The Unconventionality of Nature: Biology, from Noise to Functional Randomness

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Abstract In biology, phenotypes' variability stems from stochastic gene expression as well as from intrinsic and extrinsic fluctuations that are largely based on the contingency of evolutionary and developmental paths and on ecosystemic changes. Both forms of randomness constructively contribute to biological robustness, as resilience, far away from conventional computable dynamics, where elaboration and transmission of information are robust when they resist to noise. We first survey how fluctuations may be inserted in biochemical equations as probabilistic terms, in conjunction to diffusion or path integrals, and treated by statistical approaches to physics. Further work allows to better grasp the role of biological "resonance" (interactions between different levels of organization) and plasticity, in a highly unconventional frame that seems more suitable for biological processes. In contrast to physical conservation properties, thus symmetries, symmetry breaking is particularly relevant in biology; it provides another key component of biological historicity and of randomness as a source of diversity and, thus, of onto-phylogenetic stability and organization as these are also based on variation and adaptativity.

Keywords: noise biology, randomness, resilience, variability, diversity

1 Introduction

Conventional computing is the result of a remarkable historical path that originated in the invention of the alphabeth: discrete and meaningless signs evocate meaning by composition and by phonemes, that is by sounds, and provide by this a musical notation for the continuum of speech. This revolutionary step is an early form of dualism, an invention very far from natural phenomena: ideograms carry or recall meaning in their form, while the signs of an alphabeth are perfectly abstract and meaningless. They require phonemes and do not refer per se to the sensible world. We enriched this stepping away from the world by more passages, in history, such as the Cartesian dualism, which further separated a human mental software from physical matter, and, later, by the coding of alphabethic signs by numbers, yet another radical separation of (coded) words from meaning. Gödel and Turing brought to the limelight this later invention for the purpose of . . . showing the internal limits of the (alphabethic) writing of axioms and formal (meaningless) deductions. In order to prove their negative results, the construction of undecidable sentences and functions, they had to formally define computability and decidability. By well-known equivalence results, we know that no finitistic (alpha-numeric) re-writing system computes more functions than the ones invented by the founding fathers and, thus, that it is subject to the same limitations and incompleteness. In these computational frames, which are our fantastic, linguistic invention far away from nature and its material contingency, randomness has no place and all is done to avoid it, as "noise".

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However, these limits of formal writing and signs' manipulations may be viewed also as a contribution to understanding the key role of randomness in describing natural phenomena. As a matter of fact, randomness, in all existing physical and computational theories, may be understood as unpredictability w.r.to the intended theory. It is thus a form of (in time) undecidability w.r.to the given (more or less) formal frame (see Calude and Longo 2015; Abbott et al. 2012; Gács et al. 2011 for analyses in relation to algorithmic randomness). In other words, the (joint) analysis of (algorithmic, physical and biological) randomness crucially helps to go beyond formal deductions and computations, as given by conventional theories.
The understanding and the treatment of randomness and unpredictability is at the core of dynamical (non-linear) systems, quantum mechanics, statistical physics. We will discuss common tools for the analysis of unpredictability within some mathematical formalisms, from the Langevin approach to the Fokker-Planck equation for diffusion, from path integrals to limit theorems of probability theory related to the Law of Large Numbers. In biology, though, randomness acquires a peculiar status as it is inherent to the variability, adaptivity and diversity of life, as crucial components of its structural stability. Stochastic gene expression will be introduced as striking example that already provides hints towards a novel, hopefully more proper, definition of biological randomness; the notions of "bio-resonance" and plasticity will be further examples of this. In particular, we will first refer to "noise" in various, very relevant, conventional (physical) representations of randomness, extensively applied to biology. Then, we will stress the essential role of random events in biological processes, whose contribution to life's dynamical stability goes well beyond "noise" and suggests the need for an enriched perspective; that is, for a better, unconventional, conceptualization (and terminology), or possibly mathematization of randomness, encompassing biological variability and diversity. A comparison will be made with the revolutionary change in the laws of causality, randomness and determination proposed by quantum mechanics in the analysis of matter in microphysics. This poses the question of the suitability of the notion of "law", as inherited from classical and quantum physics, for the investigation of the dynamics of the living state of matter. A key issue for us is that physical laws are given in pre-defined phase spaces.

2 Stochasticity Modelled by Noise

Stochasticity in biological systems is largely denoted as "noise". The use of term noise implicitly assumes a way of thinking about cells shaped by the metaphor that compares genetic and metabolic pathways to signalling "circuits" (Monod 1970; Simpson et al. 2009; Maheshri and O'Shea 2007).
Models, for the sake of simplification and understanding, rely on the choice of relevant objects, properties and some defined degree of detail. In particular, a mathematical (equational) model requires the a priori choice of the pertinent observables and parameters, that is of a "phase space". In this context, invoking analogies with better characterized systems can provide qualitative insights but is not neutral in terms of conceptual implications: discussing the latter is indispensable to assess the suitability of metaphors, including the transfer of mathematical tools between scientific fields. In fact, analogies set the guiding principles for building models (to be considered "representations" first of all), in such a way to shape the mathematical formalism, and how experiments are designed and interpreted. It is thus a matter of vocabulary and, more importantly, of conceptual frameworks that may hinder progress if they prevent from formulating questions in a way pertinent to the intended domain, living beings in our case.
Concepts for studying metabolic and genetic pathways are explicitly drawn from electronic circuit theory (e.g. Bhalla 2003), the richest source of inspiration among various metaphors for signalling. The essential point, in our view, is that the emphasis is placed on particular levels of description, namely functionality and the problem of optimal processing and transmission of information. This is inherent in the very mechanism of a metaphor, which is a *meta-fero*, a transfer of meanings, a mapping to more familiar domains, that does not necessarily imply a complete superposition. Furhermore, the systematic transfer of methodology and concepts from physics to biology should be reframed in terms of dualities as well as (or rather than) similarities, as we will argue below. In the context of this metaphor, "noise" is seen as something that disrupts the system, causes a defective functioning or even the breakdown. Yet, as we will stress, biological "noise" is meant to refer also to *variability*: as a consequence, one attributes the meaning of "disturbance" to something intrinsic to life, as a component of adaptivity and diversity (plasticity is yet another element

of these aspects of biology).
Next sections are devoted to a discussion of the mathematical role of this particular notion, *noise*, in the quantitative investigation of stochastic effects in biological systems. Our aim is to focus on its theoretically and practically relevant implications once it acts as a principle to make experimental evidences intelligible, because it then contributes to modelling assumptions and to the construction of the "objectivity" to which scientific analysis is applied, in particular because it affects how we conceive the underlying causal structure.

3 Randomness and its Mathematical Formulation

The dynamics of a biochemical reaction is believed to be properly treated as a Markov jump process (i.e. changes are seen as discrete events occurring at random times and regardless of the previous chemical history) in a state or phase space specified by the number of molecules (it is a description at the level of "copy numbers"). Typically the abundance of reactants allows a quantification on a continuous scale in terms of concentrations (number/volume). We mention this aspect as, in the following sections, we will discuss the relevance of defining a pertinent phase space when laying the foundations of a theory: in existing physical theories, the laws (of a dynamics, typically) are given in a pre-defined phase space.
In the context of a deterministic macroscopic characterization of biochemical networks, variations of concentrations are assumed to occur by a continuous process and reactions are described in terms of rate equations for the species involved. This temporal evolution can be obtained applying the law of mass action, which states that the rate of a reaction is proportional to the product of the concentrations of the reactants and leads to equations in the form:

Rate of change of concentrations = Total rate of production - Total rate of consumption

Mathematically equivalent to:

$$\frac{dx_i(t)}{dt} = \sum_{j=1}^{R} S_{ij} f_j(\boldsymbol{x}) \tag{3.1}$$

where $i = 1, ..., N$ denotes the chemical species and j runs from 1 to R, the number of chemical reactions. $S_{ij} = s_{ij} - r_{ij}$ contains the stoichiometric coefficients s_{ij} for the reactants and r_{ij} for the products, while $f_j(\boldsymbol{x})$ is the macroscopic rate function for the j-th reaction and accounts for its probability.
As exhaustively explained by Gillespie (1976), in this formulation the cell is considered to be endowed with a well-mixed and spatially homogeneous environment: spatial components and inhomogeneities, compartmentalization of reactions, diffusion phenomena should be then analyzed separately. Moreover, what should be verified is that the occurrence of nonreactive (elastic) collisions or other molecular motions responsible for the maintenance of these conditions of random uniform distribution is more frequent than reactive collisions.
Differential equations for the temporal evolution of concentrations must be interpreted as a deterministic description as, once a set of initial conditions $\boldsymbol{x}_0(t_0)$ is fixed, the future evolution will be univocal. On the other hand, heterogeneous cellular behaviors are thought to be appropriately captured by stochastic models: the lack of accuracy of the deterministic models for essential biological features leads one to introduce stochasticity at the level of the description (Wilkinson 2009). Once the need for a stochastic explanation has been recognized, the first step is to resort to statistical analyses and probability theory. This is presently the only quantitative framework for taking into account any kind of *unpredictability*, either epistemic or intrinsic.
In this spirit, the primary source of stochasticity is identified with fluctuations present in all biochemical systems, as reactions occur at random times and with a random outcome: arguments based on Poisson statistics are then used to affirm that the relative amplitude of fluctuations should scale as the inverse square root of the chemical population. Stochasticity is thus expected to be enhanced by small numbers, for which fluctuations can exceed, in magnitude, the mean molecular level (Elowitz et al. 2002; Simpson et al. 2009; Swain et al. 2002; Raj and Van Oudenaarden 2008).
In light of this expected crucial role, a growing interest towards stochastic behaviors has emerged in the

