Randomness and Multi-level Interactions in Biology[1]

Marcello Buiatti
Department of Evolutionary Biology
Florence University, Florence, Italy

Giuseppe Longo
Centre Cavaillès, CNRS – Ecole Normale Supérieure, Paris
http://www.di.ens.fr/users/longo

Abstract. The dynamic instability of living systems and the "superposition" of different forms of randomness are viewed, in this paper, as components of the contingently changing, or even increasing, organization of life through ontogenesis or evolution. To this purpose, we first survey how classical and quantum physics define randomness differently. We then discuss why this requires, in our view, an enriched understanding of the effects of their concurrent presence in biological systems' dynamics. Biological randomness is then presented as an essential component of the heterogeneous determination and intrinsic unpredictability proper to life phenomena, due to the nesting of, and interaction between many levels of organization, but also as a key component of its structural stability. We will note as well that increasing organization, while increasing "order", induces growing disorder, not only by energy dispersal effects, but also by increasing variability and differentiation. Finally, we discuss the co-operation between diverse components in biological networks; this co-operation implies the presence of constraints due to the particular nature of bio-entanglement and bio-resonance, two notions to be reviewed and defined in the paper.

Keywords: classical/quantum randomness, biological randomness, critical transitions, random complexification, entropy production, network constraints, bio-resonance.

1. Introduction.

In his long struggle against creationism and finalism, J. S. Gould tackled the issue of the apparent increasing "complexity" of organisms through Evolution. The question he asked himself was: from prokaryotic to eukaryotic cells and to multi-cellular organisms, and within them towards mammals and humans, with many intermediate steps, is there something with one of the many meanings of "complexity" which "increases"? Gould's answer is very well documented in his 1998 book "Full House", where he presents the general argument for denying that progress, as a tendency towards the best, defines the history of life or even exists as a general trend at all. Following Gould's remarks, our theoretical proposal is dedicated to the role of randomness both through ontogenesis and phylogenesis. In *no way* do we claim by this that "everything in biology (in evolution, in particular) is contingent", i.e. that it is the result only of one form or another of randomness, the specifics of which we will spell out below. Instead we intend to focus on the various possible notions and instances of this *component* of biological dynamics, contingency as randomness. Randomness in Biology deserves a proper analysis, along the lines but well beyond the many deep ones carried out within the various theories of the inert. Note that classical and quantum physics each propose different forms of randomness, which we will recall. These, in our view, are both relevant for understanding biological randomness.

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As for "biological complexity", the first point to understand within this frame is that, whatever may be increasing (the notions of biological complexity are multivariate and controversial), the dynamics of the increase do not follow a direction towards a final result (a total order). It may be a partial order, like a tree expanding in all possible directions and, as Gould and Eldredge (1972) first showed, following a trend of increase in complexity. This may be followed by "stasis" or sudden reductions, generally due to environmental and, more recently, human directed changes, all happening together with crossing-overs between different branches of the evolutionary "tree of life". In particular, different evolutionary paths may give phenotypic *analogies* or similar paths producing *homologies*. "Regressions" in complexity are also possible (the loss of eyes in the cave-fish and hundreds of other well-known examples), with no predetermined orientation.

Exit, thus, finalism; we also have to drop, in evolution, any notion of "value", or whatever comparison between different organisms which would lead to directionality towards an (even local) maximum or "best". Our human hand is not "the best", nor is it "better", with respect to any other front podia, from the elephant's to the kangaroo's: they all are just the results of the diverse and possible evolutionary paths followed by the front legs of tetrapods.

If we look back to the history of Biology in the modern era, we find that the concept of finalism stems from the birth of the so-called "Modern synthesis" (Huxley, 1943) and particularly in Fisher's mathematical version of it. However, Fisher's "dogma" (1930) stating that selection works in a stable environment and therefore leads to the evolution of optimal genotypes/phenotypes, has been proven wrong since the pioneering work by Sewall Wright (1932) on the dynamics of populations living in ever-changing environments. Wright showed that different combinations of alleles can reach the same level of adaptation, introducing the concepts of non-additive effects of genes and alleles on the fitness of genomes and of an "adaptive landscape", by which is meant the landscape of fitness of different genotypes with more than one optimum. Following Wright, then, the concepts of "highest fitness" or the "best fit" have been challenged and we now talk of variable levels of adaptation to variable "environments". That is, adaptation must be analyzed within a co-constituted, far from equilibrium[2], environment, where individual organisms and the ecosystem as a whole are interacting in ever changing transitions. We will recall below some ideas of the theory of "extended critical transitions" to which we refer as a frame for understanding organisms/ecosystem dynamics (Bailly and Longo, 2011).

In the "classical" Darwinian perspective on selection, the unfit or the less adapted is eliminated. However, low or high adaptations are relative and may depend, of course, on the possible presence of the other "avatars" (Eldredge, 2008) of competitive species or variants within a population which, locally and on specific aspects may perform better or worse in reproduction, possibly in correlation to access to limited resources. However, even minor changes in the environment, undetectable at any particular time, may subsequently show that different causes may render the organism or species more or less adapted, adaptation standing as the only general criteria for natural selection. And in no way, by looking at one specific evolutionary "moment", may one predict which individuals or species will be less or more adapted in thousands or millions years. Similarly, it was totally unpredictable, from the given state of the ecosphere, whether the double jaw of some vertebrates of the Devonian (the gnathostomes) would yield the bones of the median ear of amphibians (the stegocephalia) and, then, of mammals – quoting a preferred example by Gould. Similarly, there was no way to predict the role of feathers evolving first for temperature regulation and later sustaining flight. These were possible, contingent paths, interpreted as *exaptations* (Gould's original notion), and leading to a previously non-

[2] By "far from equilibrium system" we mean a system subject to a flow of energy and/or matter.

existing function by a new use, after contingent changes, of previously existing organs or component of organs. And this is just contingency, since there is no evolutionary *necessity for life* to hear nor to fly.

Now, which scientific notion of randomness do we need to grasp the biological notions of "contingency" and of "possible" (evolutionary/ontogenetic) path? This is a crucial question never really seriously tackled by scholars of the life sciences, but needing to be analyzed if we want to advance beyond the now obsolete antinomy between total chance and total necessity proposed by Jacques Monod (1972), and recently challenged for instance by Buiatti and Buiatti (2008). Darwin himself challenged the popular concept of chance, with an anecdote proposing an original version of randomness or how contingency may contribute to biological organization: "Let an architect be compelled to build an edifice with uncut stones, fallen from a precipice. The shape of the fragments may be called accidental; yet the shape of each has been determined by the force of gravity, the nature of the rock, and the slope of the precipice, events and circumstances, all of which depend on natural laws" (Darwin, 1875: p.236). In modern terms (see below), the formation of the stones' shapes may be seen as the result of classical non-linear dynamics, with highly unpredictable (random) outcomes, later used by the evolutionary "bricolage", in Monod's terms. Yet another interesting approach is proposed in (Luisi, 2006), where contingency is understood as the encounter of independent causal paths: "Contingency, in this particular context, can be defined as the simultaneous interplay of several concomitant effects to shape an event in a given space/time situation …. For example, a tile falling on your head from a roof can be seen as a chance event, but in fact it is due to the concomitance of many independent factors such as the place where you were, the speed at which you were walking, the state of the roof, the presence of wind, etc." This recalls another pioneering notion of contingency, hinted by Spinoza in the Ethics by a very similar example: the encounter of independent causal paths.

We will compare the different notions of randomness in Physics with those implicit in these and other reflections in Biology, for the purposes of the study of contingency in the two main biological processes, development and evolution. A sound theory of biological randomness requires an analysis, in the cell, of the two known forms of physical randomness – classical and quantum randomness. As a matter of fact, quantum and "quantum-like" effects may happen jointly with classical dynamics and their proper forms of randomness, i.e. they take place simultaneously and affect each other in intracellular processes. Moreover, different levels of organization, in a multicellular organism (as well as in "colonies" of unicellular ones), may interact and produce stabilizing and destabilizing effects. As we shall see, this form of integration and regulation also includes random phenomena or amplification of randomness, and will be called "bio-resonance", in analogy to the well-established notion of resonance in physical non-linear dynamics.

As a preliminary hint towards our approach and in a rather general sense, note that for us "random" means "unpredictable in the intended theory" (note that this applies both to the Quantum and the Classical notions of randomness as discussed in sect. 2)[3].

[3] This notion of randomness as (relative) unpredictability may be seen as epistemic, since it depends on the theory, on the intended mathematical measure theory (e.g. Lebesgue measure in the mathematical spaces used) and on physical measurement, i.e. on which mathematical ways the theory is specified and relates to the "world", by measurement. Yet, it becomes intrinsic (ontological, some like to say), when the theory subsumes the issue of measurement as an integral part. This is the case of Quantum Mechanics, typically, where the theoretical frame includes indetermination, from the measurement of the energy spectrum and Planck's h, to the probability density as Schrödinger state function. We will not insist on this "epistemic vs. intrinsic (or ontological)" issue, which may depend on the reader's metaphysics. It may help though to better specify the extensive and not

2. Randomness in Physics.

Too many biologists, also on the grounds of the "Central dogma of molecular genetics" proposed by Francis Crick (1958, 1970) and thoroughly discussed within the frame of a mechanistic theory of life by Monod (1970), think that deterministic means predictable and that randomness is completely independent from determination. The situation is vastly more complex. Since the beginning of the 20th century, physicists deal with two forms of randomness, classical and quantum, in separated (actually incompatible) theories, as the classical/relativistic and the quantum fields are not unified: entanglement and Bell inequalities mathematically separate these two theories of randomness. In this section we will hint to the basic ideas on this matter, for the purpose of our analysis in Biology.

