PART 1

Randomness in all of its Aspects

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Classical, Quantum and Biological Randomness as Relative Unpredictability

We propose the thesis that randomness is unpredictability with respect to an intended theory and measurement. From this point of view, we briefly discuss various forms of randomness that physics, mathematics and computer science have proposed. Computer science allows us to discuss unpredictability in an abstract, yet very expressive way, which yields useful hierarchies of randomness and may help to relate its various forms in natural sciences. Finally, we discuss biological randomness – its peculiar nature and role in ontogenesis and in evolutionary dynamics (phylogenesis). Randomness in biology is positive as it contributes to organisms' and populations' structural stability by adaptation and diversity.

1.1. Introduction

Randomness is everywhere, for better or for worse: vagaries of weather, day-to-day fluctuations in the stock market, random motions of molecules or random genetic mutations are just a few examples. Random numbers have been used for more than 4,000 years, but they have never been in such high demand than they have in our time. What is the origin of randomness in nature and how does it relate to the only access we have to phenomena, that is, through measurement? How does randomness in nature relate to randomness in sequences of numbers? The theoretical and mathematical analysis of randomness is far from obvious. Moreover, as we will show, it depends on (and is relative to) the particular theory that is being worked on, the *intended* theoretical framework for the phenomena under investigation.

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1.1.1. *Brief historical overview*

Democritus (460–370 BCE) determined the causes of things to necessity and chance alike, justifying, for example, the fact that atoms' disorderly motion can produce an orderly cosmos. However, the first philosopher to think about randomness was most likely Epicurus (341–270 BCE), who argued that "randomness is objective, it is the proper nature of events".

For centuries, though, randomness has only been mathematically analyzed in games and gambling. Luca Pacioli (in *Summa de aritmetica, geometria, proporzioni et proporzionalita*, 1494) studied how stakes had to be divided among gamblers, particularly in the difficult case when the game stops before the end. It is worth noting that Pacioli, a top Renaissance mathematician, also invented modern bookkeeping techniques (Double Entry): human activities, from gambling to financial investments, were considered as the locus for chance. As a matter of fact, early Renaissance Florence was the place of the invention of banks, paper currency and (risky) financial investments and loans[1].

Cardano (in *De Ludo Aleae* (The Game of Dice), 1525) developed Pacioli's analysis further. His book was only published in 1663, so Fermat and Pascal independently and more rigorously rediscovered the "laws of chance" for interrupted games in a famous exchange of letters in 1654. Pascal clarified the independence of history in the games of chance, against common sense: dice do not remember the previous drawings. Probabilities were generally considered as a tool for facing the lack of knowledge in human activities: in contrast to God, we cannot predict the future nor master the consequences of our (risky) actions. For the thinkers of the scientific revolution, randomness is not in nature, which is a perfect "Cartesian Mechanism": science is meant to discover the gears of its wonderful and exact mechanics. At most, as suggested by Spinoza, two independent, well-determined trajectories may meet (a walking man and a falling tile) and produce a random event. This may be considered a weak form of "epistemic" randomness, as the union of the two systems, if known, may yield a well-determined and predictable system and encounter.

Galileo, while still studying randomness, but only for dice (*Sopra le scoperte de i dadi*, 1612), was the first to relate measurement and probabilities (1632). For him, in physical measurement, errors are unavoidable, yet small errors are the most probable. Moreover, errors distribute symmetrically around the mean value, whose reliability increases with the number of measurements.

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1 Such as the loan, in 1332, to the King of Britain Edward III who never returned it to the Bank of Bardi and Peruzzi – as all high school kids in Italy and our colleague Alberto Peruzzi in Florence know very well.

Almost two centuries later, Laplace brought Pascal's early insights to the modern rigor of probability theory (1998). He stressed the role of limited knowledge of phenomena in making predictions by equations: only a daemon with complete knowledge of all the forces in the Universe could "embrace in a single formula the movements of the greatest bodies of the universe and those of the tiniest atom; for such an intellect nothing would be uncertain and the future just like the past would be present before its eyes". The connection between incomplete knowledge of natural phenomena and randomness is made, yet no analysis of the possible "reasons" for randomness is proposed: probability theory gives a formal calculus of randomness, with no commitment on the nature of randomness. Defining randomness proved to be a hugely difficult problem which has only received acceptable answers in the last 100 years or so.

1.1.2. *Preliminary remarks*

Randomness is a tricky concept which can come in many flavors (Downey and Hirschfeldt 2010). Informally, randomness means *unpredictability, with a lack of patterns or correlations*. Why is randomness so difficult to understand and model? An intuitive understanding comes from the myriad of misconceptions and logical fallacies related to randomness, like the gambler's fallacy. In spite of the work of mathematicians since the Renaissance, there is the belief that after a coin has landed on tails 10 consecutive times, there are more chances that the coin will land on heads on the next flip. Similarly, common sense argues that there are "due" numbers in the lottery (since all numbers eventually appear, those that have not come up yet are "due", and thus more likely to come up soon). Each proposed definition of randomness seems to be doomed to be falsified by some more or less clever counter-example.

Even intuitively, the quality of randomness varies: tossing a coin may seem to produce a sequence of zeroes and ones which is less random than the randomness produced by Brownian motion. This is one of the reasons why users of randomness, like casinos, lotteries, polling firms, elections and clinical evaluations, are hard pressed to "prove" that their choices are "really" random. A new challenge is emerging, namely, to "prove randomness".

For physical systems, the randomness of a process needs to be differentiated from that of its outcome. Random (stochastic) processes have been extensively studied in probability theory, ergodic theory and information theory. Process or genesis randomness refers to such processes. On one hand, a "random" sequence does not necessarily need to be the output of a random process (e.g. a mathematically defined "random" sequence) and, conversely, a random process (e.g. a quantum random generator) is expected, but not guaranteed, to produce a "random output".

Outcome (or product) randomness provides a *prima facie* reason for the randomness of the process generating that outcome (Eagle 2005, p. 762), but, as argued in Frigg (2004, p. 431), process and outcome randomness are not extensionally equivalent. Process randomness has no mathematical formalization and can only be accessed/validated with theory or output randomness.

Measurement is a constant underlying issue: we may only associate a number with a "natural" process, by measurement. Most of the time we actually associate an interval (an approximation), an integer or a rational number as a form of counting or drawing.

Let us finally emphasize that, in spite of the existing theoretical differences in the understanding of randomness, our approach unifies the various forms of randomness in a relativized perspective:

> Randomness is unpredictability with respect to the intended theory and measurement.

We will move along this epistemological stand that will allow us to discuss and compare randomness in different theoretical contexts.

1.2. Randomness in classical dynamics

A major contribution to the contemporary understanding of randomness was given by Poincaré. By his "negative result" (his words) on the Three Body Problem (1892, relatively simple deterministic dynamics, see below), he proved that minor fluctuations or perturbations below the best possible measurement may manifest in a measurable, yet unpredictable consequence: "we then have a random phenomenon" (Poincaré 1902). This started the analysis of deterministic chaos, as his description of the phase-space trajectory derived from a nonlinear system is the first description of chaotic dynamics (Bros and Iagolnitzer 1973).