field of biological modelling. Stochastic modelling has been acknowledged as a well-established solution only since late 1990s, once experimental techniques gave precise results showing that including random terms was fundamental in order to fit experimental findings (Arkin et al. 1998).
Molecular fluctuations are usually incorporated by adding a random force term in rate equations according to the so-called *Langevin approach* (see the textbook by Van Kampen 2007 for a discussion), as follows:

$$\frac{dx_i(t)}{dt} = \sum_{j=1}^{R} S_{ij} f_j(\boldsymbol{x}) + \xi_i(t) \tag{3.2}$$

The Langevin approach consists of writing down the deterministic equations of the macroscopic behavior with an additional Langevin force term that exhibits certain properties:

- The average over an ensemble of identical (or similar) systems vanishes, i.e. $\langle \xi_i(t) \rangle = 0$ for any i.
- It stems from the instantaneous collisions between particles, so that, if variations are sufficiently rapid, they are not correlated in successive times. As a consequence, the autocorrelation is supposed to be represented by a delta function, i.e. $\langle \xi_i(t)\xi_j(t') \rangle = \Sigma_{ij}(\boldsymbol{x})\delta(t-t')$.
  This delta representation is an abstraction, but it is applied for the sake of convenience whenever the time of a collision is negligible w.r.to the relevant timescale of the dynamics.
- $\xi_i(t)$ is Gaussian distributed (i.e. completely characterized by the first two moments).

This term is often referred to as "noise" because of its unpredictable nature; on the other hand, the above properties guarantee a regular behavior in terms of averages. In particular, when the last two properties hold true, one can define a *Gaussian white noise* (*white* refers to the fact that a δ-time correlation is independent on frequency in the Fourier space).
Remarkably, this approach represents a very recurrent strategy in stochastic modelling and it has been adopted to include heuristically every type of fluctuations, also not directly connected to thermal effects in biochemistry: the properties listed above are often given *a priori*, without connections to the physical dynamics of the underlying process[4]. The structure of Langevin equation is taken as conventional justification for affirming that, whenever fluctuations are not relevant, the molecular population evolves *deterministically* according to the set of macroscopic reaction rate equations. Also at the level of mathematical description, it has been often found convenient to invoke analogies from engineering: in fact, Gaussian white noise is a useful model of noise in electronics engineering, for example for instrument errors in filtering theory and for unknown forces in control theory. The analogy in these cases connects the "noise" observed in biochemical networks to what is called "shot noise" of charge carriers in electronic devices, the random timing and discrete nature of molecular processes being the common features (Simpson et al. 2009). Adding a noise term can be conceived as a formal procedure to insert "randomness" in a deterministic equation and the description it conveys is that of an *external* force contribution. The aim is, in parallel, to switch from a deterministic description to a probabilistic one: in this way, in fact, each value is associated with a probability distribution, which is either a peaked or spread function depending on the amplitude of fluctuations, and is characterized in terms of averages.
Adding fluctuations to a dynamics otherwise predictable, enlarging the width of probability distributions reflect the first attempts along an intellectual path going from invariant to structurally stable, from repetition of identical to repetition of similar. In the resulting theoretical account of stochasticity, still a "regularity" in the sense of physics can be found (by means of the average over an hypothetical ensemble) while an always different outcome (that we would call stochastic, unpredictable) can be interpreted as "regular" given an epistemology based on variability as a major invariant, presumably more appropriate in biology (Longo and Montévil 2013).

[4] In this regard, Van Kampen critically claims an "indiscriminate application" of the Langevin approach for internal sources of stochasticity, the main reason being that fluctuations cannot be analyzed independently of the global evolution. From the mathematical point of view, in fact, the eq.(3.2) is rigorously defined only if one specifies which integration rule is chosen (either the Itô or Stratonovich convention, as explained in Van Kampen 2007).

The Langevin approach is completely equivalent to a *Fokker-Planck equation* (see Risken 1989), a diffusion equation for continuous Markov processes which turns out to be generally more tractable:

$$\frac{\partial}{\partial t}P(\boldsymbol{x},t) = -\sum_{i=1}^{N}\frac{\partial}{\partial x_i}(\boldsymbol{Sf})_i(\boldsymbol{x})P(\boldsymbol{x},t) + \sum_{i,k=1}^{N}\frac{\partial^2}{\partial x_i \partial x_k}\Sigma_{ik}(\boldsymbol{x})P(\boldsymbol{x},t) \tag{3.3}$$

The *convective* term $(\boldsymbol{Sf})_i(\boldsymbol{x})$ corresponds to the macroscopic deterministic reaction, while the *diffusion* term $\Sigma_{ik}(\boldsymbol{x})$ is meant to mimic how the noise leads the probability distribution to spread around the average value, which coincides with the deterministic one (it is also referred to as "noise-generating" term).
Simplified assumptions are usually needed to solve analytically the Fokker-Planck equation. In this regard, stochastic kinetics methods have been primarily developed for biochemical reactions that exhibit macroscopically stable stationary (or steady) states. We remark that stationarity is a condition that requires steady flows of energy and matter, thus it includes also some out-of-equilibrium, but close to equilibrium, situations. In this perspective, one analyzes small fluctuations w.r.to stationarity, for example by considering suitably large numbers of molecules and by linearizing the dynamics around the stationary states, see the Linear Noise Approximation (LNA) put forward by Van Kampen (2007). According to the solution of the Fokker-Planck equation in this case, deviations follow a Gaussian distribution, thus in average they cancel out. However, in general, intracellular biochemical processes can occur far from the thermodynamic equilibrium and from stationarity, where the noise becomes extremely significant, regardless of the average molecule copy number. Although approximations such as the LNA are very valuable tools for characterizing fluctations in many scenarios, they still fail to faithfully and accurately describe what we will highlight as "noise-induced" phenomena, i.e. the rich set of dynamical behaviors that stem from the interplay between fluctuations and nonlinearities (Elf and Ehrenberg 2003).

3.1 "Effective" Randomness

It is worth a brief discussion on the meaning of a random term and the corresponding stochastic picture, as it does not necessarily imply the "pure" randomness of the physical underlying mechanism.
As a matter of fact, fluctuation terms can be also representative of a conventional randomness in the description, canalizing the way in which the existence of ignored variables manifests itself (we shall call it "effective" randomness). This point can be exhaustively clarified through the application of *projection methods* (Zwanzig 1961) or other methods for reduced statistical descriptions (Bravi and Sollich 2015). More generally, the projection approach demonstrates that, when a separation of timescales can be identified, the exact equation for "relevant" (slow) variables may be mapped into a stochastic equation with a "random" force stemming from "irrelevant" (fast) degrees of freedom that have been traced out. In the context of this particular description, typically chosen for a matter of convenience and tractability, fast variables act *effectively* as random terms, regardless of the true physical mechanism by which they influence the system (in principle they can act as deterministic forces). Coarse graining procedures, that allow to switch between different levels of detail, rely on the same logic. Random terms indeed arise as a consequence of mapping a finer scale of description into a coarser one where only certain relevant variables are retained. For example, as explained both in conceptual and formal terms by Castiglione et al. (2008) and in the references therein, a microscopically deterministic dynamics, whose unique source of stochasticity is given by uncertain initial conditions, can be translated into a mesoscopic stochastic evolution.
A basic and powerful guiding idea of many models is to trace out degrees of freedom, so that to end up with terms of effective randomness carrying memory effects from the neglected components. This idea has been explicitly elaborated within projection methods but typically underlies several statistical approaches: it must be seen as a way of rearranging in a form suitable for further treatment the complicated contribution of both predictable and intrinsically unpredictable effects, as well as the overall uncertainty on conditions and on factors involved.
To sum up, terms of effective randomness appear as a consequence of the choice to integrate out some levels of detail, in terms both of components and dynamical processes. This randomness "intrinsic" to the formal-

ism from the mathematical point of view adds itself to the one "intrinsic" to the experimental procedure, the unavoidable uncertainty that affects each physical measure and forces one to express it by an interval.