2.1 Classical Randomness.

Laplace, after contributing to the equational determination of the gravitational systems, by the Newton-Laplace equations, conjectured the complete predictability of all "mechanical" facts (that is, of celestial mechanics and of generally deterministic systems, see Laplace's work on Celestial Mechanics, from 1799 to 1825). Yet, he was also an outstanding mathematician of probability theory, as a measure of randomness, which he considered a totally different notion from "determination" (Théorie analytique des probabilités et Philosophie des probabilités, 1812– 1814). In short, Laplace bi-partitioned all physical dynamics between deterministic *and* predictable on one side, and random, on the other. These views, similarly claimed by Lagrange and Poisson, marked the 19th century (and common sense till now). As mentioned above, Monod (1970) similarly opposed "hasard *et* nécessité", in Biology. A direct consequence of this approach has been the emphasis on the notion of "genetic program", since "computable (i.e. programmable)" coincides with "deterministic *and* predictable", see (Longo et al., 2010, or, better, Longo 2013). It is worth noting here that the Laplace's view has been directly inherited by the neo-Darwinian theory of evolution as well. According to this theory, two of the three driving forces of evolution (mutation and random drift) are described as complete and un-qualified randomness, while selection is deterministic.

In contrast to Laplace's split, classical randomness is now understood, since Poincaré (1892), as *deterministic unpredictability*, a consequence of the determination of a dynamics by non-linear equations. Poincaré started this radical change in the epistemological perspective, by a mathematical analysis of the solvability of the equations describing the interactions of at least three celestial bodies in their gravitational fields. As a consequence, the Solar system, for example, turns out to be non-additive, and the non-linearity of the equations expresses this fact. Mathematically, non-additivity (non-linearity) is enhanced as soon as more than two "bodies" (entities) interact and modify by this each mutual action (their dynamics cannot be analyzed one-by-one, then two-by-two and then summed up – as conjectured by Laplace: in this sense are non-additive). In Poincaré's analysis, the addition of one more planet to a single one rotating in a Keplerian orbit around the Sun, radically changes the system and its predictability: as intuited, but not formalized also by Newton, the new gravitational field interferes with the previous ones. Stability is then lost as perturbations below observability may, over time, affect the supposed clockwise and predictable dynamics of planets - technically, minor fluctuations are exponentially amplified by the non-linear effects. In other words, by his "negative result", as he called it, Poincaré showed that in a simple deterministic system (determined by only 12

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enough analyzed use of the words "randomness" and "contingency" in Biology, a specification that is the main purpose of this paper.

equations), stable and unstable trajectories (manifolds) may intersect in an extremely complex way, along orbits that he called “homoclines". They undergo bifurcations, where the choice of a paths may depend on non-observable events (fluctuations or perturbations below measurement).

More precisely, Poincaré proved that the orbits of non-linear systems (in the “phase space” of position and momentum) may intersect infinitely often, but also form “tight meshes ... folded upon themselves without ever intersecting themselves". As early as 1892, thus, Poincaré presented deterministic chaos and its form of complexity for the first time. He then observed that “prediction becomes impossible . . . and we have random phenomena" (Poincare, 1902), since non-measurable perturbations may lead, by the presence of homocline orbits and bifurcations, to completely different trajectories (see Longo, 2013, for a synthetic presentation and its correlation to computational undecidability – or “non-programmability”).

This is why classical randomness is described as deterministic unpredictability, since “noise”, if understood as perturbation/fluctuation below measurement, may measurably modify, after a sufficient time, a perfectly well determined trajectory. Observable randomness, in particular, appears as soon as one has a non-linear system with no analytic (i. e. no linearly approximated) solutions.

The deterministic chaos thus shows up even in our Solar system. By mathematics, it is possible to evaluate the time range of unpredictability for various planets (Laskar 1990; 1994): in rather modest astronomical times, it is provably unpredictable whether the planets will still be turning around the Sun (about one million years as for Pluto).

Philosophically, as we mentioned in the footnote above, it would be fair to say that these phenomena yield an epistemic form of randomness, since, classically, we can access to phenomena only by approximated measurements[4]. That is, by principle, classical (and relativistic, of course) measurement gives an interval: unpredictability develops in time from fluctuations/perturbations below the best possible, “incompressible” measurement (due, at least, to the thermal fluctuation). And one has a deterministic, yet non-programmable, system. Meaning that the discrete space and time programmable trajectory quickly diverges both from the physical process and its continuous representation.

Can we call the novel unity of at least three planets an “emergent systemic unity”? Is the system complex? Why not? Poincaré describes a very complex dynamics in the phase space. Yet, we shall distinguish this minimal form of physical complexity and unity from the unity and complexity of biological systems, also in the light of their specific form of randomness.

2.2 Quantum randomness.

As for quantum randomness, this is “objective” (or intrinsic to the theory), as it is correlated to quantum indetermination, a very different perspective. Note first that Schrödinger's equation is a (even linear) *determination*, but it determines the dynamics only of a *law of probability* in a (possibly infinite dimensional) space of state-functions (the Hilbert space of the state or wave functions). It is *not* the dynamics of position-momentum in ordinary space-time, as the equations of classical and relativistic systems. Thus, when measurement occurs, the equations only *allows to compute the probability* of obtaining a value, not *a value*, like in classical (and relativistic) physics. Second, in the prevailing interpretation, Heisenberg’s indetermination of position/momentum is intrinsic to the understanding of Quantum Mechanics, as a theory. This says that there is no way to determine (the product of) position

[4] Spinoza's notion of randomness, mentioned in the introduction, is a weaker form of epistemic randomness: just ignoring the existence of another deterministic, possibly predictable, chain of events. Yet, *if known,* two systems can, in principle, always be made into one. Classical measurement instead is, by principle, always an interval (i.e. approximated).

and momentum of a quanton below a given constant, Planck's h. In other words, by principle, in the theory, it is not possible to know exactly both position, p, and momentum, q, of a quanton, or the order of the measurements of p and q does not commute (the difference "pq – qp" is at least h). And these values cannot be obtained exactly by computing the Schrödinger equation since this gives only the *probabilities* of obtaining a value.

Moreover, as a consequence of "quantum entanglement" (Einstein et al., 1935), the very notion of "randomness" radically changes (see for recent reflections and many references on this point, Aspect et al., 1982, Jaeger, 2009 or Longo, et al., 2010, Bailly and Longo, 2011). Quantum entanglement was proposed by Schrödinger and mathematically specified by Einstein, Podolski and Rosen in a famous paper of 1935. Einstein's aim was to prove the "incompleteness" of quantum mechanics because of the incompatibility of entanglement with relativity theory. Entangled quanta are the result of an initial systemic unity of two quanta (given by Schrödinger's state function), which are later spatially separated. When their observable properties are measured in remote parts of space, they yield correlated probability values, as if instantaneous communication were possible. Mathematically, this is expressed by the so-called "violation of Bell inequalities", which shows that there is no way to obtain independent measurements of entangled particles. This "violation" has been empirically validated (Aspect et al., 1982) and confirmed many times since then: it is the idea that should allow Quantum Computing, eventually. In short, if two classical dice interact when flipping (they touch each other or interact by whatever physical way) and later separate, one may *independently* compute the probabilities of their expected outcomes (Bell inequalities are complied). In contrast to this, there is no way to obtain independent measurements of entangled particles (particles mathematically treated as a system), even when they are far away from each other, in space. And Einstein's paradoxical deduction, based on a pure mathematical reasoning on Schrödinger's equation, has been shown to be empirically valid: entangled yet remote particles do exist, they have been actually produced several times, since Aspect's early experiments in Paris. Thus, one has different forms of randomness in classical vs. quantum physics, as the "measure of randomness" (that is, probabilities) provably differ. This difference is one of the reasons for the incompatibility of relativistic and quantum physics.

In conclusion, there is no internal inconsistency of quantum mechanics, at least, not as intended by Einstein's proposal, but "just" an incompatibility of the two field theories and in the different understanding of randomness. In Quantum Mechanics, this is given by an intrinsic indetermination in measurement and mathematically differs from the classical one, in presence of entanglement. It happens, and this is one of our theses, that classical and quantum randomness coexists or superpose in biological events. This is a major theoretical challenge for the proposal of a rigorous notion of randomness in Biology.

3. Continua, discrete and quantum randomness in Biology.

Before discussing the presence of quantum effects (and randomness) in living organisms, let's briefly analyze some recent use in Biology of the terms of entanglement and superposition so important in general and particularly as for randomness in Quantum Physics.

As discussed in Buiatti and Buiatti (2008), living systems are intrinsically *multiverse* showing at the same time different properties. We may then argue that this concept is analogous to Schrodinger's superposition although certainly not being homologous.

Let's first refer to the history of Biology in the twentieth century. For a long time, starting from the very beginning of the twentieth century, the presence of two contrasting properties in living matter were interpreted, in many cases, as antinomies and led to harsh debates on which of the two properties

was to be considered prevailing. In Biology, the most relevant sources of discussion have been the putative antinomies "chance vs. necessity", "contingency vs. determinism" and "continuous vs. discrete". At the beginning, biological discreteness and chance were prevailing, following Mendel's discoveries and the Mutation's Theory of evolution by Hugo de Vries, against the holistic Darwinian and Galtonian vision of a continuous evolutionary change. In the same years, in Physics, Planck's law, the photoelectric effect and the discrete values of the energy spectrum of the electron seemed to contradict Maxwell's theory of Electromagnetism, based on waves in continuous fields.

The concept of the simultaneous presence of discrete and continuous patterns in Biology was introduced by the discovery by the Swedish plant geneticist Nillsson-Ehle in 1909 who showed that the continuous distribution of color intensity of wheat kernels was determined by the additive action of variable numbers of discrete genetic variants (alleles), affecting the intensity of colors. However, the coexistence of discreteness and continuity as a general feature of living systems was formally discussed and fully accepted only later on, by J.L. Lush (1945), K. Mather (1949) and I.M. Lerner (1950). A whole new discipline, Quantitative Genetics, was built and complex mathematical models were developed, in which the effects of the environment were also taken as a further interfering quantitative variable leading to the continuous distributions of phenotypes. These findings brought to accept a conceptual superposition, since they derive from the existence *at the same time* and *in the same object* of properties based on two contrasting features such as discreteness and continuity.

