Progress in Biophysics and Molecular Biology 109 (2012) 108–114

Contents lists available at SciVerse ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Review

Is information a proper observable for biological organization?

G. Longo [a,*], P.-A. Miquel [b], C. Sonnenschein [c], A.M. Soto [c]

[a] CREA, Ecole Polytechnique, 32 Boulevard Victor, 75015 Paris, France
[b] Laboratoire CEPERC, UMR CNRS, 6059, Université de Provence, France
[c] Department of Anatomy and Cellular Biology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA

ARTICLE INFO

Article history:
Available online 13 July 2012

Keywords:
Entropy
Complexity
Program
Determinism
Code
Signal

ABSTRACT

In the last century, jointly with the advent of computers, mathematical theories of information were developed. Shortly thereafter, during the ascent of molecular biology, the concept of *information* was rapidly transferred into biology at large. Several philosophers and biologists have argued against adopting this concept based on epistemological and ontological arguments, and also, because it encouraged genetic determinism. While the theories of elaboration and transmission of information are valid mathematical theories, their own logic and implicit causal structure make them inimical to biology, and because of it, their applications have and are hindering the development of a sound theory of organisms. Our analysis concentrates on the development of information theories in mathematics and on the differences between these theories regarding the relationship among complexity, information and entropy.

© 2012 Elsevier Ltd. All rights reserved.

Contents

1. Introduction 108
2. The *elaboration* of information, or how the story began 109
3. Information, entropy and negentropy in two different perspectives 109
   3.1. The analysis of *transmission* of information 109
   3.2. The analysis of *elaboration* of information 110
4. How does *information* lead to a central role for molecules? 111
   4.1. *Information* in biology and the structure of determination it imposes 111
   4.2. *Information* and the three-dimensionality of organisms 112
   4.3. The structure of determination of biological organization 113
5. Conclusion 113
   Acknowledgments 114
   References 114

1. Introduction

The concept of information has dominated biological discourse particularly in genetics and molecular biology. Although biologists have for the most part embraced this notion, others have raised objections "on the ground that enthusiasm for information in biology has been a serious theoretical wrong turn", and because "…it fosters naive genetic determinism" (Godfrey-Smith and Sterelny, 2008; Hacking, 1999). Our current analysis stems from information theories in mathematics and addresses the differences between these theories regarding the relationship among complexity, information and entropy. These differences have led to intrinsic inconsistencies and ambiguities when metaphorically applied to biology. Beyond the observables[1] known from physics,

* Corresponding author. Tel.: +33 (0) 145526420.
E-mail address: Giuseppe.Longo@ens.fr (G. Longo).

[1] A measurable property of a physical system, such as mass or momentum. In quantum mechanics, observables correspond to mathematical operators used in the calculation of measurable quantities (from http://www.thefreedictionary.com/observable).

0079-6107/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pbiomolbio.2012.06.004

there is a need for new observables in biology that would increase its intelligibility and facilitate the quantification of biological organization. *Information* was erroneously thought to be the key observable. Thus we will argue that the concept of information is not applicable to biology and point out which have been the unintended consequences of the information metaphor.

2. The *elaboration* of information, or how the story began

In 1931, Kurt Gödel, a major logician, invented the number-theoretic coding of everything. With an idea that now may seem obvious, he associated one-to-one letters to numbers and by a clever use of arithmetic properties he coded all sentences of formalized mathematics as numbers. A few years later, Alan Turing made out of this idea the fantastic Logical Computing Machine for manipulating all sentences of formal theories (Turing, 1936). He accomplished this by providing instructions, later called *programs*, also subject to being coded by numbers, that is, by sequences of zeros and ones. And thus, he invented the modern theory of *elaboration* of information. The program was encoded by the same structure as the data, a sequence of 0s and 1s. A Universal Machine could then compute with any program by using part of its memory to code for the program and another for the data. This "architect", as Schrödinger called it in 1945, uses a string of numbers as a program (Schrödinger's "plan") to carry on the computation over data, what is now called an operating system and a "compiler".

Under the form of code-script, Schrödinger first hinted at *information*[2] as the observable proposed by the newly invented Theory of Computation and of Coding (Schrödinger, 1945). This new discrete observable would be straight-forwardly found in chromosomes, the "aperiodic crystals" envisioned by Schrödinger. The base pair complementarity of DNA discovered in 1953 strengthened the force of the information metaphors and provided an uncomplicated conceptual frame for the analysis of the transmission of hereditary traits (Mendelian inheritance) and for the "reading" of a (coded) gene sequence into its corresponding protein.

