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Lev V. Beloussov

Developmental Causation: A Set of Strict Instructions or a Self-organized Morphogenetic Field?

Abstract

Two alternative versions of interpreting the developmental events are discussed. The first of them regards the development as a set of highly specific steps each of them being caused by a unique special force, or an "instruction". By this version, nothing outside the rigidly determined chain of events is presented, and the ultimate aim of a researcher is in making a list of specific instructions. The second version is centered around the notion of an extended spatio-temporal continuum (morphogenetic field). Any developmental trajectory is now considered to be the function of this continuum's geometry in Euclidean and/or phase space. Within the context of such an alternative we review the classical embryological data related to inductive phenomena and embryonic regulations. The contours of a morphogenetic field theory are sketched.

1. General outline of a problem

Anybody even superficially familiar with the development of multicellular organisms will agree that it is undoubtedly a most complicated and ordered set of non-artificial events ever observed in Nature. Within the course of development, the increasing number of embryonic cells are dividing, changing their shapes, moving and changing their internal structure (become differentiated) in a highly coordinated and regular way. Each time we are dealing with a highly specific and perfectly reproduced spatio-temporal succession. How does it come into being? In what way does each part of an embryo "recognize" what it should do at the given time moment and at the given space location?

Whether formulated in this or in other ways, these are eternal questions, known already to ancient Greek philosophers. Each cultural epoch gives them some new accents but their very essence remains much the same. Even present- day biology, so proud of its achievements, is far from answering them in an exhaustive way. But what is important we are at least able to concentrate all the tentative versions of such answers around two paradigms, each of them being of a heuristical value (i.e., non-tautological and to a reasonable extent falsifiable). My friend, a thoughtful American biologist Albert Harris, made an attempt to visualize both of them by the following pictures (Fig. 1 A, B). Being of course unable to reflect all of the nuances of both versions they seem to me quite useful for guiding a reader (especially a non-specialist) into the very heart of the problem.

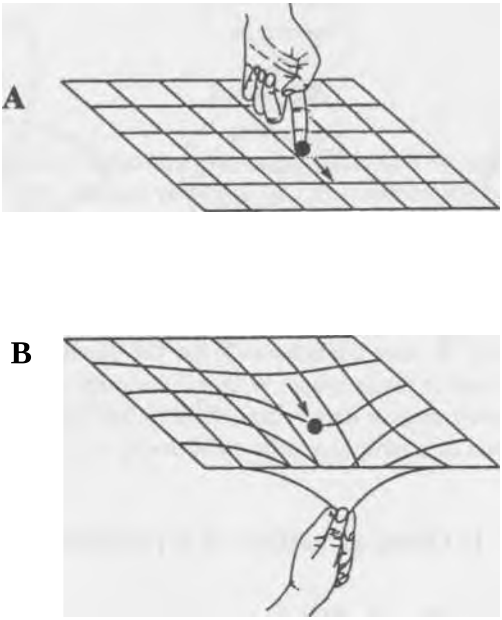

Figure 1. A, B. Allegorical representations of two interpretational versions of embryonic development. A: „instructivist“ version; B: morphogenetic field version. For comments see text (courtesy of Albert Harris).

The first version regards embryonic development as a set of highly specific steps, each of them being driven by a unique special force, or, more generally, by an “instruction”. What we define as an instruction is a statement or a physical action unambiguously generating a definite effect which can be largely non-isomorphic to its instruction. Instructions themselves are generally assumed to be also largely non-isomorphic to each other, mutually independent, and not belonging to any higher order's whole. In our illustration, an instruction corresponds to a movement of the Demiurg's finger. The instructions are assumed to be arbitrary, independent from each other, discrete, rigid and unambiguous: it is impossible to produce more than one event by one instruction (although the reverse is assumed as possible). Within a framework of an "instructivist paradigm" the ultimate goal of the research would be in making some kind of a list of specific instructions, very much like a traffic schedule, informing you at what geographical point and at what time moment you should change your train in order to reach the destination point safely. And if the traffic is working normally, no passenger in its right mind will be interested either in the locomotive's mechanics or the surrounding geography; he/she is sure that everything is strictly predetermined within the schedule. As we hope to argue later on, this version is very powerful, and even dominating (although if not always in the overt form) in the present-day science, and is deeply rooted both in epistemology and in the present-day human's psychology. From now on we shall call it the Version I.

This is contrasted to the Version II (Fig. IB), which is as follows. Instead of a set of rigid specific arbitrary instructions, it introduces the notion of a certain extended space-temporal continuum, a really observed developmental trajectory being no more than a small fraction of it. Now our interest becomes focused on the entire geometry of this continuum rather than in enumerating instructions one after another. What the Demiurg II is really performing are just changes in the continuum's geometry (deformations of the surface). The geometry is comprised both by the slope of the surface along the temporal axis T and its momentary (i.e. when T = const) relief, including valleys, crests, heights, craters, and so on. It was the outstanding British embryologist, Conrad Waddington, who introduce such a mountain allegory of development, calling it "the epigenetic landscape". Other axes symbolize either a real (physical) space, the entire continuum now being 4-dimensional, or a "phase space" describing some non- spatial characters of the developing systems (now the continuum becomes N-dimensional). In the first case we are dealing with the morphogenesis proper (that is, with the movements and rearrangements of embryonic parts without substantial changes in their internal structure), while in the second case we enter the realm of cell differentiation. Within actual development, both aspects are closely interlinked, but as a rule morphogenesis precedes and to a substantial extent determines cell differentiation. In any case, within this version's framework a task of making an instructions list becomes meaningless; instead, our main goal should be in discovering a kind of an embracing law for the entire space- temporal continuum, which we may call now a morphogenetic field. Although according to both versions the development can be regarded as a programmed process, the Ilnd Version program is quite of another kind than that of the Version I. It has a holistic character and will be completely lost in the case of splitting a system into its minor components.

Another remarkable distinction is that while within the Version I framework any instruction, that is, any single movement of the Demiurg's finger, produces only one effect, the Demiurg II, by making a crater, produces automatically a series of folds on its sides. Each of the folds may be regarded as a separate developmental trajectory. Hence, the final result may be more complicated than the initial perturbation. In this way a system acquires self-organizing properties.

