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Self-Organization, Symmetry and Morphomechanics in Development of Organisms

Lev V. Beloussov
Department of Embryology, Faculty of Biology Moscow State University
Russia

1. Introduction

This chapter may look strange for a text-book. While the usual text-books expose firmly established facts and theories, the main aim of this essay is to tell about what we *do not* know and *do not* understand and to show that this "dark area" is probably greater than the elucidated one. No less strange may look that our arguments are based to a great extent upon the data obtained long ago and for many times described but, as we try to argue, up to now adequately non-interpreted. On the other hand, the main pathway which we suggest to move along, that is the application of a self-organization theory to developmental events, is missed in conventional text-books. Taking into consideration a strange genre of this essay, the author have to apologize the potential readers for its inevitable shortages: some points may be discussed too briefly, while others too much emphasized. Nevertheless, my goal will be achieved if just single readers will realize that in the science about organic development much more than some small details are unknown and unexplained; and that the young generation of researchers has ahead a fascinating field for further studies.

2. Do we understand development?

Being an aged Professor of Moscow State University, within several decades I am reading Embryology lectures for a large class of Biology students. I was a witness of an exciting transformation of this science (which, in the hope to look more modern changed its traditional name to "Developmental Biology") from a minor and poorly known affiliation of zoology or histology to a powerful and highly respectable branch of life sciences, closely linked with genetics and molecular biology and becoming an indispensable part of stem cell research, regenerative medicine, and so on. At the first glance, everybody even to a small extent related to this science should be proud of its achievements. But nevertheless, several times during my lecture course I feel myself uneasy with my students, as if I do not tell them the whole truth. And the truth is that, in spite of all the technological achievements, we the specialists do not understand the development of organisms not so much in details, as in its main outlines. Yes, we can produce by our willing in artificial conditions some types of cells and multicellular structures, but we have to take these and other results as given, without really explaining them. Actually, we cannot answer a question which looks naïve,

but is actually very deep: *why in the course of normal development a given stage* (that is, a given set of embryonic structures) *is exchanged by another one, no less definite; or why, what looks even more miraculous, a variable set of structures comes towards quite a definite end-result* (Fig. 1).

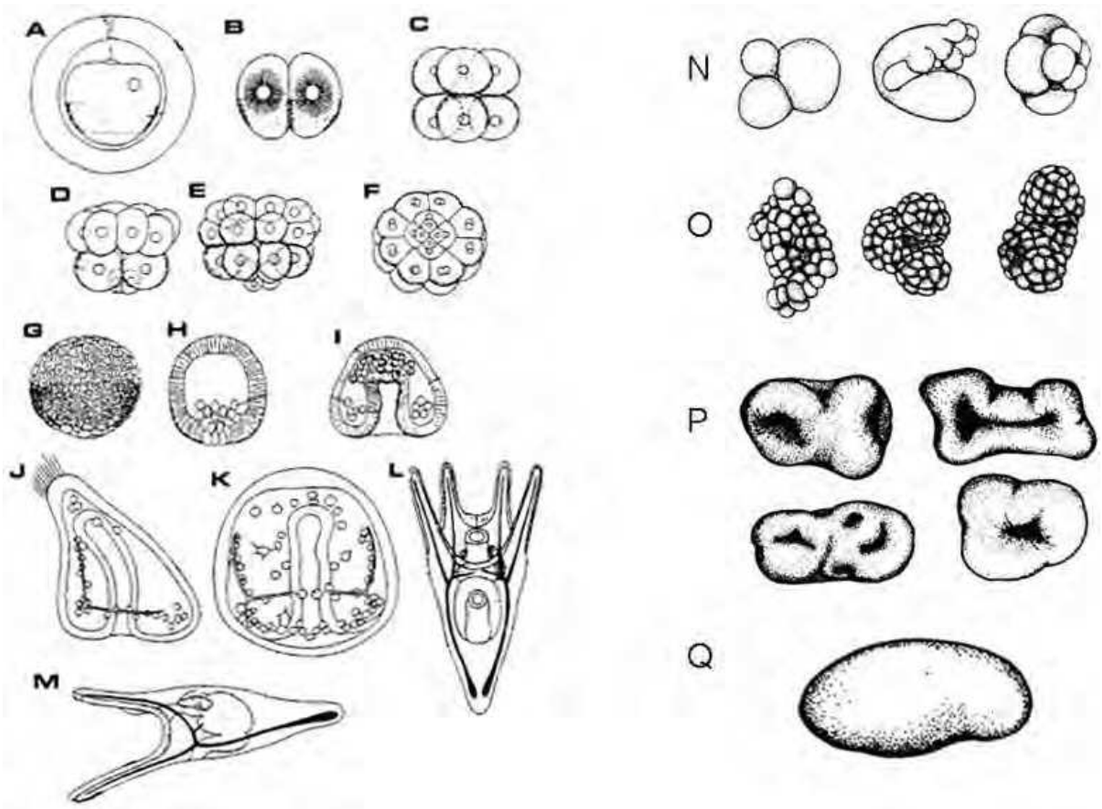

Fig. 1. Two examples of developmental successions. A-M: succesive stages of sea-urchin development.In this case the structure of each next stage is strictly determined. N-Q: development of a hydroid polyp from a cleaving egg to larva stage.The early and intermediate stages (N-P) have quite a variable structure, but the end-stage Q is the same in all the cases (From Beloussov, 2008).

True, a response to a question "why" which can satisfy us is itself in no way definite and unambiguous, especially in biology. If you ask, why a given embryonic structure is appeared at this time and location, at least three different kinds of "explanation" can be given.

First, some people will be satisfied by claiming that a given structure is arisen here and at that time moment because this is required for fulfilling its subsequent physiological functions, and/or obtaining some selective advantages, and so on. All such statements, which exchange the question "why" by "for what purpose" belong to so called teleology – a view which is looking into future for finding the reasons for what has happened just now or in the past. Teleology cannot be completely withdrawn from life sciences –for a biologist to look for goals is a respectable business. However, if we want to follow the main way taken by other natural sciences, we have to search the answers to the "why" questions in the immediate past of a given event, rather than in its future.

Just this idea became a basis for a classical causality, which is often called Laplacian, because it was formalized by the great French mathematician Pierre Simon Laplace at the beginning of XIX century and was considered for a long time to be the only one compatible with a real science. By this approach, the main aim of a science is to analyze the observed world to such an extent that it could be presented as (being split to) a chain of one-to-one cause-effects links, a single cause being able to produce no more than one event. The main task of investigator is to compile a complete list of the causes. If fulfilling this task, the surrounding world will become completely predictable: nothing new (unexpected) can happen in it.

Paradoxically, the Laplacian approach became, in the course of time, much more deeply rooted in biology, than in physical sciences, which Laplace had into mind. In particular, it has been introduced in embryology by the German embryologist Wilhelm Roux already at the end of XIX century. Up to now it remains to be the leading ideology of this science (although most of experimenters do not even suspect this).

Meanwhile, in physics since Galileo and Newton times another approach, which may be called law-centered one, took the leading positions. In a certain sense, it is opposite to the causal one, although the both developed hand by hand. While classical causality is directed towards detalization (by splitting a world into a set of as detailed as possible cause-effects relations), the law-centered approach tends to generalize, by establishing *invariable* relations between as much as possible events. For example, if two physical bodies are moving along different trajectories, this approach invites us to formulate a common law describing the both movements, while if following the classical causality we should search the specific causes for each of the movements, and even for the small parts of the trajectories. It was the law-centered approach who gave to the physical sciences a predictive power, that is, any power at all. Our main question will be - should we use this approach in developmental biology, or we are completely satisfied by a classical causality? The answer will depend mainly upon whether the successions of developmental events are underlain by perfect causal chains, determined in all their links. Let us look, whether this is the case. In doing this, we shall explore the possibilities of two mostly used versions of a causal approach. The first one claims, that the main causes of the developmental events are genes, while another ascribes a leading role to the influences of the earlier arisen embryonic structures upon the subsequent ones.

A genocentric approach seems, at the first glance, firmly substantiated, because the genes, or, if speaking more precisely, so called signaling pathways, that is the relays of protein-protein interactions, triggered by so called ligands (in most cases, products of genes activity) and switching on other genes are indispensable participants of virtually all the biological processes, including developmental ones. If blocking (knockouting) certain genes and/or signaling pathways, many developmental events will be abolished and distorted. Does it mean however that there exists one-to-one relation between a gene/signaling pathway on one hand and a given embryonic structure on the other?