Poincaré's analysis is grounded in a mathematical "tour de force". He proved the non-analyticity of the (apparently) simple system of nonlinear equations describing two planets and a Sun in their gravitational fields (three bodies). The planets disturb each other's trajectories and this gives the formal divergence of the Lindstedt-Fourier series meant to give a linear approximation of the solution of the equations. More precisely, by using his notions of bifurcations and homoclinic orbit (the intersection of a stable and an unstable manifold), he showed that the "small divisors", which make the series diverge, physically mean that an undetectable fluctuation or perturbation may be amplified to a measurable quantity by the choice of a branch, or another in a bifurcation, or a manifold along a homoclinic orbit. It is often difficult to give a physical meaning to the solution of a system of equations; it is particularly hard and inventive to make sense of the absence of a solution. Yet, this made us understand randomness as deterministic unpredictability and non-analyticity as a strong form of classical unpredictability[2].

In this classical framework, a random event has a cause, yet this cause is below measurement. Thus, Curie's principle[3] is preserved: "the asymmetries of the consequences are already present in the causes" or "symmetries are preserved" – the asymmetries in the causes are just hidden.

For decades, Poincaré's approach was quoted and developed by only a few, that is, until Kolmogorov's work in the late 1950s and Lorentz in the 1960s. Turing is one of these few: he based his seminal paper on morphogenesis (Turing 1952) on the nonlinear dynamics of forms generated by chemical reactants. His "action/reaction/diffusion system" produced different forms by spontaneous symmetry breaking. An early hint of these ideas is given by him in Turing (1950, p. 440): "The displacement of a single electron by a billionth of a centimetre at one moment might make the difference between a man being killed by an avalanche a year later, or escaping". This Poincarian remark by Turing preceded by the famous "Lorentz butterfly effect" (proposed in 1972) by 20 years on the grounds of Lorentz's work from 1961.

Once more, many like to call this form of classical randomness "epistemic" unpredictability, that is related to our knowledge of the world. We do not deal with ontologies here, although this name may be fair, with the distinction from the understanding of randomness as a very weak form of unpredictability proposed by Spinoza. Poincaré brought a fact known since Galileo into the limelight: classical measurement is an interval, by principle[4]. Measurement is the only form of access we have to the physical world, while no principle forbids, *a priori*, to join two independent Spinozian dynamics. That is, even epistemic, classical physics posits

2 The non-analyticity is stronger than the presence of positive Lyapunov exponents for a nonlinear function. These exponents can appear in the solution of a nonlinear system or directly in a function describing a dynamic. They quantify how a minor difference in initial conditions can be magnified along a trajectory. In this case, we can have a form of "controlled" randomness because the divergence of the trajectories starting within the same best measurement interval will never exceed a pre-assumed, exponentially increasing value. In the absence of (analytical) solutions, bifurcations and homoclinic orbits can lead to sudden and "uncontrolled" divergence.

3 A macroscopic cause cannot have more elements of symmetry than the effects it produces. Its informational equivalent, called data processing inequality, asserts that no manipulation of information can improve the conclusions drawn from such data (Cover and Thomas 1991).

4 Laplace was also aware of this, but Lagrange, Laplace and Fourier firmly believed that any system of Cauchy equations possessed a linear approximation (Marinucci 2011).

this limit to access and knowledge as *a priori* measurement. Then this lack of complete knowledge yields classical randomness, typically in relation to a nonlinear mathematical modeling, which produces either positive Lyapunov exponents or, more strongly, non-analyticity. In other words, classical systems (as well as relativistic ones) are deterministic, yet they may be unpredictable, in the sense that randomness is not in the world nor it is just in the eyes of the beholder, but it pops out at the interface between us and the world by *theory* and *measurement*.

By "theory" we mean the equational or functional determination, possibly by a nonlinear system of equations or evolution functions.

1.3. Quantum randomness

Quantum randomness is hailed to be more than "epistemic", that is, "intrinsic" (to the theory). However, quantum randomness is not part of the standard mathematical model of the quantum which talks about probabilities, but is about the measurement of individual observables. So, to give more sense to the first statement we need to answer (at least) the following questions: (1) What is the source of quantum randomness? (2) What is the quality of quantum randomness? (3) Is quantum randomness different from classical randomness?

A naive answer to (1) is to say that quantum mechanics has shown "without doubt" that microscopic phenomena are intrinsically random. For example, we cannot predict with certainty how long it will take for a single unstable atom in a controlled environment to decay, even if one has complete knowledge of the "laws of physics" and the atom's initial conditions. One can only calculate the probability of decay in a given time, nothing more! This is intrinsic randomness guaranteed.

But is it? What is the cause of the above quantum mechanical effect? One way to answer is to consider a more fundamental quantum phenomenon: *quantum indeterminism*. What is quantum indeterminism and where does it come from? Quantum indeterminism appears in the measurement of individual observables: it has been at the heart of quantum mechanics since Born postulated that the modulus-squared of the wave function should be interpreted as a probability density that, unlike in classical statistical physics (Myrvold 2011), expresses fundamental, irreducible indeterminism (Born 1926). For example, the measurement of the spin, "up or down", of an electron, in the standard interpretation of the theory, is considered to be pure contingency, a symmetry breaking with no antecedent, in contrast to the causal understanding of Curie's principle[5]. The nature of individual measurement outcomes in quantum mechanics was, for a period, a subject of much debate. Einstein famously dissented, stating his belief that "He does not throw dice" (Born 1969, p. 204). Over time the assumption that measurement outcomes are fundamentally indeterministic became a postulate of the quantum orthodoxy (Zeilinger 2005). Of course, this view is not unanimously accepted (see Laloë 2012).

Following Einstein's approach (Einstein *et al.* 1935), quantum indeterminism corresponds to the absence of physical reality, if reality is what is made accessible by measurement: if no unique element of physical reality corresponding to a particular physical observable (thus, measurable) quantity exists, this is reflected by the physical quantity being indeterminate. This approach needs to be more precisely formalized. The notion of *value indefiniteness*, as it appears in the theorems of Bell (Bell 1966) and, particularly, Kochen and Specker (1967), has been used as a formal model of quantum indeterminism (Abbott *et al.* 2012). The model also has empirical support as these theorems have been experimentally tested via the violation of various inequalities (Weihs *et al.* 1998). We have to be aware that, going along this path, the "belief" in quantum indeterminism rests on the assumptions used by these theorems.

An observable is *value definite* for a given quantum system in a particular state if the measurement of that observable is pre-determined to take a (potentially hidden) value. If no such pre-determined value exists, the observable is value indefinite. Formally, this notion can be represented by a *(partial) value assignment function* (see Abbott *et al.* (2012) for the complete formalism).

When should we conclude that a physical quantity is value definite? Einstein, Podolsky and Rosen (EPR) defined *physical reality* in terms of certainty of predictability in Einstein *et al.* (1935, p. 777):

> If, without in any way disturbing a system, we can predict with certainty (i.e., with probability equal to unity) the value of a physical quantity, then there exists an element of reality corresponding to that quantity.

Note that both allusions to "disturbance" and to the (numerical) value of a physical quantity refer to measurement as the only form of access to reality we have. Thus, based on this accepted notion of an element of physical reality,

5 A correlation between random events and symmetry breakings is discussed in Longo *et al.* (2015). In this case, measurement produces a value (up or down), which breaks the in-determined or in-differentiated (thus, symmetric) situation before measurement.

following (Abbott *et al.* 2012) we answer the above question by identifying the EPR notion of an "element of physical reality" with "value definiteness":

EPR principle: If, without disturbing a system in any way, we can predict with certainty the value of a physical quantity, then there exists a *definite value* prior to the observation corresponding to this physical quantity.