Similar conclusions can be drawn for some more antinomies in Biology like the antinomy we already mentioned between chance and necessity or "internal" and "external". For instance, multi-cellular organisms live within ecosystems but have an internal space (Claude Bernard's "milieu intérieur"), yet these spaces interact or cannot be strictly separated. The same concept can be extended to all the levels of the hierarchical organization of life, from molecules to the Biosphere where the behavior of objects at the higher level is influenced by those of the lower level *and vice versa*.

As for entanglement, this term, as defined by Arndt et al. (2009), "means a non-classical correlation", or a non-separability connection between physical observables, possibly then also between *physiological properties.* In a similar sense and within Biology, it has been advocated by Soto et al., (2008): meaning that two different physiological processes cannot be observed independently. For example, they stress the mutual influence of stroma and epithelium morphogeneses. That is, recombining stroma and parenchyma (usually epithelium) from different organs has provided evidence about the inductive role of the stroma over the epithelium, as well as some indications that the epithelium possesses some degree of cellular identity that is not influenced by the stroma.

It should be clear that the biological concepts of entanglement and super-position above are conceptually analogous but non homologous to quantum entanglement, as in the latter more precisely refers to (correlated) particles that are in an opposite state. However, examples of proper quantum entanglement, in biological processes, have been given and more general quantum processes are analyzed by a brand new discipline (Quantum Biology), see (Arndt et al., 2009). Reported examples are polarization-entangled photon-pairs, superconducting circuits, nuclear spins in small molecules, spin noise in atomic ensembles, trapped ions, and other systems (see also the references in Nielsen and Chuang, 2000). Note that, once established, this quantum-like connection may theoretically persist over long distances and times, unless it is perturbed by external interactions and measurements (Arndt et al., 2009). The success of Quantum Biology should be no wonder, as living systems are made of molecules and quantum chemistry certainly is a well-established field of research (see the very comprehensive review on proton coupled electron transfer in Biology by St. Reece and D.G. Noguera (2009)). For instance, electron tunneling has been observed in cellular respiration (Gray and Winkler,

2003) and electron transport along DNA has been shown by Winkler et al. (2005). The first experimental evidence for proton tunnelling has been given in 1989 (Cha et al., 1989) for the enzyme alcohol de-hydrogenase, which transfers a proton from alcohol to nicotinamide adenine dinucleotide.

Of particular interest are two more areas of investigation with an obviously relevant relationship with the origin of life and evolution, namely quantum related processes in DNA dynamics and in photosynthesis, the major biological process allowing the storage of solar energy and its usage for the construction of living matter. As for DNA, Perez et al. (2010) showed that nuclear quantum effects such as tunnelling and zero point motion destabilize rare tautomeric enol forms through the transfer of two hydrogen-bonded protons between adenine and thymine and between cytosine and guanine, thus confirming the suggestion by Watson and Crick in their 1953 paper of a role of prototropic tautomerism of bases in the induction of spontaneous point mutations. This finding was supported by earlier data obtained in 1995 on the molecular basis of the dynamics and the role of quantum tunnelling in DNA (Douhal et al.1995). These authors showed through a high resolution analysis of the cooperativity of formation of the tautomer, that the first step of tautomer formation is the shift of protons from one base to the other, a dynamical process of femtoseconds. Moreover, Noguera et al., 2004, showed that metal cations like Cu 2+ interact with DNA and influence intermolecular Proton Transfer processes. Finally, Ceròn-Carrasco et al, (2009) found that the double proton transfer affects spontaneous mutation in RNA duplexes, particularly in G-C base pairs. This is a particularly relevant discovery, since RNA duplexes, according to most theories on the origin of life, most probably played a key role in the primeval so called RNA-world.

Photosynthesis captures sunlight energy using the so-called Fenna-Matthews-Olson antenna complex containing chromophore proteins present in the chlorosome, the reaction center of the chloroplast. The energy captured is then used it to convert carbon dioxide in biomass. This process has been shown by Engel et al. (2007) to work according to quantum probability laws instead of classical laws. Collini et al. (2010) showed, through two-dimensional photo echo-spectroscopy, quantum coherent sharing of electronic oscillation across proteins at ambient temperature in photosynthetic algae. This result, in contrast with the general idea that the presence of water and high temperatures (physiological temperatures) would determine de-coherence, has been confirmed by Sarovar et al. (2010) who analyzed entanglement in multi-chromophoric light-harvesting complexes and showed that a small amount of long-range and multipartite entanglement can exist even at physiological temperatures.

Recently, quantum biological studies are being extended to other areas as shown for instance by the results of modeling of a possible radical-pair entanglement mechanism of avian magnetic orientation where birds could be “seeing” their path because of the effects of magnetic fields on cryptochrome (for more details, see (Cai J. et al., 2010)).

The general picture coming from all these results confirms the concept that the dynamics of living systems stems from an interaction between classical and quantum processes, the last being possible also at fairly high temperatures and in the presence of water as shown first and confirmed since the early work by Del Giudice (1986). Later, it was also found that stochastic metabolic activities may be induced or accelerated by quantum effects analyzed in terms of Quantum Electro-Dynamics (QED). This phenomenon may depend on the very peculiar, “(super-)coherent” structure of water in cells. Since these molecules are mostly at no more than a few μm from a membrane, they partly organize their spins and slow down their relative Brownian motion by groups, as explained in terms of QED by Del Giudice et al. (1998; 2006). As a consequence, it may be conjectured that, at constant temperature, the other molecules increase their random movements and stochastic interactions. In our view, this fact may further justify the current increasing interest in stochastic gene expression, (Kupiec, 1997; Paldi

2003; Arjun R. and van Oudenaarden R., 2008). A survey on stochastic gene expression and its consequences may be found in (Heams, 2013).

4. Interactions and different kinds of randomness in Biological systems.

The first point we want to make is that we cannot have a sound theory of biological randomness without at least relating the two forms discussed above of physical randomness, in a cell. The quantum and "quantum-like" effects we described may happen jointly to classical dynamics and their proper form of randomness, i. e. they take place simultaneously and affect each other. As far as we know, since a "unified understanding" of quantum and classical/relativistic fields and related entanglement phenomena has not yet been invented, no physical theory, so far, deals at once with the "superposition" of classical and quantum randomness.

Thus, beginning with intracellular phenomena and then with cell to cell interactions, in a tissue, one may need a classical, a quantum but also an ad hoc dynamical treatment, as it should be given concerning a largely stochastic dynamics whose structure of determination (and subsequent randomness) is far from being known. And, this is not the end.

4.1 Evolution, structure and dynamics of the multi-level organization of life.

In living systems, the formation of different levels of organization, both in embryogenesis and evolution (see later), corresponds, in principle, to a *local* decrease of entropy, since organization increases, thus leading to a decrease of randomness. That is, during these biological processes, locally, some more "order" appears in the Universe – at the price, of course, of energy consumption and, thus, of increasing entropy somewhere else. Yet, each of these "new" levels of organization has its-own non-linear (or quantum) internal dynamics, and, moreover, and this will be crucial for our analysis, these levels mutually interact (an inter-level dynamics). The novel forms of interactions between continuously differentiating new components yield a new form of randomness, which we will discuss later in sub-section 4.2 in terms of "bio-resonance".

In order to discuss these two contrasting and coexisting tendencies of life – formation of order while inducing new forms of randomness – we will first discuss the processes of increase in number, differentiation and connection of components, throughout evolution from the possible origin of life to the formation of the interacting and interwoven hierarchical organization of life in the Biosphere.

As discussed thoroughly in a review by Buiatti and Buiatti (2008), the global living system is hierarchically organized into levels of increasing complexity, from networks of molecules, to cells, to organs and organisms in pluricellular organisms, to ecosystems to the biosphere, where all levels are endowed with some general properties as well as with level dependent ones (see also Bailly and Longo, 2011).

In our view, following the hypothesis of Eigen and Schuster (1979), everything started when two kinds of macromolecules, DNA and RNA, built a dynamical micro-system capable of reciprocal replication. The next step may have been compartmentalization and the formation of primeval cells. Then, aggregation processes gave rise to colonies where, as it still happens in bacterial colonies, differentiation and cooperation followed. Later on, more complex eukaryotic cells derived from fusions between nucleated cells and others bearing two kinds of small circular genomes, namely the mitochondria, capable of respiration, and, in plants, the chloroplasts as well, capable of the only process present in living systems leading to the fixation of solar energy.

Multi-cellular organisms belonging to both plant and animal kingdoms were later born and a more complex cooperative "division of labor" between cells capable of different functions was developed in single organisms, again through complex processes of multiplication and differentiation. This hypothesis is supported by a number of thoroughly described examples of cellular multiplication and differentiation in colonies of bacteria and unicellular eukaryotes, along developmental lines which resemble cells and tissue differentiation in multi-cellular organisms, all showing composite life cycles including mono-cellular and multi-cellular stages.

Already in 1979, J.W.T. Wimpenny and J.A. Parr observed different levels of activity of a series of enzymes in the external and internal areas of *Enterobacter cloacae* large colonies.

Later on, J.C. McMichael (1992), studying the behavior of *Moraxella bovis* colonies grown between agar and polystyrene in Petri dishes, found that they were differentiated into concentric rings. In the two outer ring zones dividing bacteria formed agar surface colonies of very different morphology from that of the innermost zones, where cells were quiescent. Rieger et al., 2008 and Cepl et al., 2010, studied thoroughly the morphology and behavior of *Serratia marcescens* "bodies" as they called them, with an explicit reference to multi-cellular organisms morphology. Also *Serratia rubidaea* bodies are differentiated in areas of different colors and textures, differentiation being directed by a series of molecular signals between cells and coming from the outer area of the colonies. Differentiation then was shown to be induced by a *dynamic cooperation* between cells, where varying concentrations of signals in different areas of the colonies regulate both texture and colors.