Biologists sensed the *zeitgeist* and followed the fashion of the time, as if these notions where "causally neutral"; however, they are not. Note that Frege's and Hilbert's mathematical logic (Barwise, 1978) were proposed as a foundation of mathematics based on Arithmetic and programmatically departing from physics and its foundations (Bailly and Longo, 2011). Gödel's and Turing's work addressed questions in this purely linguistic and abstract context. Thus, from this mathematical logic perspective, the encoding of the Aristotelian "essence" of an organism into an aperiodic crystal was not supposed to bring into biology any intended "structure of physical determination" or causal relationship. Instead, it was supposed to merely imply the "soft" symbol of manipulation, typical of coding and programming, which was later associated by Crick to the principle of genetic determination. In a famous paper, Crick claimed that the transcription of the *information* contained in DNA molecules — along with its translation — takes place "in a linear order" that starts from the "genetic material" and ends with the synthesis of proteins. Thus, genetic information could be stored in DNA (or RNA) and become known by the reading of the nucleic acid sequence, and that interactions among proteins, lipids, and other chemical entities could not change it. He stated explicitly in this sense, that: "the sequence of bases determines the sequence of amino acids" (Crick, 1958).

[2] *Information* in italics denotes the use of this concept in biology in contraposition of information in mathematics.

Schrödinger rightly acknowledged the peculiar deterministic nature of his proposal when he wrote « …In calling the structure of the chromosome fibers a code-script we mean that the all-penetrating mind, once conceived by Laplace, … could tell from their structure whether the egg would develop, under suitable conditions, into a black cock or into a speckled hen…» (Schrödinger, 1945). In code-script, regardless of whether it is a matter of programming or cryptography, determination is "Laplacian", that is, it implies causality and predictability.[3] Programming and decrypting led in principle to predictable dynamics on discrete and exact data types. From Gödel's primitive *recursive* functions to portability of software, the purpose of programming is *identical iteration*. Primitive recursion is iteration plus updating a register. Programs ought to be *portable*, that is, they should iterate identically even in slightly different, but compatible, computational environments. When re-launching a program, even in a network, or when opening a webpage in say, Japan, or South Africa, one would want both the program and the website to run identically … always! And in computer networks this is hard, as space-time continua step in. Yet, it works! This is also true in cryptography: given the key, decoding must work as expected and iterate, as all ordinary bank teller machines do.

Biological phenomena, instead, do not exhibit this predictability. For example, a relatively low percentage of fertilized eggs produce live births. Also, normal cells extracted from humans rarely can be "established" in culture conditions. In addition, only one in hundreds of "nuclear transfer embryos", like Dolly, are born, and so on. Mathematically, on the other hand, codes and programs are made to work exactly. The program may be too long or its results yet unknown in practice, but *in principle*, everything should be in it. This is why, in 1945, Schrödinger wrote that if the chromosomes are indeed a code-script, once they become decoded, deterministic predictability should fully display its power. Hopefully, then, we would know in which way "the DNA code … is the *program* for the behavioral computer of this individual" (Mayr, 1961). Today, however, this Laplacian structure of determination going from the DNA to the phenotype is highly controversial. More modestly, most biologists view the genome just as a program for producing proteins (Danchin, 2003). Yet, a process is "programmable" (i.e., modeled in a faithful way by a program on discrete data types) if, and only if, it is deterministic and predictable, and thus Laplacian (Bailly and Longo, 2011).

3. Information, entropy and negentropy in two different perspectives

3.1. The analysis of transmission of information

The word "information" is absent in Schrödinger's book. However, he writes about *code-script*, meaning the "order" coded by and in an aperiodic crystal. This was an audacious proposal into the possible structure of chromosomes, especially because at that

[3] In short, a physical system is deterministic when it has a "conceivable" determination in explicit mathematical terms – equations, evolution functions… For Laplace (1749–1827), any deterministic system is *predictable* and unpredictability, as randomness, had to be analyzed in purely probabilistic terms. This turned out to be false, since, in his Geometry of Dynamical System, born from the Three Body Problem, Poincaré (1854–1912) showed that classical randomness may be understood as "unpredictable determinism". This is typically due to the role of non-observable fluctuations (fluctuations below the best physical measure) in continuous dynamics, which may produce relevant observable effects by non-linear amplifications. This was a consequence of Poincare's proof of non-analytical solvability of the equations for three celestial bodies in their gravitational fields (1890), see (Barrow-Green, 1997).

time the chemical nature of the genetic material was unknown. Later in his book, negentropy appears as opposed to entropy, that is, entropy with negative sign or "order". Schrödinger did *not* consider negentropy as information; instead, he introduced it in a footnote as a component of Gibbs free energy (Bailly and Longo, 2009).

How do information and entropy relate in physics and in information theory? After trying without success to obtain from mechanics a general theorem to prove the second law of thermodynamics, in 1896, Boltzmann related entropy to the increasing probability of the macroscopic state; that is, states go from less probable to more probable. In another sense, they go from "highly organized" (*molekular geordnet*) to "less organized" (*molekular ungeordne*) (Boltzmann, 1898). High entropy corresponds to a large number of possible different microscopic structures (microstates), which are indistinguishable to us and, thus, yield the same macrostate, which is unique at thermodynamic equilibrium (maximal entropy). At maximal entropy, there is no order, no "organization". The canonical example is the totally random mixture of two or more gas types. Thus, particularly in biology, the increasing probability of the macroscopic state may be interpreted as increasing disorder. It should be noted that Boltzmann referred to a body of gas in a fixed container that evolved in complete isolation from its environment. There is no heat or matter being exchanged by the gas during the process.