Many years ago the biologists believed, that this was just the case. One of the milestones of a first half of XX century biology was a claim: “One gene – one character” (a character was taken at that time as something static, related to an adult state). More recently, however, when the amazing technical progress permitted to trace the expression of single genes in the course of development, quite unexpected results have been obtained: it turned out that the

products of activity of the same or closely homologous genes and/or the same signaling pathways were involved in quite different developmental events and vice versa. Text-books in developmental and cell biology are full of such examples. Here are just few of them:

- "The interactions betweeen 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, 2010).
- The transcription factor Pax-6 is expressed at different times and at different levels in the telencephalon, hindbrain and spinal cord of the central nervous system; in the lens, cornea, neural and pigmented retina, lacrimal gland and conjunctiva of the eye; and in the pancreas (Alberts et al., 2003).
- In Drosophila embryos a gene Engrailed is involved in segmentation of a germ band, development of intestine, nervous system and wings. In mouse same gene participates in brain and somites development. In Echinodermata it takes part in skeleton and nervous system development (Alberts et al., 2003).
- Delta-Notch signaling pathway regulates: neuro-epithelial differentiation in insects, feather formation in birds,fates of blastomeres in Nematodes, differentiation of T-lymphocytes etc (Alberts et al., 2003).
- Hunchback gene is involved at the early stage of Drosophila development as one of so-called gap genes and at the later stages participates in development of neural system.

By summarizing: if we know everything about the genes/signaling pathways being in work in the given space/time location, we can tell nothing about what embryonic process is going on, and vice versa. This is enough for concluding that the genes/signaling pathways in spite of all their importance cannot be considered as "causes" of development; much better to say that they are tools, which can be utilized by a developing organism for quite different purposes. Certainly, the tools deserve to be studied, and such studies can be very important and useful, but they do not help us to answer our main question. Accordingly, the results of our studies will have no predictable power – we are doomed to investigate each next experimental point separately.

Let us pass to the second version of the causal approach, ascribing the main role to the interactions between embryonic rudiments. Just this version was used by Roux and his followers.

The first task which Roux decided to solve by his approach was a long standing controversy between two general views upon development. The first of them, called preformism, claimed that each structure of an adult has its own material representative from the very beginning of development, the latter being localized somewhere inside an egg or spermatozoon. By this view, from the very beginning of development an embryo is no less spatially complicated than the adult organism. The alternative view, called epigenesis, negated this idea, suggesting that an early embryo is less complicated than the advanced one, and may be even homogeneous. Roux attempted to resolve this alternative by dividing an embryo into parts: if the preformism were true, an isolated part of embryo will produce, under subsequent development, nothing else than that set of organs, which will be normally produced from this very part; if, meanwhile, a part, after its isolation, will produce another or, moreover, the larger set of organs, preformism should be rejected. Roux himself performed this procedure by killing one of two first cells (blastomeres) of a frog egg with a

heated needle. As a result, the remaining blastomere produced roughly a half of embryo. It looked, as if preformism was true. However, such a situation lasted less than for a decade. Several years later another German embryologist, Hans Driesch, separated the blastomeres of another animal, sea urchin, by more delicate technique: by using sea water lacking calcium ions he separated the blasstomeres, but kept all of them alive. The result was quite another: each of two first blastomeres, and even each of the first four ones gave rise to *entire, almost normal embryos* (although of a correspondingly diminished sizes), rather than to the parts which had to be normally developed from the isolated blastomeres (Fig. 2). This effect was called *embryonic regulations*.

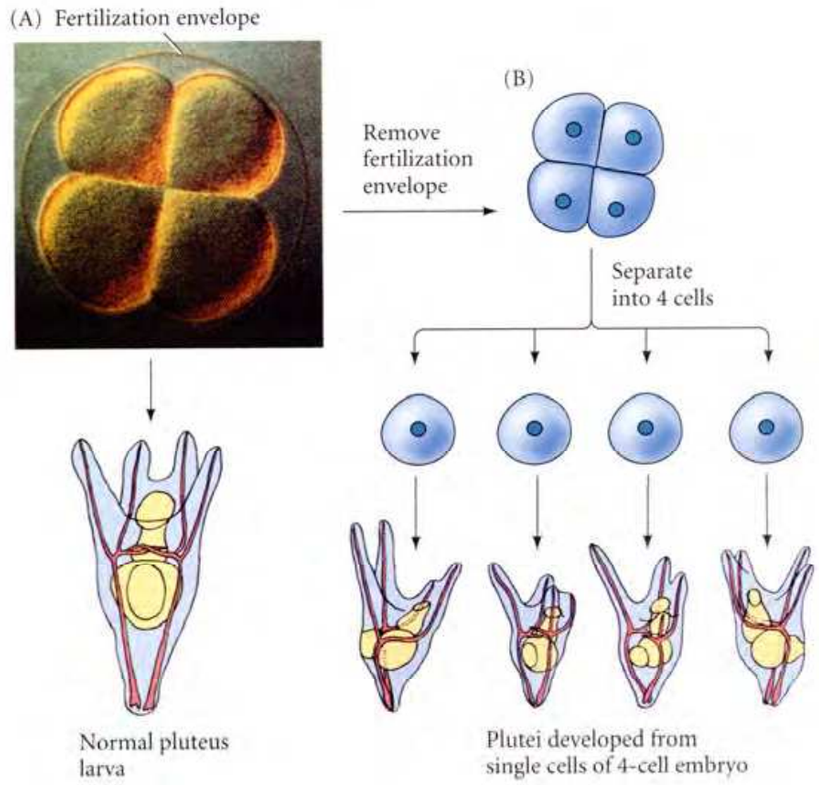

Fig. 2. A scheme of Driesch's experiment demonstrating embryonic regulations: so-called plutei larvae developed from the single blastomeres separated at 4-cell stage have roughly the same structure (at the diminished size) as the normal larva (from Gilbert, 2010, modified).

A similar result was obtained in another set of Driesch experiments, in which the blastomeres were rearranged (changed their neighbors). In spite of rearrangement, the subsequent development was going in a normal way. Since Driesch times, hundreds of such experiments have been performed at the different animal species and stages of development, obtaining in general (if omitting details, unnecessary in out context) quite similar results.

What should we derive from these experiments as related to the concept of one-to-one causal chains?

If we continue to assume that each structure of an adult or of an advanced embryo possesses its own causal chain traceable from the very beginning of development, embryonic regulations enforce us to conclude that each one of say four blastomeres contains at the same time ¼, ½ or a full set of the causal chains and, moreover, the portions of these sets contained in the same blastomere may be different in the different experiments. Taking into mind, that a blastomere "do not know" in advance, whether he will be isolated or not, and what neighbors will he have, we have to accept that embryonic regulations make the idea of one-to-one causal chains contradictory and absurd: at least during the developmental period when the regulations are taking place, any causal chains should be smoothed and lost.

Besides embryonic regulations, there are also other arguments against the existence of one-to one causal chains. One of the main ones is a so-called equifinality, illustrated by Fig. 1N-Q. It is the attainment of the same end-result of development by quite various, sometimes purely stochastic developmental pathways. A stochasticity of embryonic processes firstly emphasized already a century ago by the Russian biologist Alexander Gurwitsch, looks to be a background of many morphogenetic events, first of all those associated with branched rudiments (blood vessels, lungs, leaf veins). These structures are of a fractal nature and are hence generated in chaotic regimes, to which the notion of specific causes is completely inapplicable.

Now let us look, what conclusions from his experiments made Driesch himself. He expressed them in a laconic statement, known as Driesch law: "A fate of a part of embryo depends upon its position within a whole" [let us add: rather than upon its internal properties].