It is worth noting that, as we shall discuss later, the dynamic flow of molecular cascades also induces the primary differentiation in the embryos of most multi-cellular animals from *Drosophyla*, where it has been fully demonstrated for the first time, to mammals. In all these cases, thus, differentiation is mainly epigenetic, meaning that it is generally not due to changes in the genetic complements of the aggregating cells but to different levels of expression, from zero to a maximum, of different sets of genes in different areas of the "organism", where by organism we now mean all kinds of organization of living systems from cell colonies to plants and animals. This possible model of the intermediate steps from unicellular to multi-cellular organisms seems to be supported by two examples, a prokaryotic and an eukaryotic one, in whose life cycle, "bodies" endowed with complex cell differentiation derive from the aggregation of single cells (see the review by Dao et al. (2000)).

The two organisms are *Myxococcus Xanthus,* a prokaryote, and *Dictyostelium discoideum,* an eukaryote (an amoeba)**,** are both living in the soil and feeding on bacteria. Both have surprisingly similar general life cycles involving a process of aggregation, the use of sensor histidine kinases to regulate development, and the use of mechanisms of quorum sensing to count the number of cells before multicellular development. Bacteria and amoebas live for a large part of their cycles as individual cells, yet, while Dictyostelium feeds by phagocytosis, Myxococcus groups of cells attack other bacteria using large quantities of digestive enzymes. Therefore, while in bacterial cycles cooperation between different cells occurs also before aggregation, a collaborative behavior in Dictyostelium develops later.

Aggregation in this case is induced when nutrients start being scarce and cells start moving to join a "founder" cell through complex systems of chemiotaxis. The process is induced and regulated by the induction of cyclic AMP synthesis by low concentrations of food, the "founder" amoeba being simply the first of the population whose internal level of cyclic AMP reaches a threshold level. At that moment AMP production enters into an exponential phase and a part of it is released in the medium inducing the movement of surrounding amoebas, which will aggregate forming initially undifferentiated mounds containing an average of 100,000 cells. The mound will then differentiate leading to the formation of a slug that will move in search of a new, more favorable environment in terms of amounts of nutrients.

Once found such a suitable environment, the slug will stop its search and transform itself into a stalk and a fruiting body where cells will be changed into spores to be released. Each spore therefore will become again an amoeba and a new cycle will start. The cycle of Myxococcus Xantus is similar although the fruiting structures are much less complex.

It is worth noting here that the number of cells in the slug of Dictyostelium is far higher than those which will become spores giving rise to the amoebas of the future cycle, and this suggests the possible presence of selection processes. Now, it should be recalled that amoebas single cell populations are highly heterogeneous as they are derived from meiotic processes, a fact which prompted a series of studies of the dynamics of what may be called the "social structure and dynamics of slime moulds". Now we know (Ostrowsky et al., 2008, Flowers et al., 2010, Mehdiabadi et al., 2008, Strassmann et al., 2000) that the aggregation processes are based on kin recognition and on the selection against the possible "cheaters", that is genetically different cells liable to enter in the fruiting body and in the next generation. As shown by Van Driessche et al, (2002), about 25% of Dictyostelium genes are differentially regulated during development and in different cell types, through a cascade of signal transduction events initially triggered by the variation in cAMP concentration in time and space, based on coordinated cell to cell interactions. Thus, differentiation processes in Dictyostelium are in a way similar to those occurring in multi-cellular animals and plants, all depending on initial triggers coming from the cell environment and from epigenetic cell-to cell interactions. Interestingly, this pattern is also similar to what happens also at the population level in other social systems of multi-cellular organisms such as, for instance, bees. In this case physical and behavioral differentiation are both epigenetically induced by interactions between individuals belonging to the same community. In the case of bees, for instance, cast differentiation has been shown to derive from social behavior as suggested by the fact that "queens" and workers have the same genotypes. The different morphology, physiology and behavior of queens derives from different gene expression patterns induced by their nutrition by workers with the so-called royal jelly (see for instance Kucharski et al., 2008).

Climbing to yet higher order systems, there exist further levels of organization among different mono-specific populations of organisms (the "avatars" by Eldredge (2008), mentioned in the introduction above) that live in the same ecosystem, or in different ecosystems, all connected to each-other in the same continent and between continents through air and water.

After this brief discussion on the complex aggregation or multiplication processes followed by differentiation throughout development and evolution, we shall now discuss in which sense the increasing number of levels of organization yields further forms of randomness. In section 7, we will try to understand the role of random evolutionary paths as a possible factor explaining the increasing complexity of life, including the unicellular aggregations discussed above.

4.2 Bio-resonance.

A cell is made out of a network of interacting molecules within a membrane; colonies and tissues are made of groups of interacting cells; individual organisms are interacting with others of the same and different species in the same ecosystem and all ecosystems interact in the Biosphere.

Interactions thus happen at all levels of organization between different objects within a level, and*, internally to each level,* they are not additive. Moreover, as we shall see later, communication is both intra and inter-level and therefore a change in one level may spread its effects at the same time to higher and lower ones.

At the molecular level interactions between molecules generally lead to the formation of complexes between two or more of them with globally different but complementary conformations (as for their

non additivity, see (Ricard, 2008)). Cells interact either exchanging molecules and/or energy (gradients), like in the case of neurons, through intercellular membranes or through the reciprocal recognition and perception, as it happens for instance in the case of contact inhibition between differentiated cells. Contact inhibition is critical for the maintenance of the organization of cell networks particularly in animals where disruption may mean undesirable cell division putatively leading to cancer (Soto and Sonneschein, 1999). Exchange of molecules may be "horizontal" (within the same level of organization), "vertical" (between levels) or between the organism and the external environment. It may be mediated by the recognition of specific molecules or energetic inputs by complementary trans-membrane receptors. After recognition the receptor will change conformation and start a cascade of molecular transfers within the cell, very often leading to gene activation or repression and the active synthesis of new molecules needed for the response to the primary incoming input. Moreover, interaction may be based on exchanges of energy, matter or just *gradients* of energy and matter. For example, in a synaptic ion transfer, it is not the energy transfer that matters, but the variation of energy transfer.

To put this in another terminology and as suggested by the referee, following Lemke (2000) and Salthe (1985), each new emergent level of organization in the dynamics of a complex self-organizing system functions to re-organize the level below and this, in turn, re-structures the level above (in a "meaningful" way, in Lemke's terminology). In the 3-level paradigm of Salthe, units on level N are constituted by interactions among the units at the lower level (N-1), but that of all the possible configurations, which such interactions might produce at level N, only those actually occur which are allowed by boundary conditions set at level (N+1). As mentioned above, non-additivity (as mathematical non-linearity) applies as soon as more than two pertinent entities interact and modify by this each mutual action. This game of intra-level *and* inter-level interactions is thus at many bodies and highly non-linear. A typical consequence of non-linearity is the amplification of minor fluctuations, which is the origin of classical randomness, as explained above.

Yet there is more in these phenomena. In logical terms, we have a "higher order" form of intra- and inter-level interactions, rarely dealt with (if ever) in mathematical Physics. Poincaré's work allowed to focus on *resonance effects* between two planets and one Sun: just one (relatively simple) deterministic system or, one simple level of organization with non-linear interactions. And he invented deterministic chaos, as the result of amplification of fluctuations/perturbations below measurement[5].

Quantum Mechanics deals with randomness at its own scale, as we observed, and unification with relativistic/classical physics is far from being accomplished. In short, a lot may be said in physics even when looking at only one level of determination/organization. Mathematics generally deals with homogeneous systems, or, more precisely, the mathematical formalization of a physical phenomenon tends to "homogenize" it: a set of equations or an evolution function sets variables and observables in a unique and pre-given phase space.

On the other hand, in Biology, one has to deal with interacting, yet different levels of organization, each possessing its own (possibly mathematical) form of determination and where each determination may be non-linear or quantum, homogeneously. The further non-additivity, or non-linearity of these

[5] Technically, in Astrophysics, two planets are in maximal resonance/gravitational interference when they are on the same line with respect to the Sun. Many other forms of resonance, as a component of "divergence" of possible trajectories and, thus, of unpredictability, have been analyzed in mathematical physics. A rather general one is the Pollicott-Ruelle resonance, which applies also to open systems and is related to various forms of dynamical entropy, (Gaspard, 2007). Thus, while the first form of instability (Poincaré's) is analyzed in system at equilibrium, the second form may be extended to systems far from equilibrium.

multi-level interactions induces what we shall call *"bio-resonance"* and its subsequent proper form of randomness. Once more, minor fluctuations in one level or organization (one structure of determination, if explicitly given by mathematics) may induce major changes in another level and this may give random phenomena (i.e. unpredictable by each of the intended structure of determination, at each level and globally, if any).

Can this be reduced to a familiar form of physical randomness? May be, but for the time being, we shall discuss the physical singularity of life and the peculiar form of randomness derived from higher order interactions, while trying to conceptualize it as clearly as we can. Consider, say, that even computational and dynamic randomness (ergodicity) have been only recently (and only partially) correlated, see (Longo, 2011).

In summary, bio-resonance takes place among different levels of organization, each level having its "autonomous" activity liable to be treated with different conceptual – sometimes mathematical – tools, each with its own form of (internal) non-linearity, resonance and alike. Thus, minor changes in one level may be amplified *also* by the exchanges with another level: for example, a minor perturbation of the endocrine system may induce a cancer in a tissue (Soto and Sonnenschein, 2010).