Enter Claude Shannon, the pioneer of the theory of *transmission* of information. This theory is to be distinguished from Turing's theory of *elaboration* of information. During the 1940s, Shannon was interested in the effectiveness of transmission along a wire, and the possible dispersal of information (Shannon, 1948). He quantified information according to the probability distribution, p_i, of individual coded events. It should be noted that probability is a measure of randomness, thus, of unpredictability. In short, Shannon defined the information content of a sequence of n signs (possibly integer numbers, or even digits), as given by the inverse of the "expectation" that each sign presents; that is, the more an event is unlikely, or it has a low probability to happen, the more its occurrence is "informative". Thus, $p_i \leq 1$ is defined as the probability of event or coding sign $i = 1, \ldots, n$ in a sequence of n signs. Then, the amount of information in the sequence is given by $-\Sigma p_i \log p_i$. Now, for purely mathematical reasons, Shannon's formula happens to be analogous to Boltzmann's formalization of entropy. More specifically, for Boltzmann, entropy is a logarithmic measure of the density of possible states, given by $k_B\, \Sigma p_i \log p_i$, where k_B is the Boltzmann constant, equal to 1.38065×10^{-23} J K^{-1}. That is, the summation is over all the microstates where the system can be in, and p_i is the probability that the system is in the ith microstate. The thermodynamic equilibrium for a mixture of gases, for example, is reached when the disorder as well as the entropy is *maximal*.

In 1956, Leon Brillouin formally related Shannon's information to negative entropy, or "negentropy" (that is, I = −S, for Boltzmann's S, up to some technical changes). Information was then considered as a new "physical" dimension. Thus, for Brillouin, Shannon's information is a matter of "differential knowledge", and so is entropy as is our insight into order *vs*. disorder: these are epistemic notions. Under the Shannon–Brillouin interpretation, entropy, as a measure of disorder and of unpredictability, is an (inverse) degree of knowledge. For example, a series of coin tosses with a fair coin has maximum entropy, since there is no way to know what will come next. In summary, the Shannon–Brillouin approach provides a mathematical characterization of the relation between information, entropy and order, where.

$$\text{High entropy} = \text{low knowledge} = \text{low information} = \text{low order } (= \text{low complexity})$$

3.2. The analysis of elaboration of information

In the 1960's, Andrei Kolmogorov developed an *algorithmic* approach to the notion of information *à la* Turing (as data elaboration, not transmission). This approach became a discipline called *Algorithmic Theory of Information* which deals with the amount of information expressed by a *computer program* (Calude, 2002). For this purpose, Kolmogorov used new concepts such as "incompressibility" and "sequence complexity". In short, in Kolmogorov's theory, a sequence of numbers (0's and 1's) is *incompressible* when it *cannot be generated* by a program shorter than the sequence itself. Thus, in order to effectively describe an incompressible sequence, one must calculate it point by point. Such a sequence would contain or require the highest information: one would need a very long program to generate it, a program as long as the sequence itself. That is, an incompressible sequence has the *highest complexity*. Equivalently, it would contain no regularity that can be summarized in a description shorter than the sequence. Now, a long sequence of 0's and 1's where one detects no regularity whatsoever may be considered to be random.[4] Thus, randomness increases with the complexity and the amount of information, as disorder in a sequence. In other words, a random, incompressible finite sequence has the highest complexity and informational content. In short,

$$\text{High complexity} = \text{high information}$$

By revising a related idea of Kolmogorov, Gregory Chaitin showed that an incompressible sequence may be soundly considered totally disordered, meaning that all initial segments of an infinite sequence are incompressible if and only if the sequence is random.[5] Thus, the absence of regularities, randomness, disorder and maximal complexity are all equivalent in this algorithmic context. It stands to reason that if one wants an algorithm that gives pixel by pixel, the momentum and position of all particles of two or more mixed gases, this algorithm would be as large as the required information to give those data: no regularities allow describing them by a shorter program. Thus.

$$\text{High complexity} = \text{high information} = \text{high entropy}$$

When one applies to Kolmogorov's finite sequences the Shannon–Brillouin's notion of entropy, as derived from Boltzmann, the above equalities are obtained (Baez and Stay, in press; Hammer et al., 2000).

Finally, these two different theories, the transmission and the elaboration of information theories, consistently yield different correlations between information, entropy and order, in view of their different origins, motivations and applications. The extensive use of the words *information* and *complexity* in biology poses then the question of which set of notions and rules are being used: Shannon–Brillouin's or Kolmogorov–Chaitin's? If one uses the former, a Kolmogorov's incompressible sequence has then both the highest entropy and complexity. Therefore, the two theories of

[4] For example, the sequences "000…0" or "010101…01", even if extended for long stretches may be generated by a very short program (write all 0s or alternate 0 and 1). A sequence with no (apparent) regularities, such as one obtained by flipping a coin, can only be obtained by producing it entirely. To be precise, however, this latter case of flipping a coin, is not even a "program", but this is a different issue….