By this formulation Driesch wanted to interpret embryonic regulations in the following way. At the first step, the shape of a normal early embryo is in rough outlines and in diminished size restored. Next, each cell of a regulated embryo "recalculates" its position according to its coordinates within a new "whole" and develops according to this recalculated position, rather than follows its normal destiny. Formally such interpretation may be true, but several important questions remain unanswered. First of them is: by what means a roughly normal shape of an early embryo is restored? This process is not explained by Driesch law. Moreover, well after Driesch it was shown that a normal shape can be restored from the cells arranged in a completely chaotic manner (Fig. 3). The second question is: what are the

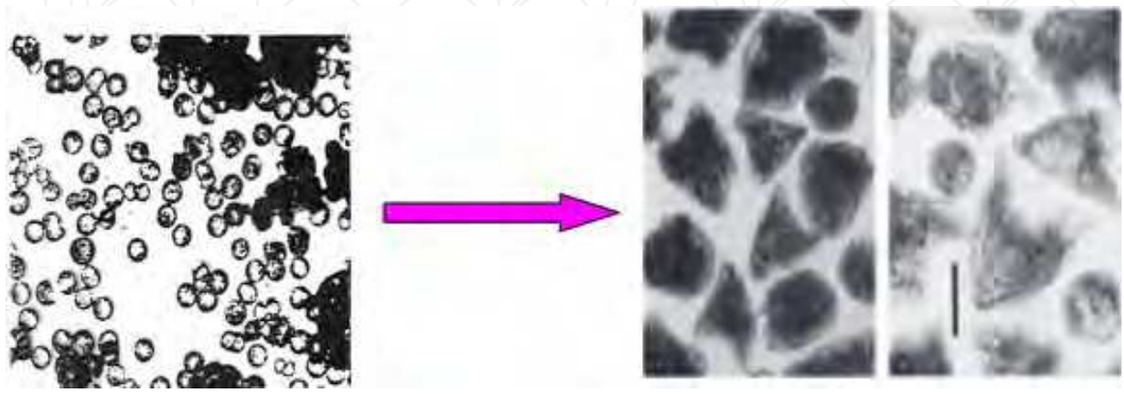

Fig. 3. Normal sea-urchin larvae can arise from completely random aggregations of embryonic cells.

reference points for the recalculation procedure? Driesch formulation – "according to a whole"- is too vague, although, as we'll see later, such a vagueness has its own justifications. Meanwhile, in a new and a most popular version of Driesch law – a concept of "positional information" (PI) (Wolpert, 1996) - the answer was another: cell positions are referred to certain special predetermined points, often defined as "sources" and "sinks" of some diffusible substances, the morphogenes. But it is easy to demonstrate that the existence of such predetermined points is incompatible with embryonic regulations. The matter is that under either partial removal or rearrangement of embryonic material all of its elements (including those which are suggested to be the reference points) take the positions, geometrically non-homologous to those occupied by the same points in normally developing embryos (Fig. 4). Moreover, so far as the early embryos are capable to

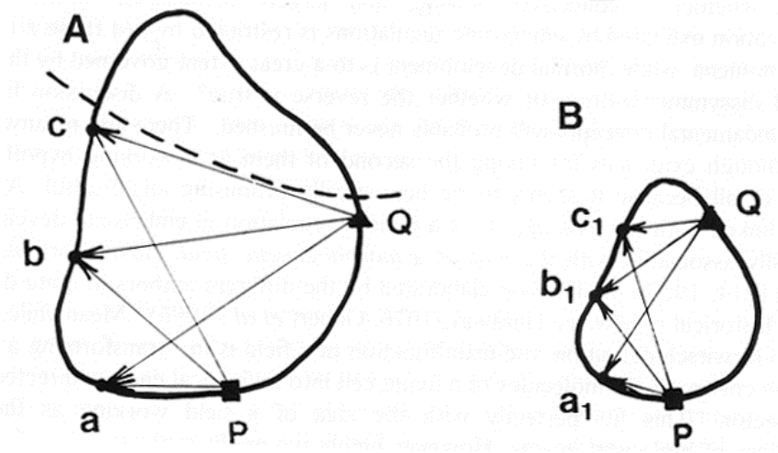

Fig. 4. Embryonic regulations are incompatible with the assumption of any prelocalized specific material elements (say, P andQ), regarded as the sources of a positional information (PI). After the dissection of an embryo part upper from a dotted line shown in A and closure of the wound (B) the positions 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 points of an embryo which occupy in A and B homologous positions (say, a and a1, b and b1, c and c1) will perceive quite different PI signals which is incompatible with embryonic regulations (from Beloussov, 1998).

regulations after the removals and rearrangements of quite different embryonic areas, any predetermined elements will take in different experiments quite different (but each time geometrically non-homologous) positions. Consequently, we have only two formal possibilities to "save" a concept of predetermined reference points: either to suggest that such a role is passed each time to the elements, occupying geometrically homologous positions, or to assume that *all* the elements of a partial or normal embryo play a role of the reference points. However, the both versions (out of which the second one looks more consistent) imply that either only the reference points or even all the embryonic elements should somehow "feel" the shape of a whole. Here we see that a vagueness of the Driesch formulation had its reasons: intuitively he felt that the regulations which he discovered cannot be explained without implying the action of something related to irreducible whole to the minor elements. In his time, when the Laplacian determinism still was in full power, such a claim looked as something inappropriate for a real science. Today it is impossible to

negate such things; moreover, the verbal expressions like "top-down causation", "emergent behavior" and "context-dependency" have been coined for describing them. However, mere words are not enough; what we need is a coherent law-centered theory explaining the arising of complexity, holistic regulations and so on. Remarkably, such a theory has been emerged already several decades ago quite outside of biology as a result of convergence of several branches of mathematics and physics. This is a self-organization theory (SOT). Before addressing to SOT directly, we must however get some knowledge of another topics – a symmetry theory (even irrespective to SOT it is very useful for any biologist).

3. Elements of a symmetry theory as related to development

In short, a symmetry theory is dealing with invariable transformations of geometric bodies, that is, with those kinds of movements which superpose a body with itself. The emphasis upon invariability makes this theory closely related to the very essence of law-centered approach.

We'll restrict ourselves to the elementary part of a symmetry theory, which is dealing with three kinds of movements: rotations, reflections and translations and explore some simple examples. It is easy to see, for example, that a rectangle superposes with itself under rotations around its center to 90^0, 180^0, 270^0 and 360^0 (that is, in four positions), a regular triangle do the same under rotations to 120^0, 240^0 and 360^0 (3 positions), while a disc superposes with itself under rotation to an infinite (∞) numbers of angles. A number of positions superposing a body with itself is defined as an *order of symmetry* (in the above cases it is a *rotational* symmetry). If, as in the case of a disc, the number of such rotations is infinite, one speaks about a *power* of a symmetry order. Passing from 2-dimensional disc to 3-dimensional sphere, we obtain a rotational symmetry power ∞/∞, what means that the rotations may go around an infinite number of central axes intersected at any angles.

The bodies possessing any order of a rotational symmetry may have or not have *reflection* (mirror) *symmetry*, its plane denoted as *m*. Thus, a combined rotation/reflection symmetry of a sphere is $\infty/\infty \cdot m$. The bodies having no mirror symmetry at all can exist in two mutually reflected modifications, which can be arbitrarily defined as left and right.

The *translational* symmetry is that of linear repeated patterns. Its order is characterized by a smaller linear shift *n*, which superposes a shifted pattern with non-shifted one. If a pattern is homogeneous along the shift direction (*n* is infinitesimal), the translational symmetry order is ∞.

After learning these definitions, we can easily see that the development of an egg towards the adult state is associated with a stepwise reduction of symmetry order (or a series of symmetry breaks, as is often told). Thus, an egg before the establishment of its polar axis has a symmetry order of a sphere ($\infty/\infty \cdot m$), after the axis establishment it is reduced up to $\infty \cdot m$, while after determination of a saggital plane (into which the antero-posterior axis of a future organism is located) it becomes $1 \cdot m$ (we ignore a right-left asymmetry, which is of a molecular origin and seems to persist throughout the entire life cycles without any fundamental perturbations). The development of advanced embryos is mostly associated with reduction of a translational symmetry order, that is, with establishment of the finite (rather than infinitesimal) *n* values. Most obvious examples are the formation of mesodermal somites out of a roughly homogeneous cell mass, or a subdivision of an initially smooth neural tube into brain vesicles.

We pay so much attention to symmetry breaks, because they are closely associated with the entire problem of causation. This linkage has been formulated by a classical principle claimed by the French physicist Pierre Curie exactly at the time when Driesch made his regulations experiments (although the both scientists did not know anything about each other). In his principle, Curie gave for the first time a strict definition of an effect and its cause. By his idea, any observable event is associated with the reduction of a symmetry order (by his words, "This is a dissymmetry, which creates an event"). Next, by Curie principle, no symmetry break can take place spontaneously, that is, without a somewhere located "dissymmetrizer", an object with the already reduced symmetry order. It is a dissymmetrizer, which fits a notion of a "cause".

By applying this concept to developmental events, we have to conclude that any step of the above mentioned symmetry breaks, according to Curie principle, demands a dissymmetrizer, located either outside or inside of an entire egg/embryo. Let us start from the earliest developmental events. At the first glance, they require external dissymmetrizers. For example, an egg polarity in the eggs of brown algae can be established by a directed illumination of an egg and the polarity of many animal eggs by the surrounding structures of an ovary. The position of a saggital plane in amphibian eggs is determined by the point of a sperm entrance, and so on. However, very accurate observations have shown, that the external agents are not necessary: the algae eggs acquire polarity under absolutely isotropic illumination and amphibian eggs can select a plane of saggital symmetry out of an infinite bunch of planes even in the absence of a spermatozoon (parthenogenesis), or if it was inserted accurately into the egg pole (where it cannot act as a dissymmetrizer).