The EPR principle justifies:

Eigenstate principle: a projection observable corresponding to the preparation basis of a quantum state is *value definite*.

The requirement called *admissibility* is used to avoid outcomes that are impossible to obtain according to quantum predictions, but which have overwhelming experimental confirmation:

Admissibility principle: definite values must not contradict the statistical quantum predictions for compatible observables of a single quantum.

Non-contextuality principle: the measurement results (when value definite) do not depend on any other compatible observable (i.e. simultaneously observable), which can be measured in parallel with the value definite observable.

The Kochen-Specker Theorem (Kochen and Specker 1967) states that no value assignment function can consistently make *all* observable values definite while maintaining the requirement that the values are assigned non-contextually. This is a global property: non-contextuality is incompatible with *all* observables being value definite. However, it is possible to localize value indefiniteness by proving that even the existence of two non-compatible value definite observables is in contradiction with admissibility and non-contextually, without requiring that all observables be value definite. As a consequence, we obtain the following "formal identification" of a value indefinite observable:

Any mismatch between preparation and measurement context leads to the measurement of a value indefinite observable.

This fact is stated formally in the following two theorems. As usual we denote the set of complex numbers by $\mathbb{C}$ and vectors in the Hilbert space $\mathbb{C}^n$ by $|.\rangle$; the projection onto the linear subspace spanned by a non-zero vector $|\varphi\rangle$ is denoted by P_φ. For more details see Laloë (2012).

THEOREM 1.1.– *Consider a quantum system prepared in the state* $|\psi\rangle$ *in dimension* $n \geq 3$ *Hilbert space* $\mathbb{C}^n$, *and let* $|\varphi\rangle$ *in any state neither parallel nor orthogonal to* $|\psi\rangle$. *Then the observable projection* P_φ *is value indefinite under any non-contextual, admissible value assignment.*

Hence, accepting that definite values *exist* for certain observables (the eigenstate principle) and behave non-contextually (non-contextuality principle) is enough to locate and *derive, rather than postulate*, quantum value indefiniteness. In fact, *value indefinite observables* are far from being scarce (Abbott *et al.* 2014b).

THEOREM 1.2.– *Assume the eigenstate principle, non-contextuality and admissibility principles. Then, the (Lebesgue) probability that an arbitrary value indefinite observable is 1.*

Theorem 1.2 says that all value definite observables can be located in a small set of probability zero. Consequently, value definite observables are not the norm, they are the exception, a long time held intuition in quantum mechanics.

The above analysis not only offers an answer to question (1) from the beginning of this section, but also indicates a procedure to generate a form of quantum random bits (Calude and Svozil 2008; Abbott *et al.* 2012, 2014a): to *locate and measure a value indefinite observable*. Quantum random number generators based on Theorem 1.1 were proposed in (Abbott *et al.* 2012, 2014a). Of course, other possible sources of quantum randomness may be identified, so we are naturally led to question (2): what is the quality of quantum randomness certified by Theorem 1.1, and, if other forms of quantum randomness exist, what qualities do they have?

To this aim we are going to look, in more detail, at the unpredictability of quantum randomness certified by Theorem 1.1. We will start by describing a non-probabilistic model of prediction – proposed in (Abbott *et al.* 2015b) – for a hypothetical experiment *E* specified effectively by an experimenter[6].

The model uses the following key elements:

1) The specification of an experiment *E* for which the outcome must be predicted.

2) A predicting agent or “predictor”, which must predict the outcome of the experiment.

6 The model does not assess the ability to make statistical predictions – as probabilistic models might – but rather the ability to predict precise measurement outcomes.

3) An extractor ξ is a physical device that the predictor uses to (uniformly) extract information pertinent to prediction that may be outside the scope of the experimental specification *E*. This could be, for example, the time, measurement of some parameter, iteration of the experiment, etc.

4) The uniform, algorithmic repetition of the experiment *E*.

In this model, a predictor is an effective (i.e. computational) method to uniformly predict the outcome of an experiment using finite information extracted (again, uniformly) from the experimental conditions along with the specification of the experiment, but independent from the results of the experiments. A predictor depends on an axiomatic, formalized theory, which allows the prediction to be made, i.e. to compute the "future". An experiment is predictable if any potential sequence of repetitions (of unbounded, but finite, length) can always be predicted correctly by such a predictor. To avoid prediction being successful just by chance, we require that the correct predictor – which can return a prediction or abstain (prediction withheld) – never makes a wrong prediction, no matter how many times it is required to make a new prediction (by repeating the experiment) and cannot abstain from making predictions indefinitely, i.e. the number of correct predictions can be made arbitrarily large by repeating the experiment enough times.

We consider a finitely specified physical experiment *E* producing a single bit $x \in \{0,1\}$. Such an experiment could, for example, be the measurement of a photon's polarization after it has passed through a 50:50 polarizing beam splitter, or simply the toss of a physical coin with initial conditions and experimental parameters specified finitely.

A particular trial of *E* is associated with the parameter λ, which fully describes the "state of the universe" in which the trial is run. This parameter is "an infinite quantity" – for example, an infinite sequence or a real number – structured in a way dependent on the intended theory. The result below, though, is independent of the theory. While λ is not in its entirety an obtainable quantity, it contains any information that may be pertinent to prediction. Any predictor can have practical access to a finite amount of this information. We can view a resource as one that can extract finite information, in order to predict the outcome of the experiment *E*.

An *extractor* is a physical device selecting a finite amount of information included in λ without altering the experiment *E*. It can be used by a predicting agent to examine the experiment and make predictions when the experiment is performed with parameter λ. So, the extractor produces a finite string of bits $\xi(\lambda)$. For example, $\xi(\lambda)$ may be an encoding of the result of the previous instantiation of *E*, or the time of day the experiment is performed.

A *predictor* for E is an algorithm (computable function) P_E which halts on every input and outputs either 0, 1 (cases in which P_E has made a prediction), or "prediction withheld". We interpret the last form of output as a refrain from making a prediction. The predictor P_E can utilize, as input, the information $\xi(\lambda)$ selected by an extractor encoding relevant information for a particular instantiation of E, but must not disturb or interact with E in any way; that is, it must be *passive*.

A predictor P_E provides a *correct prediction* using the extractor ξ for an instantiation of E with parameter λ if, when taking as input $\xi(\lambda)$, it outputs 0 or 1 (i.e. it does not refrain from making a prediction) and this output is equal to x, the result of the experiment.

Let us fix an extractor ξ. The predictor P_E is *k-correct for ξ* if there exists an $n \geq k$, such that when E is repeated n times with associated parameters $\lambda_1, \ldots, \lambda_n$ producing the outputs $x_1, x_2, \ldots, x_n$, P_E outputs the sequence $(\xi(\lambda_1))$, $P_E(\xi(\lambda_2))$, …, $P_E(\xi(\lambda_n))$ with the following two properties:

1) no prediction in the sequence is incorrect, and

2) in the sequence, there are *k correct* predictions.

The repetition of E must follow an algorithmic procedure for resetting and repeating the experiment; generally, this will consist of a succession of events, with the procedure being "prepared, performed, the result (if any) recorded and E being reset".

The definition above captures the need to avoid correct predictions by chance by forcing more and more trials and predictions. If P_E is k-correct for ξ, then the probability that such a correct sequence would be produced by chance $\binom{n}{k} \times 3^{-n}$ is bounded by $\left(\frac{2}{3}\right)^k$; hence, it tends to zero when k goes to infinity.