2. Epistemological and psychological roots of the both versions

The epistemological roots of the "instructivist" Version I can be traced back to a so-called Laplacian determinism, the approach ascribed (may be, unproperly) to be founded by a French mathematician Pierre Simon Laplace more than 200 years ago. The famous Laplace's statement was that if we could know the structure of a World in all its details (at least for just one moment of its past) we would be able to predict its future with the same degree of exactness. This was the starting point for one of the most influential research programs of the Western science defined later on as a reductionism and directed towards a straightforward progressive analysis (splitting) of a studied object in the hope of becoming able to predict its future. Under such a framework, the entire World should be represented as a rigid net, consisting of unambiguous, one-to-one cause-effects chains which in principle have nothing in common with each other. It is meanwhile worth mentioning that even in the classical physics (not to say about quantum mechanics and other modem trends), this approach was never taken too pedantically and never used for something more than a primary exploration of the complicated objects; after doing that, it should be exchanged by approaches much more similar to our Version II. What we mean is the construction of a unifying mathematical law, or a model, or a symmetry group, etc. The less specific this law/model would be the better (both falling apple and rotating planets obey the same law). Not so in biology: partly due to the real immense complexity of the biological objects and partly due to a strange belief (shared, among others, by the German embryologist Wilhelm Roux, a founder of a "Developmental Mechanics", a germ of the modem embryology) that the reductionist splitting is the main attribute of the advanced physical sciences, this approach got an immense power and has retained up to now its almost monopolistic positions. In the course of such an evolution, a substantial cause-effects isomorphism of a classical causal approach has been largely distorted; in the modem instructivist versions the causal relations could be as complicated and non-isomorphic as you want. Either an instruction is assumed to be very much detailized and complicated while its effect is brief and "simple"; or, on the contrary, the instruction can be quite short and simple (a kind of a "command"), while its consequences enormously complex. In the last case the instructions' receiver should be endowed by some extremely powerful interpretational capacities. In any case, however, an instruction is regarded as something forcibly imposed onto an instructed object rather than being derived in some way from the internal properties of the object itself or of the surrounding space.

Psychologically, Version I has some definite similarities with the modem human's mood. Most of people, especially in well-developed countries, are living now according to a strict schedule and get their bread by exactly fulfilling arbitrary instructions (just by pushing buttons) without looking much around or thinking about the global results of their activity. They well know that any deviation from the instructions will lead to a smaller or greater disaster in their life. Therefore it is very easy for them to accept that the developing organisms behave in the same manner.

As to the epistemological roots of the Version II, they are also deeply embedded in physics, both classical and modem, and most obviously in the theories of physical fields. Taking into consideration the leading role of physics in the natural sciences, it may look strange why this version is not dominated in present-day biology. If searching for the rational reasons, they may lie in disbelief that any physical theories can interpret such an extensive and ordered increase of complexity, as it is really observed during development. Either intuitively, or under a hypnosis of classical thermodynamics, many people think that the physical forces themselves cannot drive a system towards something other than a chaotic state. Hence they are inclined to suggest that the embryos cannot develop themselves otherwise than by obeying a set of ordering instructions, similarly to the human beings especially if dressed in a uniform. Interestingly, the instructivist people likes to condemn vitalism (a belief in fundamental irreducibility of biology to physics) although one cannot imagine anything more anti-physical than the development going on according to a set of instructions.

Happily, the limits of physics are not fixed forever; during the last several decades they have been considerably shifted towards what was traditionally believed as the biological estates. What we mean here is a modern selforganization theory which teaches us that a spontaneous evolution of non-linear systems far enough removed from thermodynamic equilibrium can lead, under appropriate conditions, towards certain highly ordered and stable space-temporal regimes of a reduced symmetry order, rather than to a mere destruction and white noise. The "appropriate conditions" imply the existence of dynamic perturbations (which may be highly degenerative: in many cases any positive or any negative values lead to the same final result) and, mostly important, the introduction of the parameters with the definite values. The parameters are distinguished from the dynamic variables (just reflecting the observed behavior of a system) by much greater characteristic times. The non-linear self-organizing systems obey a dualistic causal subordination: both parametrical and dynamical. Firstly the parametrical regulation comes into play, determining a set of possibilities, or potencies (that is, a set of the stable regimes which are in principally achievable). This is just what the Version II Demiurg is doing by changing the potential relief of a phase space. Only on this background the dynamic regulation can come into work, each time selecting just one of the potencies out an entire set. The above mentioned degeneracy of the required perturbations endows a system by a property of a robustness, which is also among the main features of the self-organizing system. Another related property is that the self-organized systems, contrary to deterministic ones are at least bi-level, and usually multi-level, that is, consists of the different characteristic times and space dimensions. This also relates to all living systems, certainly including the developing ones. The inability of the linear deterministic versions to reflect these properties is obvious. At best, any linear system can be regarded as a particular case (a short-termed representation) of a non-linear one, but not vice versa.

In any case, the existence of self-organizing systems overrides the above mentioned skepticism about whether a non-instructivistic (that is, driven by physical laws) ordered complication is possible. However, in coming from this point towards a really comprehensive theory of development requires a deep biological analysis. Before starting it, let as make a few remarks about the psychological roots of the relative unpopularity of a self-organizing approach.

Strange as it is, this advanced trend of the modem science, in spite of numerous claims for a wide introduction of a “non-linear way of thinking” into the modem life and even politics, has much less affinity to a modem technocracy than the deterministic one (as discussed above). Although any one modem technology employs parametric regulation, robustness, structural stability and so on, all of these properties are, so to say, very much behind the screen, and what is left for the operator are these notorious buttons. Paradoxically, the old-fashioned (Third World’s) agricultural technologies are much closer to a self-organizing ideology than the button-pushing occupations of the First World’s majority. Unfortunately, the modern genetically engineering interventions into these technologies are based, again, onto the button-pushing approach. Only slowly and unwillingly the scientific community starts to suspect that the final results of such interventions can be much more complicated, unpredictable and unfavorable than it comes from the deterministic believing,

3. Biological analysis

As was briefly mentioned, Version 1 came to the developmental biology from Wilhelm Roux' deterministic research program. Roux initially believed that the development can be effectively represented as an interplexed network of one-to-one cause-effect relations. To his credit be it said, he was never too pedantic in defending his views and willingly gave a place in his famous journal "Archiv fur Entwicklungsmechanic des Organismen" (Archiv for the Developmental Mechanics of the Organisms) to the supporters of an opposite viewpoint, Hans Driesh and Alexander Gurwitsch being the main ones among them.

A real domination of a deterministic ideology started from the discovery of a primary induction by Hans Spemann and his colleagues (1921, see Spemann, 1936). This was probably contrary to a personal, somewhat vitalistic views of the discoverer himself, but now this may be only of a historical interest. In any case, it so happened that several generations of embryologists eagerly liked to reduce development to a chain of the primary, secondary, tertiary etc inductions, the earlier induced rudiment taking at the next stage the function of the inductor, and so on. A permanent focusing on the chemical structure of inductors gave to these researches an inalienable reductionist flavor which could be justified only if the inductive chains were regarded, in a good enough approximation, as one- to-one cause-effects relations. But is it really so?