Even less are the chances to find any dissymmetrizers for the events taking place in more advanced embryos. Here, as known from embryology text-books, in very many cases one rudiment plays a role of a so called inductor which triggers the development of another one, and in most cases this process is directly or indirectly mediated by chemical agents, emitted by inductor. Usually the inductors are regarded as the "causes" of the induced organs formation, but is it so in the terms of Curie principle? It is easy to show, that virtually in all these cases the symmetry order (as a rule, translational) of an induced morphological structure is considerably reduced in relation to that of an inductor; for the cases of purely chemical induction this is obvious without any comments. In the terms more customary for biologists this means that the morphological structure of an induced rudiment cannot be derived in one-to-one manner from that of an inductor: certain factors, increasing the complexity of the induced organ and non related to inductor itself should be involved.

In general, both embryonic regulations and symmetry breaks without dissymmetrizers leads us to conclude, that in the course of development more complicated (less symmetric), although if perfectly ordered entities are emerged from less complicated (more symmetric) ones. This is incompatible with a classical causal approach, but perfectly fits to what is called self-organization. Is such a process unique for the living beings?

4. Self-organization in inanimate matter

Already more than century ago the first examples of the similar events proceeding in non-biological systems has been described by the French physicist Benard. This was the formation of cell-like structures (Benard cells) from a homogeneous viscous liquid,

intensively heated from below (Fig. 5A, D). These structures immediately disappeared after heating was stopped, or became less pronounced. As proved later by one of SOT founders, Ilya Prigogine, these structures appeared because under enough intense flow of energy the convection streams (upward shifts of heated liquid particles and downward shifts of the cooled ones) pass from a random to so-called *coherent regime*, characterized by collective movements along some common trajectories which became now energetically more advantageous than the random movements along individual tracks (Fig. 5B, C). What we see here is a real emergence of an ordered complexity from a homogeneous state or, in other words, a spontaneous (non-embedded from outside) reduction of a symmetry order: the initial infinite order of a translational symmetry is reduced up to that of *n* order, where *n* is a Benard cell diameter.

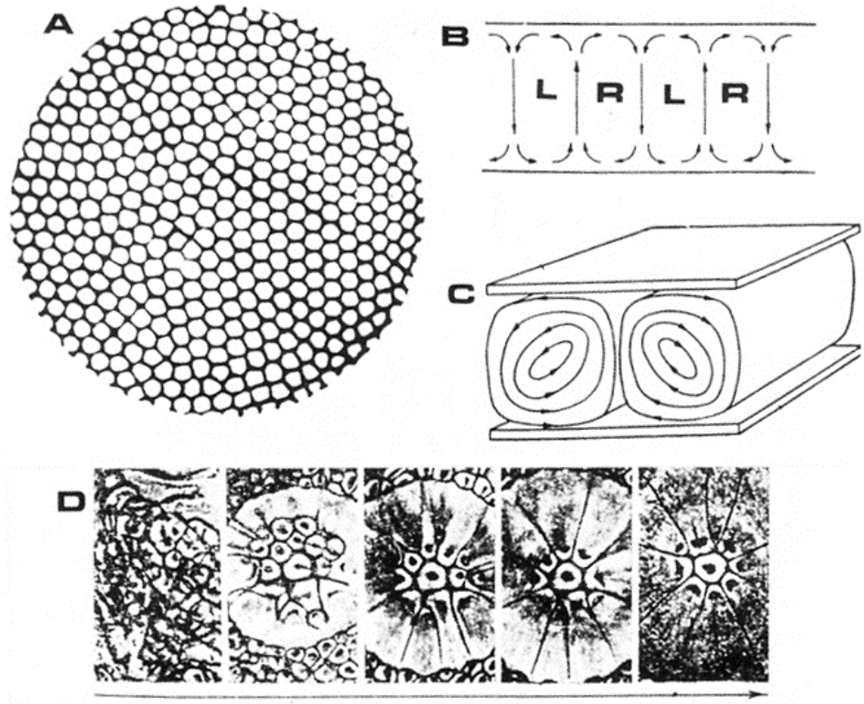

Fig. 5. Benard cells. A: general view from the top. B, C: schemes Of coherent convection streams. D: evolution of Benard cells patterns under constant heating (from left to right)

While the phenomenon of Benard cells formation did not pay much interest and was not considered as a breakthrough event, quite another was a public reaction to the occasional discovery of a fluctuating chemical reaction by the Russian chemist Boris Belousov in 1950ieth. Although firstly it was rejected by the editorial board of a scientific journal (the referee wrote that it violates the second law of thermodynamics and hence should not exist) very soon an entire research team from the Institute of Biophysics, Russian Acad. Sci. extensively elaborated this reaction, transformed it into space-unfolded "autowaves" and gave its complete theory. Because of its vividness, the reaction became very popular throughout the world: everybody could see that within a couple of minutes a series of ever complicated spiral waves appear from "nowhere", that is from a completely homogeneous state (Fig. 6).

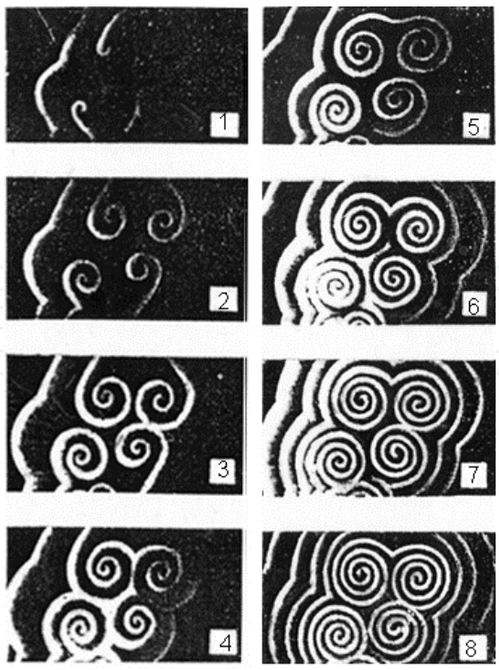

Fig. 6. Successive structures (1-8) arisen during Belousov-Zhabotinsky chemical reaction.

5. A theory of something emerged from nothing

Now we'll give a very brief and elementary review of SOT principles (for much more complete, but still popular SOT account see Capra, 1996; for a developmentally related account see Beloussov, 1998). Let the readers only slightly familiar with math be not afraid: the math will be minimal. As other great specialist in this field, Rene Thom said – "this is not the math, this is a mere drawing". Our drawings will be also minimal – most will be expressed by words.

The first point to be noticed is that contrary to classical mathematics, SOT is about a real world, which is full of so called unexpected perturbations, or a noise. Without noise none of the effects, predicted and described by SOT, will take place. For us biologists this is quite obvious: all the organisms are living in a very noisy world, which they have to resist and/or assimilate, preserving their individual, or a species-specific way of living. Such a property of a dynamic, or functional (not static!) resistance is also one of the main components of a self-organization. It is called robustness. All the natural systems are to a certain extent robust – otherwise they would not exist at all. However, robustness always has its limits, and when they are exceeded, a system abruptly passes into another state, which is as a rule also robust.

Let us express the above said by mathematical symbols. We shall see that such a transformation will very much clarify what was told before. Our main tool will be differential equations, firstly one variable linear, and then two variables nonlinear ones. Why is it necessary? The matter is, that even the simplest differential equation like

$$dx/dt = kx \tag{1}$$

has the following properties, lacking, say, in algebraic equations:

1. It describes a process, rather than a static state;
2. It contains a feedback loop: not just the right part variables affect the left part ones, but vice versa as well. The feedback may be either positive, or negative, or, in the case of two variables equations, positive-negative (±). The latter is mostly useful for self-organization.
3. Most important in our context: differential equations combine the values of quite a different order - *dx/dt* is an infinitely small part of *x*. Thus, *x* represents a whole, while *dx/dt* its small part. Correspondingly, the action of *x* upon *dx/dt* is the action of a whole upon its parts. Just formally, differential equations imply a holistic causation, which we beforehand derived from experiments. .