3.2 Path Integrals

The Fokker-Planck equation is deterministic because the value of the solution is fixed once we know the initial conditions, while stochasticity is included in the fact that it *determines* the dynamics for a law of probability, in analogy with the Schrödinger equation of quantum mechanics.
Quantum randomness manifests as unpredictable fluctuations in measurements: if we repeat an experiment under exactly identical conditions, the outcome of any measurement is found to vary with a random behavior that can be assessed only by probabilistic tools. Importantly, this is due not only to our *ignorance* (the epistemic randomness of classical dynamics), but also to Heisenberg principle. The latter states the non-commutativity of measurements (they depend on the order) and it transforms uncertainty into a *principle*, at the very root of the theory, intrinsically. On the other hand, fluctuations are not the only aspect representing randomness, which in quantum theory is accounted for by the complex nature of the wave function: remarkably, this allows a description for the interference phenomena that are observed in microscopic world and whose explanation builds on the superposition principle. This principle is formalized by the *path integral* formulation, which replaces, for calculating quantum amplitudes, the classical notion of a unique trajectory with a sum, or functional integral, over an infinity of possible trajectories.
Path integrals constitute a formalism intended to incorporate naturally interference effects stemming from wave-particle duality and the key intuition behind is to express stochasticity as an intrinsic superposition of possibilities satisfying certain given boundary conditions. This idea can be traced back to the theory of stochastic processes and can be attributed to Wiener (1976), who introduced the integral named after him for the study of Brownian motion and diffusion processes.
The *Wiener integral*, involving Brownian walks, can be regarded as the first historical evaluation of a statistical path integral and, as well, it provides the basis for a rigorous formulation of quantum mechanics in terms of path integrals, to which stochastic processes are related upon transition to imaginary time. In fact, quantum mechanics relies on real-time (Minkowskian-time) path integrals: by performing a Wick rotation (i.e. an analytical continuation of the integral to an imaginary time variable) one recovers the Wiener integral, that in this way can be immediately interpreted as an Euclidean-time (imaginary time) path integral giving a transition probability for the process. In addition, once integrated over boundary configurations, this path integral turns out to resemble a statistical partition function: this connection between quantum mechanics and statistical mechanics (globally discussed e.g. by Kleinert 2009) is deeply rooted in the theory and not just dependent on the path integrals formulation. It is demonstrated also by the fact (well known to Schrödinger) that the equation bearing his name coincides with a diffusion equation with an imaginary diffusion constant (or, analogously, in imaginary time). The complete path integral formalization for non-relativistic quantum theory was developed by Feynman (1948), who also showed the equivalence of this formulation to the one of Schrödinger differential equation and to the algebraic one of Heisenberg matrices. In quantum mechanics, the probability of an observable (a real quantity) is given by the squared module of a complex number, the probability amplitude. As a consequence of the superposition principle, Feynman's conjecture theorizes that the probability amplitude can be calculated by a sum of all conceivable and alternative ways of evolution in configuration space, in other words, a sum over all *histories* of the system. Each one is weighted by an exponential term whose imaginary phase is given by the classical action for that history divided by the Planck constant $\hbar$. Thus, according to Feynman's interpretation, the classical action is postulated to contribute as a phase acquired by the system during the time evolution: quantum path integrals are in fact denoted as *oscillatory*. This is in opposition to Wiener integrals, where the action in the exponential still represents a particular history but is not multiplied by the imaginary unit: the probability of each path is thus encoded by an exponential decay, the well-known Boltzmann factor of statistical mechanics (Sethna 2006). By this idea of histories with varying phases, the path integral formulation offers a convenient framework for deducing the classical limit of quantum theory. For instance, when the classical action is much larger than the Planck constant, the exponent becomes a very rapidly varying function, positive and negative deviations w.r.to the classical history are suppressed by destructive interference and the path integral can be evaluated

by *stationary phase method* (therefore a justification of classical variational principle is also included). The classic limit of quantum path integrals corresponds to the deterministic limit in stochastic path integrals, which is the one that selects the most probable path by minimizing the action.
Both in the quantum and stochastic context, path integrals do no bring conceptual novelties strictly speaking, they are rather a reformulation of the existing theory in a different form[5]. Nevertheless such a different form looks suitable for performing mathematical manipulations and in particular it frames in intuitive terms a common way of thinking about randomness. The interplay between real and complex numbers, objectified by the Wick rotation, is fundamental in transforming a representation of a properly quantum randomness to the one of diffusive processes, but still the same formal framework can summarize both: an inherent coexistence of possibilities is assumed to characterize quantum systems as well as classical systems commonly denoted as *stochastic*.

4 Stochastic Gene Expression

Since the pioneering work by Kupiec (1983) and more recently (see Raj and Van Oudenaarden 2008; Maheshri and O'Shea 2007; Swain et al. 2002), it has been acknowledged that gene expression is best described as a stochastic process, the evidence being that, even in presence of homogeneous and reproducible experimental conditions, single-cell measurements display a significant degree of heterogeneity. This is interpreted as a phenomenon due to stochasticity, or "noise", intended as unpredictability about the outcome and occurrence of chemical reactions: the idea that noise can influence cell fates was thus developed starting from experimental observation of cell-to-cell differences in gene expression levels. In 1940 Delbrück put forward, for the first time, the hypothesis that fluctuations in biological molecule populations, typically consisting of few copies, can have a relevant impact on cellular physiology: later he proposed this might explain, in part, the variability observed in the number of viruses produced per phage-infected cell (Delbrück 1945). The notion of stochastic gene expression has become well established and widely accepted only more recently, since means of a systematic experimental investigation became available (many of early experiments were in fact limited by the difficulties inherent to measuring gene expression in single cells and needed the development of new tools to manipulate organisms genetically). Since then, it has motivated a great research effort and resulted in a long series of publications in the context of "noise biology" (e.g. Rao et al. 2002; Simpson et al. 2009). Among the first experiments aimed at identifying factors influencing gene expression, we recall the studies of Elowitz et al. (2002), who introduced the distinction between extrinsic and intrinsic noise (see next section).
From a quantitative point of view, a measure of the noise affecting a state variable is given by the Coefficient of Variation (CV), a dimensionless quantity defined as standard deviation of the distribution divided by the mean value (we refer to Simpson et al. 2009; Swain et al. 2002 for formulas): this definition implies examining an ensemble of trajectories at a single time or points of a single trajectories over time, given that ergodicity holds true (i.e. time averages and population averages are interchangeable). The "noise" of a stochastic variable thus is identified with fluctuations with respect to the average over the whole statistical ensemble, usually composed by different cells. Already this definition implies that cells can be regarded as independent and identical realizations of the same system, forcing then a symmetry that is far from being verified in biology, as it will be discussed. By means of the Central Limit Theorem and the Law of Large Numbers (LLN), fluctuations are expected to scale as the inverse of the square root of the number of molecules, thus they correspond only to small corrections to the mean value and can be neglected with respect to the latter. In other words, fluctuations average out as the numbers of molecules increases. Once defined the CV as measure of stochasticity, it can be compared with the noise-type term of the Langevin approach, a term, we remark, that reflects and imposes a probabilistic description. Note that, in the context of experimental characterization, noise is found to have a structure that consists of magnitude (i.e. the size of excursions with respect to mean value) and autocorrelation (a characteristic time scale that quantifies the duration of effects due to fluctuations): both are important in determining biological consequences. However,

[5] Almost ironically, Feynman (1948) notices in this regard: "There are, therefore, no fundamentally new results. However, there is a pleasure in recognizing old things from a new point of view".

in biological systems, low copy numbers of crucial components, like DNA or of some molecular types in a cell, prevent from the application of the same argument and motivates the interest for fluctuations, as we will acknwoledge below[6].