The confidence we have in a k-correct predictor increases as k approaches infinity. If P_E is k-correct for ξ for all k, then P_E never makes an incorrect prediction and the number of correct predictions can be made arbitrarily large by repeating E enough times. In this case, we simply say that P_E is correct for ξ. The infinity used in the above definition is *potential*, not actual: its role is to arbitrarily guarantee many correct predictions.

This definition of correctness allows P_E to refrain from predicting when it is unable to. A predictor P_E which is correct for ξ is, when using the extracted information $\xi(\lambda)$, guaranteed to always be capable of providing more correct predictions for E, so it will not output "prediction withheld" indefinitely. Furthermore, although P_E is technically only used a finite, but arbitrarily large, number of times, the definition guarantees that, in the hypothetical scenario where it is executed infinitely many times, P_E will provide infinitely many correct predictions and not a single incorrect one.

Finally, we define the prediction of a single bit produced by an individual trial of the experiment *E*. The outcome *x* of a single trial of the experiment *E* performed with parameter λ is predictable (with certainty) if there exist an extractor ξ and a predictor P_E which is correct for ⇠, and P_E (ξ (λ)) = x.

By applying the model of unpredictability described above to quantum measurement outcomes obtained by measuring a value indefinite observable, for example, obtained using Theorem 1.1, we obtain a formal certification of the unpredictability of those outcomes:

THEOREM 1.3. (Abbott *et al.* 2015b) – *Assume the EPR and Eigenstate principles. If E is an experiment measuring a quantum value indefinite observable, then for every predictor P_E using any extractor ξ, P_E is not correct for ξ.*

THEOREM 1.4. (Abbott *et al.* 2015b) – *Assume the EPR and Eigenstate principles. In an infinite independent repetition of an experiment E measuring a quantum value indefinite observable which generates an infinite sequence of outcomes $x = x_1x_2\ldots$, no single bit x_i can be predicted with certainty.*

According to Theorems 1.3 and 1.4, the outcome of measuring a value indefinite observable is "maximally unpredictable". We can measure the degree of unpredictability using the computational power of the predictor.

In particular, we can consider weaker or stronger predictors than those used in Theorems 1.3 and 1.4, which have the power of a Turing machine (Abbott *et al.* 2015a). This "relativistic" understanding of unpredictability (fix the reference system and the invariant preserving transformations is the approach proposed by Einstein's relativity theory) allows us to obtain "maximal unpredictability", but not absolutely, only relative to a theory, no more and no less. In particular, and from this perspective, Theorem 1.3 should not be interpreted as a statement that quantum measurement outcomes are "true random"[7] in any absolute sense: true randomness – in the sense that no correlations exist between successive measurement results – is mathematically impossible as we will show in section 1.5 in a "theory invariant way", that is, for sequences of pure digits, independent of the measurements (classical, quantum, etc.) that they may have been derived from, if any. Finally, question (3) will be discussed in section 1.6.2.

7 Eagle argued that a physical process is random if it is "maximally unpredictable" (Eagle 2005).

1.4. Randomness in biology

Biological randomness is an even more complex issue. Both in phylogenesis and ontogenesis, randomness enhances variability and diversity; hence, it is core to biological dynamics. Each cell reproduction yields a (slightly) random distribution of proteomes[8], DNA and membrane changes, both largely due to random effects. In Longo and Montévil (2014a), this is described as a fundamental "critical transition", whose sensitivity to minor fluctuations, at transition, contributes to the formation of new coherence structures, within the cell and in its ecosystem. Typically, in a multicellular organism, the reconstruction of the cellular micro-environment, at cell doubling, from collagen to cell-to-cell connection and to the general tensegrity structure of the tissular matrix, all yield a changing coherence which contributes to variability and adaptation, from embryogenesis to aging. A similar phenomenon may be observed in an animal or plant ecosystem, a system yet to be described by a lesser coherence of the structure of correlations, in comparison to the global coherence of an organism[9].

Similarly, the irregularity in the morphogenesis of organs may be ascribed to randomness at the various levels concerned (cell reproduction and frictions/interactions in a tissue). Still, this is functional, as the irregularities of lung alveolus or of branching in vascular systems enhance ontogenetic adaptation (Fleury and Gordon 2012). Thus, we do not call these intrinsically random aspects of onto-phylogenesis "noise", but consider them as essential components of biological stability, a permanent production of diversity (Bravi Longo 2015). A population is stable because it is diverse "by low numbers": 1,000 individuals of an animal species in a valley are more stable if they are diverse. From low numbers in proteome splitting to populations, this contribution of randomness to stability is very different from stability derived from stochasticity in physics, typically in statistical physics, where it depends on huge numbers.

We next discuss a few different manifestations of randomness in biology and stress their positive role. Note that, as for the "nature" of randomness in biology, one must refer, at least, to both quantum and classical phenomena.

First, there exists massive evidence of the role of quantum random phenomena at the molecular level, with phenotypic effects (see Buiatti and Longo 2013 for an

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8 Some molecular types are present in a few tenths or hundreds of molecules. Brownian motion may suffice to split them in slightly but non-irrelevantly different numbers.

9 An organism is an ecosystem inhabited by about 10^{14} bacteria, for example, and by an immune system, which in itself is an ecosystem (Flajnik and Kasahara 2010). Yet an ecosystem is not an organism: it has no relative metric stability (distance from its constituents), nor general organs of regulation and action, such as the nervous system found in animals.

introduction). A brand new discipline, quantum biology, studies applications of "non-trivial" quantum features such as superposition, non-locality, entanglement and tunneling to biological objects and problems (Ball 2011). "Tentative" examples include: (1) the absorbance of frequency-specific radiation, i.e. photosynthesis and vision; (2) the conversion of chemical energy into motion; and, (3) DNA mutation and activation of DNA transposons.

In principle, quantum coherence – a mathematical invariant for the wave function of each part of a system – would be destroyed almost instantly in the realm of a cell. Still, evidence of quantum coherence was found in the initial stage of photosynthesis (O'Reilly and Olaya-Castro 2014). Then, the problem remains: how can quantum coherence last long enough in a poorly controlled environment at ambient temperatures to be useful in photosynthesis? The issue is open, but it is possible that the organismal context (the cell) amplifies quantum phenomena by intracellular forms of "bio-resonance", a notion defined below.

Moreover, it has been shown that double proton transfer affects spontaneous mutation in RNA duplexes (Kwon and Zewail 2007). This suggests that the "indeterminism" in a mutation may also be given by *quantum randomness amplified by classical dynamics* (classical randomness, see section 1.6).

Thus, quantum events coexist with classical dynamics, including classical randomness, a hardly treated combination in physics – they should be understood in conjunction, for lack of a unified understanding of the respective fields. Finally, both forms of randomness contribute to the interference between levels of organization, due to regulation and integration, called bio-resonance in Buiatti and Longo (2013). Bio-resonance is part of the stabilization of organismal and ecosystemic structures, but may also be viewed as a form of proper biological randomness, when enhancing unpredictability. It corresponds to the interaction of different levels of organization, each possessing its own form of determination. Cell networks in tissues, organs as the result of morphogenetic processes, including intracellular organelles, are each given different forms of statistical or equational descriptions, mostly totally unrelated. However, an organ is made of tissues, and both levels interact during their genesis, as well as along their continual regeneration.