Let us now add a free member "*-A*" to eq. (1), obtaining

$$dx/dt = kx - A \tag{1a}$$

and make a graph (Fig. 7A), depicting by arrows the directions of *dx/dt* . We'll get what is called the vector field (in this case 1-dimensional). Owing the presence of a free member, we have a stationary point $dx/dt = 0$ at $x = A/k$, from which the vectors *dx/dt* are *diverged*. Correspondingly, if we reverse the signs of the right part members, getting

$$dx/dt = - kx + A \tag{1b}$$

the vectors will be *converged* towards the point with the same coordinates (Fig. 7B). This is enough for coming to the main notions of SOT: those of a dynamic (or Lyapunov) *stability/instability*. The solution (stationary point) in eq (1a) is unstable, because any infinitesimal shift from this point will bring us away without any chance to return back. On the contrary, in the framework of (1b) equation after any shift we'll come back to the stationary point, which is unlimitedly stable. We call this kind of stability/instability dynamic because it relates to the variable *x,* which dynamics is just traced in the equations. Besides these *dynamic variable(s),* in all the equations another kind of values is always present and plays a leading role: those are so called *parameters*, which either do not change at all their values, or change them in an order more slowly than the dynamic variables. A distinction between dynamic variables and parameters is very important, because it relates to the fundamental concept of the *structural-dynamic levels*. This concept, belonging to so called systems theory, claims that a surrounding world (both animate and non-animate) is stratified into a number of more or less discrete levels distinguishing from each other by characteristic times (Tch) and characteristic dimensions (Lch) of the related events; the both hierarchies are, as a rule, roughly parallel to each other. In this language, the parameters, at least by Tch criteria, should be attributed to a much higher level than the dynamic variables. As concerning Lch it is crucial that in the developing organisms the dynamic variables are always the collective entities: all the developmental events are based upon the action of many cells, or many molecules, occupying different positions. As a rule, all the members of this collective share the same parameters values (otherwise this would not be a common system). Correspondingly, the area of the parameters action (the parameters Lch) is also greater than Lch for each one dynamic variable.

In eq (1a, 1b) the parameters are represented by *k* and *A* values. Even in these simplest equations they are playing the main role and, remarkably, do it in quite a robust manner. Namely, there are the signs (+ or -) rather than the absolute values of the both parameters

which decide whether the solution will be stable or unstable: it is easy to see, for example, that only eq (1b) rather than (1a) has stable solutions. At the same time, in the immediate vicinity of $k = 0$ just very small shifts of k values are enough for switching a solution from stable to unstable, and vice versa. In other words, in relation to the shift of, say, parameter k eq (1) is unstable at $k \approx 0$ and stable in all the other areas. This is another kind of stability/instability, which is called *parametric*, or *structural*. A notion of a structural stability very adequately represents such biological realities as, for example, a morphology of a taxon, because it reflects at the same time a preservation of a general "Bauplan" and some considerable, but nevertheless limited fluctuations.

The notions of stability/instability (both dynamic and parametric) and their regulation are of a primary importance for understanding the developmental transformations and their relations to causality. When we notice, as mentioned above, that at least some of the symmetry breaks look to be proceeded "spontaneously", this actually means that the preceded symmetry order has lost its dynamical stability and hence can be broken by negligibly small perturbations (of a noise intensity), to which a developing organism is insensible during stable periods. By the way, this means that Curie principle formally keeps its validity during instability periods as well, but at that time the "causes" are so small that cannot be distinguished from the ever presented noise.

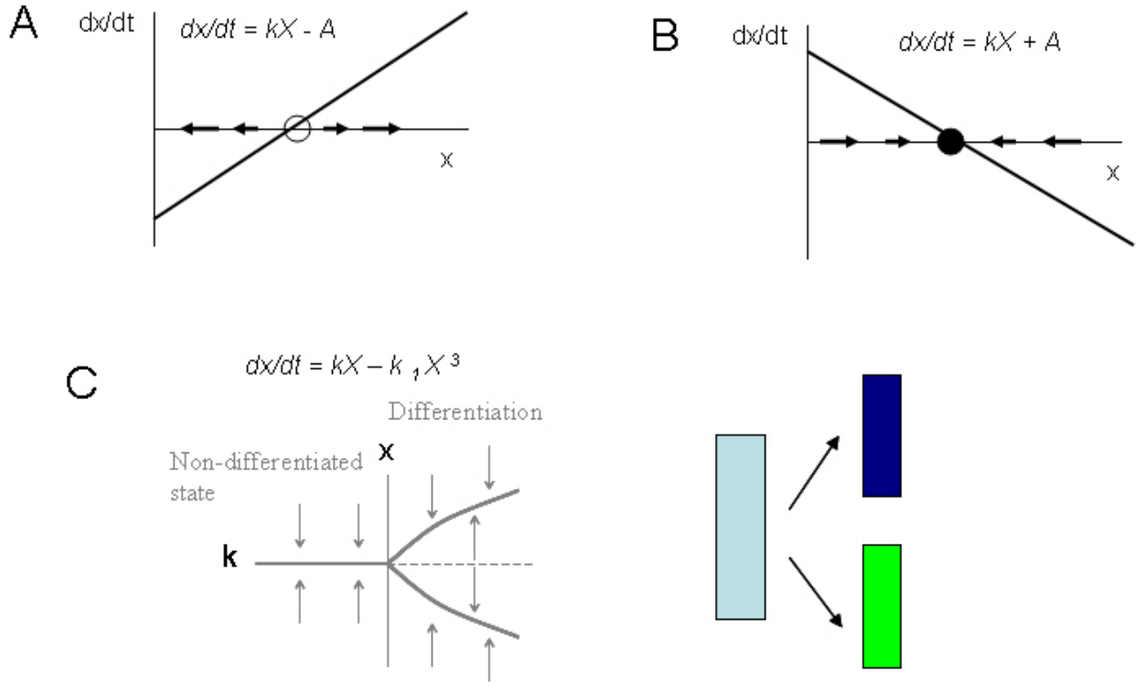

Fig. 7. Vector fields and solutions of some simple differential equations. A, B: linear equations. In A the solution is unstable (empty circle, vectors diverging), while in B it is stable (filled circle, vectors converging). C: under $k < 0$ there is only one stable solution $x = 0$, while under $k > 0$ this solution becomes unstable while two stable solutions appear in exchange. A transition from negative to positive k values corresponds to that from a single non-differentiated to a differentiated state (colored scheme to the right). For more details see text.

Under these conditions, it is meaningless to look for the "causes" in their classical sense. What we need to know instead is why at the given moment an embryonic structure has lost its previous stability. Meanwhile, we know already, that the loss (or acquiring) of stability is provided by the changes of the parameters values. This conclusion is of a direct methodological usage: instead of splitting the studied systems into ever smaller parts in pursuit of ever escaping causes, we should concentrate our interest onto macroscopic levels, to which the parameters belong.

For illustrating the role of parametric regulation in more details, we have to go from linear to non-linear equations. This shift is not just formal: it means that we pass from independently acting elements to interacting ones (those which either enhance, or inhibit each other, or make the both things together). In other words, non-linearity means *cooperative interactions*, most of all important for developmental events. A simple example: suggest that N identical elements affect the event A. If these elements are independent of each other, their action upon A is proportional to N, while if N elements enhance each other, it is proportional to $N(N-1) \approx kN^2$.

We miss a quadratic non-linearity and come directly to the 3-rd order one, as providing one of the best illustrations of developmental processes. Consider the equation

$$dx/dt = kx - k_1x^3 (k_1 > 0) \quad (2)$$

which describes a first order positive feedback between kx and dx/dt and 3-rd order negative feedback between k_1x^3 and dx/dt . It can be easily tested, that under $k < 0$ eq (2) has only one rational solution $x_1 = 0$ which is stable, while under $k > 0$ this solution becomes unstable, while two new stable symmetric solutions appear:

$$x_2, x_3 = \pm \sqrt{k/k_1}$$

(Fig. 7C). The main property of this model is that when k parameter in his rightwards movement reaches positive values, a number of stable solutions increases from one to two. Accordingly, it is a simplest model of the complexity increase, or of the reduction of a symmetry order (under $k < 0$ the sole stable solution $x_1 = 0$ is the axis of a rotational and reflection symmetry, while under positive k none of the stable solutions x_2, x_3 can play this role). In biological language this is just what we define as differentiation. The most important lesson from this model is that such a crucial step is under a full parametric control. That does not mean that the dynamic variables play no role at all, but this role is parametrically dependent. Namely, only under $k > 0$ the dynamic variables can select one of two vacant stable solutions. But they do it in quite a robust manner, without being obliged to take precise values: under any $x > 0$ the positive solution is selected, while under any $x < 0$ the negative one. Therefore:

(1) there are the parameters which determine the number and the values of stable solutions, that is, stable states, *potentially achievable* by a system; (2) among these, the actual states are selected by the dynamic variables in quite a robust manner: each stable state is a "basin of attraction" of infinitesimal number of the dynamic variables values.

By the way, these conclusions undermine a myth of an extremely precise organization of the living beings: the main condition for surviving and keeping their individuality is a small

number of potentially achievable and highly robust stable states, rather than a precise arrangement of the dynamic variables, which never exists.