Owing to a great amount of works in this field, we definitely know now
that:

- There is nothing like "one inductor - one organ" rule. On the one hand, the same organ can be induced by quite different agents, some of them being definitely non-specific. For example, an amphibian limb, during its normal development hardly has any discrete inductor at all; but it can be easily induced by a rudiment of an internal ear (otic vesicle), nasal placode and even a piece of a cellophane transplanted to a flank region of an embryo although the above mentioned rudiments have nothing in common with the limb and cannot induce it in their normal locations. On the other hand, these same inductors, including highly purified chemical substances (belonging to the group of so-called growth factors) generate quite different effects in the different types of cells. Similarly, the "classical" inductors produce different effects while being transplanted into different embryonic regions.
- At no size scale are there any traces of one-to-one correspondence between the spatial structure of an inductor and of an induced organ: just a small piece of an inductor, or the inductor dissociated into single cells and then re-associated, etc produce no less perfect result than an intact whole inductor.

- The symmetry order of an induced organ or a set of organs is as a rule lower than that of the inductor. Therefore, the causal link between an inductor and an induced organ cannot be one-to-one: instead, it implies a real complication in betw een.
- There are a lot of developmental processes that are going on without discrete inductors.

A list of the deviations from a strict determinism cannot be more representative! We may be sure that the inductors do not act in the same way as the Demiurg I alone, that is, accurately moving an imaging body from one specific point of a flat surface to another. Much closer to the reality is to regard the inductors as combining the activities of the Demiurg II, modifying the potential relief of a system, with very much degenerated (lazy and imprecise) actions of our Demiurg I, just slightly pushing the imaging bodies into already molded valleys and craters (for more detailed analysis see Beloussov, 1998). But if accepting this viewpoint, the investigations of the inductor-associated events should be much more concentrated on the structure of the morphogenetic field rather than the molecular constituents of the inductive substances.

The same way of reasoning can be applied to a much larger class of phenomena, namely to that of a cell signalling. The more we know about the signalling pathways, the more they look as an immensely perplexed network of molecular events, some of them enhancing and some suppressing each other (see, e.g. Pawson & Saxton, 1999). How can it be that so rapid and specific responses (quite different under the different “cell contexts”, as some authors cautiously remark) which we really observe, are produced as a result of these networks’ action? Is it possible to interprete these results in the terms of an intrinsic specificity of each next step of such networks, without implying some holistic governing principle? It would be the same as if assuming that several, and even many Demiurgs I are pushing their balls along the same surface hoping to avoid any unexpected collisions and deviations so that each ball will reach safely its specific destination site. Certainly, such expectations will be futile. Retaining within the Version I framework, it would be quite difficult to understand why the nature invented so complicated networks instead of a small number of strictly determined pathways. Let us now invite the Demiurg II to come into play and to incline a bit the surface (in different ways under the different “cell contexts”). Now everything becomes much more reasonable: the overall direction of the balls’ movement is determined by the surface deformation while the multiplicity of the pathways increases the reliability to reach this final goal (if one way is hampered, another works) without having a risk to take a wrong direction. Or, in other words: the micro-processes (the individual links of a network) provide a local, rather imprecise dynamics, while the macroscopic factors (those deforming the surface’ relief) establish a directiveness by spending very low amount of energy. For self-organizing systems such a dualistic subordination is quite ubiquitous (Beloussov, 1998, p. 43), but for biology this approach is still unaccustomed.

A new outburst of determinism is associated with the introduction of fascinating new techniques permitting us to visualize the domains of gene expression in developing embryos. A powerful tendency has emerged to regard development as a deterministic chain of genes' expression, implying that the products of the firstly expressed genes induce the subsequently expressed ones, and so on. It is easy to see that logically it is much the same as in the case of inductive chains. Hence, one should not be very much astonished to meet here the same difficulties. Thus, a developmental sequence of gene expression is associated, in most cases, with a regular complication (reduction of symmetry order) of the arisen patterns. For example, in Drosophila development a smooth gradient of the maternal gene products is exchanged by few wide expression bands of so called *gap* genes, these ones by several narrow stripes of *pair-rule* genes and, next, by a 2-fold number of the *segment polarity* genes' stripes. Even if there is a direct causal connection between the subsequent genetical patterns, it cannot be one-to-one. On the other hand, innumerable examples show us that the morphogenetic results of the same genes' expression can be largely different, as depending, say, from the developmental stages or the rudiment's specificity: "the interactions between msx-1 and msx-2 homeodomain proteins characterize the formation of teeth in the jaw field, the progress zone in the limb field, and the neural retina in the eye" (Gilbert et al., 1996). Generally, in the related species the development of homologous organs can be associated with the expression of largely non-homologous genes, and vice versa (Wray and Abouheif, 1998). Also, a morphological result of a given gene's action can be more complicated (less symmetrical) than the shape of the gene's expression domain: in the *Arabidopsis* plant a gene responsible for the number of flower's petals is homogeneously expressed throughout all of the petals' whorl (Goodwin, 1994, pp. 126-128). All of this strongly argues against a strict one-to-one deterministic relations between genes and morphological structures and supports the idea of the higher organizational levels' involvement in regulating space-temporal parts of gene expression (in this respect see also Nijhout, 1990). Much more detailed analysis of the role of morphogenetic fields in genes' expression is required. Meanwhile, in the terms of a self-organization theory the role of genome is quite obvious: due to a high degree of its spatio-temporal uniformity it perfectly fits the category of the parameters. Such a role is very respectable. Nevertheless, to identify the genes without knowing anything about the morphogenetic field is logically equivalent to determining the numerical values of parameters in one of the equations of physics, except without having even a vague idea of the nature of the equation itself, into which these parameters are to be fitted. Obviously, that would mean knowing nothing at all. On the other hand, the reverse is not true: one can make some more or less definite probabilistic predictions based on knowing only the general form of an equation, even before knowing the values of its various parameters.

4. Multiplicity of developmental trajectories and positional dependence

According to Version I, for each embryonic element there exists a unique “correct” and highly specific developmental trajectory with everything outside being treated as “wrong” (aberrant, pathological). Meanwhile, Version II implies the existence of an entire “cloud” of permissible trajectories, differing from each other only by their probabilities. Within some spatio-temporal domains of development the trajectories can be to a some extent converged while in other cases diverged, but a multiplicity of the potentially achievable trajectories is always here.