Moreover, each system or level is integrated and regulated by all the other elements of the *same* as well as of *different* levels of organization - while affecting them. Thus, the other fundamental aspect we want to stress here is that bio-resonance, based on integrating and regulating interactions, has both a stabilizing and a destabilizing role, in contrast to the physical "parallel" notions, mostly related to divergence and instability. Typically, the cellular dialogue in a healthy tissue, the tissue's matrix, the collagen, the subsequent tensegrity ... all control, stabilize and canalize cells' reproduction and variation. And the entire organism regulates local phenomena by the hormonal, neural, immune systems, by a two/many ways interaction.

4.2.1 Homeorhesis and regulation

For a better understanding of the basics of this discussion we shall introduce here further concepts that are typical of living systems, analogous but not necessarily homologous to similar and well known ones in physical theories.

Biological objects are, as discussed by Waddington, "homeorhetic", as opposed to homeo-static, in the sense that, during their cycles, they keep changing. Moreover, their onto-phylogenetic path is largely unpredictable, though preserving, as long as possible, the internal coherence of an organism and its relations to the ecosystem. It is unpredictable because of the random effects at each level and of the bio-resonance effects between different levels. In a very informal sense, an organism develops within an attractor, as a locally unstable yet globally stable structure, whose space is limited by the genetic structure, the phenotypic plasticity of components, also partially heritable, and by the dynamics of the connections (including regulation and integration, both being aspects of bio-resonance). As we mentioned above and as also suggested by Arndt et al. (2009), these connections between components and levels of organization can in a way be analyzed in terms of the concept of "bio-entanglement", to which one should add bio-resonance, particularly when coherence rules are due to interactions among different levels of organization. In all cases, the specific and general structural and dynamical "rules" of bio-entanglement and bio-resonance have been and are evolving in time under the pressure of processes of "extended selection", a term recently suggested by one of us (Buiatti, 2011) including classical selection by the environment, but also "internal selection" (Bateson, 1979), that is selection imposed by the internal coherence at each level of organization of living networks. The concept of internal selection is always correlated with that of co-evolution of the components of networks at all

levels of organization, already implicitly mentioned by Charles Darwin in his "laws of correlated variations". Therefore each living system is endowed with specific levels of robustness and resilience shaping the attractor permanently in a state of critical transition, as hinted below.

This is why, the analysis of biological processes in terms of interactivity and non-linearity is sound, as both in classical and quantum dynamics there surely are plenty of interactive, non-additive systems, all major challenges for mathematical intelligibility, but it is still insufficient (or *incomplete*). Their complexity is not comparable with the biological complexity, first because those physical dynamics are always described at one (mathematically homogeneous) level of determination, while an organism contains many such (interacting) levels. Second, because, if the description of an organism as a permanent (extended) critical transitions is pertinent, as suggested in (Bailly and Longo, 2011; Longo and Montevil, 2011) and some more discussed below, then any reasonable measurement of its complexity in the physical terms of one level of organization would be mathematically "infinite"[6].

We may here recall, as an example of the difficult task of measuring living networks, the interesting but not sufficient analysis of their structure by Barabasi and his group (2004) (see (Fox-Keller, 2005) for a critique of this approach). Networks are described as structures largely inspired by computers' networks, with their hubs and "scale invariants", and are only defined from a formal point of view, without entering into the discussion of their specific and material dynamics. Furthermore, in this approach, they are analyzed at only one level of organization, determined by the mathematics of networks, based on two key assumptions: a principle of "preferential attachment" and the maintenance of the "mean number of connections" at each node. It is then possible that the world-wide web and the cellular metabolic networks yield similar results and are shown to obey to the same or similar rules, when one does not take into account what happens in their multilevel contexts. Moreover, and this is interesting, when dynamical functions are added to these "small-world" models, simulation experiments yield results common to classical physical non-linear system. This is very useful to understand some very (too) general behaviors, but not sufficient, say, to understand how life dynamics take place: once more, just one level of internal interactions is isolated from the multilevel interactions, and the material structure of the hubs and links (they are living cells and ever changing synapsis) is not taken into account. In a sense, as a consequence of Galileo's analysis, we understood that a falling dog is accelerated like a stone, due to a major physical invariant, this is good to know, yet it doesn't say much about the biology of dogs.

An example of further, remarkable, physical insight is given by the continuous dynamics of morphogenesis. Since Turing's 1952 work and by completely different mathematical tools from the ones mentioned above, these investigations opened the way to very important analyses of organs' formation. They equally apply to any physical action/reaction/diffusion system. However, organ formation takes place under the severe constraints imposed by DNA, in an organism that integrates and regulates the dynamics. Once more, the mathematics of morphogenesis and phyllotaxis, even in its most refined way, see (Jean, 1994), describes one level of organization. In general, this is the level of organs, which exchange energy or matter and are thus "shaped" by physical constraints. The situation is also similar to that of critical phenomena applied to Biology, where universality laws only give relevant information on common physical features of critical transitions (Bak et al., 1988).

In conclusion, these approaches, though very interesting, are based on strong physico-mathematical assumptions and crucially deal with just one *homogeneous* mathematical structure of determination.

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[6] In physical criticality, several observables or their derivatives diverge, at the transition point, see (Binney et al., 1992); this mathematically infinite complexity is a non-obvious issue, possibly to be further explored, for a better understanding of the biological vs. physical notions of complexity: infinity is a useful, precise and robust concept in mathematics.

Thus, they stop on the verge of the proper complexity of the *heterogeneous*, many level organization of living entities, mutually integrated and regulated. A property that begins at least with the single living cells and more so with colonies, symbiosis and cenobiosis of bacteria and unicellular eukaryotes, as we hinted above. We insist here in this heterogeneity in particular from the point of view of the random phenomena that may depend on it, as a component of bio-resonance.

As a matter of fact, the biological challenge begins when one deals, for instance, with a metabolic network in a cell, but must take into account the fact that it belongs to a cellular network composing a tissue, which is part of an organ, integrated in and regulated by an organism and so on, as discussed before, where all the different levels of organization are inter-regulated by cascades of events in all directions, exposed and reacting to matter and energy inputs coming both from the living and the inert components of the systems. Moreover, all dynamics involve interference and superposition between classical non-linear and quantum processes, as well as the stabilizing/destabilizing effect of bio-resonance and its contribution to randomness.

This is the conceptual, first, then the mathematical analysis, if possible, we have to work at, in order to grasp the proper complexity of the living state of matter, well beyond, but including, the non-linear, interactive structures of physical dynamics and networks.

5. Complicated/complex

A non-linear system may be also obtained by a bottom-up artificial construction: consider for instance a double pendulum, connected to a spring pulling on a non-linear oscillator … the "whole" yields a highly unpredictable non-linear machine. One may even insert such a device into a network of similar machines leading to even more complicated structures. Is such a system complex or just "complicated"? Yes, the machine is complex, if non-linearity of interactions is considered a sufficient characterization of complexity. No, and it should be better called "complicated", if we consider *complex* an object only when it has a multi-level structure of determination. That is, as we mentioned in the previous section, when each level being understood through different conceptual/mathematical tools, and when it is, at the same time, "ordered *and* disordered, regular *and* irregular, variant *and* invariant, stable *and* instable, integrated *and* differentiated" (a description of complexity proposed by Edelman (1987)). To complete the story we may add to this list of conceptual oppositions, "far from equilibrium *and* maintaining some components at equilibrium, dissipative *and* conservative, self-organized *and* subject to constraints, entropic *and* anti-entropic, in critical singularities *and* extended to an interval of criticality" (see below). Some networks, may satisfy part of the first list of opposite properties, but still, physical networks and morphogenetic dynamics are generally treated as equilibrium systems and do not satisfy the second list of conceptual oppositions. These antinomies are at the core of the biological theoretizing, as this must take into account opposing constraints and interacting levels, which yield a coherent and ever changing dynamics. The latter may be understood only by focusing on this challenging game of conceptual oppositions.

In particular, this second group of co-existing opposites may be properly found only in the presence of different levels of organization, that is, molecular, cellular, tissues' levels, composing organs of an organism and so on. Integration and regulation are due to the key fact that all levels, with the exception of the molecular one, are constructed also top-down**,** their "components" being a priori integrated as they originate from a pre-existing organization. That is, in an organism, integration and regulation are not obtained by adding cells, tissues, organs, but by differentiation from an original "organism", one zygote cell. The embryogenesis of an evolved multi-cellular organism is not the result of adding a leg

or a brain, as we can add a wheel or a computer to the pendulum/spring/oscillator device above or as we can add further nodes, hubs and links to an artificial network like the World Wide Web for example. The apparent exceptions to this rule, such as a bacterium taking up a plasmid or, more similarly to organogenesis, the formation of the slug of Dictyostelium mentioned in sect. 4.1, may suggest the ever changing dynamics of unicellular organisms and the way multicellular ones appeared during evolution: organisms' formation uses both bottom-up and top-down dynamics. In the latter case, one sees a process of aggregation that substitutes the first cell divisions of a zygote in the formation of an embryo. In a slug, this process leads to a mass of undifferentiated cells genetically homogeneous with the rare exception of some "non-kin" "cheaters". Thus, also in this case, differentiation occurs later, through chemical exchanges between cells and with the "environment". These exchanges are as well crucial in the well-known examples of Drosophila and humans.

In conclusion, even in the formation of bacterial colonies, differentiation, leading to organismal structures, is essentially an epigenetic phenomenon, which applies to already aggregated and genetically kin cells, and it is not obtained by addition of an extra device, like in artificial/physical constructions, from clocks to computer networks. Bottom-up, top-down dynamics all coexist in Biology, as well as middle-out (Noble, 2010) and symbiotic processes, when evolutionary convenience joins previously autonomous organisms.

It may be thus fair to call "complicated" the physical multi-level devices liable to be constructed essentially bottom-up, and reserve the word "complex" to living structures, as a result of biological evolution, in particular in presence of the phenomena hinted above, that is:

1. bio-entanglement;
2. bio-resonance:
3. the join of top-down, bottom-up construction, symbiosis ..., based on differentiation and/or integration from one or a few (genetically homogeneous) individual cells.

