domain. Solving and obtaining the reflective domain is used as a new transition rule (Gunji et al., 1997), and during this process the unfolding is collapsed into the fractal spatiotemporal structure. According to this approach, the fixed point x for the operation of determination of A and A^-, denoted by F can be expressed as an infinite recursion, $x = F(F(F(\ldots F(x)\ldots)))$, by mapping $x = F(x)$ onto $x = F(x)$ and presented as a point in two-dimensional space. The operation of F is the contraction in a two-dimensional domain, indicating either A or A^- (Kitabayashi et al., 1999). If validity of A is denoted by m, the invariance of validity with respect to contraction is expressed as $f(m)*m = constant$, where m is the value of validity and $f(m)$ is the probability of m. If distribution of $f(m)$ does not have an off-set peak, m directly means the rank. Then $f(m)*m = c$ represents what is called the Zipf's law, i.e. $\log(f(m)) = -\log(m) + c$ (Kitabayashi et al., 1999). A similar formula was introduced by Mandelbrot (1982) for the fractal structure. Actually fractal is an iteration arising from the set of complex numbers by squaring them, i.e. by reflecting them into the 2D space. The third dimension is a reflection over this 2D domain. As a result, the 3D + T structure appears (more details in Igamberdiev, 2004).

In biological morphogenesis, the preceding motif unit is transferred into the subsequent one by a certain generic similarity transformation g, that can be reduced to a simple rule such as $F_{n+1} = g*F_n$. The finite representation of actualization forms a coordinate scale inherent to any individual morphological form. These coordinate scales can be transformed by simple recursive rules via rescaling (Thompson D'Arcy, 1917). The limit of actualization fits optimality of the structure being actualized, thus it provides the existence of optimal solutions for design. If we take the simplest and most general way of transformation when a new domain is composed of two previous (two-dimensional transformation), the two sequential values are composed to get the third value. Thus the next value is composed from the two previous values when they are memorized: $F_{n+2} = F_n + F_{n+1}$. This means that certain recursive limits appear as fundamental parameters of *memorization in the course of unfolding process*. In many cases of biological morphogenesis the configuration of golden section is realized as the limit ($n \to \infty$) of this process:

$$\Phi = \lim \left(\frac{F_{n+1}}{F_n} \right) = \frac{1 + 5^{1/2}}{2} = 1.618\ldots$$

The solution for F_n depends only on the number of recursions addressing the fixed point and described by the Binet's Fibonacci number formula:

$$F_n = \frac{(1 + 5^{1/2})^n - (1 - 5^{1/2})^n}{(2^n \times 5^{1/2})}$$

The Fibonacci numbers represent possible solutions for morphogenetic problems, as numbers of ways of picking sets in recursive process with the formation of corresponding spatial patterns (Brousseau, 1972). Important series (referring to three-dimensional unfolding) appear when three neighboring elements F_n, F_{n+1}, F_{n+2} of the Fibonacci are taken as lengths of three sequential segments (as appeared in the sequential past $(t-1)$, present (t) and future $(t+1)$ times). They represent the ratio defined as the wurf having its "golden wurf" limit W (Petukhov, 1989):

$$W = \lim \frac{(F_n + F_{n+1})(F_{n+1} + F_{n+2})}{F_{n+1}(F_n + F_{n+1} + F_{n+2})} = \frac{\Phi^2}{2} = \frac{3 + 5^{1/2}}{4} = 1.309\ldots$$

The value of golden wurf as a limit of the recursive unfolding process will arise from the combination of three sequential segments with the values 1, Φ and Φ^2, i.e. it follows from the memorization of limits of recursion in the Fibonacci series (Petukhov, 1989). The golden section and the golden wurf constants represent fundamental values of infinite recursion when the next element is formed by the operation on the sequentially appearing elements within the reflective loop and occur in many morphogenetic patterns.

8. Conclusion

The problem of actualization of biological forms (morphogenesis) can be understood in frames of limiting conditions which define possible emergent (self-generating) phenomena. Functional activity of biosystems emerges via non-programmable generation of computable events. The basic process determining morphogenetic phenomena is a prolonged conformational relaxation governed by the cytoskeleton and generally leading not to the restoration of the initial state (as in the metabolic homeostatic flux control) but to its hyper-restoration that increases curvilinearity of

the system and leads to successive spatiotemporal development (homeorhesis). The conformational relaxation holds the quantum mechanical coherence for macroscopic time intervals and causes ultraweak emission of coherent photons. This emission can be a unifying factor for providing morphogenetic phenomena forming a parametric field governing emergence of new structures. Biomechanical and coherent events during the morphogenetic relaxation appear in concordance and represent the mesoscopic phenomenon of the same nature as the well-known wave-particle dualism of the quantum mechanics. The coherent events percolate from elementary submolecular level to organismic entities by generating a dynamic morphogenesis network. Successive spatiotemporal structures, being closed at the macroscopic level, can be studied without addressing molecular level events, as transformations in the curvilinear space reproducing specific parameters such as the golden ratio and the golden wurf, which appear as fundamental objective constants of morphogenetic processes. In biosystems, physically embodied reflective loops consistently reproduce the fundamental parameters such as the golden ratio and the golden wurf.

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