[5] In other words, Kolmogorov's notion may be extended up to infinity. Under certain conditions, technically given by Chaitin as being "prefix-free" (Calude, 2002), exactly the finite initial segments of an infinite random sequence [certified by passing all effective tests of randomness, *à la* Martin-Löf (Calude, 2002); (Martin-Löf, 1966)], are incompressible. But this may have little impact in biology because no infinite DNA, RNA or protein sequences are known so far.

information propose opposite understandings of the relation between complexity, information and entropy, namely:

1. *Transmission* (Shannon–Brillouin): highly improbable, the highest information, the highest order (thus, conversely: highest entropy, higher probability). In other words, information becomes negentropy and it is co-variant with order (and complexity):

$$\text{negentropy} = \text{information} = \text{order}(= \text{complexity})$$

2. *Programming* (Turing–Kolmogorov–Chaitin): an organized (ordered) message is compressible. Thus, it contains less information. In other words, information and complexity are positively correlated to disorder (and entropy), and conversely, they are contra-variant with order:

$$\text{complexity} = \text{information} = \text{disorder}(= \text{entropy})$$

What are the consequences of these opposite meanings for the use of information in biology? And on which of these two theoretical frames is the biological reference to information based? Are we dealing with:

1. Shannon–Brillouin, where a highly ordered/organized organism would contain highest *information* and lowest entropy (as it seems reasonable)? or
2. Kolmogorov–Chaitin's programming approach, where complexity grows with disorder?

If *information* is used in the sense of Shannon–Brillouin, since the informational content of the code script is meant to encode biological organization, then biological organization should be understood as the opposite of entropy (that is, as negentropy). Conversely, if we assume that the DNA is a program (meaning a code-script with its own "plan and architect") then the DNA should contain in a compressed form the complex *information* of an organized individual. In this case, the use of the joint notions of *information* and of *program* leads to the Turing–Kolmogorov–Chaitin approach. Thus, a maximally disordered gas (maximal entropy) would have maximal complexity: as observed above, it would require a very long program to describe the position/momentum of *each individual* particle. Biologically, this is rather absurd because a mouse would be less complex than a gas of the same volume: it would contain less *information*. In any case, these two alternatives yield a real metaphorical/theoretical confusion.

4. How does *information* lead to a central role for molecules?

Which of the two notions of *information* are biologists referring to: elaboration or transmission? A biologist who would want to keep the idea of "coded information" should then propose a precise, scientific notion of *information*. For example, which would be the informational content of a continuous anatomical deformation (a continuous change in a shape)? To avoid this confusion, it has been claimed that the use of "information" is just metaphorical and that it does not refer to existing theories. By their implicit referential content, metaphors may force a way of thinking with no explicit bases that would allow a critical insight.

Since the '50s, in view of the increasing importance of both theories of *elaboration* and *transmission*, *information* is understood as being encoded by digits, or, equivalently, by discrete data types. In this context, anything else is considered as noise and may only increase entropy as disorder. If a wire or a computer are compressed, pulled or twisted, these actions will *not* increase the *information* that they are transmitting or elaborating, neither in practice nor in principle. The very robust Shannon's entropy principle would forbid it. On the other hand, all along embryogenesis, compression, dilation, shearing, pulling, twisting and continuous deformations significantly and causally contribute to development. Thus, the metaphorical use of *information* encourages the observer to think in terms of discrete structures, that is, of molecules only, including DNA. Therefore, molecules become the loci of *information* coded by digits, or the paradigm for discreteness in the living. And, we insist that the fundamental principle of Shannon's digital information – the information-theoretic application of the second law of thermodynamics – states that *information* cannot be increased *but* by adding digits. So, the "constraints" or the interactions in living organisms, given by either the cells, the different levels of organization and/or by the ecosystems cannot causally and positively contribute to the generation and maintenance of the organism unless they are digitally encoded as molecular signs.

In sum, the *information* theoretic approach in biology seems to ignore the principles common to computability and of transmission theory, in which the main conceptual invariant is "perfect iteration on discrete data types", from primitive recursion, to portability of software to the algorithms for data transmission (Longo, 2009a).

4.1. Information in biology and the structure of determination it imposes

Early into the Molecular Biology Revolution, it was pointed out that the relationship between genes and phenotypes was not univocal; in fact, it was vague and misleading (Hull, 1974). In reality, it was about "the many (genes) and the many (phenotypes)." This non-univocal (many to many) correspondence *a fortiori* poses problems because the idea of "coding" implies Laplacian determination. This lack of univocal correspondence between a given gene and its protein, has already been highlighted in eukaryotes by the existence of introns and exons in DNA whereby the corresponding pre-mRNA is spliced, the introns are removed and the exons are joined together to generate the mRNA that will eventually be translated into a protein. Alternative splicing produces different proteins from the same DNA sequence which, again, reinforces the fact that the DNA-protein relationship is not univocal. Moreover, against what was postulated by Anfinsen (1973), protein folding is not entirely determined from its amino acid sequence either[6] (Kang and Kini, 2009).

