



# Embryonic Development in Light of Controlled Chaos Dynamics and Quantum Electrodynamics

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## Abstract

Biological systems are necessarily dissipative structures in the long run, and dissipative structures are far from equilibrium and homeostasis: order (periodicity) and disorder (non-linear variability) are “*coexisting dynamic states*”. The common epistemological habit of modern molecular biology is to reduce an observed phenotype or function to a molecular entity, such as a gene, protein or pathway, which have become the embodiment of causation in biology. In the emerging framework of gene network architecture the *attractor nature* of distinct cell phenotypes, explains a series of cell behaviors that are not easily accounted for by linear molecular pathways. It explains why cell-type specific genome-wide expression profiles, defined by the values of thousands of variables, are so reliably established during differentiation as if orchestrated by an invisible hand: the *self-organizing* and *self-stabilizing* property of biologically significant gene expression profiles is a natural feature conferred by *attractors*. In the *human placental mammal*, the embryonic cell cycle and intrauterine development process rests on one of the most effective dynamics to regulate the living, sometimes approaching and sometimes diverging chaos, *i.e.* a *controlled chaos dynamics*. Biological system’s development, namely each stage of the embryo development, is characterized by the presence of one-to-many *attractors*, toward which the developmental dynamic variables trajectories are rapidly approaching from all the points of its phase space. Symmetry propagation and symmetry breaking are essential processes in biological morphogenesis, in metazoan evolution and development. Within embryogenesis, the *amniotic fluid* (AF) should be treated as biological water in a super-coherent state and may act as an inherently dynamical entity endowed by a proper non-linear dynamics, that creates a biochemistry not governed by random collisions between molecules, but by a code of mutual recognition and recall among molecules based on long-distance electromagnetic interaction. For convenience, a GLOSSARY of terms extrapolated from the body of the text can be consulted at the end of the article.

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## Subject Areas

Bioengineering, Biophysics

## Keywords

Controlled Chaos Dynamics, Attractors, Super-Coherent State of Biological Water, Gene Regulatory Network, Symmetry Breaking

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## 1. Premises

The epistemological bases of experimental science (natural philosophy) are laid in Europe by G. Galilei, F. Bacon, I. Newton, G. W. Leibniz, R. Descartes, J. Kepler. Strengthened by the idea that the universe is a work created by God, the fathers of modern science thought that doing experimental science meant researching the laws of nature put into place by the creative and ordering mind of God the creator. Thus, modern science was born in the light of theology with a view to determining the rules and principles of the divine universal order. The necessity of the divine order of nature translated, therefore, into the necessity of the logical order of scientific knowledge (theological empiricism). The presence of the theological and teleological order in the structure and dynamics of natural phenomena influenced the thought of biologists and doctors to such an extent that C. Bernard, a great nineteenth-century physiologist, considered the founding father of experimental medicine, dictated the rule of “Constancy of the milieu intérieur”, or the law of “constant equilibrium in living matter”. The Bernardian conception was defined with the term “homeostasis” by G. W. Cannon, meaning the return of biological functions to the “quo ante” state after stimulatory or inhibitory perturbations. The homeostatic vision of vital phenomena has had as an epistemological consequence a systematization, structural and topological, of biological systems in “linear axes”, that is, in axial systems to action (feed-forward) and to retroaction (feed-back), with an active and responsive dynamics of the type proportionate, one-to-one, and therefore linear. Furthermore, the homeostatic view of biological physiology has had as a methodological consequence the mathematical and statistical conception of biological systems in phenomena with dynamism and limited variability of a predictable and, therefore, linear type. In fact, only by virtue of the linearity in dynamism and variability could it be conceived that each action of the “actor” component should correspond to a proportionate reaction of the “reactor” component, which would lead to the return to the original equilibrium. (...)

The serious epistemological error of modern science lies precisely in the fact that it has not taken into due consideration that in every variable phenomenon, especially if it has complex dynamics, there is a certain degree of intrinsic unpredictability that we can call “disorder or chaos”. The disorder, in this case, must be understood as unpredictable variability that is found in the structure of

all the dynamic phenomena of nature, or a number of states of the system that are not predictable. Therefore, disorder must be seen as an attribute of nonlinear variability in dynamic phenomena, including biological ones. Consequently, the disorder should not be confused with the “noise” which represents the unpredictable result of the randomness of “chance”. The unpredictability of chaos should therefore not be confused with the unpredictability of the case. From this, it follows that the order (periodicity) is not “neg-entropic”, the opposite of the entropy disorder of evolving systems. In other words, the variability is not a variation of the equilibrium, but the equilibrium is, if anything, the loss of the variability.

The disorder, *i.e.* non-linear variability, has been and is still being assimilated to randomness, error, noise, which probabilistically affect all measurements, even the most precise, if repeated. It follows that the methods of Euclidean analytical mathematics and conventional parametric statistics of modern science, in principle, consider extreme anomalous phenomena (the singularities or catastrophes of the mathematics of chaos), which are found in the dynamics of inorganic and organic events, as a result of randomness, and, therefore, as not being part of the variable structure of the system (outliers). In fact, “chance” has no structure, it is disorganized, it is amorphous. It is evenly arranged in the regions furthest from the center of the mean value. The “chaos”, on the other hand, denounces a structure that is arranged with an orientation starting from a point of minimal difference. The order, therefore, lies in what lies within certain boundaries of variability around the most frequent value or the central location value of the distribution. As in the analytical approach, also in the probabilistic statistical approach, everything that lies beyond the extreme limits of distribution is considered a probable result of chance. Ultimately, both the analytical and the statistical approaches are valid and capable of studying the “centrality” of repeating phenomena, but, in principle, they are unable to study the “peripherality” of what is repeated. The unpredictable, therefore, is such due to the methodological limitation of current scientific methods which are not suitable for documenting the unpredictability. (...)

Biological systems are necessarily dissipative structures in the long run, and dissipative structures are, by definition, far from equilibrium and homeostasis: order (periodicity) and disorder (non-linear variability) are “coexisting dynamic states”. The structure of the disorder is the fractal (see GLOSSARY). The fractal iteration of the disorder is perfectly periodic. Disorder, therefore, finds its way of being simultaneous with order in the iterative structure of a periodic variation [1] (translation from Italian is mine).

## 2. Introduction

The countless structural and functional solutions that characterize biological varieties, produced in the course of phylogenetic (see GLOSSARY) diversification via pre-adaptation (*exaptation* – see GLOSSARY) and adaptation dynamics,

represent as many *dissipative systems* (see GLOSSARY) far from thermodynamic equilibrium, that rely on the availability of *anticipatory systems* (see GLOSSARY). That is, biological systems are *non-linear dissipative systems* [2] embedded by *super-complex anticipatory systems* (see GLOSSARY) relying on thermodynamics of non-equilibrium, at the phase boundary between chaotic and ordered (coherent) regimes. The state maintained at the verge of chaos turns out to be, in some sense, rather stable. This peculiar state is defined as a *self-organized criticality* [3].