The first two properties are made possible by the last one, which forces integration, in existing organisms. Note that bio-entanglement and bio-resonance are also part of the constraints, thus they contribute to differentiation and its control.

It should be recalled that, as mentioned before, bio-entanglement and bio-resonance provide a further understanding of the "correlated variation" mentioned by Darwin or, with an updated term, to co-evolution.

In other words organisms are "physiologically entangled" with each other and within themselves. Yet, while physical entanglement is expressed in terms of quantum measurement and the possibility of instantaneous knowledge of the result of a remote measure from a local one, by this notion we mean here that there is no *physiological measurement* of an organ's activity that may be derived nor isolated from the values of the others' activity. No reasonable physiological measurement can be made on a brain, say, which is isolated in a flowerpot, as in most network approaches to neural systems. Similarly, the physiological analysis of a lung or a vascular system does not make sense away from an organism. In other words, at variance with physical entanglement, "physiological entanglement" in an evolved organism means the simultaneous and correlated dynamics of different components through the mutual exchange of energy and matter.

Nesting and coupling different levels of organization, proper randomness (due to classical/quantum coexistence and to inter-level bio-resonance effects), entanglement of components as superposition of physiological activities …. The blend of all these peculiar conditions yields the proper complexity of the living state of matter.

6. More on biological randomness.

As mentioned above, classical randomness is deterministic unpredictability in equilibrium dynamics. In case of non-linear interactions, the system may yield highly unstable trajectories, yet constantly remaining at equilibrium. These systems are conservative and their trajectories may be mathematically analyzed (yet not predicted) by extremizing a functional (a lagrangian or hamiltonian), that is, they go along an optimal trajectory, a geodesic, in a suitable phase space.

In an equilibrium non-linear dynamics, a trajectory is stable when it is not modified by minor fluctuations/perturbations. It is unstable, when it is subject to the too well known (and so badly understood) "butterfly effect", whose mathematics we owe first to Poincaré and his analysis of the planetary determination. This effect is more rigorously called "sensitivity to initial and border conditions", but two more mathematical properties are required for classical deterministic chaos, as better specified in the 1970s, (see Devaney (1989)).

In Biology, living systems dynamics are not a matter of stable or unstable equilibrium, but of *far from equilibrium* processes, i.e. which undergo a flow of energy or matter, yet they are "structurally stable" systems[7]. This hard to understand simultaneous structural stability and non-conservative behavior is a blend of stability and instability due to the coexistence of opposite properties such as "order/disorder … integration/differentiation" mentioned above. Typically, integration and differentiation stabilize and destabilize, preserve and modify symmetries, since they maintain the global stability, while allowing the permanent reconstruction of the living system as exemplified by the organism, an object which continuously passes throughout "critical states". That is, an organism is not "just" a process, a dynamics: it is a permanent passage through a critical transition, which is a peculiar bifurcation where, at least locally, it re-organizes itself. For instance, each mitosis breaks symmetries: the two "new" cells differ from the original one and from each other. This bifurcation is fully general as it applies to cell division across the phyla; it is critical in the sense that, in particular, it continually changes symmetries by breaking existing and constructing new ones (Longo and Montévil, 2011). Mathematically, this changes the invariants (which are mathematical symmetries), yet it may preserve the changing homeorhetic stability of the global structure, be it an organism or an ecosystem, while exploring new paths, through variability and differentiation: an organisms, an ecosystem is continually and always (slightly) differently reconstructed. This exploration of (possibly new) "possibilities" takes place at all levels of organization, through evolution and ontogenesis. It is an essential component of biological plasticity and adaptability.

But … what are the "possibilities"? Let us focus on evolution, the key process for the understanding of the specificity of biological randomness and its differences with respect to the known forms of physical randomness. From the superposition of classical and quantum randomness, in a cell, an organism, an ecosystem, and by bio-resonance at different levels of organization, stems, in Biology, the need of a third, stronger, notion of randomness. A form of randomness where the very list of possibilities to be explored is not already given, as it usually is in Physics. When flipping a coin or throwing dies, we know in advance the list of two or six possible outcomes. Even in quantum Physics, the list of possibilities is mathematically pre-given, be it an infinite space like a Focks' space that accommodates all the highly unpredictable, but possible creation of new particles. In Biology, it is the very "phase space" of evolution, the space of possible phenotypes, as pertinent observables, which is highly unpredictable or randomly co-constituted, as proposed in (Longo et al., 2012). This

[7] Under stress, some organisms may survive in a quasi-equilibrium state, see (Minsky et al., 2002).

mathematical challenge is not treated by current physical theories: at most, they deal with dynamically parametrized dimensions for a pre-defined phase space, as in statistical physics. One of the reasons for this yet to be studied form of unpredictability in biological theoretizing, thus of biological randomness, may be given in terms of quantum randomness. A key point of the so called "standard interpretation" of Quantum Mechanics (in the opinion of these authors, the most interesting one), there are no "hidden variables". In short, unpredictability in *classical* dynamics pops out from a "hidden" fluctuation or perturbation (below measurement) – and this may be considered a hidden variable. In Quantum Physics instead the theoretical originality and relevance is based on the fact that, for example, the spin up or down of an electron is *pure contingency*. It has no hidden cause, it is *a-causal,* it is as it is. It seems as if it were difficult to many to leave Descartes, Leibniz and Spinoza's universe, where "every event has a cause" (they all agree on this, yet their agreement is an exception – Poincaré and Einstein as well remained in this causal frame). If the relevance of quantum phenomena in biology is confirmed, as it seems, then a mutation or a molecular cascade may be the result of a quantum a-causal event. And the molecular dynamics may have somatic/phenotypic consequences. If the latter is compatible with the internal and external ecosytems, we would then have a radically unpredictable change of the biological observables, the phenotypes, thus of the pertinent phase space, as observed in (Longo et al., 2012).

Moreover, in reference to Physics, many are still talking of "equilibrium dynamics" (and we also did so in reference to deterministic chaos) and molecular biologists are hardly digesting Poincaré's discovery that an equilibrium dynamics may be highly unstable, thus random, yet deterministic. As we said, the still dominating Monod's alternative (Chance and Necessity), suggests that deterministic means "necessary" thus predictable (i. e. programmable) and that randomness is a very different issue, due to noise.

From our perspective, in Biology, the situation is rather different. As we recalled above and it is widely acknowledged (but not always applied), living objects are far form equilibrium, dissipative systems. This is so for one single organism as well as for an ecosystem. In some cases the system may be stationary or in a steady state (constant input/output flow of energy), or, at least, this is a reasonable working assumption, in order at least to write thermo-dynamical balance equations. On the ground of this mathematical assumption, some aspects of evolution have been analyzed (Bailly and Longo, 2009) and the notion of "extended critical transition" was proposed (Bailly and Longo, 2008, 2011; Longo and Montevil, 2011). In short, an organism continually undergoes a phase transition, which is critical, in the sense of changing, locally or globally, the symmetries and the (values of) some observables. A physical example is provided by the transition from water to ice. If water is vaporized, the formation of a snow flake is a radical re-organization of the previously homogeneous distribution of droplets. Moreover, the specific symmetries of a given snow flake depend on minor fluctuations at the transition. Similarly, minor fluctuation at mitosis, distribute differently the proteome of two resulting cells. Minor differences may be present also in the DNA. This sensitivity to the context at transition may contribute to cell differentiation; it surely contributes to diversity (in unicellular, first, but also in multicellular organisms).

Note now that most physical transitions may be reversed and that they are mathematically described by isolated points. One may consider the "density" of mitoses in a multi-cellular organism, as better expressed by the mathematical density of transition points, in an interval of all pertinent parameters (time, energy, pressure … mitosis happens in time, under certain conditions of all the other physical parameters). This is the basic intuition of "extended criticality", but the reader should consult the texts above for more.

In this context of potentially high sensitive transitions, the dynamics of the dissipative, far from equilibrium structuring of living matter, may propagate downwards, to the molecular level or upwards

to the higher order levels: that is, non-equilibria may downward or upward affect and destabilize or, more soundly, des-equilibrate other levels. For instance in the case of interacting cells (in a tissue, say), “disorder” (or the failure of the cells' dialogical connections) can propagate downwards to the physical dynamics of molecules, and this disorder may even derive from the organism (endocrine disruption, for example). Conversely, as everybody agrees, disorder may go from molecules (mutations, typically) to the whole organism, the latter being the key component for the exploration of diversity, proper for instance of the Evo-Devo systems.

However, the regulating role of the system may stabilize unstable or even pathological dynamics. For example, a normal tissue is likely to normalize a cell isolated from a cancer tissue. More precisely, as observed by (Maffini et al., 2005), the cell belonging to the cancer tissue may retain in its transplanted site its already acquired mutations, its chromosomal aberrations and/or other intrinsic cell properties, but would "behave" according to the norms of proliferation and motility imposed by the tissue in which it was transplanted. That is, the surrounding normal tissue will take over the control of the proliferation and motility of the isolated cell coming from a cancer tissue.

Let us now consider a few examples of upward/downward bio-resonance inducing an increase in variability. As discussed at length by Zeh et al. (2009), eukaryotic genomes contrary to prokaryotic ones have a very low relative amount of sequences coding for RNA or proteins: non-coding ones cover the vast majority of DNA. In humans for instance coding DNA is only about 3%, the rest is considered to be non-coding but containing a large number of transposons (about 45%), that is mobile elements capable of “jumping” from one location to another in the genome, inserting themselves and dispersing their copies in a quasi-random distribution. A condition for the insertion is the production of cuts, by the activation of cutting enzyme. The result is a modification of the whole sequence where the transposon will be inserted. Moreover, some classes of transposons, such as the so-called “helitrons”, often carry with them parts of the sequence of the original insertion site, thus re-arranging the genome and changing the order of genes. This often means permanent changes in expression levels of the host sequence with putatively relevant heritable changes in the phenotype of the organism affected. Now, transposons are generally kept silent by the organism through a process involving the addition of a methyl group to their DNA, but in the case of stress de-methylation occurs and transposon mobility is restored suddenly. This increases the mutation frequencies in a random yet partially controlled way, since the (only) constraint to randomness is given by the fact that, in general, transposons tend to insert themselves in GC-rich regions of DNA.