The lack of correspondence at specific sites between DNA and mRNA in cells from the same individual also points to a breach on the presumed determination by DNA of the protein sequence (Li et al., 2011). In fact, the lack of correspondence cited above is also manifested at the protein level. In addition to errors, which usually are corrected by the process called "proof-reading", and changes due to "RNA editing", almost half of the changes were transversions (substitutions of a purine for a pyrimidine) which are not accounted for by the editing process. Parenthetically, the terms "proof-reading" and "editing" belong to the informational and linguistic nomenclature and were borrowed by molecular biologists who were persuaded that DNA carried *information*.

An additional experimental finding that contradicts the ideas a) that *information* is stored in DNA, b) that information is "coded"

[6] "In essence, the determinants of correct folding (or in the case of amyloidogenesis, protein misfolding) are neither completely understood nor can they be simplistically limited to structural features on the sequence" (Kang and Kini, 2009).

and c) that DNA contains a "program" is the stochastic nature of gene expression. Originally proposed by Jean-Jacques Kupiec in the 1980's (Kupiec, 1983) the stochasticity of gene expression is now supported by a body of experimental data. For example, protein and mRNA copy numbers vary from cell to cell in isogenic bacterial populations, and in a given single cell, protein and mRNA copy numbers for any given gene are uncorrelated (Taniguchi et al., 2010). Those supporting the *information* paradigm in biology call these fluctuations "noise", implying that a perfect Laplacian determinacy of the digital information paradigm meets the "imperfect" physical reality of the cell. For low-copy number mRNAs and proteins, these fluctuations are called intrinsic noise, and it is believed to be due to the few copies of gene activating protein molecules that interact stochastically (Tyagi, 2010). For more abundant proteins, the noise is called extrinsic and is attributed to variable metabolic capacities among cells (i.e., number of ribosomes and polymerase molecules), so that 2 proteins subjected to this type of noise fluctuate in time in a correlated mode.

Adding to the fact that mRNA levels fluctuate in genetically identical cells, the lack of correspondence between a mRNA and its corresponding protein may be due either to the different half-life of their mRNA (very short lived in bacteria) and proteins (significantly longer half-lives) or to the random passage of protein molecules to the daughter cells following the division of the mother cell. This "noisiness" seems to be even higher in mammalian cells. This is attributed to random changes in chromatin packing that would either allow or exclude access of the "gene-activating" proteins to the "control" regions of genes. For example, "gene activating proteins can gain access to these regions only during random episodes in which local chromatin becomes loose," (Tyagi, 2010). Additionally, "If gene activation does indeed correspond to chromatin remodeling, this points to the possibility that the nucleation of chromatin decondensation at a gene locus may be an inherently random event that does not require the presence of transcription factors but, once initiated, requires those factors to sustain the decondensed state" (Raj et al., 2006).

In summary, the experimental data reviewed above led to the question: If *information* is digital, and randomness massively contributes to gene expression, where is Schrödinger' architect, or, for that matter, Turing's "compiler (universal machine)"? Or even, in which Shannonian universe is information randomly extracted from a source?

4.2. Information and the three-dimensionality of organisms

In Francois Jacob words: "For it is during embryonic development that the instructions contained in the genetic program of an organism are expressed, that the genotype is converted into phenotype" (Jacob, 1982). Almost 20 years later, John Maynard-Smith, while recognizing that the similarities between a computer program and the so-called "developmental program" were superficial, stated: "There is, however, one feature of the control of development which closely resembles both a computer program, and verbal instructions. This is the symbolic nature of the process…" (Maynard-Smith, 1999). These views still prevail in the field of developmental biology. They rely on an assumed privileged causal role attributed to DNA whereby differential gene expression and morphogenic field effects due to homeotic gene control determine shape and function. Moreover, the prevailing experimental approach (knock-outs), consisting of deleting a gene (a discrete DNA fragment) and looking for the resulting phenotype, has not revealed how shape arises during morphogenesis (Davies, 2009).