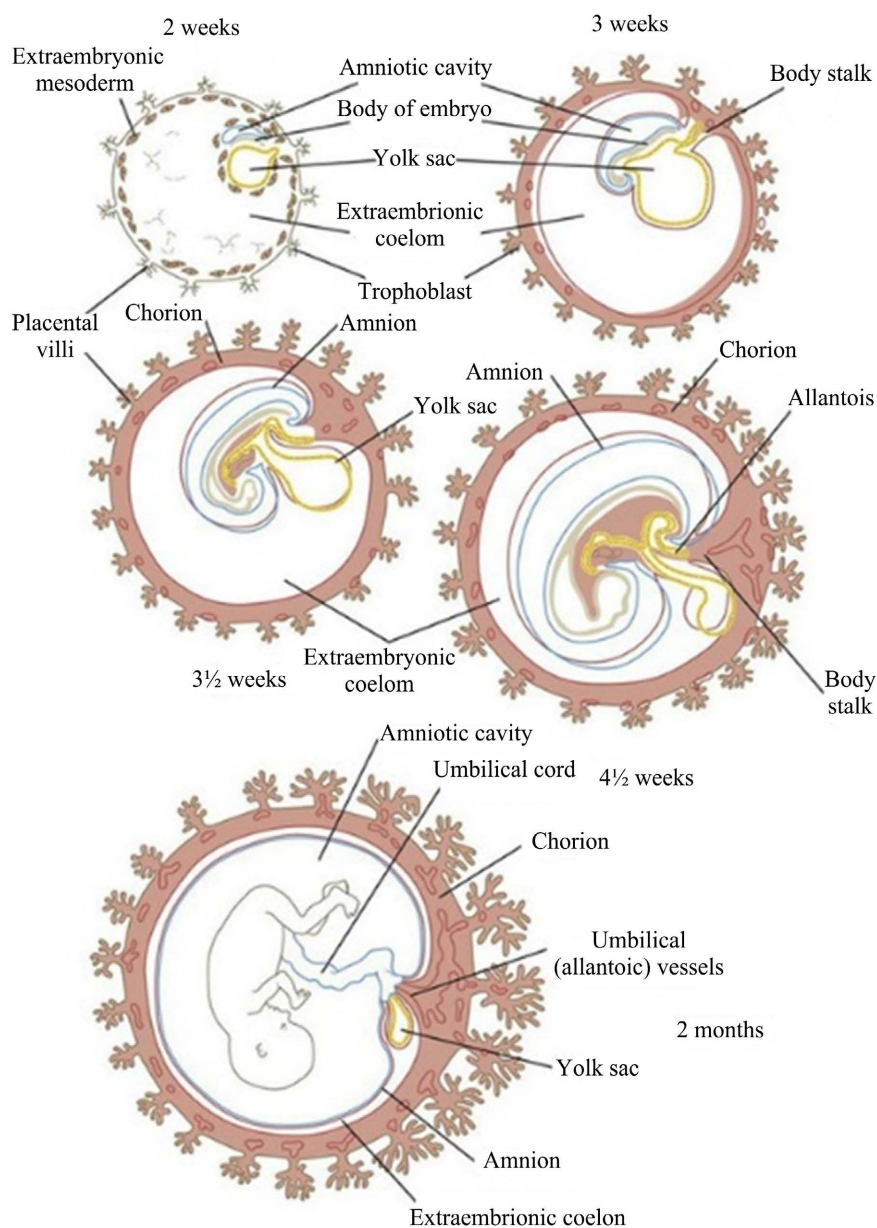
In the *human placental mammal*, the embryonic cell cycle and intrauterine development process rests on one of the most effective dynamics to regulate the living, sometimes approaching and sometimes diverging chaos, *i.e.* a *controlled chaos dynamics* [4] (also coined as *deterministic chaos*).

Each stage of embryo development is characterized by the presence of one-to-many *attractors* [5] (see GLOSSARY), toward which the developmental dynamic variables trajectories are rapidly approaching from all the points of its phase-space, and occurs among three main phases or periods, namely the *pre-embryonic period* (zygote → merula → blastocyst), ranging from fertilization to the 9<sup>th</sup> gestational day; the *embryonic period* (blastocyst → embryo), from the 10<sup>th</sup> gestational day to the 12<sup>th</sup> week of gestation; the *fetal period* (embryo → fetus), from the 13<sup>th</sup> week of gestation to term.

The primary structure of the embryo is trilaminar, consisting of endoderm, mesoderm and ectoderm, and the morphogenesis of the main apparatus of the body starts during the first half of the embryonic period. The development, first embryonal and then fetal [Figure 1], takes place inside a bag (ectodermal amniotic membrane or *amnios* → mesodermal chorionic membrane → amniochorionic membrane → chorionic villi epithelial mantle → *placenta*) filled with *amniotic fluid* (AF), composed for 98% by a *glassy* and *super-coherent state* of *biological water* (see par. 2), mineral salts, amino acids, lipids and various kinds of ions, stem cells and proteins.

The AF increases progressively in relation to embryonic/fetal growth, and until the 10<sup>th</sup> week of gestation is formed essentially by maternal plasmatic ultra-filtrate. From the 10<sup>th</sup> to the 20<sup>th</sup> gestational week, it has a composition very similar to that of the fetal plasma, which diffuses into the amniotic fluid through the thin and nonkeratinized embryonic/fetal skin. The third quarter is largely formed by the urine and by cutaneous and lung transudation of the fetus.

Commonly, the function assigned to AF is that of cushion and settling tank of embryonic and fetal metabolic degradation, nevertheless, recent studies have revealed that it also performs an immune action [6] and occupies a leading role in the *embryo morphogenesis* [7], *neurogenesis* (AF contains numerous neurotrophic factors secreted by amniotic cells, thus exerts a neurotrophic effects on fetal neurodevelopment during pregnancy [8]) and *CNS morphogenesis*. Further, within embryogenesis AF may act, as will be discussed in paragraph 2, as an inherently dynamical entity endowed by proper non-linear dynamics, that creates a biochemistry not governed by random collisions between molecules,



**Figure 1.** Embryonic development from 2nd to 8th gestational week. Between 2nd and 5th gestational week is observable an amniotic cavity in which it welcomed the embryo, and a chorionic cavity (extraembryonic coelom) in which the yolk sac is incorporated. From the 8<sup>th</sup> gestational week the yolk sac undergoes a rapid process of involution, chorionic cavity is progressively reduced becoming interstitial space/interstitial fluid, located between the amnion and chorionic membrane, which between the 12<sup>th</sup> and 13<sup>th</sup> week shape the amnio-chorionic membrane. Image source:

<http://clinicalgate.com/placenta-and-extraembryonic-membranes/>.

but by a code of mutual recognition and recall among molecules based on long-distance electromagnetic interaction.