Is such a view experimentally supported? Just this problem (although formulated in other terms) was deeply analyzed by Hans Driesch (1921). He coined the concepts and terminology of “presumptive significance” (PS) - which is what a given part of an embryo produces in its normal development - and which is contrasted by a set of “prospective potencies” (PPs), that refer to whatever the given part of the embryo can give rise to under any of various experimental conditions. Driesch generalized his experimental data by claiming that PPs are as a rule greater than PS, and this simple statement turned out to be true for an overwhelming majority of cases. In other words, one can always find an early enough developmental period so that, for a given part of the embryo, PPs> PS. Sooner or later, it becomes true that PP = PS; this transition is called embryonic determination. But the existence of a preceding period of time, characterized by this stated inequality is of primary importance. It is precisely the period when the main developmental game is played.

Some new techniques give us nice corroborations of these old ideas. For example Dale and Slack (1987) reported that by labeling the individual blastomeres of a frog’s egg at the 32-cell stage one can show that both their PSs and their positions inside embryo are quite variable, even though the embryos as wholes remain identical. Hence, not only the allegorical developmental trajectories in a phase space of developmental characters (based on the experiments concerning embryonic regulation), but also the real cells’ trajectories in the physical space of normal embryos - both appear to be considerably indeterministic. Furthermore, the variability of the trajectories is increased during mostly crucial periods of development, for example gastrulation (Cherdantzev and Scobeyeva, 1994). From an ordinary viewpoint, that would seem to be no less dangerous and absurd as to let go of a steering-wheel just at a cross-road! But let us remember that in old times peasants, if losing their way in the darkness or in a snow-storm did exactly this: they loosened their horse' reins permitting the horse to find a way itself. Again an example from the Third World!

Another point is that the developmental precision is as a rule greater at upper levels, as compared with lower levels. Combinations of imprecise activities by individual cells, in any cases produce as net results precise enough macroscopic organs. It is very difficult to imagine our Demiurg I succeeding in producing a precise pattern out of disorderly moving balls. Meanwhile, that creates no problem for our Demiurg II: he simply makes a crater and lets the balls fall in, one after another, without having to pay much attention to their individual dynamics.

Nevertheless, even the multiplicity of these alternate developmental trajectories cannot be regarded as sufficient evidence for the existence of a continuous field. There may be, instead, a kind of a discrete multiplicity without any holistic, systemic properties, somewhat similar to a telephone switchboard with a huge amount of independent numbers. Let us discuss this switchboard/ field alternative by analyzing the fundamental phenomena of embryonic regulations (Fig. 2).

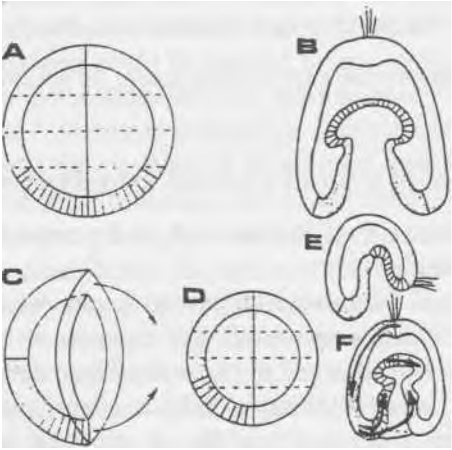

Figure 2. Embryonic regulations in sea urchin embryos. A: a "fate map" of an early blastula, showing the localization of different rudiments. Within the normal development (B) the hatched area will give rise to coelomic sacs, the dotted one to the endoderm and the empty one to the ectoderm. After cutting off half of an early embryo (C) the rested hemisphere is spontaneously closed into a complete sphere (curved arrows) and the fate map becomes as shown in D. If further development would go on according to pre- established cell fates, a monster like that shown in E would be arisen. Nevertheless the developing embryo is of a normal structure although of a reduced scale (B). For achieving this result, the cells' fates should be shifted according to new cells' positions as shown schematically by arrows in F.

If detached from one another, the two first blastomeres of a sea-urchin egg will each divide as normal, producing thereby a hemispherical half-blastula (Fig. 2C). Soon this is closed by joining its opposite poles (Fig. 2D). This mini-blastula (compare with the normal one, Fig. 2A) can give rise, in a good percent of cases, to a pretty normal and properly proportioned embryo (Fig. 2F, cf Fig. 2B). This is precisely what is meant by "embryonic regulation". It could be seen a priori (and had been repeatedly tested in labeling experiments) that this regulation could not take place if any part of an embryo would develop according to its PS: if the latter were true, nothing except a monster like that shown in Fig. 2E could possibly emerge. In which way, even formally, can such regulation be described? For this purpose, Driesch used the allegory of a geographical coordinate grid imposed onto a normal embryo. Now a developmental fate of each of its part (that is, what part of the body each will finally produce) can be related one-to-one with this part's coordinates. Then let us do the same with a smaller sized embryo, developed as a result of regulation, making use of a coordinate grid whose dimensions have been correspondingly diminished. We will see that in the case of regulation (and only in this case) the relations between the developmental fates of all the parts and their coordinates will be identical to those in the normal development. Meanwhile, the presumptive significance of all the parts have will have been drastically changed. Hence,

> The fate of an embryonic part is a function of its position within a whole
>
> (Driesch, 1921)

(and not, let us add, of this part's internal individual properties)

This is a famous law of Driesch and, at the same time, a first rudiment of a morphogenetic field theory.

Driesch himself formulated his law in a very laconic and uncertain form, leaving many questions unanswered. For example - what does the notion of "fate" really mean: is it identical to the entire future developmental trajectory, or just to a small fraction of it? What actually is a "part", what are its spatial limits, should it contain any entities of the different structural levels? And, finally, what is the "position", what are the reference points for its specification?

We shall concentrate our discussion on this last issue, because it is central to the.popular "positional information" concept (Wolpert, 1969).

About 3 decades ago Lewis Wolpert aimed to renew Driesch's concept and to liberate it from what he among many others considered as anachronistic vitalistic trash. In this latter category, in his opinion, belonged its vague notion of position referred to a "whole". Wolpert re-edited Driesch's concept by postulating the existence of certain specialized elements of an embryo which are the sources of "positional information" (PI), this latter assumed to be spread throughout an embryonic body in a more or less linear gradient fashion. Thus defined PI gradients have usually been identified with the concentration gradients of some (mostly unknown) chemicals, called the “morphogens”, and suggested to be emitted by PI sources. All the embryonic parts supposedly perceive PI independently from each other according to their positions and then “interpret” it with the use of their genomes. What we call development is, according to this view, just the interpretation of PI.