Remarkably, most of the above said can be easily translated into embryological language.

One of the most important notions of embryology is indeed that of a *competence*: briefly speaking, this is a capability of a given embryo region at a given stage to develop into more than one direction. Now we may see that in SOT language it corresponds to that region of the parameters values, which has more than one stable solution. Therefore, the existence or the absence of a competence should be regulated parametrically. The next step after reaching the region of competence will be to come into the "attraction basin" of a definite solution. This event corresponds to what is defined in embryology as *determination*, and we can conclude that it is a matter of dynamic regulation. Same will be true for the final reaching of a stable state; in embryological language this is *differentiation*.

At the end of this section, let us briefly describe, even missing formulae, some more complicated self-organizing systems. Biologically very important class of systems is described by 2-variables (X and Y) non-linear differential equations, where Tch for Y are in an order smaller than for X: therefore, if including the parameters, these systems are at least three-leveled. In addition, the variables are interconnected by (+, -) feedbacks: a slower variable X inhibits a fast variable Y, while the latter enhances the first one. As a result, in a wide range of the values of a single controlling parameter we get so called autooscillations, that is, non-damped regular fluctuations of the both variables values. Complementing this system by a linear dependence between Y and dx/dt, we transform ever persisting autooscillations into a so-called trigger regime with two stable states, exchanging each other after finite perturbations of one of the variables. The arisen structures may be either only time-dependent, or in addition space-unfolded. In the latter case one has to assume that at least one of the variables is diffusing through space (it may exemplify not only a chemical substance, but also a certain physical state). In any case, all of these either purely temporal, or spatial-temporal structures are able to create, under a proper range of controlling parameters, quite stable patterns out a completely homogeneous state; note however that the patterns are stable until the supply of dynamic variables will continue.

6. Application of SOT to embryonic development

The first person to be mentioned here is Conrad Waddington, a British scientist who, even before SOT emerged in its present form, suggested a very stimulating allegory of development, that of a mountain landscape, consisting of valleys (which symbolize stable developmental trajectories) and crusts (imaging unstable states between valleys) (for recent account see Goldberg et al., 2007). There is also a tale that it was Waddington who asked a famous mathematician Alan Turing whether it is possible to construct a model generating a macroscopic order out of a completely homogeneous state. Turing did so postulating feedback interactions and diffusion of two reagents (Turing, 1952). His model became quite famous, even if it had no relations to any real biological process. An entire series of models, aiming to imitate biological realities have been constructed later on by Gierer and Meinhardt (Meinhardt, 1980). In general, the models postulated feedback interactions between two chemical substances, one of them (the activator) stimulating the development of a certain structure, while another (the inhibitor) suppressing the activator. Necessary was also the

inequality of the both components diffusion rates: the inhibitor should diffuse much more rapidly than the activator.

These models permitted to reproduce a number of biomorphic patterns, mostly periodic ones and in particular those related to surface designs. Also, they introduced an important principle: "short-range activation – long range inhibition" - which seems to be a wide-spread tool for pattern formation, although not necessarily connected with diffusible chemical substances. Meanwhile, the authors were fully satisfied by reproducing some single steps of development, without expressing any interest to model more or less prolonged chains of events. As a result, the initial conditions and the relations between postulated chemical substances and morphological structures which they assume to "activate" or "inhibit" had to be taken each time in quite an arbitrary way.

7. Mechanically-based self-organization (morphomechanics)

Much closer to biological realities and less connected with arbitrary assumptions became another class of models, emerged since 1980ieth. The main acting agents in these models were *mechanical stresses* (MS), generated by embryonic cells. Even a priori MS looked to be good candidates for being involved into regulatory circuits by the following reasons at least:

- they belong to universal (largely non-specific) natural agents;
- they are acting at the same time on quite different structural levels, from molecular to that of whole organisms;
- MS create very effective feedbacks with geometry of stressed bodies: any changes in MS pattern affect geometry in a well-predicted way, and vice versa. As D'Arcy Thompson told in his classical book "On Growth and Form" (last edition: Thompson, 1961) "Form is a diagram of forces".

As discovered during several last decades, embryonic tissues of all the studied animals, from lower invertebrates to human beings are mechanically stressed (same, even to a greater extent is true for plants). Embryonic MS are of different origin. In early development the main stressing force is turgor pressure in embryonic cavities (blastocoel, subgerminal cavity), which is born due to ion pumping and which stretches the surrounding cell layers. At the advanced stages most of stresses are caused by collective movements of many dozens of cells. Cell proliferation also contributes to MS. It is of a particular importance, that MS are arranged along ordered patterns, remaining topologically invariable during successive developmental periods and drastically changing in between. They never are uniformly spread throughout the developing embryos, but are generated in a certain part and transmitted by rigid structures to others.

Already several decades ago the German anatomist Bleschmidt described a large set of MS patterns emerging in human development, and claimed that "the general rules… that are applicable to man … have much in common with the rules of the developmental movements that take place in animals and even in plants" (Bleschmidt and Gasser, 1978). In advanced embryos he distinguished 8 different kinds of MS fields which participate in development of practically all the organs. Some of them are depicted in Fig.8A-C. Modulations of MS patterns (relaxation, reorientation, changes in MS values) in amphibian and chicken embryos lead to grave developmental anomalies. A number of fetus pathologies are also mechano-dependent.

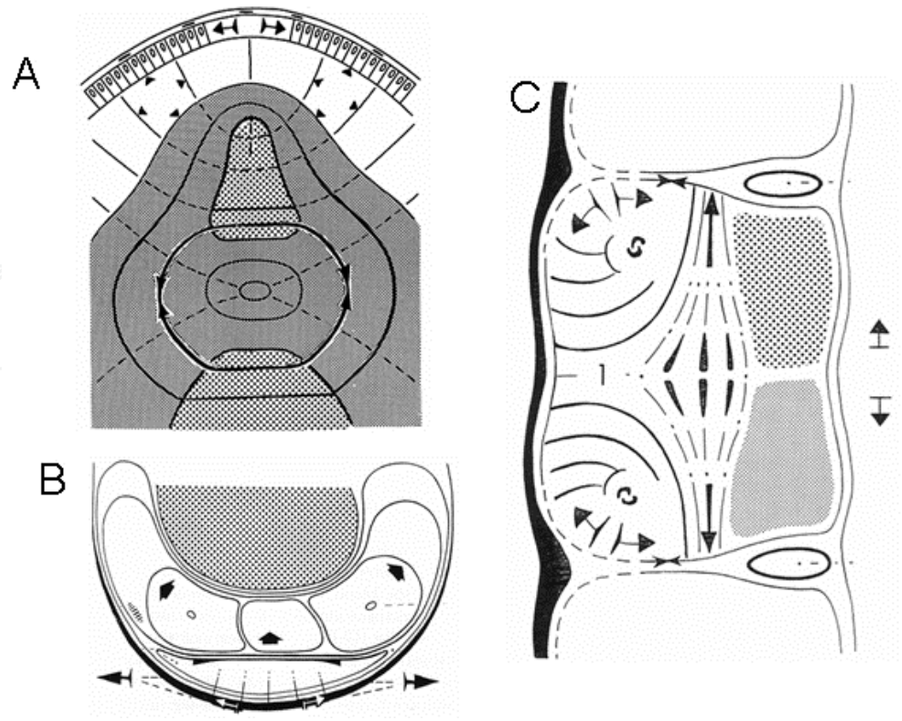

Fig. 8. Some examples of "biokinetic" schemes of human embryos anlagen by Blechschmidt and Hasser (1978). A: a rudiment of a finger; B: heel pad of 5 months fetus; C: a somite with surrounding tissues. Diverging and converging arrows depict stretching areas and those resisting to stretch, correspondingly. The main idea is that all the anlagen have their own patterns of mechanical stresses.