In multicellular organisms of the animal kingdom (from *Metazoa* to *Homo*), the distribution of the various functions among different and increasingly specialized tissues is integrated by the *Nervous Tissue* (NT), whose functional unit

(in association with *glial cells*<sup>1</sup>) is the *nervous cell*, i.e.:

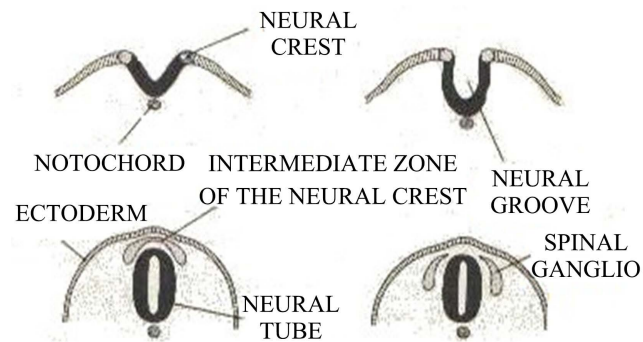
- A *generator of electromagnetic radiation* in ultrahigh range of frequencies with the wavelength comparable with linear dimensions of the cell itself;
- A *rhythmogenic center* with exogenic modulated frequency;
- A *receptor unit* playing selective function on *state variations* (stimuli) and *functional interface* between innervated tissues;
- Engaged in supporting and integrating the *energy-transfer* function exerted by the catalytic cellular core (CCC), formed by the Golgi apparatus, the centrosome (MTOC, Microtubule Organizing Center [13]) and microtubules<sup>2</sup> (the structural units of the cell cytoskeleton, polymerized protein highly polarized).

In the human placental mammal *embryo neurogenesis* is a complicated process of generating functional neurons from neural (→neurospheres, composed of free-floating clusters of neural stem or progenitor cells) [8] and glial precursors, very active in the pre-natal period (→CNS development) and relatively active in post-natal period (→neuronal repair processes) [15], which involves, in addition to neural and glial precursors, mature glial cells, the *cerebrospinal fluid* (CSF), the AF and ependymal cells<sup>3</sup>. Glial cells, and in particular *astroglial cells* (astroglial lineage), occupy a prominent place both in *neurogenesis* and in the evolution and architecture of the CNS, its *morphogenesis*, a complex process that takes place through the same sequence of stages in all vertebrate embryos, which involve two of the three germ layers: mesoderm and ectoderm (the first induces morphological changes in the latter so that it can differentiate to become neural tube). The CNS appears at the beginning of the 3<sup>rd</sup> gestational week as stretched ectodermal thickening, the neural plate, located in the dorsal-central region of the embryo, in front of Hensen's node and the primitive streak. The neural plate is lifted, forming two reliefs, the neural crests. These crests are then joined incorporating part of the AF in which the embryo is immersed, giving shape to a tubular structure, the neural tube [Figure 2]. The AF incorporated in the neural tube is then turned into CSF [Figure 3], initially by the *neuroepithelial cells* (NECs) and by the *radial glial cells* (RGCs), and subsequently by the *choroid plexuses* (CHPs), small vasculo-nervous spongy structures located in the cerebral ventricles (in the laterals two, in the third and fourth ventricle), which start to develop when the embryo reaches the 8 mm (9<sup>th</sup> week of gestation).

<sup>1</sup>Until recent times it was thought that the nerve cell was the only functional unit of the Nervous System (NS). It is now believed that this role should be partly shared with other cells belonging to the NS, the *glial cells* [9] (e.g. they regulate the neuronal synaptic responses associated with learning and memory processes, and share with neurons the role of mediators in the genesis of brain functional skills [10] [11] [12]).

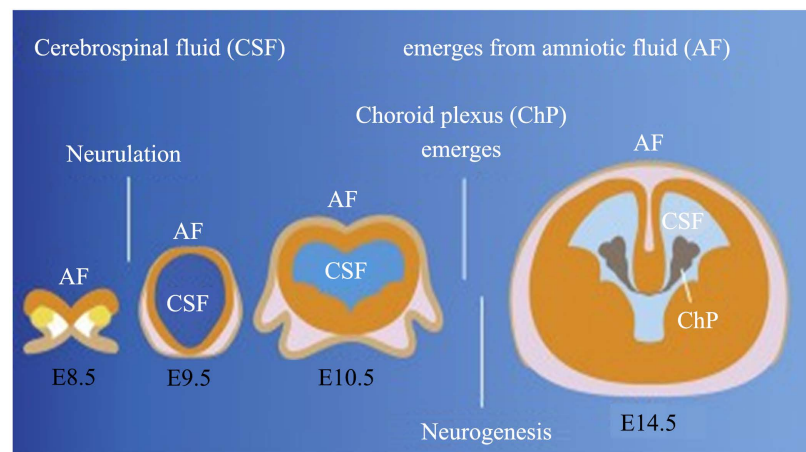
<sup>2</sup>It should be noted that Hameroff and Penrose's *Orchestrated objective reduction* (Orch OR) theory attributes *consciousness* to "orchestrated" quantum computations in microtubules inside brain neurons, rather than the conventional view that it is a product of connections between neurons [14].

<sup>3</sup>Specialized epithelial cells, which create a selectively permeable barrier (ependyma) between the CSF and nervous tissue, and that, according to recent studies, can generate *neuro-stem cells* (NSCs), pluripotent cells that can differentiate and become neurons or glial cells.



**Figure 2.** The CNS originates in the 3<sup>rd</sup> gestational week from the neural plate, a thickening of the fetus dorsal ectoderm in the shape of racket, in front of Hensen's node and the primitive streak. The neural plate thickens and bends becoming neural groove, which by closing form the neural tube, inside of which is incorporated the AF, which is converted into CSF, initially by neuroepithelial cells (NECs) and by radial glial cells (RGCs), and subsequently by the choroid plexuses (ChPs). Image source (modified):

<http://www.albinismo.it/info-scientifiche-albinismo-35/melanociti>.