4.1 Extrinsic-Intrinsic Noise

In the attempt to clarify and interpret results of experiments, two categories have been defined: *extrinsic* noise and *intrinsic* noise. Both types of noise are claimed to be necessary to justify the observed amount of variability and both are suggested to appear in intracellular reactions involving small numbers of reactants (see Elowitz et al. 2002; Wilkinson 2009; Raj and Van Oudenaarden 2008).
First of all, to make progress in terms of understanding and interpretation, it is essential to provide a brief overview of the biological context in relation to which the subdivision intrinsic-extrinsic has been introduced. In this regard, the fundamental work was done by Elowitz et al. (2002), whose aim was to proceed with a quantitative study of gene expression variability in *Escherichia Coli*. They injected 2 copies of the same promoter into a single cell genome, one responsible for the expression of the cyan fluorescent protein (CFP) and the other for the yellow fluorescent protein (YFP). Under different experimental conditions, the two fluorescent species could either fluctuate indipendently (something observable in the very diversified resulting colors of bacteria) or in a correlated way, giving rise to a more homogenoeus population. According to the definition of CV, noise can be quantified looking at the distribution of a state variable (in this case, the relative number of proteins in living cells that can be estimated from fluorescence intensity): uncorrelated fluctuations define the intrinsic noise, the extrinsic component is detected through correlated flucuations. Correlated changes in expression are believed to result from fluctuations of global expression capacity, while uncorrelated variations in protein levels affect copies independently. In this way, if both promoters can be reasonably assumed independent and statistically equivalent in the expression, intrinsic noise is taken as proportional to the difference in the number of each protein within a single cell, while cell-to-cell differences in total fluorescent protein expression account for the extrinsic noise. Both the intrinsic and extrinsic component of noise could be thus determined from plots of CFP versus YFP fluorescence intensity in individual cells, where correlated and uncorrelated deviations actually appear as orthogonal contributions to total noise. The intrinsic noise is classified as the one due to stochasticity of biochemistry inherent in translation and transcription events: it incorporates and expresses the stochastic nature of gene-specific biochemical reactions, which consist of collisions occurring at random times.
On the other hand, cellular variation is known to be predominantly generated by multiple interactions of the system of interest with other stochastic systems, within the cell and in the environment, that become experimentally detectable as extrinsic fluctuations. As a consequence, several studies (see Shahrezaei et al. 2008; Huang et al. 2010) have focused on models that include random terms of both intrinsic and extrinsic type: in particular, the authors claim that extrinsic noise is essential for the sake of a biologically realistic picture. While the treatment for intrinsic stochasticity is relatively well established, the attempts of mathematical formalization of extrinsic stochasticity are still at the beginning. A hypothesis widely accepted on the basis of experimental evidence (Shahrezaei et al. 2008) is to characterize extrinsic noise as nonspecific (it affects equally each component of the system, so that mathematically it modifies the dynamics as multiplicative noise) and colored (the autocorrelation time is not negligible: it exhibits a substantial lifetime, comparable to the cell cycle).
Many factors are believed to be sources of extrinsic noise: cell-to-cell differences in morphology, organelle composition and molecular population structure, microenvironmental changes in temperature, pression, chemicals, radiation, nutrients, influences from upstream regulators that are unknown or neglected at a certain level of description. As a result, in stochastic representations including extrinsic fluctuations, a connotation of "effective" for randomness should be implicitly assumed: effective randomness, in fact, concentrates contributions of unknown initial and boundary conditions. The idea is to focus on a certain subsystem, so that

[6] The intuition beyond can be traced back to E. Schrödinger's words: "Incredibly small groups of atoms, much too small to display exact statistical laws, do play a dominating role in the very orderly and lawful events within a living organism", *What is Life* (1944).

external but connected degrees of freedom can be taken into account as "random" terms in the equations of that particular subsystem, even if in principle they act deterministically (Bravi and Sollich 2015). The importance, in generating extrinsic fluctuations, of variation both in intracellular and extracellular environments lays a great stress on the role of contexts (intracellular crowding, tissue organization) and history (cell divisions cause an accumulation of differences) in cell dynamics. In other words, extrinsic noise expresses the fact that a cell is not an autonomous entity, it is embedded in an organism and maintains connections with it by regulation and integration mechanisms in several directions. In fact, looking at the cells population level, variability is not found to be simply the sum of independent stochastic events occuring at the intracellular level, as it is not averaged out by large numbers: gene expression itself seems to depend also on a collective dynamics of the whole population (see Stolovicki and Braun 2011).
To summarize, firstly we reconsider the importance of stochasticity on the basis of the LLN, which provides an explanation for what in physics is called "intrinsic" noise, as it stems from the very nature of components of the systems and not from external perturbations. In biological data, additional sources of heterogeneity force to introduce a "noise" accounting for the orthogonal contribution in observations: to remark this opposition, it is called "extrinsic". Paradoxically, at a more detailed analysis, the discussion about the different factors contributing to extrinsic noise reveals that, biologically speaking, it can be regarded as more *intrinsic* than the "intrinsic" noise: in fact, it emerges as an operational and mathematical way to take into account the fundamental *specificity* of biological objects. It is thus be considered *intrinsic to the theory* by remote analogy to its treatment in quantum mechanics. In addition, one is somehow forced to resort to the (too) inclusive category of extrinsic noise because of the lack of experimental techniques to isolate all the different factors we listed.
In the overall perspective, extrinsic noise seems a problem still to exhaustively unravel and this, possibly, suggests a change of viewpoint, as we will propose below: reframing the question itself into an alternative epistemology, the one of the living beings, which accounts for the structures of determination inherent to biology and for an autonomous definition of randomness. Sticking to this idea, history and contexts, as well as internal constraints of integration and regulation mechanisms, can be thought to *constrain* possible evolutionary paths that dynamically arise in the interaction with the environment rather than to *determine* the outcome (as determinism requires that the same effects derive from the same causes). The role of constraints, in reference to "enablement", both to be defined below, seems crucial in biology, as we will hint in the sequel. Our emphasis on the peculiar biological meaning of "noise" may become particularly relevant in connection to the new discipline we mentioned, whose denomination is exactly "noise biology".

5 Noise Biology

Understanding the role of biological "noise" is in some sense an attempt to address the interplay order-disorder, an unresolved problem in biology since Schrödinger (1944): this constitutes the main focus of "noise biology", a rapidly expanding field. As we observed, noise biology relies on engineering approaches to systems biology, in which networks of biochemical processes are conceptualized as circuits. Noise as a disturbance effect is the consequence of the use (and, let us say, abuse) of the electronic circuit metaphor: as we will discuss later, it focuses on functionality features and thus tends to identify the action of factors that do not fall into this category as a disruption. On the other hand, many are the studies that offer alternative points of view with respect to the one of noise as detrimental to organisms, the convincing argument being that, if what is called noise exerted only perturbative effects, there wouldn't be the interesting "noise-induced" phenomena that we observe in metabolism, stress response, growth (Raj and Van Oudenaarden 2008; Eldar and Elowitz 2010). Some examples are epigenetic influences in developmental processes (see Buiatti 2011) and "noise-driven" cell fates (see Arkin et al. 1998; Rao et al. 2002; Bhogale et al. 2014; Munsky et al. 2014). Among the most striking "noise-induced" phenomena, we should then mention self-organizational properties and the spontaneous emergence of patterns in morphogenesis (e.g. see Meyer and Roeder 2014 for a review): random fluctuations, such as inhomogeneities in the spatial distribution of chemical species, can in fact initiate tissue differentiation and patterning mechanisms by breaking the symmetry between cells. Interestingly this research direction is in part reminiscent of what Prigogine (1984) introduced as "order by fluctuations"

and, in particular, it continues Turing's studies on pattern formation in reaction-diffusion systems (1952). Even in this different perspective, the vocabulary often used still derives from the electronic circuit metaphor and thus inherits some notion of "optimality" in the design, a problematic notion itself when referred to organisms (Longo and Montévil 2013). The basic assumption of noise biology is that natural selection has "optimized" the distribution of noise to populations, shaping molecular processes in such a way to "resist" or to functionally "exploit" noise (Vilar et al. 2002; Rao et al. 2002): the aim of noise biology is to understand this distribution, statistical properties of random variables being informative about selective mechanisms that drove such evolution.

The emerging scenario is consistent with the characterization of "canalized" biological randomness previously proposed. In the noise biology literature, heterogeneity is often denoted as "*biased* by environmental and intracellular signals [...] *ordered*" (Rao et al. 2002), "*adjusted* during functional evolution" (Snijder and Pelkmans 2011). In particular, the integration of functional modules and regulatory features are assumed to filter and shape noise, the result being a "*cultivated* noise" or an "environmentally *tuned* heterogeneity in a cell population" (Rao et al. 2002). For instance, stochastic behaviors are inevitably affected by the crowded, diffusion-limiting, highly structured and compartmentalized intracellular media and by molecular mechanisms of regulation and compensation, such as *feedback* and *feedforward* loops (in feed-back loops the output comes back as input, while in feed-forward information is unidirectional). Also at the tissue level, mechanical stresses can either control or amplify cell growth heterogeneity, as suggested by Uyttewaal et al. (2012). In general, noise takes part in the evolutionary and adaptive dynamics thus its "functional role" has been extensively claimed. In this context, the focus is on its interplay with nonlinearities, which leads to phenomena of stochastic amplification, stochastic dumping and focusing of oscillations (see Paulsson et al. 2000). An example worth mentioning is the circadian rhythm, i.e. the biochemical mechanism oscillating in phase with the photoperiod, for which stochastic models are shown (see Guerriero et al. 2012 for plant circadian clock) to better capture experimental observations. Stochasticity ensures a faster, thus more efficient, synchronization to variations in photoperiod and buffers fluctuations in various environmental factors, such as light intensity and temperature. In summary, stochasticity, by facilitating the response to external changes, provides organisms with an increased plasticity and it is directly linked to metabolism and survival through the role played by circadian rhythms in photosynthesis.