Second, for classical randomness, besides the cell-to-cell interactions within an organism (or among multicellular organisms in an ecosystem) or the various forms of bio-resonance (Buiatti and Longo 2013), let us focus on macromolecules' Brownian motion. As a key aspect of this approach, we observe that Brownian motion and related forms of random molecular paths and interactions must be given a fundamental and positive role in biology. This random activity corresponds to the thermic level in a cell, thus to a relevant component of the available energy: it turns out to be crucial for gene expression.

The functional role of stochastic effects has long since been known in enzyme induction (Novick and Weiner 1957), and even theorized for gene expression (Kupiec 1983). In the last decade (Elowitz *et al.* 2002), stochastic gene expression finally came into the limelight. The existing analyses are largely based on the classical Brownian motion (Arjun and van Oudenaarden 2008), while local quantum effects cannot be excluded.

> Increasingly, researchers have found that even genetically identical individuals can be very different, and that some of the most striking sources of this variability are random fluctuations in the expression of individual genes. Fundamentally, this is because the expression of a gene involves the discrete and inherently random biochemical reactions involved in the production of mRNA and proteins. The fact that DNA (and hence the genes encoded therein) is present in very low numbers means that these fluctuations do not just average away but can instead lead to easily detectable differences between otherwise identical cells; in other words, gene expression must be thought of as a stochastic process. (Arjun and van Oudenaarden 2008)

Different degrees of stochasticity in gene expression have been observed – with major differences in ranges of expression – in the same population (in the same organ or even tissue) (Chang *et al.* 2008).

A major consequence that we can derive from this view is the key role that we can attribute to this relevant component of the available energy, *heath*. The cell also uses it for gene expression instead of opposing to it. As a matter of fact, the view that DNA is a set of “instructions” (a program) proposes an understanding of the cascades from DNA to RNA to proteins in terms of a deterministic and predictable, thus programmable, sequence of stereospecific interactions (physico-chemical and geometric exact correspondences). That is, gene expression or genetic “information” is physically transmitted by these exact correspondences: stereospecificity is actually “necessary” for this (Monod 1970). The random movement of macromolecules is an obstacle that the “program” constantly fights. Indeed, both Shannon’s transmission and Turing’s elaboration of information, in spite of their theoretical differences, are both designed to oppose noise (see Longo *et al.* 2012b). Instead, in stochastic gene expression, Brownian motion, thus heath, is viewed as a positive contribution to the role of DNA.

Clearly, randomness, in a cell, an organism and an ecosystem, is highly constrained. The compartmentalization in a cell, the membrane, the tissue tensegrity structure, the integration and regulation by and within an organism, all contribute to restricting and canalizing randomness. Consider that an organism like ours has about 10^{13} cells, divided into many smaller parts, including nuclei: few physical structures are so compartmentalized. So, the very "sticky" oscillating and randomly moving macromolecules are forced within viable channels. Sometimes, though, it may not work, or it may work differently. This belongs to the exploration proper to biological dynamics: a "hopeful monster" (Dietrich 2003), if viable in a changing ecosystem, may yield a new possibility in ontogenesis, or even a new branch in evolution.

Activation of gene transcription, in these quasi-chaotic environments, with quasi-turbulent enthalpic oscillations of macro-molecules, is thus canalized by the cell structure, in particular in eukaryotic cells, and by the more or less restricted assembly of the protein complexes that initiate it (Kupiec 2010). In short, proteins can interact with multiple partners (they are "sticky") causing a great number of combinatorial possibilities. Yet, protein networks have a central hub where the connection density is the strongest and this peculiar canalization further forces statistical regularities (Bork *et al.* 2004). The various forms of canalization mentioned in the literature include some resulting from environmental constraints, which are increasingly acknowledged to produce "downwards" or Lamarckian inheritance or adaptation, mostly by a regulation of gene expression (Richards 2006). Even mutations may be both random and not random, highly constrained or even induced by the environment. For example, organismal activities, from tissular stresses to proteomic changes, can alter genomic sequences in response to environmental perturbations (Shapiro 2011).

By this role of constrained stochasticity in gene expression, molecular randomness in cells becomes a key source of the cell's activity. As we hinted above, Brownian motion, in particular, must be viewed as a positive component of the cell's dynamics (Munsky *et al.* 2009), instead of being considered as "noise" that opposes the elaboration of the genetic "program" or the transmission of genetic "information" by exact stereospecific macro-molecular interactions. Thus, this view radically departs from the understanding of the cell as a "Cartesian Mechanism" occasionally disturbed by noise (Monod 1970), as we give heath a constitutive, not a "disturbing" role (also for gene expression and not only for some molecular/enzymatic reactions).

The role of stochasticity in gene expression is increasingly accepted in genetics and may be generally summarized by saying that "macromolecular interactions, in a cell, are largely stochastic, they must be given in probabilities and the values of these probabilities depend on the context" (Longo and Montévil 2015). The DNA then becomes an immensely important physico-chemical trace of history, continually used by the cell and the organism. Its organization is stochastically used, but in a very canalized way, depending on the epigenetic context, to produce proteins and, at the organismal level, biological organization from a given cell. Random phenomena, Brownian random paths first, crucially contribute to this.

There is a third issue that is worth being mentioned. Following Gould (1997), we recall how the increasing phenotypic complexity along evolution (organisms become more "complex", if this notion is soundly defined) may be justified as a random complexification of the early bacteria along an asymmetric diffusion. The key point is to invent the right phase space for this analysis, as we hint: the tridimensional space of "biomass × complexity × time" (Longo and Montévil 2014b).

Note that the available energy consumption and transformation, thus entropy production, are the unavoidable physical processes underlying all biological activities, including reproduction with variation and motility, organisms' "default state" (Longo *et al.* 2015). Now, entropy production goes with energy dispersal, which is realized by random paths, as with any diffusion in physics.

At the origin of life, bacterial exponential proliferation was (relatively) unconstrained, as other forms of life did not contrast it. Increasing diversity, even in bacteria, by random differentiation started the early divergence of life, a process that would never stop – and a principle for Darwin. However, it also produced competition within a limited ecosystem and a slower exponential growth.

Gould (1989, 1997) uses the idea of random diversification to understand a blatant but often denied fact: life becomes increasingly "complex", if one accords a reasonable meaning to this notion. The increasing complexity of biological structures, whatever this may mean, has often been denied in order to oppose finalist and anthropocentric perspectives, where life is described as *aiming* at *Homo sapiens*, particularly at the reader of this chapter, the highest result of the (possibly intelligent) evolutionary path (or Design).

It is a fact that, under many reasonable measures, an eukaryotic cell is more complex than a bacterium; a metazoan, with its differentiated cells, tissues and organs, is more complex than a cell and that, by counting neurons and their connections, cell networks in mammals are more complex than in early triploblast (which have three tissues layers), and these have more complex networks of all sorts than diplobasts (like jellyfish, a very ancient life form). This nonlinear increase can be quantified by counting tissue differentiations, networks and more, as very informally suggested by Gould and more precisely quantified in (Bailly and Longo 2009) (see Longo and Montévil 2014b for a survey). The point is: how are we to understand this change toward complexity without invoking global aims?

Gould provides a remarkable, but very informal answer to this question. He bases it on the analysis of the asymmetric random diffusion of life, as constrained proliferation and diversification. Asymmetric because, by a common assumption, life cannot be less complex than bacterial life[10]. We may understand Gould's analysis by the general principle: *any asymmetric random diffusion propagates, by local interactions, the original symmetry breaking along the diffusion*.