**Figure 3.** Cerebrospinal fluid (CSF) early development from amniotic fluid (AF). As the *neural tube* closes, it envelops AF that fills the lumen and is later actively modified. Early in development, *neuroepithelial cells* (NECs) and *radial glial cells* (RGCs) contribute to the composition of this liquid milieu, but this task soon falls to the *choroid plexuses* (ChPs). The ChPs are folded structures residing in the brain ventricles that consist of a single layer of highly active epithelium sandwiching an elaborate vascular network. This vascular-neural composite controls the passage of molecules into the CSF, which impacts *neurogenic zones* throughout life. Image source (modified):

<http://vector.childrenshospital.org/2015/12/how-amniotic-and-cerebrospinal-fluids-talk-to-the-developing-brain-proteomics/>.

During embryonic development, the vast majority of neurons and a large number of glial cells are generated in the germinal zones or germinal matrices or *Neurogenic Niche* [16] [17], the micro-anatomical environment that depending on the period of neuronal development (prenatal → postnatal) may contain endothelial cells, ependymal cells, stem cells, astrocytes, microglia, neurons and mature descendants of adult neural precursors, and that functionally controls their development *in vivo*. In the early phases of cytogenesis, the germinal zones

are located primarily at the ventricles surface (*ventricular zone*, VZ). While embryonic development proceeds, on the surface of VZ forms a germinal *subventricular zone* (SVZ)<sup>4</sup>, which together form the *ventricular-subventricular zones* (V-SVZs) [18] [19] [20].

As the cerebral hemispheres enlarge, and the distance to be travelled by the cells increases, most of the neurons that will form the cerebral cortex migrate to their destinations along specialized *radial glial fibers* (RGFs) that span the entire thickness of the hemisphere from the ventricular surface to the pia<sup>5</sup>.

After birth neurogenesis is carried out by the specialized activity of the neurogerminative *subgranular zone* (SGZ) of the dentate gyrus of the hippocampus [17] [21] [22].

### 3. Long-Range Spatial Organization during Embryo Development

The stages of embryo development require the integration of two ordering actions, namely a network that generates sustained oscillations (patterns for the cell-cycle clock in developmental processes) and a control mechanism that produces robust spatial synchronization. While considerable research has addressed oscillatory behavior in different biological contexts, the question of how embryos are synchronized across large spatial dimensions has yet to be addressed, namely: *how genes are activated in certain spatial regions and how the distribution of functional biomolecules and cell types is orchestrated and coordinated to result in large-scale pattern and its regulation?*

Simple diffusion alone and short-range forces are insufficient to communicate the stage of the cell cycle over typical embryonic length scales (0.1 - 1 mm), even if morpho-mechanochemical models are of different opinion. Indeed, these models imply the existence of long-lived mechanical stresses, mainly tensile and compressive stresses (which depend, according to [23], on the elasticity of the cell surface, linear tensions at the junctions between individual cells and the active contractility of the cell perimeter caused by the action of actomyosin rings) which through chains of short-range interactions, create at any stages mechanically stressed multicellular communities (permanently maintained normal tensile patterns are indispensable for providing a long-range morphological order), that bind together the different level processes [2].

One system-focused answers on how embryos are synchronized across large

<sup>4</sup>The cells that will form the deep cerebellar nuclei and the Purkinje cells of the cerebellar cortex are generated in germinal zones in the subventricular region of the fourth ventricle. The cells that form the deep cerebral nuclei are formed along the ventricular surface of the diencephalon (the future third ventricle) and from the ganglionic eminence of the telencephalon (the future site of the caudate nucleus). The diencephalic germinal zone will produce cells that form the thalamus, hypothalamus, and globus pallidus, whereas the cells produced in the ganglionic eminence will form the striatum (caudate nucleus and putamen), amygdaloid complex, and claustrum.

<sup>5</sup>The orderly production and migration of the cells, from the germinal zone to the cerebral cortex along the RGFs, led to the concept of *neuronal-glial vertical units*. This units includes the germinal zone which produces the cells destined for a certain region of the cortex, the cells themselves, and the bundles of radial glial fibers which guide the cells to their final destination.



spatial dimensions is provided, e.g., by the so-called *morphogenic field theory* [24] [25] [26] [27], which suggests that a pervasive field of influence induces *long-range spatial organization* in plant and animal development [28] [29] and guides both structure and function. That is, the formation of new space-temporal structures during the development of organisms and the behavior of both individual cells and rudimentary organs is controlled by a field of forces common to all elements of an embryo [30].

What this force field consist of? The morphogenic field theory suggests that chemical signaling is supplemented by electromagnetic signaling in driving and organizing the structure and function of cells, tissues, organs and the whole organism [31] [32].

The electromagnetic signalling role in relation to embryogenesis can be better understood within the Quantum Field Theory (QFT) system of correlations, with biological fields having a very complex *chreod* (attractor path) from the zygote to the fully grown individual, pierced by many points of symmetry breaking, and within the Quantum ElectroDynamic's (QED) properties of the *super-coherent state of biological water* [33] [34], of which the AF is mostly composed (until the 10<sup>th</sup> week of gestation its composition is given by maternal plasmatic ultra-filtrate and from the 10<sup>th</sup> to the 20<sup>th</sup> gestational week by a fluid very similar to that of the fetal plasma).

As discussed in [33] [34], over the last 80 years evidence has been accumulated on the influence of electromagnetic fields (EMFs) on living organisms, showing that the electrodynamic field plays an important role in the establishment of coherence, directional transport, organization of morphological structures, interactions, information sharing, and brain activity. The frequencies of the involved EMFs cover different intervals corresponding to the different scales present in the organisms. The exceptional electrical polarity of biological objects and long-range interactions suggest a basic role of the endogenous EMF generated by living cells, a role that finds its place in a physical vision that addresses biological dynamics as an interplay of chemical processes and EMF interactions, that is, as an array of EMF assisted biochemical reactions. Excited longitudinal polar oscillations in microtubules in eukaryotic cells generate the endogenous EMF [35]. The metabolic activity of mitochondria connected with *water ordering*, forms conditions for excitation.