The result of this process is therefore the production of new variability, which may affect the functionality of genes endowed of critical functions, such as, for instance the tumor suppression genes, whose inactivation may reportedly lead to cancer, according to the so called Somatic Mutation Theory (Sorsa, 1980). In this case, inter-level resonance is both upward and downward. External stress from the environment may induce transposon jumping within cells (downward), but this induction of a random event, through transposons’ activation in cells, will change the cell itself and it may contribute to its uncontrolled proliferation and, possibly, to cancer with higher frequency. The amplification of these random, molecular events, in the multilevel interaction, is, in our terminology, a component of bio-resonance. That is, these events may happen within a cell, but in humans, for instance, they may have negative effects on the whole organism as a consequence of this inter-cellullar, intra-organismal bio-resonance (inter-level bio-resonance), although they are induced by an external, possibly minor, input. The alternative, more recent approach to carcinogenesis, TOFT in (Sonnenschein and Soto,

1999), even more closely relies on the disruptive role of global, organismal failure in the control of cell proliferation.

Another interesting example of bio-resonance may be found in the well-known process of development in animals from the fertilized egg to the whole organism (for a thorough discussion of animal development, see (Gerhart and Kirschner, 1999)). In Drosophyla, but also in mammals like humans, the developmental process is activated by the "injection" into the fertilized egg of RNAs and proteins orginating from maternal genes and coming from mother cells in an antero-posterior and dorso-ventral direction. This generates concurrent concentration gradients leading to an oscillator that induces the formation of segments of the pupa within which other gradients are formed. These gradients regulate the differentiation of cells, which are all submitted, along the two axes, to different ratios between the regulatory molecules. In this case, the inducing molecules come from the upper level (the body of the mother), yet they activate the lower cellular level and induce differentiation. This is surprisingly similar to the phenomenon discussed above concerning Dictyostelium, where molecular gradients induce differentiation and allow the formation of new connections, thus new organization, as integration of differentiated cells. Conversely, a "pure" upward effects of bio-resonance can happen when a mistake in DNA replication may induce a mutation in a differentiated cell leading to cell division and inducing, as in the example discussed before, cancer, a syndrome dramatically modifying the whole organism and its interactions with the environment. Also under the different approach to cancer mentioned above (Sonnenschein, Soto, 1999), this is seen as the result of the failure of cells' dialogue in a tissue, that is as a problem in the tissue's coherence structure, possibly induced by an incoming carcinogen, which deregulates the controlled proliferation of cells, thus affecting an organ's function and, possibly, the entire organism. Yet another case may be a downward process like a change in a few connections between neurons, a process not happening only as a response to external agents but which may derive as well from the internal dynamics of the brain. A change like this, of course, since the brain is the central controller of the whole body, may modify several organismal processes in an unpredictable way.

Of course, these interactions are regulated and integrated within an organism, while containing major random phenomena not only because of the non-linear molecular, intracellular, interactions (which may include the possible quantum randomness discussed above) and the inter-cellular ones, but also because the whole organismal dynamics is submitted to unpredictable environmental changes. This dynamics, then, cannot be described, let alone predicted, by focusing only on just one given level of determination and randomness, that is on molecular cascades or on cells or even on developing organism as a whole. As a consequence, the analysis of randomness as well, in Biology, cannot be isolated from a context: it is always a more or less highly canalized phenomenon. Even the Brownian motion of molecules, in a cell, in highly canalized by membranes and compartimentalization or even by the coherence structure of water (see sect. 3). And this is a crucial and fully general point. In particular, the many-folded forms of randomness, which manifest themselves within integrating and regulating activity, are at the core of variability and diversity, thus of evolution and development. That is, they also contribute to the peculiar stability of phylogenesis and ontogenesis. As a matter of fact, these are possible since they are adaptive and constantly explore possibly diverging paths, under different and ever changing constraints.

As for bio-resonance, to put it in very common terms, this is due to dynamical connections between components of living systems and may lead to "butterfly effects" all through the multilevel organization of life, as the increase in magnitude of their dynamics is liable to induce a "discontinuous pattern of change", thus a new organization, if viable. The notion of discontinuous pattern of change,

contrary to the continuous Darwinian evolution of Darwin and Galton, has been proposed for the first time by Richard Goldschmidt (1940), a German Jewish embryologist escaped to USA, considered to be a "heretic" for a long time. Goldschmidt challenged the corpuscular hypothesis of the structure of genes, proposed by the followers of the "Modern Synthesis", by attributing mutations to chromosome re-arrangements and introducing the concept of what he called "Hopeful Monsters". That is, he observed that organisms may abruptly change their whole organization following not a so-called singular "macro-mutation" as proposed by many, but a change in a network of genes endowed with an amplification effect (see (Thyssen, 2009), for a thorough overview). As discussed by Dietrich (2000), Goldschmidt's hypothesis was supported by a series of data on Drosophyla development, but for a long time his work was almost forgotten by neo-darwinists, although one of the founders of the Modern Synthesis (R. Sewall Wright) discussed Goldschmidt's intuition and managed to connect it with the prevailing theories. The situation changed completely when N. Eldredge and S.J. Gould challenged the gradualistic hypothesis of the neo-darwinists on the basis of paleontological data showing the alternation, throughout evolution, of periods of relative "stasis" and fast change. Nowadays the researchers working within the frame of the recent discipline called Evo-Devo are finding compelling evidence that mutations in key-nodes of organismal networks will result in the death of the organism or in its drastic change, due to the high number of connections of the modified component, which leads to a butterfly effect on the whole network. In the language of this paper, this means that intra-organismal bio-resonance may amplify and extend the effect of a single change producing hopeful monsters liable to enter in a different "valley" of the Waddingtonian landscape or even in a new one (see for instance (A.P. Moeller and J.P. Swaddle, 1997) for a discussion on asymmetry and stability in evolution). Needless to say, although a large part of the work on these processes has been carried out by developmental geneticists and embryologists, the initiating events of these downwards and upwards cascade of changes may happen at all levels of the organization of life from molecules to the Biosphere.

7. Anti-entropy

In physics, entropy production is associated to energy dispersal, which does not need to produce disorder, in an inert structure. All diffusion processes, though, are based on random paths, thus the key role of randomness in thermodynamics. In Biology, there exist two forms of entropy production. One is due to the many thermodynamical processes that occur at all levels of organization, to be associated to energy flows and/or production. By the second principle of thermodynamics, applied to far from equilibrium, open (dissipative) systems, these flows and activities produce energy dispersion, thus physical entropy. The other form is properly biological and is due to *variability*, both as individual and evolutionary variability and as cell differentiation (these two notions are related, of course). This second form of "increasing disorder", thus of entropy production, may coexist with increasing order: when one has two cells instead of one by mitosis, the order, locally, increases (at the expenses of energy, of course, in an open system). Yet, since, in reproduction, cells always change/differ and/or differentiate, this process induces *also* some disorder. A perfect symmetry of the two new cells would just be an increase of order, yet variability, thus some disorder or lack of symmetry, is a key component of the process (see (Longo, Montévil, 2012) for more details on this peculiar form of entropy/disorder production, always associated to increasing biological order).

Of course, the reductionist may tell us that this fact may be understood in physical terms. Yes, but no physical theory, so far, deals with non-identical proliferation as a core theoretical invariant.

Crystallo-graphy, for instance, analyzes crystals' generation and their symmetries, but "imperfection" is hardly the main theoretical invariant.

In Biology, instead, both variability and organization need to be theoretically described, in their multi level structuring, in order to understand the survival and evolution of organisms (Buiatti and Buiatti, 2008). In order to deal with these opposing concepts, viewed as disorder vs. order, Bailly and Longo (2009) have introduced the notion of *anti-entropy,* as a way to quantify the formation and maintenance of biological complexity and as a form of order locally opposing to entropy production. More specifically, anti-entropy is proposed as a proper observable of life, quantitavely represented by the numbers that may be associated to these structures:

- cellular networks (number of nodes, hubs, links …);
- the fractal dimension and number of connected components of organs[8];
- the number of tissue's differentiations

(we refer to (Bailly, Longo, 2009; Longo, Montévil, 2012) for a more detailed treatment of these quantities).