Furthermore, fluctuations act in connection with positive feedbacks in cell fate-selection mechanisms, yielding to the so called noise-mediated or stochastic "switches" (Raj and Van Oudenaarden 2008): a positive feedback loop can lead to multiple stationary solutions (multistability) and stochastic fluctuations have the potential to switch between them, causing a variation in the phenotype. Such mechanisms are considered an evidence of functional advantage of noise to respond to environmental changes. The paradigmatic (and firstly studied) system in this regard is the λ-phage lysis-lysogeny decision circuit, where the "noise" canalizes the effect of the environment in such a way to enable the decision between the lytic and lysogenic pathway (Arkin et al. 1998). Other examples can be listed in metabolism and nutrient uptake, such as the lactose-pathway switch in *E.coli* (Bhogale et al. 2014), or in connection to fate selection in viral infection, such as the Pyelonephritis-Associated Pili (PAP) epigenetic switch in *E. Coli* (Munsky et al. 2014). Variability is thus enhanced by networks that can produce multiple, mutually exclusive profiles of gene expression: this fact, in combination with other processes of randomly expressing genes and silencing others, is thought to have a selective advantage, as it allows organisms to display phenotypic variants also in uniform genetic and environmental conditions (Wilkinson 2009). These phenomena can be thought to belong to the class of "variability generators" introduced by Buiatti and Buiatti (2008) and described as exploration tools of the phase space that are essential for the adaptation to changing contexts. This is relevant in the perspective further developped below, that the very phase space is co-constructed by the changing biological structures and their interaction with the ecosystem.

6 Robustness from Noise and Beyond Noise

Dialectically, the problem of "noise" cannot be separated from the one of "robustness": this is often meant as an inherent noise-rejecting property, given implicitly the assumption that a noise-resistant system is likely to exhibit robustness. Many key properties of biological systems, from phenotypes to the capability of performing some task, are recognized to be "robust" in the sense of relatively insensitive to the precise values of biochemical parameters: the degree of robustness can be thus quantitatively and systematically investigated by methods connected to sensitivity analysis (Barkai et al. 1997). Relying on the analogy with an electronic circuit, robustness is described as crucial to ensure a proper functioning of "signal" transduction networks in "noisy" conditions. The explanation of biological robustness in absence of large numbers, not possible by invoking arguments from physics, is attempted rather by focusing on "design" features of biochemical networks (a way of proceeding more akin to engineering). The metaphor biosystem-circuit provides thus the framework to accommodate the interplay between robustness, noise and their respective roles for a reliable operational outcome but, importantly, in such a framework they are conceived as seemingly conflicting notions. "Noise", by enlarging the range of parameters, contributes to variability and, as a consequence, a potential advantage in terms of adaptiveness to changing environments can be argued for (see e.g. Rao et al. 2002): one can indeed analyze robustness in close connection with organisms internal plasticity (Buiatti and Buiatti 2008) and randomness as a key component of structural stability (Longo and Montévil 2013).
Attempts to include a property of robustness into models account for the "individuality" of living objects that strikingly emerges in observations: examples of this evidence are some features of chemotactic response (Barkai et al. 1997), such as adaptation time and steady state tumbling frequency, that vary significantly from one bacterium to another in genetically identical populations, or phyllotaxis (Mirabet et al. 2012), as the arrangement of leaves and flowers is widely diversified both at inter and intra-plant scale. In our perspective, robustness expresses and justifies a notion of organisms as systems endowed with a high degree of historical specificity: it allows changes over time, while preserving varying degrees of individuality, from bacteria to large vertebrates. By virtue of this correspondence, robustness can be regarded as an intrinsic property, as far as variability and individuality within the constraints of structural stability are inherent to life. Thus, stochasticity, far from being just "noise", plays a constructive role towards robustness, by promoting and underlying the adaptive responses of an organism to the environment. Remarkably, this potential positive contribution of randomness is grounded not only in statistical properties but it holds true both by large and by small numbers, in contrast to physics, as we will argue below.
In biology one needs to enrich the notion of robustness with respect to other disciplines (see Lesne 2008 for an extensive review of the notion of robustness in biology): for example one should add forms of "functional", "structural" robustness that stem from regulation mechanisms and are shaped by the evolutionary history (e.g. feedbacks in stochastic "switches" and in morphogenesis act towards a stabilization and a reinforcement of the phenotypic path selected by fluctuations). In particular, the definition of robustness should not be limited simply to "feature persistence" but should include also the meaning of "resilience", to be intended as persistent dynamic reconstruction of a viable coherence structure, viable also because adaptive and diverse, thus changing.

7 Proper Biological Randomness

It should be clear by now that the need to capture heterogeneity, which manifests itself as unpredictability with respect to the deterministic formalism, leads to resort to stochastic models. In particular, a description in probabilistic terms of biochemistry has been the starting point for the physico-mathematical investigation and characterization of biological randomness.
In spite of the major interest of this investigation, we consider it still essentially incomplete (where incompleteness does not mean at all useless). The perspective we want to hint here is based on an attempt to include randomness in the "structure of determination" of biological dynamics, intrinsically. In a sense, we can still refer to mathematical physics, methodologically, for a paradigmatic change of this kind: Schrödinger equation gives the deterministic dynamics of . . . a law (an amplitude) of probability. By this, quantum randomness is integrated in the mathematical determination. We are far from being able to propose a similar

mathematical novelty, in biology, as first a change in the theoretical frame, including terminology, is required. A preliminary, apparently minor, point is the idea of avoiding the reference to "noise", when appreciating the role of random events in biology. As we stressed and as we will further stress below, in biology, randomness is an integral part of variability, thus of adaptation and diversity, both in reference to small numbers and to large numbers. Randomness contributes by this to biological structural stability, as a peculiar form of resilience. It is an evolutionary fact that a population of a few thousand animals is more stable if diverse; but diversity in large populations as well, or in species, contributes to stability, far away from the "averaging out" proper to noise in stochastic dynamics in physics. That is, both within an organism and in the ecosystem, diversity, variability and number of components play a diverse role, as we will hint. And randomness, as a component of variability, adaptation and diversity, becomes functional *as such* to biological dynamics.

7.1 Examples of the Functionality of Diversity in Large Numbers

Within an organism, variability may contribute in different ways to its structural stability. It is largely claimed that the average functionality of hepathocytes (liver cells) only matters (Pocock 2006). So, variability seems averaged out in this organ made of a few hundred million cells, a number considered "large" in biological applications of statistical physics. Similarly, as for the lungs' function, only the average functionality of lung's cell seems to matter. Yet, at a closer insight, both interindividual and intraindividual diversity of the fractal and alveoli's structure and cells' diversity of lungs in mammals (about five hundred million alveoli, in an adult human), contributes to the adaptivity of the lungs' functionality in different contexts: the direct interface with the atmosphere better adapts to atmospheric changes by its diversity. Even more so, the about 10^9 leukocytes in the immune system, yet another large number, are effective exactly because of their variety and diversity: they are produced as a result of variability generators (Buiatti and Buiatti 2004) and subsequently selected when binding antigens. The immune system is a true evolutionary system within an organism, where diversity within each leukocytes' population, and between populations, is at the core of its functionality and is enhanced by selection (Thomas et al. 2008). Thus, variability, which fluctuates over about 10^{15} potentially different cell receptors, is the opposite of noise to be averaged out. In conclusion, the biological functionality of randomness is highly unconventional w.r.to physics, by the peculiar role of adaptivity and diversity, and a reference to two out of these three examples, say, just in terms of "noise" may be highly misleading.

In biology, a novel and specific notion of randomness has been claimed (see Buiatti and Longo 2013; Longo and Montévil 2013, 2014). This is also due to the need to work simultaneously at different levels of organization, that is to grasp, in a unified way, cellular, tissue, organ, organismal levels, possibly within an evolutionary context. In physics, different scales are enough to force different theories, so far: quantum and relativistic fields are still not unified to describe gravity; classical and quantum randomness are treated differently (they are dealt with different probabilities, in view of the violation of Bell inequalities, see Aspect et al. 1982); hydrodynamics is far from being understood in terms of quantum physics – in spite of water being formed by simple molecules (Chibbaro et al. 2014). This lack of unity, in physics, is relevant for biological theorizing, since both quantum and classical randomness are present at the molecular level (see Buiatti and Longo 2013 for references and a discussion); water, say, has also a relevant role, including by its peculiar "coherence" in the highly compartimentalized structures of eukariota, due to Quantum Electro-Dynamics effects (Del Giudice and Preparata 1998). Moreover, many researchers analyze cell networks in terms of statistical physics, while others work in morphogenesis of organs in terms of non-linear dynamics, since Turing's 1952 paper (Fleury and Gordon 2011).
From an epistemic perspective, these different levels of analysis may be soundly called "different levels of organization" as they require, so far, different mathematical, even conceptual, possibly incompatible, tools. The reduction to the molecular level is a myth that is in contrast to the history of physics, where theoreticians proposed "unifications" (Newton, Boltzmann) not reductions and still search for unification (relativistic vs. quantum fields). Moreover, this myth leads to incomplete theories even at the molecular level, as any relevant molecular cascade, in an organism, be it just a cell, *causally depends on the context*. In particular, macromolecular interactions are largely stochastic, must then be given in probabilities and these probabilities

depend on the context. For example, macromolecular syntheses may be "constrained" by enzymes in different ways; a simple pressure on the cell or its nucleus, "constrains" or "canalizes" stochastic gene expression (Farge et al. 2009; Swain et al. 2002; Raj and Van Oudenaarden 2008).