Liquid water molecules cannot be assumed to be bound by purely static interactions (H-bonds, electric dipole-dipole interaction). Their binding is actually induced by the time-dependent radiative long-range endogenous EMF. Short-range static bonds, such as H-bonds, then set in as a consequence of the molecule condensation induced by such long-range radiative fields. An ensemble of molecules interacting with the radiative EMF acquires, above a density threshold and below a critical temperature, a new non-trivial minimum energy state, different from the usual one where the oscillations of the molecules are uncorrelated and the EMF is vanishing. The new minimum energy state implies a configuration of the system where all molecules enclosed within a variable re-

gion, denominated Coherence Domain (CD) if its wavelength  $\lambda$  is that of the trapped EMF and Exclusion Zone (EZ) if wider (coherence among multiple CDs), oscillate in unison in tune with an EMF trapped within the CD/EZ. The persistence in time of extremely low frequency (ELF) magnetic fields guarantees a steady excitation of the *glassy* and *super-coherent state* of *biological water* CD/EZ and correspondingly of the biochemical activity catalyzed by them. CD/EZ oscillates on a frequency common to the trapped EMF and the biological water molecules and this frequency changes when energy is stored in the CD/EZ. When the oscillation frequency of the CD/EZ matches the oscillation frequency of some non-aqueous molecular species present on the CD/EZ boundaries, these “guest” molecules become members of the CD and are able to catch the whole stored energy, which becomes activation energy of the guest molecules; consequently, the CD/EZ gets discharged and a new cycle of oscillation could start [36]. In order to load energy in the *super-coherent state* of *biological water* CD/EZ, *i.e.* in order to energetically excite the cloud (vortex) of quasi-free electrons kept orbiting at the periphery of the water CD/EZ by the internal EMF inhomogeneity<sup>6</sup> (residual positively charged ionized molecules sink toward the centre of the CD/EZ and the CD/EZ become a spherical - or a hybrid between a circular cavity and a dipole, an excitable unit made of two complementary phase-points capacitor of quantum nature, able to trap electromagnetic energy through coherence), a resonant alternating magnetic field is needed. In animals, such as the humans, this field can be produced by the Nervous System (nervous cell is a *generator of electromagnetic radiation* in ultrahigh range of frequencies with the wave length comparable with linear dimensions of the cell itself). Elementary organisms, such as bacteria and virus, but also plants (*vegetal cell network*) should use environmental fields. Good candidates are the Schumann modes of the geomagnetic field. These modes are the stationary modes produced by the magnetic activity (lightnings or else) occurring in the shell whose boundaries are the surface of the Earth and the conductive ionosphere, which acts as a mirror wall for the wavelengths higher than several hundreds of meters<sup>7</sup> [36].

<sup>6</sup>Ions close to water CD/EZ are attracted by the EMF trapped in the domains and kept orbiting around the domain moving at a circular speed proportional to the so called cyclotron frequency  $\nu_c$ . Since DNA and also proteins are polyelectrolytes, they are surrounded by a cloud of positive counter-ions; ions having a cyclotron frequency in the interval between 1 and 100 Hz play an important role. By applying a magnetic field, having a frequency which matches the ion cyclotron frequency, on a system where ions are present, these ions are extracted from their orbits [37] [38]. Due to the conservation of angular momentum, the extraction of ions from the cyclotron orbits produces a rotational motion of the *quasi free* electrons of the water CDs, which therefore become energetically excited [39] [40].

<sup>7</sup>It is interesting to observe that, should the cyclotron orbits around the water shell be saturated by an ion species which does not match the Schumann resonances, the activity of the biological system would be inhibited. This prediction is in agreement with facts since we know that there are ions promoting biological activity and ions inhibiting it. The above conclusion holds, of course, if the only EMF background is the natural one (Schumann modes) or an artificial EMF background with frequencies similar to the Schumann ones; should an artificial EMF background with a different frequency distribution be present, a reshuffling of the favorable and unfavorable ion species would occur. This feature could provide a rationale for the observed impact of ELF fields on the physiological activity.

Due to its composition (at least until the 20<sup>th</sup> gestational week), AF should be treated as *biological water in a super-coherent state*, and within embryogenesis may act as an inherently dynamical entity endowed by a proper non-linear dynamics, that creates, as discussed above, a biochemistry not governed by random collisions between molecules, but by a code of mutual recognition and recall among molecules based on long-distance electromagnetic interaction. This is also the role that continues to be played throughout life by the CSF (which, as earlier mentioned, is AF incorporated in the neural tube and turned into CSF during the early phase of CNS formation) in relation to the CNS activity. This consideration implies that chemical interactions are highly dependent on the dynamics governing the field, which can modify and eventually supersede classical chemical reactions [41], and that the overall chemical reactivity can be significantly modulated by biophysical – not chemical – factors, such as long-distance electromagnetic interaction.

We have, therefore, a *non-stationary coherent regime*, but that evolves over time, generating in turn a time-dependent biochemical framework whose function is to optimize the intrauterine development process, e.g.:

- ✓ Allow for aggregation in response to nutrient deprivation,
- ✓ Allow for the transmission of information over large length scales at rates far greater than allowed by simple diffusion,
- ✓ Give rise to complex spatial patterns linked to high-order torus (fractal-like) topology<sup>8</sup> (fractal algorithm with the development of a set of similar scale-invariant modules is an effective way of morphogenesis based on a relatively small genetic program [42]).

Such *non-stationary coherent regime* can be drawn as a macroscopic system described by QFT in terms of *coherent Bose-Einstein condensate* (BEC – see GLOSSARY) [43].

#### 4. Gene Regulatory Network's Basin of Attraction

The common epistemological habit of modern molecular biology is to reduce an observed phenotype or function to a molecular entity (Democritus atomistic ontology), such as a gene, protein or pathway, which have become the embodiment of causation in biology. This reductionist-mechanistic and Darwinist view, obviates the need for a more encompassing and integrative view for examining morphogenesis in the broader context of development. Instead, any novel phenotypic feature (*hall mark*) that a cell acquires is conveniently explained by a specific lasting molecular mechanics. Interestingly, while one will automatically

<sup>8</sup>According to the theorem of elementary topology, any closed surface in three-dimensional space is homeomorphic (topologically equivalent) to the sphere with a certain number ( $\mathbf{p}$ ) of handles. If there are no topological surgeries (cutting and gluing of epithelial sheets), the genus of the surface ( $p$ ) is a topological invariant, and any geometrical deformations such as surface curvature, linear and angle values are not essential. The closed surfaces of the genus  $p = 0$  (sphere),  $p = 1$  (torus),  $p = 2$  (double torus, or *pretzel*) and so on give a topological classification. The topological differences between these surfaces are fundamental and qualitative. Mechanical stress  $\mathbf{p}$  is a vector and is defined as the average force per unit area  $S$  that some particle of a given body exerts on adjacent particle across an imaginary surface that separates them [2].

seek to determine the gene driving the molecular mechanics responsible for a cell's novel phenotypic feature, nobody will doubt that normal cells as distinct as a stem cell, a mature neuron, a blood cell, or an epithelial cell, all share the very same genome. This opens an intriguing question: *how can the same set of genetic instructions produce a variety of discrete, persistent (non-genetically inherited) cell phenotypes?* [44].