Organisms and their cells live in a world of three dimensions; this world is physical, and not a string of zeros and ones.[7] Life of a metazoan begins with fertilization when a cell resulting from the union of a female and a male gamete, a zygote, is formed. The zygote is both a cell and an organism. This dual identity means that organization levels are entangled from the very beginning of development. The zygote divides, producing more cells (blastomeres), which are organized in a three-dimensional pattern. These blastomeres start a process arbitrarily called "differentiation" by virtue of their relative position and their history, which is the result of interactions with their neighboring cells. This reciprocity makes it difficult to establish detailed cause and effect relationships. Differential proliferation rates and movement imply that the "neighbors" of any given cell may also change as development progresses. Movement and cell interactions create physical forces that shape developmental processes (see below). Biomechanics plays a role on the maintenance of tissue integrity during development by a synergy between balanced tension and compression components. From the macro-scale to the nano-scale, organisms are also shaped by tension, i.e., a balanced push and pull (Ingber, 2003). As a result of these cell–cell and cell–matrix interactions diverse tissues are generated (epithelium, muscle, nerve, connective) at different points during organogenesis. Level entanglement also takes place here, as blood vessels (which are organs) appear in the midst of tissues (connective tissue) and organs.

Below are a few examples of how physical forces create shapes and structures at all levels of organization.

a) Hemodynamic forces (pressure) are required for the development of portions of the heart and vessels (Gilbert, 2011; Lucitti et al., 2007).
b) Tension forces align chondrocytes and compression forces induce several genes required for articular cartilage to differentiate and produce matrix (Tang et al., 2004).
c) Mechanical cues from the skeletal muscles determine the final shape and size of bones (Muller, 2003; Rot-Nikcevic et al., 2007).
d) Grinding food shapes the jaw. If infant monkeys are given soft food, their lower jaw becomes smaller than usual (Corruccini and Beecher, 1984). Parenthetically, orthodontics is based on the fact that tension results in bone apposition while compression results in bone resorption.
e) In tubular organs, mechanical tension due to the hydrostatic pressure of the liquid that fills these structures causes the development of smooth muscle (Jakkaraju et al., 2003).
f) DNA is mechanically and geometrically constrained by the chromatin fiber structure. This fact provides insight on the relationship between physical properties and biological function: "…the feedback loop between the DNA and the chromatin fiber levels can be seen as the result of adaptive evolution: both levels have evolved jointly … In doing so, evolution gradually turned physico-chemical properties into biological functions" (Lesne and Victor, 2006). This last example poses a dilemma: if DNA was digital information, the torsion forces resulting from the structure of the chromatin fiber could only decrease information, as explained above regarding the "noise" introduced by physical deformation of

[7] Several dimensions continua, with "physically natural" topologies, cannot be encoded in lower dimensions. Cartesian dimension is a "topological invariant". Thus, linear discrete coding can only account for discrete many dimensional structures and misses what can be better or only accounted for by the mathematics of continua, such as movement and deformation (Longo, 2009b).

the hardware and the transmission cable. Thus, how would such physicochemical properties positively contribute to the genesis of biological functions if physical deformations would just be noise? In conclusion, these experimental facts strongly indicate that it is misleading to look for a developmental program or *information* in the sense of a "code-script" within the genome.

4.3. The structure of determination of biological organization

In the classic information theoretical context, causation follows a bottom-up direction: digits as elementary and simple components, *completely determine* information; if this concept of information is applied to biology it would bring with it a bottom-up, Laplacian structure of determination operating from DNA to biological forms or phenotypes. Instead, we posit that there is no privileged causal level in biology. In addition to upward causation, cellular and tissue events occurring before the expression of a particular set of genes may act reciprocally (simultaneously), but also downwardly modifying the expression of these genes at a later time. This concept of downward causation can be used without any logical circularity when considering that a chronological operator "before/after" is acting in biology (Soto et al., 2008). Biological events are not objects completely described by their properties. They are nothing but processes (Soto et al., 2008). An instance of downward causation has been extensively studied during gastrulation of the Drosophila embryo (Farge, 2003). In this causal chain, molecular and cellular events lead to germ band extension, which in turn generates physical stress inducing the next molecular event (*twist* induction in stomodeal cells). This is an emergent phenomenon; in other words, a group of moving cells produces compression on another group of cells that respond to this force by expressing the gene product *twist*, triggering in this way a downward causal chain, starting from the physical level and acting upon the molecular (genetic) one.

A compelling example of causal reciprocity is provided by carcinogenesis studies. The view that cancer is a cell-based disease caused by DNA mutations in genes that "control" cell proliferation has dominated the scientific literature of the last half a century; this was coincidental with the hegemony of the bottom-up *information*/molecular approach to biological organization (Hanahan and Weinberg, 2000). An alternative view is that cancer is a tissue-level phenomenon akin to development gone awry (Sonnenschein and Soto, 2008; Soto and Sonnenschein, 2011). From this latter perspective, cancer results from altered chemical and physical interactions between the parenchyma and stroma of organs (Maffini et al., 2004). They include cell to cell junctions, adhesion forces among cells and between cells and matrix, tissue rigidity and fiber organization within the matrix. This view, contrary to its mutation-centered counterpart, explains the fact that cancer is reversible, as suggested by normalization of teratocarcinoma cells injected into blastocysts, embryonal carcinoma cells injected into the mammary gland, mammary carcinoma cells recombined with normal mammary gland stroma, hepatocellular carcinomas injected into normal liver, highly malignant melanoma cells injected into Zebra fish embryos, etc. These are examples where cancerous cells reverse their "malignant" properties when placed within normal tissues (Bussard et al., 2010; Coleman et al., 1997; Kasemeier-Kulesa et al., 2008; Maffini et al., 2005; Mintz and Ilmensee, 1975). In sum, these examples illustrate that the structure of determination of biological entities is not Laplacian as required by the information theories discussed above. Biological organization is not determined by bottom-up interactions of discrete molecular components, but by complex causal networks, including *simultaneous* bottom-up *and* top-down causality.