In order to deal with the physical singularity of these phenomena, the notions of "bio-resonance" and "enablement" have been proposed (Buiatti and Longo 2013; Longo et al. 2012a). These notions are proper to organismal biology and evolution and significantly change the biological "structure of determination", in particular in relation to randomness; they enrich by this the contribution by bio-chemistry, summarized in the previous sections. Bio-resonance has been proposed in analogy to the role of "planetary" resonance in the non-linear analyses of the planetary system: it is the gravitational interaction between planets that "destabilizes" the dynamics by a non-linear amplification of minor fluctuations and perturbations, in particular when planets are aligned with the sun (a sort of noise that destabilizes the perfect clockwork of Creation). This happens though at just one scale, at one level of mathematical description. Bio-resonance instead concerns the interactions, by integration and regulation, between different levels of organization, thus possibly between different mathematical analyses, within an organism. Moreover, on one side, (minor) fluctuations at one level may affect other levels – an endocrine perturbation, say, may change the control of cell reproduction in a tissue, a possible cause of cancer (Soto and Sonnenschein 2010). On the other, bio-resonance enhances regulation and correlates variations, by integration of cells, in a tissue, in an organ, in an organism. By this, it contributes to stabilization of an organism, which continually undergoes Darwin's correlated variations, also in ontogenesis, though in a more constrained way than at the evolutionary space-time scale.

As for enablement (Longo et al. 2012a; Longo and Montévil 2013), its epistemological novelty resides in enriching deterministic causality: phylogenetic and developmental paths are selected according to their "compatibility" in a (phase) space of phylogenetic and morphogenetic trajectories dynamically "co-constituted" with the environment (Longo and Montévil 2014). In short, an ecosystem *enables*, does not causes, in general, the formation of a new phenotype (possibly a species). In light of Darwin's first principle, the default state for biological entities, since they are endowed with a replicative structure, is given by "proliferation with *variation*", as we will stress in the conclusion, following Longo et al. (2015). Then, some variants, some hopeful monsters as suggested by Goldsmith, often produced by sudden bursts of variability (Eldredge and Gould 1972) may be enabled by the (changing) environment. Note that, by modifying the default state, from inertia to Darwin's descent with modification, the causal analysis of an evolutionary and ontogenetic dynamics must be extended to an analysis of "what enables". A doctor who understands the *cause* of a pneunomia in a bacterium, must also consider the state of the lungs or the general health conditions of the patient that *enabled* the infection to develop – bacteria a priori reproduce with variations and are generally present in an organism: a healthy lung and immune system control their reproduction and do not enable them beyond a viable level.

As for the dynamic nature of the enabling environment and of the organisms that grow in it and compose it, note that, since a quantum event at a molecular level may induce a phenotypic change, a possibility mentioned above, the latter has at least the same nature of unpredictability as the quantum event, though manifested at a very different scale and level of organization. Thus, if one takes as observables the ones proposed since Darwin, namely organisms and phenotypes, in a broad sense, these are a consequence of the dynamics and cannot be pre-given, even not a space of possibilities. This is in sharp contrast with the theoretical attitude in physics, where one of the major duties of theory building is the preliminary invention of the "proper" phase space: the dynamics and its laws will follow, possibly given by equations or evolution functions within those spaces. It should be clear that these may be infinite or even infinite dimensional, such as Hilbert spaces in quantum mechanics, yet they are mathematically pre-defined to the dynamics (by their symmetries, they can be axiomatically defined, by finitely many words). In some cases, in statistical physics, the (finite) dimension may change, yet the new dimensions have the same observable properties as the others and the probabilities of each change of phase space are known (Sethna 2006).

Enablement, compatibility, dynamic and unpredictable co-constitution of the phase space contribute to set up a new conceptual framework to understand and justify variability and diversity as intrinsic properties of life: they are not just "noise", or perturbations within a pre-given frame. Also the analysis of the "living state of the matter" proposed by Buiatti and Buiatti (2004) pays particular attention to variability generators

or internal random generators, a set of phenomena and mechanisms that enable organisms to produce new possible paths and variants on which selection processes act or that are enabled. These generators are at the core of plasticity, adaptiveness, evolvability. As we mentioned, within an organism, the immune system is the most typical case of a contribution to biological viability and stability based on variability generators, thus on diversity.
In summary, randomness in biology must be considered as a constitutive component of stability, also or mostly by the peculiar biological role of adaptivity and diversity. It is a massive but "canalized" phenomenon, summarizing the pressure due to internal constraints and to environmental conditions, in such a way that the analysis cannot be performed regardless of the context. Internal mechanisms of integration and regulation, to which upward and downward processes contribute, establish an intertwining of local and global scales in organisms and canalize biological evolutionary and developmental dynamics. They appear as constitutive aspects of the concept of "bio-resonance", proposed in order to include in the description both constraints and amplification of randomness between epistemic organizational levels. Furthermore, living systems are open, they continually interact with the ecosystem, exchanging energy and matter and dynamically modifying their configuration jointly to the ever changing environment. In biology, histories and contexts, "accidents" that are usually neglected in physics, contribute to biological determination (Longo and Montévil 2013): two books and several papers (see Longo's web page) propose a perspective on these aspects of organismal dynamics that need to be taken into consideration, even in investigations at a molecular level.
Note, finally, that the law of large numbers (LLN), in physics, justifies the interest in potential effects of randomness in small populations, as it indirectly stresses the potential role of fluctuations for low numbers and the possibilities of change as opposite to "averaging them out", proper to fluctuations in large numbers of entities. However, LLN does not provide tools for a satisfactory treatment of this phenomenon for low numbers, while it precludes the understanding of functional diversity by randomness in large numbers (see the immune system above). In other words, the LLN implication that fluctuations are negligible is rather a retrieval of the fully deterministic macroscopic model and its "classical" stability. In addition, the statistical theory behind LLN subsumes indipendent copy number fluctuations[7] as sole source of "noise" and this is not sufficient in biology, as we tried to make clear also by the description of intrinsic and extrinsic components of noise in the previous section and by the examples and notions in this section.
In summary, from our perspective, biological randomness plays an essential explanatory role, in presence of both large and low numbers, by the role of variability, diversity and adaptivity. By focusing on these randomness related components of *biological stability*, we stressed a rather unconvential aspect of life dynamics in comparison both to physical or computational ones. The mathematical form of randomness appropriate to biology reasonably needs a more systematic elaboration and definition, as it should condense the conceptual novelties briefly described here and be conceived as proper to the very dynamics of life.

8 Symmetries

The role of symmetries, in mathematics and physics, is well-known. By symmetry we mean both a regularity in a structure, which may present an invariance with respect to some transformations, and a trasformation that preserves some properties of the intended object. In a sense, in a discipline largely based on invariants and invariance preserving transformations, mathematics, symmetries have this peculiar double status of being both invariants and transformations. By their definition, symmetries are organized as a group, in the intended space. In mathematics and physics, from Euclid to Grothendieck, from Archimedes to Einstein and Weyl or contemporary physics, symmetries are at the core of knowledge construction. Our 3-dimensional continuum possesses a fundamental (rotational and translational) symmetry (groups O(3) and R3) which permeates all physical theories. Lorentz and Poincaré symmetry groups in relativity and gauge groups for elementary particles are at the core of contemporary physics. Symmetries appear in crystals and quasicrystals, in self-similarity for fractals, dynamical systems and statistical mechanics, in monodromies for differential

[7] As a preliminary evidence, recent experiments (see Salman et al. 2012) suggest that the fitted curves for protein abundance resemble limit distributions of strongly correlated stochastic variables: this would reflect the spatial and temporal interdependence of processes regulating gene expression.

equations .... Even more fundamentally, conservation properties, of energy and momentum, are symmetries in the equations (Noether's theorems): these properties allow to write the Hamiltonian, an omnipresent tool in mathematical physics. Similarly, in electromagnetism, inversing charges does not alter the equations (a symmetry), or the aim of the recent experiments on the Higgs boson was to witness a symmetry breaking in fundamental fields in particle physics.