Following this epistemological habit, the claim that the course of development is “genetically programmed” is commonly accepted as an absolute truth, even in spite of the lack of proper understanding of what the “program of development” actually means. So exciting were the successes in deciphering the key roles of genes in “controlling” the development of embryonic rudiments that all the instructions for “make it through” looked to be in our hands. Only closer to our days, it became realized that our belief to govern development by switching on or off any genes or signaling pathways is the same as operating an electronic device by pushing its buttons without having even a slight idea on how it actually works. Anyway, our present-day image on genetic regulation of development contains two great negations [2]: 1) even complete knowledge of genome structure cannot tell us what gene will be expressed in a given space/time location; 2) even from exhaustive knowledge of space/temporal schedule of genes expression, one cannot predict what morphological structures will be formed in these definite locations.

Actually, such a situation is in generally acknowledged, but the conclusion is in most cases expressed in an allegoric form, by claiming that genes action is “context-dependent”.

A gene expression pattern reflects the state of a *gene regulatory network* (GRN), and as a whole, is dynamic: it develops in time due to the mutual regulation between the genes of each others' expression and settles down into an *equilibrium state* that complies with the regulatory interactions. The ability of small gene regulatory circuits to produce more than one *stable equilibrium state* (stable pattern of expression of all genes in the circuit) was first proposed by Max Delbruck in 1948 [45], and later by Jacob and Monod [46] and others to explain differentiation into a multitude of *stable phenotypic states*. In the 1960s Kauffman showed that a complex network of up to hundred thousand of mutually regulating genes can under certain conditions produce hundreds of stable equilibrium states, termed *attractors* [47] [48]. Kauffman proposed that attractor states correspond to the gene expression profiles associated with each cell type [49].

The *state space* of a GRN is therefore the space that contains all theoretically possible gene expression patterns (network states of that GRN). Each point in the (high-dimensional) state space represents one gene expression pattern of the GRN and moves around as the expression patterns change. The attractor state is a particular point in the state space and has particular properties: as a stable equilibrium state, it resembles that of a *lowest energy state* at the bottom of a *potential well* which represents the *basin of attraction*. Thus the attractor state is

surrounded by unstable states and is *self-stabilizing*. A new perspective not available in the traditional paradigm of linear causative pathways takes shape. In the emerging framework of gene network architecture the attractor nature of distinct cell phenotypes, most obviously, the cell types, explains a series of cell behaviors that are not easily accounted for by linear molecular pathways. It explains why cell-type specific genome-wide expression profiles, defined by the values of thousands of variables, are so reliably established during differentiation as if orchestrated by an invisible hand: the *self-organizing and self-stabilizing* property of biologically significant gene expression profiles is a natural feature conferred by attractors. Hence, cell-type specific gene expression patterns are robust to noise, re-establishing themselves after small perturbations (imposed changes of expression levels of individual genes) and can be reached in principle via an almost infinite number of paths. Conversely, they are capable of undergoing drastic quasi-discontinuous transitions to other specific stable expression profiles via genome-wide changes of gene expression. Such transitions occur when cells encounter the proper cell fate regulatory signals that, via branching signal transduction pathways change the expression of a specific set of genes of the network, or due to sufficiently high random fluctuations of gene expression levels. In a simplified picture, attractor transitions underlie the cell phenotype switching during development [50].

The existence of high-dimensional attractor states defined by  $N =$  thousands of genes across the genome and their correspondence to particular cell types has recently been experimentally verified. Using microarrays for dynamic gene expression profiling the “attraction” of trajectories from different directions in state space towards a common final state of a differentiated cell, as well as the relaxation back to the bottom of the potential well after local perturbations are both indicative of attractors [51]. Such self-propelled convergence of high-dimensional trajectories (gene expression profile change) is a necessary signature of an attractor [52]. The biochemical cascade underlying the cell cycle, *i.e.* the dynamic behavior of this biochemical system, it can be visualized by a limit cycle, a double limit cycle, or a strange attractor, traced out by its trajectory in phase space [4].

Within this overall framework, the simple clock, representing the *embryonic cell cycle*, is described as a *limit cycle*. A doubling of the limit-cycle period takes place during embryonic development. Subsequently, a breakdown of the double cycle occurs, and a strange attractor is born, whose attraction domain is sufficiently large enough to stabilize the process of cell divisions. The transition to a system with strange attractor means that complicated nonperiodic oscillations, whose details are very sensitive to small changes in the initial conditions, can be observed. In other words, phase trajectories on the strange attractor are unstable. However, the average characteristics of this behavior are stable and do not depend on the initial conditions (they vary within a given domain). From a general point of view, and using computer simulations, one can see that the sys-

tem of a single or a double limit cycle, as well as that of a strange attractor are structurally stable (robust) systems. The property of structural stability is absent only for the bifurcation values of the system's parameters [4].

## 5. Morphogenesis Rest on Symmetry Breaking

The existence of a strange attractor with an unlimited reservoir of periods may be an important property of multicellular organisms, where the proper structure and function of the adult organism is depends strongly on intricate developmental processes as well as on sophisticated *homeostatic mechanisms*. It seems that chaos is able to favor the sudden emergence of partial synchronization processes related to different realities significant for the system in which it acts. Therefore, by increasing the degrees of freedom of the system, it would seem to play a functional role of flexibility in switching to different stable activation states for some time variation ( $\Delta t$ ) other than zero. This functional role finds a partial one confirms, for example, when the state of activation of the cerebral cortex is observed during an epileptic seizure [53]. In these conditions, in fact, the system appears strongly synchronized in rather large areas and for relatively longer times than the changes of state that they occur as a result of other mental events.

The functional role played by (deterministic) chaos on the system resembles that of the officer giving the order to break the pass when a military platoon is about to cross a bridge. The synchronized walk would quickly bring the whole structure to oscillate with a destructive resonance. In this case, the duty officer gives the order to desynchronize the gear to avoid disastrous effects.

It is possible that the nervous system, like any other biological system, in their evolutionary history, has developed its own internal strategies to “randomize” the states of activation and avoid the disastrous effects of the synchrony that we can observe, e.g., during epileptic attacks. The importance of desynchronization is even more evident when considering the phenomena of muscle activation where a vast synchronization of activation in different motor neurons would lead to undesirable tremors [54], thus preventing the fine adjustment of movement and orientation in space.

Embryonic development occurs when a single cell (the fertilized egg) reliably self-assembles a highly complex model appropriate to its species. During later life, multicellular creatures must maintain their pattern – an active process of *morphostasis* that works to maintain the whole while individual tissues age or are damaged by diseases or traumatic injury.