5. Conclusion

The adoption of the *information* theoretical approach failed to provide biology with a pertinent observable for understanding and measuring organization. On the contrary, the concepts linked to *information* such as code, program, signal, etc, have hindered the comprehension both of physical dynamics and of biological organization. First and foremost, *information* in biology has been used merely as a metaphor since it has not been properly formalized. Thus, its relationship with organization, complexity and entropy remains unclear and unspecified. As pointed originally by Ricoeur (1975), and then by Hacking (1999), every living metaphor involves a structural tension between heterogeneous semantic areas. Metaphors shift (*phora*) from one attested universe of reference to another one that is partially created or constructed by this initial tension. They can be useful to knowledge, but they deal with imagination and fiction. As such they create substitutes for their literal equivalent. Thus, a naked tree is not naked, and a genetic program is not a program. When metaphors have been used too often, they die (Ricoeur, 1975): people cease to be aware that the metaphoric use of the words is not a literal one. They become illegitimate forms of predication and of discourse.

Discrete information is unidimensional (it can be coded in one dimension). It gives an understanding of causality which may be plainly called Laplacian because it sees determination (instruction, program …) and randomness (noise), as conceptually opposed components of development (Monod, 1970).[8] When transposed to biology these characteristics hinder the understanding of organisms as 3 dimensional physical objects and of diversity and variability, a consequence of randomness, as a constitutive aspect of structural stability in biology.

Information deals with data and not with dynamics. The digital bent of *information* is static and bottom-up; it biases the study of causality towards molecules and excludes dynamics, interactions as well as contextual dependencies that are better understood by non-discrete and global perspectives. Again, in all theories of information, *in principle*, physical forces can only *reduce* digital information by creating noise (the bending, the torsions, the pressures… discussed above). These theoretical considerations about *information* have practical consequences that should be of concern to experimentalists. The biomedical literature of the last half-century has given molecules, particularly DNA, a privileged role in causation. In cancer research, for example, DNA mutations were considered the "cause" of cancer with not much progress to flaunt. Instead, development and carcinogenesis, as particular instances of biological dynamics and organization, are multilevel phenomena that are best understood at the mesoscopic hierarchical level where the phenomenon of interest is observed (Bizzarri et al., 2011). From there on, one could gingerly move up and down in search of additional causal links. Hence, there is no favored causation level, because vital phenomena are the result of multiple and reciprocal causality (Gilbert and Sarkar, 2000; Noble, 2006).

In sum, explanations in biology should be pursued through an explicit search for a proper biological observable, present at the right level of organization (Bailly and Longo, 2009). Meanwhile, biologists should embrace the complexity and the unity of the organism and seek explanations at or nearby the mesoscopic level while strictly avoiding the use of the words coding, program and signal to denote biophysical and biochemical processes and biological functions.

[8] In contrast, Poincare in the 19th century had already integrated randomness into non-linear deterministic dynamics.

Acknowledgments

This work was supported by grants from the Avon Foundation and the NIH (ES015182, ES012301 and ES08314). We are grateful to Mael Montevil for his critical reading of the manuscript and to Cheryl Schaeberle for her excellent editorial assistance.

The authors have no competing financial interests to declare.