In biology, symmetries allow to understand macromolecular interactions, as well as global structures, such as organisms' bauplans. Yet, *symmetry breaking* as well has a crucial *theoretical* role in biology, as we will hint in the next section. An interesting connection that may help to move from physics to biology, is given by the notion of "critical transition", where both symmetries and their breaking play a key role. This notion has been used, in between physics and biology, since the '80s (see Longo and Montévil 2014 for a survey and details on the following remarks). The main idea is to split first the microscopic and the macroscopic descriptions. The microscopic level may be described by the same equations in different macroscopic states and these equations satisfy certain symmetries (for example, no particular direction in magnetization at high temperature, nor in a fluid). At the transition point, i.e. at a given value of the control parameter (temperature, say), these symmetries are broken and a precise direction dominates in magnetization, in crystal formation .... The space of description changes, at the pertinent scale, as well as its symmetries. Yet, in existing physical theories, this space may be pre-given. Crystals and snow flakes, a typical formation of a coherence structure at a critical transition, yield new, but pre-listable symmetries, in a new, but expected, space of observables, due to forces already present in molecular interaction, but ineffective till the Brownian motion is above a certain threshold. At critical transitions, along the intended parameters, pertinent objects change, yet they may be measured according to pre-given observables.

In the statistical approach to thermodynamics, one can observe a similarly consistent role in the definition of a phase space, at the thermodynamic limit, and this in connection to the "averaging out" of some key features which, in that limit, can be regarded just as microscopic details. Note also that, in this approach, the probability of deviating from the most probable state decreases exponentially, depending on the number of lower-level entities (this result is known as the "fluctuation theorem"). On the grounds of some fundamental assumptions, such as the thermodynamic limit (the assumption of an infinite number of particles leads to a coincidence of averages and macroscopic states) and ergodicity (that is a symmetry assumption between time average and phase space average), the theory allows to go from the properties of a trajectory to the properties of the phase space and vice versa[8].

More generally, the description of a suitable phase space where "trajectories", in a broad sense, may be described, even in presence of critical transitions or asymptotic constructions, is a key issue of the theoretical investigation in physics. As we already observed, since Newton and Kant, we understood physical knowledge as built in "a priori" defined (phase) spaces, where one can describe the intended dynamics by equations and evolution functions, that is once fixed the pertinent parameters and observables. Newton, in space and time, then in suitable, yet different, phase spaces, Hamilton, Poincaré, Gibbs, Boltzman, Einstein, Schrödinger ... gave us the beautiful theories that frame physical theories. Let us see more closely a further key role of symmetries in this very robust methodology.

Physical and mathematical objects are *generic*, that is they are invariants in experiments and theories, in a given (abstract) space of observables and objects. As for mathematics, it should be clear that a right triangle or a Banach space are generic: a proof of their properties on one of them, gives them "for all". In physics, a measurement on a falling stone or an electron may be iterated identically, always, in any similar context, within physical approximation, for any stone or electron. This is a theoretical symmetry (a

[8] In these contexts, mean values analyses (or central limit theorems) are generally valid. However, in the complex case of second-order phase transitions, in thermodynamics, these analyses fail. For example, the transition between macroscopic order versus disorder in ferro-paramagnetic transitions, does not occur progressively but at a precise (critical) temperature. At that point, fluctuations at every scale dominate and this expresses a tendency to obtain magnetic alignments of every size. Moreover, some physical quantities become infinite, such as susceptibility to an external field. As a consequence of the dominating fluctuations, close or at the transition, mean value analyses fail (Longo et al. 2012b; Toulouse et al. 1977). This may be of interest for biological theoretizing, yet, in this case as well, the phase space is pre-given.

invariance property of objects that may be interchanged, are generic, in the theory – as given by equations, evolution functions ...), which is also crucial for measurement. As Galileo observed in "Dialoghi sopra i massimi sistemi": errors in measurement are unavoidable, yet small errors are the most probable; errors distribute symmetrically around the mean value; reliability increases with the number of measurements. The symmetries of a Gaussian and the genericity of the physical objects formalize Galileo's early insight.

9 Symmetry Breaking

9.1 Measurement

In order to stress the singularity of biological experiments and subsequent theoretizing, observe first that Galileo's remarks are fundamentally wrong in biology, from cells to plants and animals, and this constitutes a major challenge for experimental work. Indeed, biological objects are *specific*, that is, they are the result of a history, they are individuated and diverse, they are not interchangeable (symmetric). By an extraordinary attention to experimental protocols, biologists care of the history of each organism they work on: its phylogeny, up to a very high number of generations, and its ontogeny are closely considered in order to perform and compare experiments. So mice and cells are internationally numbered, described and used according to these histories. Typically, when increasing the number of experiments, one may be forced to go beyond the (limited) number of organisms with the same phylogenetic history, and this may give very different reactions in a given experiment. Then "errors" and their distance may increase with the number of experiments. The point, of course, is that these are not errors, a priori, but may correspond to increasing interindividual diversity, when a population increases. Similarly, exceptions to mean values are not to be discarded, as they may correspond to an exploration by variability of new onto-phylogenetic paths. As we observed, biologists "symmetrize" (a terminology by M. Montévil in ongoing strongly needed theoretical reflections on biological measurement) as much as they can the objects of experiments, typically by common histories and strictly controlled environments, but the comparative analysis of variability is also a component of the empirical investigation: the fact that Polynesian and Polish patients may react very differently to a molecule is an important information, per se. Specificity of organisms breaks a fundamental symmetry assumption in mathematics and physics, genericity, an invariance under objects' transformations, in experiments and in theories.

9.2 Extended Criticality

A conceptualization of the permanent reconstruction of the coherence structure of an organism, as a state of "extended critical transition" proper to biological onto-phylogenetic trajectories is summarized in Longo and Montévil (2014), following some previous papers (downloadable). Each cell reproduction, in particular in a multicellular organism, yields a critical transition. At the "bifurcation", it produces a new coherence structure of intercellular context, where two similar (almost symmetric, but inherently asymmetric) cells reorganize cell-to-cell connections as well as collagen, tissue's matrix .... The sensitivity to the context of the new symmetries formed at the transition, plus the asymmetric distribution of DNA and proteomes, facilitates cellular differentiation and variation: a minor change in the context (different distance from the source of energy, different pressure ...) may influence the cell fate. Adaptation is a further consequence of this unstable/stable dynamics, as, at criticality, a cell, an organ may better adjust to organismal or ecosystemic changes (see Mora and Bialek 2011, where also some biological functions are described as poised at criticality[9]).

In this perspective, a biological trajectory of an organism is a cascade of symmetry changes of ... a fundamentally symmetric, i.e. locally coherent, structure, yet continually changing its proper coherence (its symmetries). This viewpoint focuses on the contingency of structural stability in biology, but does not exclude stability from the theoretical construction. We just stress the role of time and of changes in an understanding

[9] In reference to a previous footnote, this situation is closer to second order criticality than to the statistical "averaging out".

of the resilience, thus of a form of stability, in biological dynamics, on the grounds of a permanent dialogue with physical theories, both by a methodological transfer and by conceptual dualities. Note, typically, that the continual changes of symmetries do not allow to describe biological trajectories as the optimal result of conservation properties (energy, momentum or alike), like in physics. As a consequence of these properties, in physics, the trajectories are geodetics (optimal paths) in a pre-given phase space, thus they are specific[10]. We claim instead that trajectories, in biology, in evolution in particular, are *generic*, that is they are "possible" ones, as a consequence of Darwin's principle of descent with modification and of enablement or selection, in a co-constructed ecosystem as phase space, where pertinent observables and parameters are subject to change[11]. Moreover, a phylogenetic trajectory is the "sum" of ontogenetic trajectories, where each of these trajectories is an extended critical path (ontogeny is an extended critical interval, in the life span, with time as a control parameter, see Longo and Montévil 2014).
Table 1, below, summarizes the conceptual dualities w.r.to physics that guide the theoretical attempts in biology mentioned here. We already hinted to the dualities in the first three lines that are extensively treated in the references. In the next section, a few ideas will be given on the dualites not yet discussed. This will allow to further stress the functional role of randomness in biology.

PHYSICS	**BIOLOGY**
randomness is **non deterministic** or deterministic non predictability **within a pre-given phase space**	**randomness** is **intrinsic indetermination** given also by changing phase spaces (ontogenesis and phylogenesis)
specific trajectories (geodetics) and **generic objects**	**generic trajectories** (possible/compatible with ecosystem) and **specific objects**
point-wise criticality	**extended criticality**
reversible time (or irreversible for degradation-simplified thermodynamics)	**double irreversibility of time** (thermodynamics and phenotypic complexity constitution)

Table 1. A possible theoretical differentiation between inert and living state of matter is described through some conceptual dualities, based on the work in Longo and Montévil (2014).

[10] Geodetics are usually derived by variational or equivalent methods that allow to write a Hamiltonian or extremize a Lagrangian functional that are given in terms of conservation properties.

[11] Note that not only measurable phenotypes, as observables, may change, but pertinent parameters as well: air vibrations at audible frequencies were irrelevant before the formation of hears, in early vertebrates with a double jaw (Allin 1975).