The early *amniote embryo* is shaped by unabated tissue motion. In particular, all early developmental milestones in amniotes involve large (millimeter-scale) morphogenetic movements, including gastrulation, left-right symmetry breaking, neurulation, segmentation and caudal axis extension. These early landmark events create the foundation for organogenesis by sculpting the vertebrate body plan and transporting organ precursors to appropriate destinations within the

embryo.

*Morphogenesis*, i.e. the ability of living systems to self-organize simultaneously on many scales to produce the exquisitely complex pattern that underlies function, is one of the most interesting aspects of biology. In morphogenesis, intricate, mathematically precise natural architectures develop from simple, symmetrical initial states that show no traces of the patterns to come. Symmetry propagation and symmetry breaking are essential processes in biological morphogenesis, in metazoan evolution and development. Analyzing the behavior and property of individual cells alone cannot unravel the complexities of morphogenesis: fluctuating *extracellular matrix* (ECM) material properties and collective biological motion govern the tissue-scale deformations that shape early amniote embryos and their organ primordia. An appreciation of both cell-autonomous and tissue-level motion perspectives is needed to understand the biomechanical mechanisms that shape amniote embryos and, potentially, non-amniote embryos [55] [56].

Symmetry Theory (ST) it may be regarded as a compact model of any law-oriented science, aiming to search for invariable basis within a set of varying events. ST therefore is dealing with the so-called invariable transformations, keeping constant some properties of a body which in other relations is changing. The transformations used for testing the invariability are the movements in a broad sense, including so-called isometric transformations keeping the form and the dimensions of the object constant as well as the different kinds of deformations.

The symmetry orders exchange between different levels is directly related to morphogenesis. In classical biology (both zoology and botany), the notions of symmetry are used in most cases for comparing static forms belonging to different taxonomic groups. Accordingly, the compared symmetries are related as a rule to higher structural levels only.

Classical self-assembly relates mostly to preservation and increase rather than decrease of the symmetry order. For creating a complicated space-temporal organization of embryos, the reverse dynamics associated with symmetry breaks will be necessary. Symmetry breakdown is one of the fundamental processes of development. Like breaking a mirror, the initially smooth, continuous surface or shape with a high degree of symmetry is transformed into one with less symmetry due to the appearance of new structures and forms. With continued growth and development, the pattern may remain essentially the same in its general characteristics, but it is initially composed of hundreds, then tens of thousands, and then millions to billions of cells in the final mature form. Various scalar and vector fields on subcellular, cellular, and supracellular levels of biological organization are manifested in heterogeneous distribution of structural components, in biochemical gradients, in vectorized subcellular transport and other functional activities, in ionic fluxes and accompanying electric fields, in fields of mechanical tensions, in directed cell movement, etc.

The self-reduction of symmetry order is linked to *cell polarization*<sup>9</sup> and is also referred to as *spontaneous breakdown of symmetry* (SBS), or spontaneous breaking symmetry. In Quantum Field Theory (QFT) it is well known that the ordering of the elementary components of a system is achieved as a result of the SBS and constitutes the observable manifestation of coherence. According to QFT, the dynamics of a system is described by a set of field equations that are postulated to contain all the characteristic features of the system. The fields represent the elementary components of the system, e.g., the electromagnetic field (EMF), the atomic and molecular system's constituents, their electric charges, and dipole moments, etc. In general, one may consider transformations, e.g. rotations, reflections, and translations (linear shifts), of the fields such that the field equations do not change their form when the fields undergo the said transformations. The dynamics is then said to be invariant under the considered transformations, and these are named symmetry transformations of the dynamics. It may happen that under the action of some external perturbation, the state of minimum energy of the system (vacuum), is not symmetric under the symmetry transformations of the dynamics. Then, the symmetry is said to be spontaneously broken. Spontaneously means that the system is driven into the non-symmetric state by its own (internal) dynamics, not forced by the external perturbation which only acts as a trigger. SBS allows the transition from the microscopic scale of the elementary components to the macroscopic scale of the system behavior.

Topological and symmetry transformations are determined genetically and epigenetically. Molecular genetics and biochemistry have focused on unraveling the role of biochemical messengers in this process, and are beginning to understand the role of tensile forces [2] and adhesion [57]. It is well established that molecular signals and genetic expression play essential roles in both plant and animal development. While the involvements of specific genetic expressions are well established in plant animal organogenesis, it remains largely unknown how genes are activated in certain spatial regions and how the distribution of functional biomolecules and cell types can form in dynamic spatial patterns (the spatial organization of evolutionary advanced animals may be represented topologically as an outer epithelial envelope of a certain genus  $\mathbf{p}$  embracing a number of inner closed epithelial surfaces embedded inside the outer envelope [42]).

Physiologically, symmetry breaking in biological systems is guided by certain *cues*, stimuli that are either intrinsic, also known as *landmarks*, or extrinsic, such as gradients of signaling molecules detected by sensors. Stimulus-induced transitions provide the ability to sense and amplify environmental cues that exceed the

<sup>9</sup>Cell polarity is based upon a complicated and up to now not completely untangled web of negative and positive feedbacks related to different levels; among them, mechanical feedbacks, in most cases tensile, seem to play the leading role in a large-scale integration of lower levels ones. For these feedbacks to be effective, the entire cell should be either in an unstable state, or on the verge of stability. In both cases, it behaves as a nonlinear system. Being still rudimentary on the levels of cytoskeleton and single molecular structures, nonlinear properties are expressed in full scale at the upper structural levels of cell organization.



level of background noise. Under normal physiological conditions, biological systems are maintained within the region of parameters corresponding to the *bistable state* posed for the stimulus-induced symmetry breaking, and are endowed by the existence of *spontaneous cell-intrinsic symmetry-breaking mechanisms* to initiate the symmetry-breaking transition [58].

## 6. Conclusions

In light of controlled chaos dynamics and Quantum Electrodynamics we discussed how the embryo development is characterized by the presence of one-to-many *attractors*, by symmetry propagation and symmetry breaking processes and by the *amniotic fluid* acting as an inherently dynamical entity endowed by a proper non-linear dynamics, that creates a biochemistry not governed by random collisions between molecules, but by a code of mutual recognition and recall among molecules based on long-distance electromagnetic interaction.

We therefore attempted to answer two main questions:

- How genes are activated in certain spatial regions and how the distribution of functional biomolecules and cell types is orchestrated and coordinated to result in large-scale pattern and its regulation?
- How can the same set of genetic instructions produce a variety of discrete, persistent (non-genetically inherited) cell phenotypes?