Although at first glance the PI concept looks similar to that of a morphogenetic field, they are actually almost antipodes. Whereas the latter class of theory deals with a continuum of possibilities much larger than those realized within the course of development, the PI concept implies a restricted set of interpretable positions. From the PI point of view it would be meaningless to ask what will happen with an embryonic element situated outside of this set. Together with the postulated mutual independence of the embryonic parts and their necessarily immense internal interpretational capacities that this would require, the PI scheme is actually much closer to a telephone switchboard allegory than to any kind of field. By endowing the different embryonic parts with such immense interpretational capacities, the PI concept merely pushes aside the main developmental enigmas rather than elucidate them. In this way we come back to the instructivistic versions of a “command type”. In addition, it is also quite unclear how such explanations could be applied to any multilevel events.

Let us next discuss the assumption that special embryonic elements play the role of PI sources. Based on simple geometrical considerations, for the purpose of defining unambiguously the position of an element within a 2-dimensional space, it is enough to have two PI sources, that do not coincide with a symmetry axis. All of the important morphological features (with the exception of left- right handedness) can be described in the space of this dimensionality. In many papers on amphibian embryology, one of these sources is identified with the vegetal pole (so-called Nieuwkoop’s inductive center) while another one with the dorsal blastoporal lip (so-called Spemann’s organizer). It is often postulated that these two centers create concentration gradients of certain substances which specify the position of any embryonic part and hence its developmental fate.

Is such a scheme compatible with actual embryonic regulation? We already know that the regulations are associated with topological transformations (e.g., rolling of a hemisphere into a closed sphere) which shift any arbitrary taken pairs of points into positions geometrically non-homologous to their positions prior to dislocation (Fig. 3). Consequently, all PI patterns referred to any pair of somehow specified points will be different in the case of the normally developed versus the regulated embryos. But this should be, according to the PI concept itself, incompatible with the development of regulating embryos. Certainly, this conclusion will be valid in all the cases when the number of PI sources greater than 1. We have to conclude that *embryonic regulation events are incompatible with the existence of any discrete pre-established sources of PI.* At the same time, the initial Driesch' idea that the *fate-determining positions of the elements should be referred to the indivisible whole* (rather than any discrete pair of elements) completely maintains its validity.

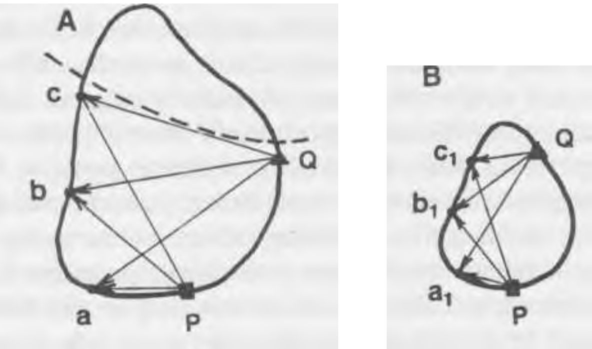

Figure 3. Embryonic regulations are incompatible with the assumption of any pre-localized material elements (say, P and Q, frame A) regarded as sources of a positional information (PI). After the dissection of a part upper to the dotted line (A) and closure of the wound (B) the positions of the elements P and Q (as well as all the others) will become geometrically non-homologous to the same elements' positions in A. As a result, any embryonic element occupying in A and B the homologous positions (say, a and a,, b and b_P c and c,) will perceive quite different PI signals. From the viewpoint of the PI concept (but not from that of the Driesch' law, if taking literally!) this is incompatible with embryonic regulations.

However (such is a common dialectic of a scientific development), very much contrary to Driesch's personal vitalistic views, any such kind of a whole- part relations can instead be perfectly based upon pure mechanics. For example, as pointed out by Martynov (1982), a flattened rotational ellipsoid covered by an elastic shell will produce a series of the vertical folds when stretched by an internal pressure and a series of the horizontal folds as a result of shrinkage. The number of the folds depends unambiguously upon the ratio of the long semi-axis to the shell's thickness, being thus a function of a mere shell's geometry, that is, of holistic properties of an inorganic body. Whether this model does or does not correspond to any actual morphogenetic phenomena, it shows the capability of mechanical forces to produce complicated, regular and geometry-dependent patterns without the need for any kind of PI in Wolpert's sense: no special PI sources are assumed to exist anywhere. On a similar mechanistic basis, Green et al. (1996) developed highly elaborated models of flower morphogenesis.

Let us take now hydroid polyps, one of the favorite objects of PI people, concerning which they usually postulate the existence of a PI gradient, oriented along the apico-basal direction in these roughly uniaxial organisms. They propose that all of developmental processes occurring in these species are functions of position within this gradient. But is such a gradient a real necessity? As shown elsewhere (Beloussov et al., 1989), the hydroids' morphogenesis is driven by the periodical cooperative osmotic swelling-deswelling of their cells, causing hydrostatic pressure pulses within cell layers. The pulses deform a visco-elastic membrane covering the rudiments. The entire shape-forming process roughly resembles the process of glass-blowing, in as much as both are effectively regulated by the pattern of pressure pulses: sudden brief pressure pulses produce narrow tubular structures while more prolonged blows lead to the creation of wide vessels with flattened bottoms. In hydroids the patterns of the pressure pulses are both species- and stage-specific and can be also modified experimentally (Beloussov et al., 1993).

As shown by modeling (Beloussov and Lakirev, 1991), these very same forces are sufficient for transforming even quite smooth initial shapes into much more complicated and realistic ones, the shell's elasticity and the patterns of pressure pulsations being the main ordering parameters (Fig. 4).