10 Symmetry Breaking, Randomness and Time

10.1 Biological Time

Longo and Montévil (2015) observe the co-existence, in existing physical theories, of symmetry breaking, random events and (local) irreversibility of time. In short, measurement as projection of the state vector in quantum mechanics, bifurcations in classical non-linear dynamics, diffusions by random paths ..., as symmetry breakings, are all associated to random events (or probability values) and are time irreversible. By a direct analogy, in this case, it should be clear that the approach hinted here to biological trajectories in terms of cascades of symmetry changes further stresses the omnipresent and constituive role of randomness in biology. But also the irreversibility of time turns out to be crucial. Of course, there are plenty of thermodynamic effects, in an unicellular organisms as well as in elephants, since energy is used and transformed everywhere. Yet and once more, the physical singularity of life pops out also by the peculiar irreversibility of time that we consider needed for an appropiate theorizing.

First, energy dispersal, as understood in thermodynamics, has a major relevance in biology. The decrease of entalpic oscillations of a macromolecule may have little physical interest, in particular because, by pumping energy, one may restaure the previous situation (like in two mixing gazes, where a centrifugue may separate again the gazes). Yet, in a cell, decreasing oscillations of macromolecules may reduce stochastic interactions and biochemical activities, thus it may irreversibly affect gene expression and metabolic stability (the increasing instability of the latter is often considered at the heart of aging, see Olshansky and Rattan 2005). This stresses the relevance of the thermodynamic irreversibility in biological processes. Second, the very setting up and mantainance of biological organization is a highly irreversible process. Everybody understands that a theory that would allow to conceive a backwards film of embryogenesis should be immediately discarded. Let's examine this point more closely.

As we recalled above, each cell division, on one side, increases order, as having two cells instead of one enriches the order or the organization of the universe; on the other, it produces a slight disorder. The asymmetric division of the proteome, which, for many molecular types that are present in low numbers, does not average out, similarly as for the differences in DNA copies, in the partitioned membrane ... yield irreversible symmetry breakings. This slight production of disorder is also a form of entropy production, while it comes with the production of order "per se", not just by the use of energy. Now, cell division is not proper only to embryogenesis, but it is a critical transition that continually occurs in ontogenesis, by billions of times everyday in a large metazoan. A close analysis of the relevance of this two forms of entropy production for aging is developped by Bailly and Longo (2009). Let's just mention here that this may help to stress a difference between monocellular and multicellular organisms. In a monocellular organism, the entropy produced by the energy transformation processes or at asymmetric reproductions is mostly released in the exterior environment. Some traces of aging are then found in asymmetries in the new membranes – a new vs. an older part – which happens to be the border between interior and exterior, where flows pass through, see (Lindner et al. 2008; Stewart et al. 2005)). In a metazoan, the entropy produced, under all of its forms, is also but inevitably transferred to the environing cells, to the tissue, to the organism. It may contribute to decrease collagen tension and the global tensegrity structures of tissues. It may affect metabolic stability in other cells as well as the oxidative stress (Romano et al. 2010). As this is an additive effect, it increases exponentially: while negligible in embryogenesis and youth, it prevails over the slower reconstruction of organization with aging. Note, here, that we do not want to ascribe aging entirely to this double form of entropy production, as the debate on the nature of aging, a multifactorial process, is extremely open and lively. We just propose a possible further element for the controversial role of many factors, some of which may be unified by this analysis, which differs but is compatible with other recent proposals. In particular, the generation of more connective tissues, a possible biological response to degradation, is another challenging component of aging, (Miquel 2014). Note finally that even the analysis of the entropic component of aging cannot be based on the averaging out of fluctuations or the centrality of means. It is based instead on the key role of reproductive variability as such and the slight creation of disorder associated to it, also during the (re-)construction of order. Moreover, the distinction between thermodynamic irreversibility and the irreversibility of the very setting up and mantainance of organization, encourages to single-out a second observable time, in the same

dimension of the physical arrow of time, yet proper to biological investigations: the time of (re-)construction of the organization (in physics, the dimension of energy contains different observable forms of energy). Biological clocks and internal rhythms in organisms provide a natural measurement for this second observable time, at least along metazoans' life span, as they scan it in a relatively independent way from thermodynamic time (Longo and Montévil 2014). Once more, random events are at the core of it and have a constitutive, functional role.

10.2 Plasticity and Variation

So far, variability in biology has been implicitly assumed as the result of random variation at some level of organization, beginning of course, with DNA, from mutations to stochastic gene expression. However, there is an increasing awareness of Lamarckian effects in phylogenesis. Acquired or epigenetic inheritance has been observed in cyliates (Nowacki and Landweber 2009). Proteomic changes due to different environmental levels in lactose are reportedly inherited for several generations (Robert et al. 2010). It is well known that methylation and demethylation, which affect gene expression, may be induced by environmental factors, including emotional situations, from rats to humans. In other words, Darwin's principle of descent with modification is not only based on random effects, but may also be induced by contextual interactions and result in acquired inheritance. In this perspective, *canalization by constraints* may be another suitable concept for the relation between biological dynamics and their contour or internal conditions. Some recent experiences in microgravity (Bizzarri et al. 2014) show that unicellular eukariota develop wild cytoskeleta when they reproduce in geo-stationary satellites. The idea is that gravity constrains development: typically, it canalizes cytoskeletal growth towards relatively flat structures as well as it selects negatively shapes that are unsuitable for subsistance or movement. When this constraint is reduced or disappears, descent with modification yields a larger variety of enabled structures. One may consider then the resulting forms as due to the plasticity of organismal development, as cytoskeleta seem shaped, not just selected, also by gravity. Biological plasticity, of course, reaches its highest point in (large) brains, where the continual dynamics of neurons and their connections undergoes deformations and even critical transitions (Werner 2007) as a consequence of brain's interaction with the ecosystem. In short, from individual eukariota to large organisms, their neural systems at least, both phylogenesis and ontogenesis extensively present random variations as well as forms of induced or canalized changes by plasticity, where selection or enablement apply.

11 Conclusion and Opening: some Principles of Biological Organization

Cell proliferation has been called "ground state" in the context of embryonic stem cells, because it is inherent to the system, and does not require stimulation (Wray et al. 2010). Morevoer, all cells move. In pioneering work on cancer (Soto and Sonnenschein 1999) proposed to consider proliferation and motility as default state of all cells, also within organisms, where this default state is highly constrained. Even neurons or heart's cells, which are known not to reproduce or to reproduce very rarely, when extracted from their organismal context proliferate at high pace. As we already mentioned, in Darwin's theory, reproduction is always *with modification* and will happen as long as there are sufficient available nutrients – up to potentially covering Earth, says Darwin. The addition of "modification" is thus fundamental; variation begins at the cell division that generates two overall similar, but not identical cells. Adding modification at reproduction is at the core of this paper not just in view of random molecular events (Kupiec 1983; Raj and Van Oudenaarden 2008), but also by the plasticity mentioned above. In Longo et al. (2015), this has been synthesized as a default state of all organisms:

Proliferation with variation and motility

and as a Framing Principle:

Life phenomena are never identical iterations of a morphogenetic process

Generating diversity from a single cell, be it LUCA (Last Common Universal Ancestor) or a zygote, is an essential component of phylogenesis and ontogenesis. The Framing Principle is a way to express a principle of iterated organization at all scales and levels, not just cells and organisms. For example, branching morphogenesis in organs is an ubiquitous iterative process that generates a repetitive, yet always changing pattern, e.g. branching angles vary (in vascular systems, in ducts of all sorts). This is due to the combined action of the default state of the cells producing the corresponding tissues and the varying pressures, frictions ... in the context.

An analysis of "organization with variation" has been recently proposed by Montévil and Mossio (2015), where an explicit distinction betweeen causal relations and constraints provides a major conceptual clarification. By the introduction of characteristic times for processes within an organism and by the role given to variation and scales, their novel diagrammatic approach to ontogenesis may open the way to new mathematical ideas, which may add relevant theoretical understanding to the transfer of tools from physics. We recall that the work at the right scale of observation has been the key step originating all theories in physics, from falling bodies and celestial mechanics to thermodynamics and quantum mechanics or hydrodynamics, originally all based on very different or incompatible principles (and many are still now). Then, new and suitable principles and mathematical tools where invented, both for the analysis at the intended scale or, later, for theoretical unifications, whenever possible, as there has been no "reduction" in physics, but remarkable unifications – even the (partial) understanding of some chemical laws in terms of quantum mechanics should be viewed in this way (Chibbaro et al. 2014). Thus, we shouldn't just use conventional tools from mathematical physics in the analysis of the living state of matter, but also develop intrinsic insights and possibly new mathematics, following the methodology of physics along history, including the choice of a suitable scale – with the cell as least component, in this perspective. Unification will then be possible, as a long term project, like within physics, but if one does not have two or more theories, there is nothing to unify. The analysis of the conceptual dualities summarized above (see also Table 1) and the peculiar yet comparable role of randomness in different contexts may be a way to this.

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