The solution to the first question is provided by assuming that at least until the third quarter gestational period the *glassy* and *super-coherent state* of amniotic fluid (AF) may act as an inherently dynamical entity endowed by a proper non-linear dynamics, that creates a biochemistry not governed by random collisions between molecules, but by a code of mutual recognition and recall among molecules based on long-distance electromagnetic interaction. A role that continues to be played throughout life by the CSF (which is AF incorporated into the neural tube during the early phase of CNS formation) in relation to the CNS activity.

The solution to the second question is provided by assuming that a gene expression pattern reflects the state of a *gene regulatory network* (GRN), and as a whole, is dynamic: it develops in time due to the mutual regulation between the genes of each others' expression and settles down into an *equilibrium state*, termed *attractor*, that complies with the regulatory interactions. The *state space* of a GRN is therefore the space that contains all theoretically possible gene expression patterns (network states of that GRN). Each point in the (high-dimensional) state space represents one gene expression pattern of the GRN and moves around as the expression patterns change. The attractor state is a particular point in the state space and has particular properties. Thus the attractor state is surrounded by unstable states and is *self-stabilizing*. The attractor nature of distinct cell phenotypes explains why cell-type specific genome-wide expression profiles, defined by the values of thousands of variables, are so reliable.

bly established during differentiation, as if orchestrated by the *self-organizing* and *self-stabilizing* property of biologically significant gene expression profiles conferred by attractors.

### Statement

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The Author does not have any known or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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## Glossary

**Fractal:** In structures that on a small scale repeat the structure examined on a larger scale, the minimized iteration of the real can take place inside or outside the object itself, so that the parts will always be similar to their whole, as well as the parts of the parts, and so on (geometric synecdoche). In other words, the whole is reflected in its parts and vice versa. In the repetition of itself, the object is assumed as a “dimension to be minimized”, so that it topologically produces its shrunken image, similar in shape and orientation, which is a fraction of it, it is its “fractal”. The fractal of itself iterates in the space of states for “geometric relationships” between the points that make up the image in terms of “affine transformations” (AT) that do not alter the basic structure of what it iterates (topological representation). Affine transformations are functions that maintain the similarity and homothety of the object being iterated (topological homeomorphism), consisting of rotations, translations, elongations, shortenings, etc. The fractal has immeasurable magnitude and imperfect proportions.

**Phylogeny.** *Phylogeny* should be understood as the process of diversification and integration to which undergoes the Earth’s biological phenomenon, as a coral unit, from its origin, in relation to all the intermediate solutions between *adaptation* and *exaptation*, to all the *dissipative/anticipatory* structures/systems solutions and to all the *state transitions* (bifurcations), induced by macroscopic and microscopic *state variations*, that have affected it, relying on the *poietic action* (which produces development and structure) exerted by *self-organization*, and maintained in a state at the verge of chaos (*self-organized criticality*) by a *basin of attraction of the chaotic type with different attractors (riddled basin of attraction)*.

**Exaptation:** The concept of *exaptation* was introduced by paleontologists Stephen Gould and Elisabeth Vrba in 1982, to indicate the possibility that in nature the relationship between organs and functions is potentially redundant, in order to allow that a tract developed for a certain adaptive reason, can be “co-opted” or converted to a function even completely independent from the previous one. This functional cooptation, which complements and does not replace the gradual action of implementation of natural selection, was named by Charles Darwin “*pre-adaptation*” and was renamed by Gould and Vrba with the neologism *exaptation*, means precisely that some innovations, appeared during the course of phylogeny, may not be the result of a process of selection toward that specific function, but the reuse for other purposes of an existing structure.

**Dissipative systems:** Far from equilibrium, the smallest fluctuations of a system’s stationary state can lead to completely different behaviors on a macroscopic scale. A myriad of crisis or bifurcations points can lead the system, in an apparently random way, to new stationary states. These not uniform states of structural organization, varying in time or space (or both), were called by Ilya Prigogine *dissipative structures*, and their spontaneous evolution, *self-organization*.

**Anticipatory systems:** Anticipatory systems are commune to all biological



systems. The ability shown by natural anticipatory systems consists in being able to foresee, with a variable but still significant margin of uncertainty, to which environmental perturbations the biological system could undergo, and behave accordingly.

**Super-complex anticipatory systems:** Complexity, as usually understood, refers to chaotic systems, *i.e.* to systems which are deterministic and sensible to their initial conditions. So understood, complex systems are entirely past-governed and are apparently unable to include anticipatory behaviour. In order to distinguish anticipatory systems from entirely past-governed systems, the concept of *super-complexity* has been introduced. Super-complexity can be regarded as the most general property of living systems, including aspects like their constitution, reproduction and autonomy. In short, complex systems are systems: 1) requiring a double form of composition (the *bottom-up* type of composition from elements to the system), and the *top-down* form from (a previous stage of) the system to its elements; 2) capable of both regeneration and self-reproduction by reproducing the elements of which they are made (*autopoiesis*); 3) endowed with autonomy.

**Attractor:** A pole of syntropic stabilization, locally unstable but globally stable, which introduces a variable and convergent quota of information in the dynamics of a system, favouring the establishment of correlative patterns (coherence). In performing its polarizing action on the dynamics of the confinement processes, attractor stabilizes a warp of polarized hysteresis domains embedded by a weft of self-recombining mnemonic-like processes of a chaotic type. The quantitative measure of its ability to stabilize a warp of polarized hysteresis domains embedded by correlative patterns between self-recombining mnemonic-like processes of the chaotic type, is referred to as *mnemotropy*, while the qualitative measure of its ability is referred to as *mnemotropic action*. It is very common for dynamical systems to have more than one attractor. For each such attractor, its *basin of attraction* is the set of initial conditions leading to long-time behavior that approaches that attractor. Thus, the qualitative behavior of the long-time motion of a given system can be fundamentally different depending on which basin of attraction the initial condition lies in (e.g., attractors can correspond to *periodic*, *quasiperiodic* or *chaotic* behaviors of different types).

**Bose-Einstein condensate:** The bosons that condense in a crystal are called the *phonons*, *i.e.* the *quanta of the elastic waves* responsible of the ordering in crystals; in the magnets, they are called the *magnons*, namely the *quanta of the spin waves* in magnets; in water, they are called “*dipole wave quanta*” (DWQ), the *quanta of the fluctuating molecular dipole waves*, and so on. The ordered patterns we observe at a macroscopic scale in these systems are sustained and generated by *long range correlations* maintained by these waves. One would never be able to construct any of these systems by using short range interaction among the nearest neighbours. Short range interaction, if it is there, is made possible by the long range one which brings “near” the components (e.g., making possible the formation of H-bonds in water). Decoherence in Quantum Me-

chanic (QM) would forbid the existence of crystals, magnets, superconductors, etc. However, these systems do exist and are observed since they are QFT systems.