The point is to propose a pertinent (phase) space for this diffusive phenomenon. For example, in a liquid, a drop of dye against a (left) wall diffuses in space (toward the right) when the particles bump against each other locally. That is, particles transitively inherit the original (left) wall asymmetry and propagate it *globally* by *local* random interactions. By considering the diffusion of *biomass*, after the early formation (and explosion) of life, over complexity, one can then apply the principle above to this fundamental evolutionary dynamic: biomass asymmetrically diffuses over complexity in time. Then, there is no need for a global design or aim: the random paths that compose *any* diffusion, also in this case, help to understand a random growth of complexity, on average. On average, as there may be local inversion in complexity, the asymmetry is randomly forced to "higher complexity", a notion to be defined formally, of course.

In Bailly and Longo (2009), and more informally in Longo and Montévil (2014b), a close definition of phenotypic complexity was given, by counting fractal dimensions, networks, tissue differentiations, etc., hence, a mathematical analysis of this phenomenon was developed. In short, in the suitable phase space, that is "biomass × complexity × time", we can give a diffusion equation with real coefficients, inspired by Schrödinger's equation (which is a diffusion equation, but in a Hilbert space). In a sense, while Schrödinger's equation is a *diffusion* of a law (an amplitude) of probability, the potential of variability of biomass over complexity in time was analyzed when the biological or phenotypic complexity was quantified, in a tentative but precise way, as hinted above (and better specified in the references).

Note that the idea that the complexity (however defined) of living organisms increases with time has been more recently adopted in Shanahan (2012) as a principle. It is thus assumed that there is a trend toward complexification and that this is intrinsic to evolution, while Darwin only assumed the divergence of characters. The very strong "principle" in Shanahan (2012), instead, may be *derived*, if one gives a due role to randomness, along an asymmetric diffusion, also in evolution.

10 Some may prefer to consider viruses as the least form of life. The issue is controversial, but it would not change Gould's and our perspective at all: we only need a minimum biological complexity which differs from inert matter.

A further but indirect fall-out of this approach to phenotypic complexity results from some recent collaborations with biologists of cancer (see Longo *et al.* 2015). We must first distinguish the notion of complexity, based on “counting” some key anatomical features, from biological organization. The first is given by the “anatomy” of a dead animal, and the second usually refers to the functional activities of a living organism. It seems that cancer is the only disease that diminishes functional organization by increasing complexity. When tissue is infected by cancer, ducts in glands, villi in epithelia, etc., increase in topological numbers (e.g. ducts have more lumina) and fractal dimensions (as for villi). This very growth of mathematical complexity reduces functionality, by reduced flow rates, thus the biological organization. This is probably a minor remark, but in the very obscure etiology of cancer, it may provide a hallmark for this devastating disease.

1.5. Random sequences: a theory invariant approach

Sequences are the simplest mathematical infinite objects. We use them to discuss some subtle differences in the quality of randomness. In evaluating the quality of randomness of the following four examples, we employ various tests of randomness for sequences, i.e. formal tests modeling properties or symptoms intuitively associated with randomness.

The *Champernowne sequence*, 012345678910111213, is random with respect to the statistical test which checks equal frequency – a clearly necessary condition of randomness[11]. Indeed, the digits 0, 1, 2, …, 9 appear with the right frequency 10^{-1}, every string of two digits, like 23 or 00 appears with the frequency 10^{-2}, and by a classical result of Champernowne (1933), every string – say 366647888599991 00200030405060234234 or 00000000000000000000000000000000000 – appears with the frequency $10^{-(\text{length of string})}$ (10^{-35} in our examples). Is the condition sufficient to declare the Champernowne sequence random? Of course not. The Champernowne sequence is generated by a very simple algorithm – just concatenate all strings on the alphabet {0, 1, 2, 3, …, 9} in increasing length order and use the lexicographical order for all strings of the same length. This algorithm allows for a prefect prediction of every element of this sequence, ruling out its randomness. A similar situation appears if we concatenate the prime numbers in base 10 obtaining the *Copeland-Erdös sequence* 235711131719232931374143 (Copeland and Erdös 1946).

11 This was the definition of chance informally proposed by Borel (1909): the proportion of times that a finite sequence is in an infinite (even very long) sequence corresponds (approximately) to the probability that such a sequence occurs during a particular test.

Now consider your favorite programing language L and note that each syntactically correct program has an end-marker (end or stop, for example) which makes correct programs self-delimited. We now define the binary *halting sequence* $H(L) = h_1h_2\ldots h_n\cdots$: enumerate all strings over the alphabet used by L in the same way as we did for the Champernowne sequence and define $h_i = 1$ if the ith string considered as a program stops and $h_i = 0$ otherwise. Most strings are not syntactically correct programs, so they will not halt: only some syntactically correct programs halt. The Church-Turing theorem – on the undecidability of the halting problem (Cooper 2004) – states that there is no algorithm which can correctly calculate (predict) all the bits of the sequence $H(L)$; so from the point of view of this randomness test, the sequence is random. Does $H(L)$ pass the frequency test? The answer is negative.

The Champernowne sequence and the halting sequence are both non-random, because each fails to pass a randomness test. However, each sequence passes a non-trivial random test. The test passed by the Champernowne sequence is “statistical”, more quantitative, and the test passed by the halting sequence is more qualitative. Which sequence is “more random”?

Using the same programing language L we can define the *Omega sequence* as the binary expansion $\Omega(L) = \omega_1\omega_2\ldots\ \omega_n\ldots$ of the Omega number, the halting probability of L:

$$\sum_{halts} 2^{-(length\ of\ p)}$$

It has been proved that the Omega sequence passes both the frequency and the incomputability tests; hence, it is “more random” than the Champernowne, Copeland-Erdös and halting sequences (Calude 2002; Downey and Hirschfeldt 2010). In fact, the Omega sequence passes an infinity of distinct tests of randomness called Martin-Löf tests – technically making it Martin-Löf random (Calude 2002; Downey and Hirschfeldt 2010), one of the most robust and interesting forms of randomness.

Have we finally found the “true” definition of randomness? The answer is negative. A simple way to see it is via the following infinite set of computable correlations present in almost all sequences, including the Omega sequence (Calude and Staiger 2014), but not in all sequences: that is, for almost all infinite sequences, an integer $k > 1$ exists (depending on the sequence), such that for every $m \geq 1$:

$$\omega_{m+1}\,\omega_{m+2}\ldots\omega_{mk} \neq 000\ldots0 \ \ m(k-1) \text{ times}$$

In other words, every substring $\omega_{m+1}\,\omega_{m+2}\ldots\omega_{mk}$ has to contain at least one 1, for all $m \geq 1$, a "non-randomness" phenomenon no Martin-Löf test can detect. A more general result appears in Calude and Staiger (2014, Theorem 2.2).

So, the quest for a better definition continues! What about considering not just an incremental improvement over the previous definition, but a definition of "true randomness" or "perfect randomness"? If we are confined to just one intuitive meaning of randomness – the lack of correlations – the question becomes: Are there binary infinite sequences with no correlations? The answer is negative, so our quest is doomed to fail: there is no true randomness. We can prove this statement using the Ramsey[12] theory (see Graham and Spencer (1990) and Soifer (2011)) or the algorithmic information theory (Calude 2002).