Most important, self-generated MS affect each other, creating feedbacks. Harris and coworkers (1984) evidenced the presence of such feedbacks by observing cell cultures seeded onto highly elastic substrates which the cells were able to stretch by their own contractile forces (Fig. 9A, B). As a result, homogeneously seeded cells became rearranged into regular clusters (Fig. 9C). This is a real self-organization (reduction of symmetry order) created by a feedback between short range adhesive interactions, tending to clump cells together into a tight cluster and long range stretching forces which extend the substrate and hence decrease cell density. Within the model framework, the adhesive forces correspond to short range activation, while the stretching forces to the long range inhibition of Gierer-Meinhardt models. Therefore, mathematics is roughly the same, but physics quite another – mechanics instead of chemistry! Quite similar, although if independently developed approach has been used in Belintzev et al. (1987) model, aiming to reproduce a segregation of initially homogeneous epithelial layers into the domains of columnar and flattened cells. In this model a role of short range activation was played by so called contact cell polarization (CCP) – cell-cell transmission of a tendency to become columnar. At the same time, long range inhibition, similarly to Harris et al. model, was provided by mechanical tension, arisen in the epithelial layer with fixed ends just because of CCP. Hence, again we have here a mechanically based (+, -) feedback. This model is of a special interest, because (unexpectedly to the authors) it became able to reproduce some main properties of embryonic regulations, namely preservation of proportions under different absolute

dimensions of a layer. This became possible, because the model equation contains a member, referring to holistic (independent from individual elements) property of a layer: this is the average cell polarization throughout the entire layer. Thus, the model can be considered as a mathematical expression of the Driesch law.

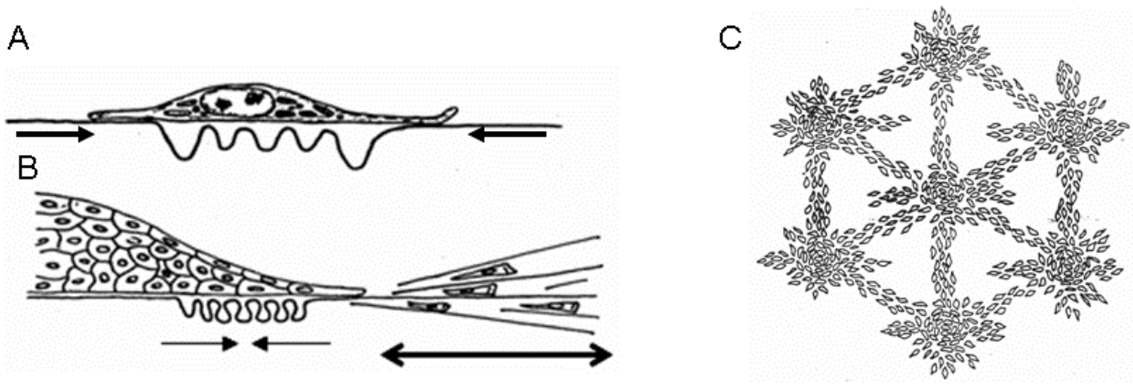

Fig. 9. Formation of regular cell clusters onto an elastic substrate. A: a single crawling cell shrinks the underlain substrate and hence stretches that located outside. B: a large cluster of adhered cells (to the left) stretches the cells located outside (to the right). C: a regular cell pattern arisen in the dermal layer of chicken embryo under the similar mechanical conditions (from Harris et al., 1984, with the authors' permission).

The described models made the first steps away from a purely static view upon development: we began to understand, why a given stage is exchanged by the next one. However, the modeled chains were too short and very soon abrupt. Is it possible to use a mechanically-based approach for reproducing much more prolonged developmental successions, including the above models as particular cases? Such an attempt has been performed by our research group about two decades ago (at the initial stage of this enterprise very important contribution was made by Dr. Jay Mittenthal from Illinois University, USA).

Our main idea was very simple. It is well known that any organism, deviated by any external perturbation (including certainly mechanical forces) from its normal functioning, tries to diminish the results of perturbation up to their complete annihilation. We modify this almost trivial statement by adding that any part of a developing organism affected by a mechanical force (coming normally from another part of the same embryo) not only tends to restore its initial stress value, but do it with a certain overshoot. This assumption, called the hypothesis of MS hyper-restoration (HR), permitted to make several predictions, opened for experimental and model testing (Beloussov and Grabovsky, 2006; Beloussov, 2008).

For example, according to this model, a stretching of a tissue piece by an external force should produce the active reaction which firstly diminishes stretching and then, as a part of HR response, generates the internal pressure force, directed along a previous stretching (Fig. 10A). As a rule, this is done by so called cell intercalation, that is, cells insertion between each other in the direction, perpendicular to stretching (Fig. 10C). Accordingly, if a tissue piece is relaxed or, the more, compressed, its cells should actively contract in the direction of relaxation/compression, tending to produce tension is this very direction (Fig. 10B, D). If applying these predictions to a cell sheet bent by external force, we should expect that its

concave (compressed) side will be actively contracted, while the convex (stretched) one extended. As a result, their cooperative action will actively increase the folding, just triggered by external force.

Importantly, these reactions are connected by feedbacks with each other. Among them, one of the main can be called "contraction-extension" (CE) feedback. As any other self-organizing event, it starts from a fluctuation – in this case, of a stretching/compression stress along cell layer. For example, if a part A of a layer is stretched slightly more than a neighboring part B and the layers edges are firmly fixed, at the next time period part A will be actively extended and hence compresses the part B. The latter will respond to this by active contraction, even more stretching A, and vice versa. The modeling showed (Beloussov & Grabovsky, 2006), that the results of these interactions crucially depend upon one of the parameters, a so called threshold stretching stress (TSS), that is the minimal stretching stress required for generating the internal pressure. If TSS is taken large enough, a layer will be segregated into single alternated domains of columnar and flattened cells. Just this situation corresponds to Belintzev et al. model. Under TSS decrease the number of alternative cell domains is increased while under very small TSS no stationary structures are produced: instead, a series of running waves is generated. This exemplifies a parametric dependence of morphogenesis.

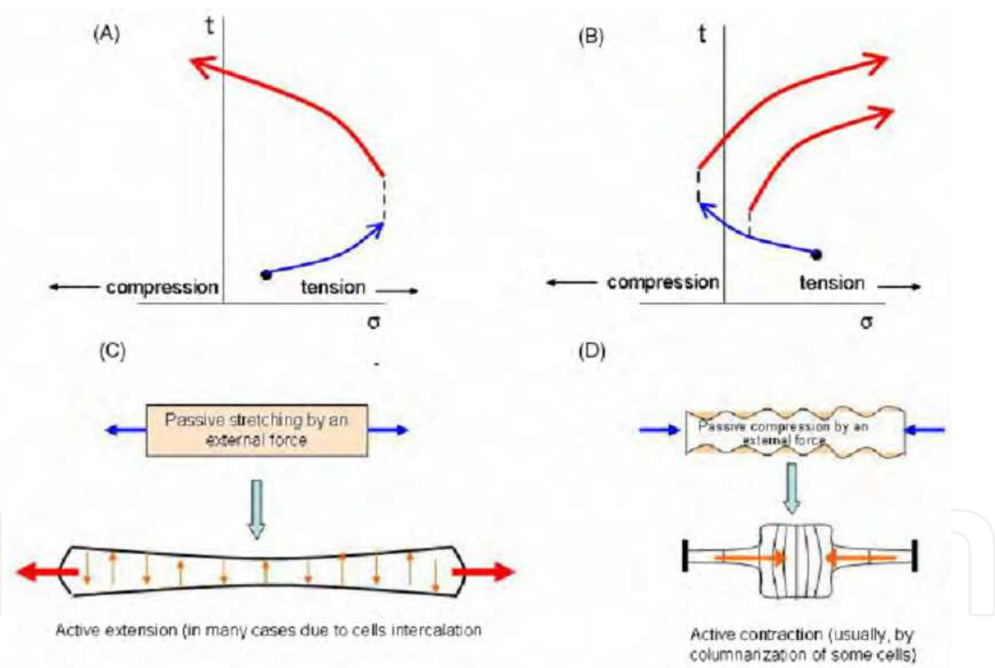

Fig. 10. Model of hyperrestoration of mechanical stresses. A, B: schemes of the responses to stretching and to relaxation/compression, correspondingly. Horizontal axis: mechanical stress (compression to the left, tension to the right). Vertical axis: time. C: a typical way for a response to stretching (cell intercalation). D: response to relaxation by tangential contraction (columnarization) of some neighboring cells. Vertical bars: firmly fixed edges.

Now let us reproduce in very broad outlines a more or less prolonged (but still uncomplete) chain of morphogenetic events. We start from so called "idealized blastula" stage, a spherically symmetric body with the walls of equal thickness which surround a concentric

cavity and are stretched by the turgor pressure within the latter. Why during normal development a blastula stage embryo will not stop at this stage but passes instead towards a more complicated (less symmetric) form? By our suggestion, this is because, according to CE-feedback, a spherical symmetry of blastula is unstable: even small local variations in its wall thickness will produce the corresponding differences of tensile stresses: thinner parts will be stretched to a greater extent and hence produce the greatest internal pressure, actively extending themselves and compressing the resting part(s) of the cavity wall. At the next step the mostly compressed part will generate, according to above said, the active contraction force. This delimits the start of the next stage, called gastrulation. In general, such a contraction can be achieved by different ways. The first of them is emigration of some cells from the compressed part inside the blastula cavity. This is typical for some lower Invertebrates (Cnidaria). Another one is the folding of a compressed part of a cell sheet; it is more elaborated type of gastrulation, called invagination. However, the folding itself may go in different geometric ways: the extreme ones are exemplified by a creation of a straight slit (Fig. 11A), and a circular fold (Fig. 11E). Take a sheet of paper and try to reproduce each of them. You will see how easy is to make a slit-like fold, while to make a circular one is virtually impossible – so much radial folds are arisen around! In order to smooth out the folds, the excessive cells should be removed (emigrated) from the folded area. In principle, CE-feedback can provide such a mechanism, but it is to be well tuned. On the contrary, a slit-like folding does not demand so refined regulation.