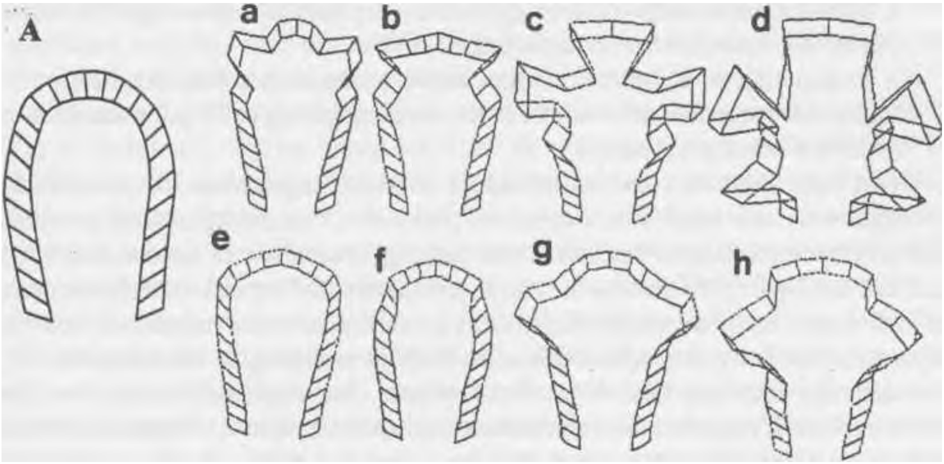

Figure 4. Modeling of hydranth's morphogenesis regarded as a function of a pulsating hydrostatic pressure within an epithelial layer. Leftwards is the initial shape (A), to the right are the modelled final shapes *(a - h).* Upper row *(a - d)* shows the shapes modeled under smaller elasticity coefficient of an epithelial layer, as compared with those shown in the lower row (e - *h).* Shapes *a-d* and e - *h* are arranged from left to the right proportionally to the growth pulsations' parameters (the extension/retraction ratios per pulsation). As a result, without using any kind of a positional information gradient a family of rather realistic shapes is obtained (from Beloussov and Lakirev, 1991).

Is there any need for PI in this construction? Should any element (a swelling-deswelling cell) “know” and, what is more, “interpret” its position within any gradient? We can see, that a realistic morphogenetic model can be built entirely without using such assumptions.

Our last example deals with a broad category of morphogenesis (mostly of Vertebrate embryos) which pass via stages of so-called columnarized cell domains: those include neural and sensory rudiments, along with as several others (columnarization means an extensive increase in the cell’s length/width ratio). These domains are formed in quite definite regions of the embryo, at specific definite periods of its development, and their linear (or 2-dimensional) extension is highly controlled. We will ask again, whether the formations of the domains imply PI, that is, whether an embryonic cell, before becoming columnarized, determines, independently of others, its position within a certain PI gradient and then behaves according to the “interpreted” position.

According to a model developed by Belintzev et al. (1987) the formation of the polarized cells’ domains out of an initially flat and homogeneous cell layer is regarded as a self-organizing process. It is triggered by a parametrical loss of stability of the initial homogeneity and (under certain parameters values) by local perturbations which have no need to be precisely localized.

Three main events are postulated to be involved here:

- a local (intracellular) bistable dynamics (a potential cell’s capacity to be either isodiametric or columnarized);
- a propagation of a columnarization impulse from one cell to another;
- an overall tangential tension of a layer, restricting each cell’s columnarization (this is a holistic property).

Not only does this model reproduce a stable segregation of an initially homogeneous cell layer into a columnarized and a flattened part, but provides also its scale-invariance.That means that the lengths relations of the columnarized and flattened parts are always the same, irrespective of the absolute dimensions of cell layer. In other words, the model (contrary to many others) is able to reproduce perfectly Driesch’s regulation without resorting to anything like PI, that depends upon any kind of localized sources. As mentioned above, even the perturbations, if required, can have rather vague localization. And each individual cell should not “know”, or perceive anything except the degree of its own columnarization and the amount of tangential tension throughout an entire layer. It is the interaction between the local and the global states (via propagating processes) that makes the whole play.

The common feature of all these examples presented above is that instead of vague and overburdened notions of “fate”, we introduce, for each next developmental step, quite definite physical values, for example changes in a local curvature (first two examples) or cell columnarization. We are also aimed to reproduce rather short, although finite, periods of development. Such are indispensable steps towards a general theory of morphogenesis.

5. Contours of morphogenetic fields

We hope that the above presented arguments are enough for accepting, at least in general, Version II while regarding Version I, in the best case, as a quite a particular solution. In other words, there is serious evidence for introducing in our picture of development the image of a spatio-temporal continuum of the developmental pathways, located both in the physical and in the phase space; this is just what we denote, in this context, as a morphogenetic field (MF). Now our next and the most principal step will be in removing from Fig. 2B the Demiurg, that is, in transforming MF into a self-organizing dynamic structure.

For doing this, we must explore firstly what should be a working body of the MF. Clearly, it should be a kind of an active medium, far removed from a thermodynamic equilibrium, opened for parametrization by the various slow and extra-slow variables, dependent upon an overall geometry of an embryo and, at the same time, structurally stable under a number of (mostly local) perturbations. This active medium should be interlinked (both in a space and in a time) by repeated non-linear feedback just permitting the development to go forth in a self- regulated way. In order not to fall down into the "instructionist" paradigm, the feedback relations should be as simple and uniform as possible.

Present-day biology knows two main candidates for such an active continuum: (1) a chemically active liquid medium characterized by a diffusion and by inhibitory and activatory feedback; (2) a mechanically stressed „active" solid body, with the similar feedback mediated by mechanical stresses. In no way one of these models excludes another, but the choice between them is nevertheless very important. In spite of some valuable conclusions firstly formulated in the terms of a chemical concept (this is, before all, the idea of a long-range inhibition and a short-range activation, see Meinhardt, 1982), it has some indelible properties of an "instructivisf ' approach, insofar it reduces the developmental processes to a set of specific reactions, largely non-isomorphic to the postulated chemical influences. On the other hand, the concepts which imply mechanics are much more unifying, less specific, more close to isomorphic ones and resonate better with the modem physical trends.

The mechanical stresses are indeed directly related to the shape changes to the extent the latter may be considered as the results of the stress relaxations. The evidences are given elsewhere (Beloussov, 1998, pp. 133-137) that a number of morphogenetic processes can be regarded indeed as "quasi-relaxations" of the stressed states. But how these latter are achieved? Is it possible to combine together the relaxational and the stress-generating morphogenetic tendencies within a common framework? Such an attempt has been made several years ago by Jay Mittenthal and me. We suggested, that an embryonic cell, or a tissue piece is able to memorize somehow its own mechanical stress value (S_Q) and while being shifted from it by any external force (either artificial, or generated by another region of the same embryo) tends actively to restore S_o but, by doing so, usually overshoots it to the opposite side. We have denoted this feature as a stress hyperrestoration (HR) and the whole concept as a HR hypothesis.