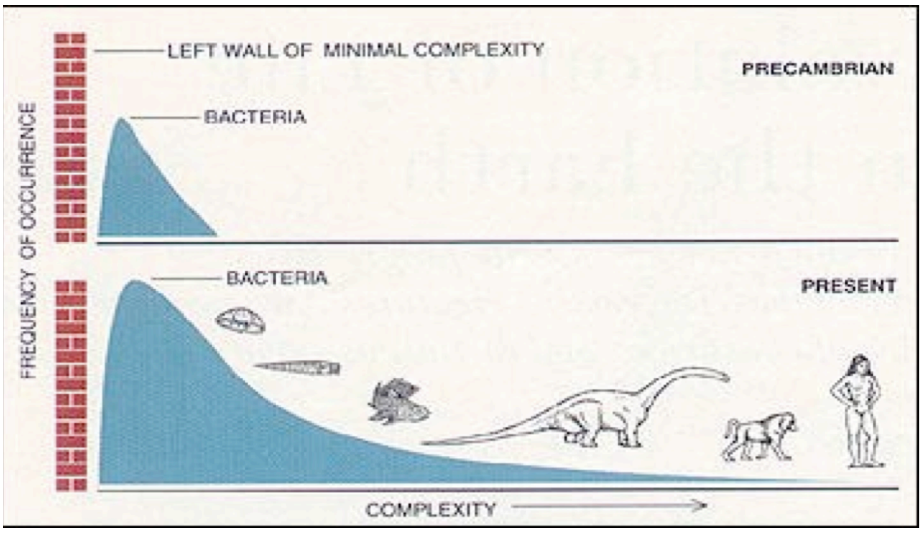
This is a largely incomplete list of items of what could be called proper *biological complexity* and provides just a preliminary "mathematical skeleton" of the much richer complexity of life. The idea is that the construction of connections and of level of organization is at the core of life and this, mathematically, opposes to entropy growth: it is anti-entropy. Of course, one may add lots of further phenotypic properties that popped out along evolution: networks within and among groups and populations (ants or bees' organizations, for instance) and much more. Its increase or just its maintenance corresponds to a decrease of entropy: anti-entropy increases or maintains organization, by opposing entropy increase. Yet, anti-entropy is not negentropy: typically, the sum of an equal amount of entropy and negentropy gives 0, a simple singularity, in all the theories where the latter is considered (Shannon, Brillouin, Kolmogorov …). Instead, one finds positive anti-entropy only in a living entity, where it adds to the inevitable production of entropy in a non-obvious singularity, that is in extended critical transitions, as proposed in (Bailly and Longo, 2008; 2011), (Longo and Montevil, 2011). The name, but just the name, is inspired by the notion of "anti-matter" in Quantum Physics, as the sum of equal matter and anti-matter does not give 0 (when encountering, a particle and an anti-particle produce gamma rays – this is how anti-matter was discovered and it beautifully justified a symmetry: Dirac's negative solution for the electron's equation).

As far as evolution is concerned, Bailly and Longo (2009) transferred Schrödinger's analysis of quantum dynamics from the dynamics of a "law of probability" to an analysis of increasing phenotypic complexity along evolution as the dynamics of a "potential of variability". Schrödinger's equation may be actually understood as a diffusion equation of the state function over a very abstract space (a Hilbert space – far away from ordinary space-time). The idea is to describe the increase of biological complexity as the random asymmetric diffusion of the density of biomass over time and anti-entropy, yet another very abstract phase space (diffusions, in physics, usually takes place in time and *space*, or of matter within another matter – thus in space). The asymmetry formalizes Gould's notion of "left wall" of biological complexity (bacterial complexity), see (Gould, 1998).

This approach is a way of specifying this dynamics of an abstract potential of variability of the bio-mass, restricted to its diffusion over this peculiar space of observables (time and anti-entropy). The

[8] To give a few examples, mammals lungs have a fractal dimension greater than 2, while the lungs of a frog have a 2-dimensional surface. As for organs' "connected components", primates may have up to 600 muscles, while a horse or a cow at most 400. But of course, the number of tissue types (differentiantions) is the main (epistemic) measure (see references).

punctuated equilibria of Gould and Eldredge, within this frame, can be explained as the effect of the disruption of more or less steady anti-entropy constitutive dynamics due to bio-resonance, leading to a (short, but "extended critical") time interval of increased variability at the end of which there may be a new organization of the system, in Waddingtonian terms. In other words, Bailly and Longo (2008) approach mathematizes Gould's idea that the diffusion of life entails increasing complexity just because of the original symmetry breaking due to the formation of the first living entity, which is considered, by principle, of "least complexity" (an arbitrary, but sound, axiomatic choice). Gould calls this asymmetry, the "left wall of life", or its origin, whatever this may have been. As already mentioned, any diffusion is based on random paths. They randomly propagate the original complexity, by local interactions, from the initial symmetry breaking, due, in this case, to the existence of the "left wall" (the least, bacterial complexity). Humans, thus, are just one of the possible outcomes of the random complexification of bacteria, via many intermediate random explorations, mostly unsuccessful. Yet, these random explorations are, on average, slightly biased towards increasing complexity, as they propagate the original asymmetry. That is, occasionally, the random distribution of changes yields a more complex structure, which happens to be successful, slightly more often than simpler ones. Intuitively, the ecological niches of simpler organisms are slightly more occupied, thus another "simple" new organism has slightly less chances to survive than a more complex one. And this phenomenon yields the contingent increase of complexity described by Gould, just by local "bumps" towards the right, similarly to the local asymmetric bouncing towards the right of the particles of a gas randomly diffusing from an explosion against a wall on the left.



From (Gould, 1998)

Gould (1998) has no sound representation of time in his empirical drawings of the "biomass over complexity" curve. By a dual use of time and energy with respect to Schrödinger's operational approach, the time dependence of the curb could be explicitly given in (Bailly and Longo, 2009) (in short, time is considered as an operator and energy a parameter, the opposite of what is done in Quantum Mechanics). And the curb fits the original explosion of bacteria, as well as the fact that bacteria remain the relatively dominating biomass, still now (the paper is downoloadable).

Of course, as we said, a random diffusion means that phenotypic complexity may equally decrease (loss of legs in tetrapods, say, see the introduction), yet, on average, over time, it does increase. It also means that there is no aim, but pure contingency, and that this contingency acts locally, by a random, yet slightly biased local effect – no global orientation towards increasing complexity, no aim, no target. Contingency, as the non-additive combination of various forms of randomness, is a relevant component of the understanding of evolution. Inheritance of structurally stable phenotypes and organisms, and selection are, of course, further, non-independent, components.

Conclusion and opening

This paper is a discussion of the various notions of randomness one may refer to in biology, aiming to give a more precise definition of the widely used notion of "contingency". We first and informally surveyed the different mathematical meanings of randomness in physics. Typically, mathematics and empirical evidence allow one to distinguish between classical and quantum randomness, by Bell inequalities and their violation. In biology, both the classical and the quantum notions seem needed in order to grasp molecular dynamics, well beyond their technical separation in most physical approaches. Moreover, we stressed that a biological organism may only be viewed, so far, as mathematically inhomogeneous, in the sense that different levels of organization are treated, whenever this is possible and pertinent, by different mathematical tools (e.g. non-linear morphogenetic equations for organogenesis, statistical physics for networks of cells, etc.). In principle, mathematical structures of determination seem to be able to deal with (or they *impose*) homogeneity on the intended phenomenal level. The biological challenge instead is that integration and regulation are at the core of the robustness or the very existence of an organism, and this is grounded on inter-level phenomena. In this properly biological conceptual space we situated our proposed notion of bio-resonance as the locus of stabilizing and destabilizing interactions, and where a proper form of biological randomness seems to manifest itself.

One of the consequences of our approach is a further justification of the view expressed in (Longo et al., 2012). In biology, randomness must be situated also in the passage from one space of observables to another, through time. That is, if one takes as a suitable phase space (the space of observable and parameters) the Darwinian space of phenotypes, the unpredictable change may be due to the appearance or disappearance of organisms and/or phenotypes. This goes well beyond the pre-given phase spaces in which physical dynamics and randomness take place. As we mentioned above, randomness, in physics, refers to the unpredictable *value* of a pre-given observable: recall, say, coin tossing and an electron's spin up or down. Or, at most, in statistical physics, what may change is the unpredictable *number* of dimensions of a fixed type of observable – the number of particles and their already listed properties, typically. In biological evolution, we observe the qualitative change of the very phase space, to be expressed as the addition of a new, qualitatively different, biological dimension (having hearing or feathers or a sonar system). Moreover, no physically meaningful mathematical infinity can take care of this biological unpredictability. In physics, not only are ordinary (Cartesian) spaces of course infinite, but the dimensions as well of a mathematical space may be infinitely many (as for Hilbert spaces in Quantum Mechanics). The point is that their mathematical symmetries allow a finite description (by a few axioms, say). Infinity thus is not the issue. In (Longo et al., 2012), it is thus claimed that evolutionary observables are "incompressible" in time, in the sense that they cannot be listed before their appearance. In our view, the key role in biology of symmetry changes, as described in (Longo, Montévil, 2011), see also (Moeller and Swaddle, 1997), is the mathematical reason for this incompressibility. This opens the way to a new conceptual and mathematical challenge: describing

biological randomness also as unpredictability of the very phase space, in the presence of dynamics where variability, adaptability and diversity are among the main invariants and contribute to the structural stability of organisms and species.

In conclusion, one may soundly understand the formation of complex biological structures in terms of random explorations of continually new possibilities. In order to be viable, though, these must be integrated and regulated in an organism, or form a coherent structure, in a niche, in an ecosystem, as life is a complex blend of various forms of contingency and determination. Organization or order and complexity, possibly as anti-entropy, as opposing random dispersals, are also at the core of any understanding of biology. For example, the formation of organism-like colonies of differentiated and integrated bacteria or unicellular organisms we mentioned above, is the result of the *random exploration by variability* of a possible *organization* of life – of newly organized life, of course. There was no need as for colonies to be formed, yet they turned out to be possible, thus, given enough time, they happened. Yet, most explorations fail; some yield a (even slightly) more complex structure, which has (slightly) more chances to be viable, by the random propagation of the diffusive asymmetry explained in the last section. The key conceptual opposition here is that, in biology, order follows both from disorder (e.g. random variations in evolution, stochastic gene expression) *and* from inherited order (the DNA, the zygote, the ecosystem); moreover, new or reconstructed order (anti-entropy production) always creates some disorder, by random distributions and differences beginning with the asymmetries in each mitosis (thus, by producing some entropy), see (Longo, Montévil, 2012).

But which mathematical form of randomness have we been talking about? As for the global, largely qualitative analysis of evolutionary increase in complexity we just recalled, all the forms we mentioned in this paper are combined. Yet, a more precise mathematical specification of the novel form of biological randomness, possibly along the theoretical approach proposed in this paper, in terms of bio-entanglement and bio-resonance for example, may further help towards a better understand the dynamics of life.

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