Here is an illustration of the Ramsey-type argument. Let $s_1 \ldots s_n$ be a binary string. A *monochromatic* arithmetic progression of length *k* is a substring $s_i\, s_{i+t}\, s_{i+2t} \ldots s_{i+(k-1)t}$, $i \geq 1$ and $i + (k-1)\,t \leq n$ with all characters equal (0 or 1) for some $t > 0$. The string 01100110 contains no arithmetic progression of length 3 because the positions 1, 4, 5, 8 (for 0) and 2, 3, 6, 7 (for 1) do not contain an arithmetic progression of length 3; however, both strings 011001100 and 011001101 do: 1, 5, 9 for 0 and 3, 6, 9 for 1.

THEOREM 1.5.– Van der Waerden. *Every infinite binary sequence contains arbitrarily long monochromatic arithmetic progressions.*

This is one of the many results in Ramsey theory (Soifer 2011): it shows that in *any sequence* there are arbitrary long simple correlations. We note the power of this type of result: the property stated is true for *any sequence* (in contrast with typical results in probability theory where the property is true for *almost all sequences*). Graham and Spencer, well-known experts in this field, subtitled their *Scientific American* presentation of Ramsey Theory (Graham and Spencer 1990) with the following sentence:

> Complete disorder is an impossibility. Every large[13] set of numbers, points or objects necessarily contains a highly regular pattern.

Even if "true randomness" does not exist, can our intuition on randomness be cast in more rigorous terms? Randomness plays an essential role in probability theory, the mathematical calculus of random events. Kolmogorov axiomatic probability theory assigns probabilities to sets of outcomes and shows how to

12 The British mathematician and logician Frank P. Ramsey studied *conditions under which order must appear*.

13 The adjective "large" has precise definitions for both finite and infinite sets.

calculate with such probabilities; it assumes randomness, but does not distinguish between individually random and non-random elements. So, we are led to ask: is it possible to study classes of random sequences with precise "randomness/symptoms" of randomness? So far we have discussed two symptoms of randomness: statistical frequency and incomputability. More general symptoms are unpredictability (of which incomputability is a necessary but not sufficient form), incompressibility and typicality.

Algorithmic information theory (AIT) (Calude 2002; Downey and Hirschfeldt 2010), which was developed in the 1960s, provides a close analysis of randomness for sequences of numbers, either given by an abstract or a concrete (machine) computation, or produced by a series of physical measurements. By this, it provides a unique tool for a comparative analysis between different forms of randomness. AIT also shows that there is no infinite sequence passing all tests of randomness, so another proof that "true randomness" does not exist.

As we can guess from the discussion of the four sequences above, randomness can be refuted, but cannot be mathematically proved: we can never be sure that a sequence is "random", there are only forms and degrees of randomness (Calude 2002; Downey and Hirschfeldt 2010).

Finally, note that similarly to randomness in classical dynamics, which was made intelligible by Poincaré's negative result, AIT is also rooted in a negative result: Gödel's incompleteness theorem. As recalled above, a random sequence is a highly incomputable sequence. That is, algorithmic randomness is in a certain sense a refinement of Gödel's undecidability, as it gives a fine hierarchy of incomputable sets that may be related, as we will hint below, to relevant forms of randomness in natural sciences.

1.6. Classical and quantum randomness revisited

1.6.1. *Classical versus algorithmic randomness*

As we recalled in section 1.2, classical dynamical systems propose a form of randomness as unpredictability relative to a specific mathematical model and to the properties of measurement. Along these lines, Laskar (1994) recently gave an evaluation of the unpredictability of the position (and momentum) of planets in the Solar system, a system that has motivated all classical work since Newton and Laplace (their dynamics are unpredictable at relatively short astronomical time). How can one relate this form of deterministic unpredictability to algorithmic randomness, which is a form of pure mathematical incomputability? The first requires an interface between mathematical determination, by equations or evolution functions, and "physical reality" as accessed by measurement. The latter is a formal, asymptotic notion.

A mathematical relation may be established by considering Birkhoff ergodicity. This is a pure mathematical notion as it does not (explicitly) involve physical measurement, yet it applies to the nonlinear systems where one may refer to Poincaré's analysis or its variants, that is, to weaker forms of chaos based on positive Lyapunov exponents (see footnote 2) or sensitivity to initial conditions and "mixing" (see paragraph below). Birkhoff's notion is derived from his famous theorem and it roughly says that a trajectory, starting from a given point and with respect to a given observable quantity, is random when the value of a given observable over time coincides asymptotically with its value over space[14].

A survey of recent results that relate deterministic randomness – under the form of Birkhoff randomness for dynamical systems – to algorithmic randomness is presented in Longo (2012). This was mostly based on the relation between dynamical randomness and a weak form of Martin-Löf algorithmic randomness (due to Schnorr) (Galatolo *et al.* 2010; Gàcs *et al.* 2011). A subtle difference may be proved, by observing that some "typically" Birkhoff random points are not Martin-Löf random, some are even "pseudo-random", in the sense that they are actually computable. By restricting, in a physically sound way, the class of dynamical systems examined, a correspondence between points that satisfy the Birkhoff ergodic theorem and Martin-Löf randomness has been obtained in Franklin and Towsner (2014). These results require an "effectivization" of the spaces and dynamical theory, a non-obvious work, proper to all meaningful dynamical systems, as the language in which we talk about them is "effective": we formally write equations, solve them, when possible, and compute values, all by suitable algorithms. All of these results are asymptotic as they transfer the issue of the relation between theory and physical measurement to the limit behavior of a trajectory, as determined by the theory: a deterministic system sensitive to initial (or border) conditions, a mathematical notion, produces random infinite paths. To obtain these results it is enough to assume weak forms of deterministic chaos, such as the presence of dense trajectories, i.e. topological transitivity or mixing. The level of their sensitivity is reflected in the level of randomness of the trajectories, in the words of Franklin and Towsner (2014):

> Algorithmic randomness gives a precise way of characterizing how sensitive the ergodic theorem is to small changes in the underlying function.

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14 Consider a gas particle and its momentum: the average value of the momentum over time (the time integral) is asymptotically assumed to coincide with the average *momenta* of all particles in the given, sufficiently large, volume (the space integral).

1.6.2. *Quantum versus algorithmic randomness*

We already summarized some of the connections between quantum and algorithmic unpredictability. The issue is increasingly in the limelight since there is a high demand for "random generators" in computing. Computers generate "random numbers" produced by algorithms and computer manufacturers took a long time to realize that randomness produced by software is only pseudo-random, that is, the generated sequences are perfectly computable, with no apparent regularity.

This form of randomness mimics the human perception of randomness well, but its quality is rather low because computability destroys many symptoms of randomness, e.g. unpredictability[15]. One of the reasons is that pseudo-random generators "silently fail over time, introducing biases that corrupt randomness" (Anthes 2011, p. 15).

Although, today, no computer or software manufacturer claims that their products can generate truly random numbers, these mathematically unfounded claims have re-appeared for randomness produced with physical experiments. They appear in papers published in prestigious journals, like Deutsch's famous paper (Deutsch 1985), which describes two quantum random generators (3.1) and (3.2) which produce "true randomness" or the *Nature 2010* editorial (titled *True Randomness Demonstrated* (Pironio *et al.* 2010)). Companies market "true random bits" which are produced by a "True Random Number Generator Exploiting Quantum Physics" (ID Quantique) or a "True Random Number Generator" (MAGIQ). "True randomness" does not necessarily come from the quantum. For example, "RANDOM.ORG offers true random numbers to anyone on the Internet" (Random.Org) using atmospheric noise.