The elementary HR reactions (Fig. 5A, B) can go by different pathways, depending mainly upon the border conditions (see for details Beloussov et al., 1994). As to reaction A, the most ubiquitous way for its active branch (taking place when the tissue edges are firmly fixed) is associated with a cooperative columnarization of some cells and flattening of the others (a process described by Belintzev et al., 1987, model). In this way the relaxed cell layer is effectively re-tensed. Reaction B is going usually via so-called cell intercalation, that is, a mutual insertion of cells in the direction perpendicular to the stretching of a layer. After releasing the imposed tension (this is just what we defined as a quasirelaxation), cell intercalation produces a substantial pressure which gives a sample with at least semi-fixed edges either a dumb-bell or a segmented shape. In the both reactions, a shift towards left is associated with the increase of a symmetry order on the individual cell's level and its decrease on a holistic level (a relaxed cell layer produces a lot of irregular folds and a cell intercalation decreases the translational symmetry order). On the other hand, the rightwards shifts correspond to a symmetry decrease on the single cells' level (isodiametric cells are transformed into columnarized and oblique ones) and increase it on the holistic level (cell layer's borders are smoothed and aligned). Such an interlevel's symmetry exchange is a remarkable process noticed by theoreticians some times ago (Shubnikov and Koptzik, 1972).

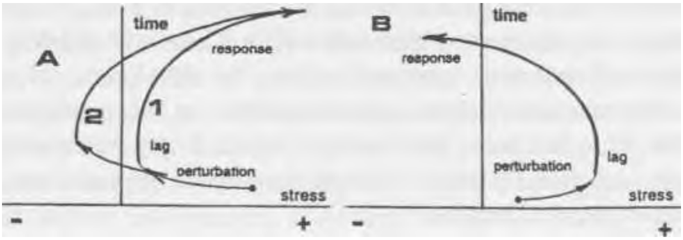

Figure 5. The loops of stress hyperrestoration. Horizontal axis: mechanical stress (positive are tensile stresses and negative are compression stresses). Vertical axis: time. In frame A loop 1 does not imply the compression of a sample while loop 2 passes via compressed state (as it takes place in hydroid polyps). For more details see Beloussov, 1998.

What is of a primary importance for MF theory, is that both branches of HR reactions are perfectly coupled with each other. This can be demonstrated in various ways. Firstly, one may expect the generation of stress auto-oscillations (“+, feedback): reaction A generates reaction B, and so on. This is similar to the model of the “cytogel” oscillations suggested by Oster and Odell (1984). That may take place when the entire mechanically isolated system is simultaneously involved into any one of the HR reactions. More realistic and wide-spread is the situation when just a part of a system is involved, at the given time period, into one of the branches of either A or B reaction. In such a way several kinds of morphogenetically important feedback can be produced. All of them obey the following general scheme: an active contraction generates in its vicinity a passive expansion, this latter is transformed (as a kind of reaction B) into an active, intercalation-like process which in its turn relaxes (or slightly compresses) the former contraction zone, stimulating its further contraction (reaction A), and so on. Such a contraction-extension feedback may be called the main algorithm of a MF since it is valid for all the levels, from single cells or cell membrane’ areas up to vast multicellular collectives. Being able to create regular structures even if starting from completely homogeneous initial conditions, it provides different results as depending upon more specific border conditions. For example, a slight curvature initiated by an external force will be actively enhanced because a stretched convex surface tends to relax stretching by a further insertion of a cell material, while a compressed concave surface will be contracted for restoring its initial tension. As shown elsewhere (Beloussov, 1998), a succession of the inter-coupled HR reactions may interprete, in a qualitative approximation, rather prolonged periods of morphogenesis. Such an interpretation is illustrated by Fig. 6. As a comparison, an instructivist (genocentric) version of the same developmental period is given in Fig. 7.

HR concept has multiple relations with a developmental time. It implies, that a given embryonic part has some memory about its mechanical past, combined with the perception of its present-moment mechanical state. This bom some interesting problems on the relations between “past” and “present” which go back to the Bergsonian “active memory”: “a cognition of all the efforts of the past laid down in present is certainly also a memory, but a memory... always directed towards action, settled down in the present and having into mind only future... Actually, it does not represent our past, it plays it through...” (Bergson, 1896). Such a memory can be regarded as a rudiment of purposeful behavior. Most probably, it is located within cell membrane and a cytoskeleton. Manipulating with stretching-relaxation of the pieces of amphibian’s embryonic tissues we have found that they need about 30 min for memorizing its newly acquired mechanical state: this is just the time required for these elements’ reconstructions.

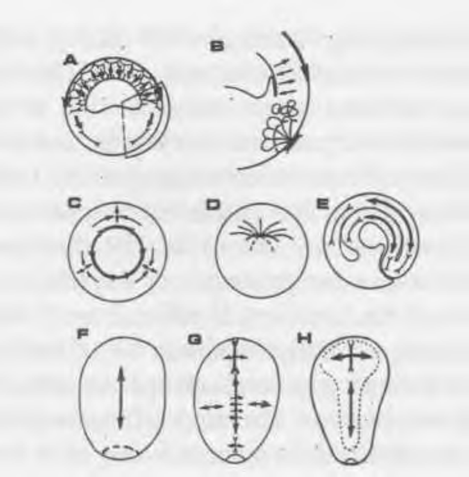

Figure 6. A-H. Development of an amphibian embryo from blastula to neurula stage interpreted within the morphogenetic fields framework, as identified with the fields of mechanical stresses. Emphasized should be the relations between passive stresses and active forces which are driving forth the development and provide its spatio-temporal specificity. The aim of this illustration is just to give an overview of such an approach. For detailed description see Beloussov, 1998.

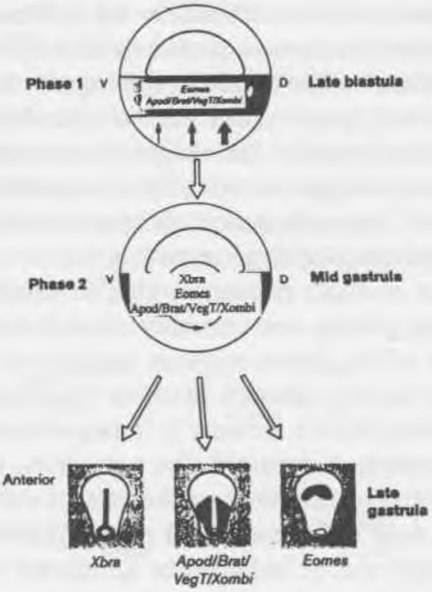

Figure 7. A more conventional, “genocentric” view of the same period of amphibians’ development as illustrated by Fig. 6. Now a researcher is interested in tracing a sequence of genes’ expression and in the diffusional gradients (shown by dense arrows, upper frame) without paying attention to the physical forces and to their spatio-temporal distribution, (from Stenrnard et al., 1997, modified).