Nature employed the both ways: the first one is typical, for example, to Annelides and Arthropoda (belonging to a large group called Protostomia), while the second one for Echinodermata and Chordata (belonging to so called Deuterostomia). Interestingly, some lower Invertebrates, belonging to the type Cnidaria, took a variable intermediate way (Fig. 11B). In any case, the geometry of gastrulation very much affects subsequent development. The laterally compressed slit-like Protostomia blastopores should actively elongate themselves along the slit axis, compresses their polar regions (which later on transform to the oral and anal openings) but to a very small extent affects mechanically the rest of embryo (Fig. 11C, D). On the contrary, a gradually contracted hoop-like blastopore of Deuterostomia embryos creates around it a diverged radial tensile field, being extended over the entire embryonic surface and thus involving it into a coordinated morphogenesis (Fig. 11F).

Meanwhile, a uniform mode of a circular blastopore contraction is also unstable: similarly to what took place at the blastula stage, even small local irregularities in contraction rate along the blastopore periphery should subdivide it into the compression and extension zones. As a result, an ideal circular symmetry will be sooner or later broken and the blastopore together with its surroundings will acquire either a radial symmetry of n order, depicted by a symbol $n \cdot m$, or a mirror symmetry $1 \cdot m$. The latter mode of symmetry means formation of dorso-ventrality, still rudimentary in Echinodermata but fully expressed in Chordata. The dorsal line is that of a maximal active extension of embryonic body. Along this line another CE-feedback is created: its posterior part becomes extended, while the anterior one relaxed/compressed. This latter region transforms into a transversely extended head (Fig. 11H, h).

Later on the body of Vertebrate embryos becomes segregated into more or less independently developing territories ("fields of organs") into which the similar events are taking place in diminished scales. It will be a fascinating and as yet almost untouched field of studies to construct self-organizing models for all of them.

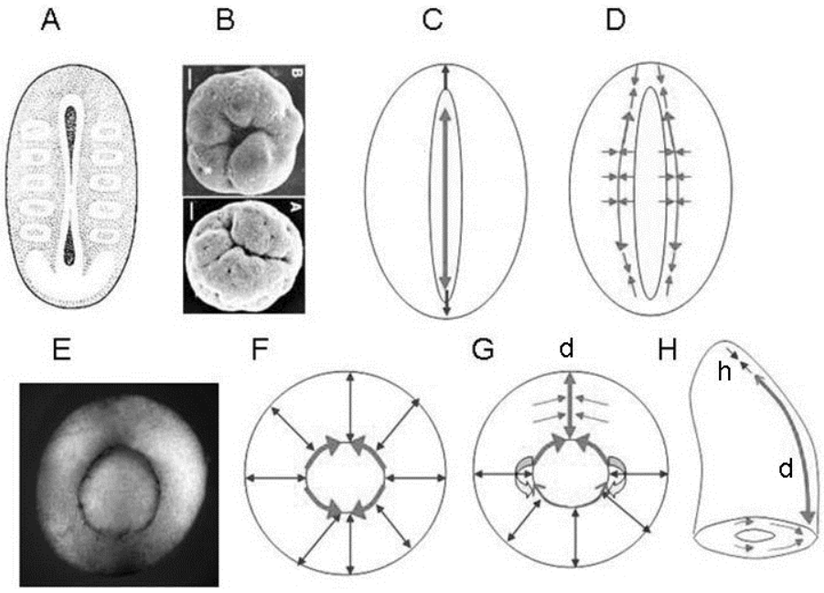

Fig. 11. Formation and mechanical role of slit-like and circular blastopores. A: typical blastopore of Protostomia. B: irregular blastopores of Cnidarian embryos. C, D: tensile fields in the vicinity of slit-like blastopores. E: circular blastopore of amphibian embryo. F-H: transformation of a radially symmetric tensile field around a circular blastopore (F) into *1 m* symmetry field with a dominating dorsal axis (G, H). H is a view from the left. d: dorsal side, h: head region.

8. Few words in conclusion

The main message of this essay is that the classical causal approach, continued to be used (even if unconsciously) by overwhelming majority of investigators cannot explain the main properties of development – the arising of more complex entities from less complex and even homogeneous ones and the associated "top-down causation" – influence of an irreducible whole upon its parts. As a result, a present-day developmental biology looks, even in the best cases, as a list of separate "instructions" of how to make this or that structure rather than a science with its own laws and predictive power. On the other hand, SOT, one of the leading branches of the modern knowledge, turned out to be quite suitable for promoting developmental biology to perform a desired transformation. To the present time, however, only the first steps on this way have been made. What we need now, is not so much a construction of specific models, but a general understanding of the nature of feedbacks, parameters and dynamic variables mostly involved in development. To a great extent this is related to a widely used notion of "genetic information". We have already seen, that it is far from being specific (an old concept "one gene – one morphological structure" is fully incompatible with modern data). Meanwhile, SOT opens a much more rational way for qualify it more properly: so far as genomes belong to the most constant components of the life cycles and the genetic factors are dealing, first of all, with the rates of molecular processes, it looks reasonable to attribute to genetic factors the role of the highest order parameters (those having the largest Tch and Lch). Within such a framework, the role of "genetic information" is quite powerful, but non-addressed: knowing the parameters' values but being non-informed about the structure of the feedback loops into which they are involved, we cannot tell anything about the role which is played by the first ones (as a rule, these roles should be quite multiple). The

parameters themselves, if taken out of the context of an associated equation or, at least, of a feedback contour are, so to say, blind – they have no definite meaning at all. If continuing to apply the notion of information to developmental events (although this never can be done with a desired degree of precision), we have to conclude, that it is smoothed between several structural levels: not only DNA and proteins, but also morphological structures and embryo geometry bear an essential amount of "information", irreducible to other levels events. Or, in other words, the biological information is embedded in wide contexts, rather than in single elements. By believing that the solution of all the developmental mysteries can be reached by splitting embryos in ever diminished parts, we may miss the very essence, which is resided onto meso- and macroscopic, rather than microscopic level.

Our last question will be of a utilitarian nature: why do we need to pay any efforts by transforming biology into a law-centered science, if already in its present-day state it gives so many results, useful for medicine and biotechnology? True, as a great physicist Boltzman told, nothing is more practical than a good theory. But is this citation applicable to biology? Nobody can be sure of it, but the attempt is worth to be performed. In any case, one can hardly be content to see the science about the most complicated, ordered and aesthetically perfect natural processes using a methodology not very different from that of a medieval alchemy.

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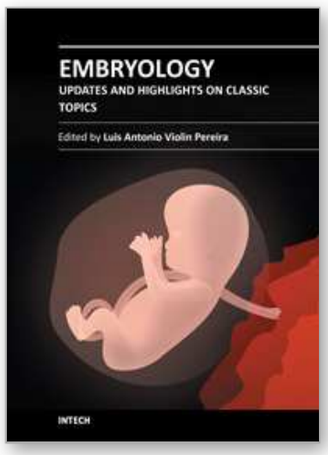

Embryology - Updates and Highlights on Classic Topics
Edited by Prof. Luis Violin Pereira

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Embryology is a branch of science concerned with the morphological aspects of organismal development. The genomic and molecular revolution of the second half of the 20th century, together with the classic descriptive aspects of this science have allowed greater integration in our understanding of many developmental events. Through such integration, modern embryology seeks to provide practical knowledge that can be applied to assisted reproduction, stem cell therapy, birth defects, fetal surgery and other fields. This book focuses on human embryology and aims to provide an up-to-date source of information on a variety of selected topics. The book consists of nine chapters organized into three sections, namely: 1) gametes and infertility, 2) implantation, placentation and early development, and 3) perspectives in embryology. The contents of this book should be of interest to biology and medical students, clinical embryologists, laboratory researchers, obstetricians and urologists, developmental biologists, molecular geneticists and anyone who wishes to know more about recent advances in human development.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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