Evaluating the quality of quantum randomness can now be done in a more precise framework. In particular, we can answer the question: is a sequence produced by repeated outcomes of measurements of a value indefinite observable computable? The answer is negative, in a strong sense (Calude and Svozil 2008; Abbott *et al.* 2012):

THEOREM 1.6.– *The sequence obtained by indefinitely repeating the measurement of a value indefinite observable, under the conditions of Theorem 1.1, produces a*

15 It is not unreasonable to hypothesize that pseudo-randomness reflects its creators' subjective "understanding" and "projection" of randomness. Psychologists have known for a long time that people tend to distrust streaks in a series of random bits; hence, they imagine a coin flipping sequence alternates between heads and tails much too often for its own sake of "randomness". As we said, the gambler's fallacy is an example.

bi-immune sequence (a strong form of incomputable sequence for which any algorithm can compute only finitely many exact bits).

Incomputability appears *maximally* in two forms:

– *Individualized*: no single bit can be predicted with certainty (Theorem 1.4), i.e. an algorithmic computation of a single bit, even if correct, cannot be formally certified;

– *asymptotic* (Theorem 1.6): only finitely many bits can be correctly predicted via an algorithmic computation.

It is an open question whether a sequence (such as Theorem 1.6) is Martin-Löf random or Schnorr random (Calude 2002; Downey and Hirschfeldt 2010).

1.7. Conclusion and opening: toward a proper biological randomness

The relevance of randomness in mathematics and in natural sciences further vindicates Poincaré's views against Hilbert's. The first has stressed (since 1890) his interest in negative results, such as his Three Body Theorem, and further claimed in *Science et Méthode* (1908) that "… unsolvable problems have become the most interesting and raised further problems to which we could not think before".

This is in sharp contrast with Hilbert's credo – motivated by his 1900 conjecture on the formal provability (decidability) of consistency of arithmetic – presented in his address to the 1930 Königsberg Conference[16] (Hilbert 1930):

> For the mathematician, there is no unsolvable problem. In contrast to the foolish *Ignorabimus*, our credo is: We must know, We shall know.

As a matter of fact, the investigation of theoretical *ignorabimus*, e.g. the analysis of randomness, opened the way to a new type of knowledge, which does not need to give yes or no answers, but raises new questions and proposes new perspectives and, possibly, answers – based on the role of randomness, for example, a demonstrable mathematical unpredictability from which the geometry of Poincaré's dynamic systems is derived, or even the subsequent notions of an attractor, etc. Hilbert was certainly aware of Poincaré's unpredictability, but (or thus?) he limited his conjectures of completeness and decidability to formal systems, i.e. to *pure mathematical statements*. Poincaré's result instead, as recalled above, makes sense at the interface of mathematics and the physical world; for an analysis of the

16 Incidentally, the same conference at which Gödel presented his famous *incompleteness* theorem.

methodological links with Gödel's theorem, purely mathematical, and Einstein's result on the alleged incompleteness of quantum mechanics, see Longo (2018).

The results mentioned in section 1.6.1 turn, by using Birkhoff randomness in dynamical systems, physico-mathematical unpredictability into a pure mathematical form: they give relevant relations between the two frames, by embedding the *formal theory* of some physical dynamics into a computational frame, in order to analyze unpredictability with respect to that theory.

As for biology, the analysis of randomness at all levels of biological organization, from molecular activities to organismal interactions, clearly plays an increasing role in contemporary work. Still, we are far from a sound unified frame. First, because of the lack of unity even in the fragments of advanced physical analysis in molecular biology (typically, the superposition of classical and quantum randomness in a cell), to which one should add the hydrodynamical effect and the so-called "coherence" of water in cells pioneered by del Giudice (2007).

Second, biology has to face another fundamental problem. If one assumes a Darwinian perspective and considers phenotypes and organisms as proper biological observables, then the evolutionary dynamics imply a change to the very space of (parameters and) observables. That is, a phylogenetic analysis cannot be based on the *a priori* physical knowledge, the so-called condition of possibility for physico-mathematical theories: space-time and the pertinent observable, i.e. the phase space. In other words, a phylogenetic path cannot be analyzed in a pre-given phase space, like in all physical theories, including quantum mechanics, where self-adjoint operators in a Hilbert space describe observables. Evolution, by the complex blend of organisms and their ecosystem, co-constitutes its own phase space and this in a (highly) unpredictable way. Thus, random events, in biology, do not just "modify" the numerical values of an observable in a pre-given phase space, like in physics: they modify the very biological observables, the phenotypes, which is more closely argued in Longo and Montévil (2014b). If we are right, this poses a major challenge. In the analysis of evolutionary dynamics, randomness may not be measurable by probabilities (Longo *et al.* 2012a; Longo and Montévil 2014a). This departs from the many centuries of discussion on chance only expressed by probabilities.

If the reader were observing Burgess fauna, some 520 million years ago (Gould 1989), they would not be able to attribute probabilities to the changes of survival of Anomalocaris or Hallucigenia, or to one of the little chordates, nor their probabilities to become a squid, a bivalve or a kangaroo. To the challenges of synchronic measurement, proper to physical state determined systems, such as the ones we examined above, one has to add the even harder approximation of diachronic measurement, in view of the relevance of history in the determination of the biological state of affairs (Longo 2017).

Note that in section 1.4 we could have made a synthetic prediction: phenotypic complexity increases along evolution by a random, but asymmetric, diffusion. This conclusion would have been based on a global evaluation, a sum of all the numbers we associated with biological forms (fractal dimensions, networks' numbers, tissue folding … all summed up). In no way, however, can you "project" this global value into specific phenotypes. There is no way to know if the increasing complexity could be due to the transformation of the lungs of early tetrapods into swim bladders and gills (branchia), or of their "twin-jointed jaw" into the mammalian auditory ossicles (Luo 2011).

Can AIT be of any help to meet this challenge? From a highly epistemic perspective, one may say that the phenotypes cannot be described before they appear. Thus, they form an incompressible list of described/describable phenotypes, at each moment of the evolutionary process. It seems hard to turn such a contingent/linguistic statement into an objective scientific analysis.

In contrast to AIT, in which randomness is developed for infinite sequences of numbers, in a measurement independent way, any study of randomness in a specific context, physical or biological, for example, depends on the *intended theory* which includes its *main assumptions* (see, for example, section 1.3 for the "principles" used in the analysis of quantum randomness and for the theory-and-measurement-dependent notion of the predictor).

As a consequence, our focus on unpredictability and randomness in natural sciences, where access to knowledge crucially requires physical or biological measurement, cannot and should not be interpreted as an argument that "the world is random" and even less that it is "computable" – we, historical and linguistic humans, effectively write our theories and compute them in order to predict (see Calude *et al.* 2012 for a discussion on the hypothesis of a lawless (physical) Universe).

We used (strong forms of) relative unpredictability as a tool to compare different forms of determination and stability in natural sciences, sometimes by a conceptual or mathematical duality (showing the "relevance of negative results"), other times by stressing the role of randomness in the robustness or resilience of phenomena. The ways we acquire knowledge may be enlightened by this approach, also in view of the role of symmetries and invariance in mathematical modeling and of the strong connections between spontaneous symmetry breaking and random events discussed in Longo and Montévil (2015).

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