Along with that, the duration of HR feedback is also of primary importance. Generally, the greater be the time duration of an active response the larger should be the arisen structure. On the other hand, almost never a HR feedback can be exhaustively characterized by a single characteristic time: usually it comprises more or less complicated spatio-temporal hierarchy. For example (Beloussov et al., 1999), the intercalation response to a stretch turned out to be at least bi-level: firstly, in 30 min after stretch there were just single cells to become elongated in the stretch direction and contracted transversely while in about 2 h later the reaction was reinforced by the transversely oriented cooperative cell movements. While the first response can be described in the single cells' coordinates, the second one requires a coordinate set firmly associated with an entire explant. Generally, within the course of evolution, the relatively short-time responses linked with small structural units are exchanged and/or supplemented by those with greater space- time values. Those are just the temporal characteristics of the HR reactions and other associated mechano-chemical events which are the real targets of the slowly varying chemical factors of morphogenesis, including the immediate products of a genetic activity, playing a role of the parameters.

6. What about phase space?

Up to now we were dealing with morphogenesis *per se,* that is, the process of cell movements and rearrangements, shape changes etc, all of them exclusively described within a physical (Euclidean) space. Besides these processes however the embryonic cells also undergo differentiation, that is, they can change a lot of their internal structural properties and produce special kinds of protein molecules due to activation of certain parts of their genomes. All of these processes are undoubtedly linked with morphogenesis and, consequently, with the fields of mechanical stresses: if the latter are perturbed, cell differentiation patterns become quite variable and imprecise (Yermakov and Beloussov, 1998). On the other hand, for being formally described, cell differentiation processes require N-dimensional phase space, which should be superimposed onto the physical one. In what way can the first one be organized?

One can hardly doubt that the crucial events of cell differentiation involve the activity of a so-called transcriptional level, that is, some modulations of a genome, non-associated with any irreversible changes of a primary DNA structure. Now our question will be: can the modulated states be identified with some stable regimes of a common "genomic field", or we are doomed instead to retain the traditional viewpoint regarding DNA as a mosaic of independent genes? In other words, we exploit again the Version I/Version II controversy, now within the genomic phase space.

Several recently obtained sets of data may be of interest in this respect. Firstly, Lima-de-Faria (1983) introduced the concept of the functionally different DNA domains and showed that thus defined nucleotide sequences are arranged along DNA strands in quite a rigid order. Next, we refer to exciting data demonstrating the fractal, that is, different scales' (including very large ones) correlations of DNA sequences. As argued by Havlin et al. (1995) such fractal correlations are mostly typical for non-coding sequences (introns), resembling thus "the disordered state of matter near critical point. On the other hand, coding sequences typically consist of a few lengthy [correlation] regions... resembling domains in the system in the ferromagnet state" (op. cit., p. 186). Let us remember that the introns are lacking in Prokaryota, poorly represented in Protista but are progressively developed throughout the evolution of Metazoa. This correlates with an increased improvement of the transcriptional regulation of cell differentiation. What might be the regulatory role of the introns? By the same authors, the number of the different energy minima within a polymer chain depends upon the periodicity (i.e., correlations) within the polymer's structure. Protein molecules, as being aperiodic, have only one global energy minimum. On the contrary, the intron-containing DNA strands may have many of them, arranged in a hierarchic order (due to fractal periodicity). Each one's accessibility will largely depend upon the previous "history" of the DNA strand, imprinted in its conformational changes. If suggesting that any epigenetically stable differentiated state corresponds to a certain energy minimum, we'll obtain a multilevel potential relief of a DNA strand very similar to that postulated for the morphogenetic field proper. The signals (perturbations) shifting the genome from one locally stable state to another may be, under these conditions, largely non-specific. Such are, for example, the mechanical factors known to affect genes' expression in a number of cell types (see, e.g., Opas, 1994; Jones et al., 1995; Chirurcel et al., 1998). These influences are probably mediated by a direct connection of the cytoskeleton's filaments with the nuclear matrix. In any case, such small influences can affect in a regular manner DNA organization only if the latter one is metastable.

7. Epilogue: enlarging the context

Let us return to our allegory of a button-pushing person, exemplifying Version I. Strange as it may seem, this miserable image has had quite powerful prototypes in human history. The Renaissance superman, a conqueror of an alien world as well as Goethe's Faust changing his entire life in an unnatural way were among his precursors. In common for all of them is the artificiality of their living pathways, their alienation from the natural and historical surroundings and the desire to change these in a forcible way. Totalitarian ideologies, ecological catastrophes and a feeling of solitude are among the consequences. Is it then the only model, or at least the mostly effective model of life for creative persons?

History and psychology of art better argue for the opposite. The greatest artists of all the times, by their own evidence, felt themselves much more as mediators, evoking from the surrounding space-time certain latent voices or images (non-apprehensible for the ordinary people), rather than the authentic inventors of their masterpieces. True, the classical masters did not like to show us the very process of such an evoking of harmonies from a sound space, feeling themselves obliged to expose to the listeners only the final, highly ordered results. But some exceptions can be found, and probably the most important ones are the last Beethoven Sonatas. Remember for example, how a celestial, and a very definite *Arioso* theme from the 31st Sonata has emerged out of a fluctuating uncertainty of the preceding *Adagio, ma non troppo',* or, on the opposite, how a C-dur leitmotive from the 32nd Sonata is plunged gradually into an all- enveloping sound web. XX century artists are more open in this respect. Two interconnected figures of Russian art can be mentioned here: the composer Alexander Scryabin, and his admirer and follower, the poet Boris Pasternak. Most of Scryabin's music, especially from his late period, is just the evoking and then a rapid decline of different voices raised from an Eternal Chaos, as he himself commented in the lines preceding his 5th Sonata:

> I appeal you to a life, you hidden aspirations!
> You, drowned in dark depths of a creative spirit,
> You, timorous germs of life,
> I bring a daring to you!

And 50 years later Boris Pasternak, who worked during all his life, according to an acute remark of a critic (Bezrodny, 1996), “at the verge of a sound and a noise” appealed to his reader “to live without imposture” in order to attract “the love of space”.

Doesn't all of this fit only the world model of Version II, with its fluctuating space-temporal continuum being the source of all the organized structures? Could it be, that the artists recognized this intuitively much earlier than (or independently from) the scientists, who approached the same conclusions in the modem theories of a physical vacuum, or in the concepts of morphogenetic field? And isn't it also possible, that such a view brings us to a much more deep and optimistic concept of Freedom (as a selection between multiple pathways, all of them being in harmony with the fundamental space-time properties) as opposed to the opposite concept, identifying Freedom with “all permitted”?

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