References

Anfinsen, C.B., 1973. Principles that govern the folding of protein chains. Science 181, 223–230.
Baez, J., Stay, M. Algorithmic thermodynamics. Mathematical Structures in Computer Science, in press.
Bailly, F., Longo, G., 2009. Biological organization and anti-entropy. J. Biol. Syst. 17, 63–96.
Bailly, F., Longo, G., 2011. Mathematics and Natural Sciences: The Physical Singularity of Life. Imperial College Press, London.
Barrow-Green, J., 1997. Poincaré and the Three Body Problem. American Mathematical Society Bookstore, Providence.
Barwise, J., 1978. Handbook of Mathematical Logic. North Holland, Amsterdam.
Bizzarri, M., Giuliani, A., Cucina, A., D'Anselmi, F., Soto, A.M., Sonnenschein, C., 2011. Fractal analysis in a systems biology approach to cancer. Semin. Cancer Biol. 21, 175–182.
Boltzmann, L., 1898. Vorlesungen über Gas Theorie. JA Barth, Leipzig.
Bussard, K.M., Boulanger, C.A., Booth, B.W., Bruno, R.D., Smith, G.H., 2010. Reprogramming human cancer cells in the mouse mammary gland. Cancer Res. 70, 6336–6343.
Calude, C., 2002. Information and Randomness. Springer-Verlag, Berlin.
Coleman, W., Wennerberg, A.E., Smith, G.J., Grisham, J.W., 1997. Regulation of the differentiation of diploid and aneuploid rat liver epithelial (stem-like) cells by the liver microenvironment. Am. J. Pathol. 142, 1373–1382.
Corruccini, R.S., Beecher, R.M., 1984. Occlusofacial morphological integration lowered in baboons raised on soft diet. J. Craniofac. Genet. Dev. Biol. 4, 135–142.
Crick, F., 1958. On protein synthesis. Symp. Soc. Exp. Biol. 12, 138–163.
Danchin, A., 2003. The Delphic Boat: What Genomes Tell Us. Harvard University Press, Cambridge.
Davies, J., 2009. Regulation, necessity, and the misinterpretation of knockouts. BioEssays 31, 826–830.
Farge, E., 2003. Mechanical induction of twist in the Drosophila foregut/stomodeal primordium. Curr. Biol. 13, 1365–1377.
Gilbert, S.F., 2011. Pressure as a developmental agent. In: Developmental Biology: A Companion to Developmental Biology. http://9e.devbio.com/article.php?ch=18&id=303.
Gilbert, S.F., Sarkar, S., 2000. Embracing complexity: organism for the 21st century. Dev. Dyn. 219, 1–9.
Godfrey-Smith, Peter, Sterelny, Kim, 2008. In: Zalta, Edward N. (Ed.), "Biological information", the Stanford Encyclopedia of Philosophy. <http://plato.stanford.edu/archives/fall2008/entries/information-biological/> (Fall 2008 Edition).
Hacking, I., 1999. The Social Construction of What? Harvard University Press, Cambridge.
Hammer, D., Romashchenko, A., Shen, A., Vereshchagin, N., 2000. Inequalities for Shannon entropy and Kolmogorov complexity. J. Comput. Syst. Sci. 60, 442–464.
Hanahan, D., Weinberg, R.A., 2000. The hallmarks of cancer. Cell 100, 57–70.
Hull, D., 1974. The Philosophy of Biological Science. Prentice Hall, Englewood Cliffs, NJ.
Ingber, D.E., 2003. Tensegrity II. How structural networks influence cellular information processing networks. J. Cell Sci. 116, 1397–1408.
Jacob, F., 1982. The Possible and the Actual. University of Washington Press, Seattle, WA.
Jakkaraju, S., Zhe, X., Schuger, L., 2003. Role of stretch in activation of smooth muscle cell lineage. Trends Cardiovasc. Med. 13, 330–335.
Kang, T.S., Kini, R.M., 2009. Structural determinants of protein folding. Cell Mol. Life Sci. 66, 2341–2361.
Kasemeier-Kulesa, J.C., Teddy, J.M., Postovit, L.M., Seftor, E.A., Seftor, R.E., Hendrix, M.J., Kulesa, P.M., 2008. Reprogramming multipotent tumor cells with the embryonic neural crest microenvironment. Dev. Dyn. 237, 2657–2666.
Kupiec, J.J., 1983. A probabilistic theory for cell differentiation, embryonic mortality and DNA C-value paradox. Specul. Sci. Technol. 6, 471–478.
Lesne, A., Victor, J.M., 2006. Chromatin fiber functional organization: some plausible models. Eur. Phys. J. E. Soft Matter 19, 279–290.
Li, M., Wang, I.X., Li, Y., Bruzel, A., Richards, A.L., Toung, J.M., Cheung, V.G., 2011. Widespread RNA and DNA sequence differences in the human transcriptome. Science 333, 53–58.
Longo, G., 2009a. Critique of computational reason in the natural sciences. In: Gelenbe, E., Kahane, J.-P. (Eds.), Fundamental Concepts in Computer Science. Imperial College Press/World Scientific, London, pp. 43–70.
Longo, G., 2009b. From exact sciences to life phenomena: following Schrödinger and turing on programs. Inf. Comput. 207, 545–558.
Lucitti, J.L., Jones, E.A., Huang, C., Chen, J., Fraser, S.E., Dickinson, M.E., 2007. Vascular remodeling of the mouse yolk sac requires hemodynamic force. Development 134, 3317–3326.
Maffini, M.V., Calabro, J.M., Soto, A.M., Sonnenschein, C., 2005. Stromal regulation of neoplastic development: age-dependent normalization of neoplastic mammary cells by mammary stroma. Am. J. Pathol. 167, 1405–1410.
Maffini, M.V., Soto, A.M., Calabro, J.M., Ucci, A.A., Sonnenschein, C., 2004. The stroma as a crucial target in rat mammary gland carcinogenesis. J. Cell Sci. 117, 1495–1502.
Martin-Löf, P., 1966. The definition of random sequences. Infect. Control 9, 602–619.
Maynard-Smith, J., 1999. The 1999 Crafoord prize lectures. The idea of information in biology. Q. Rev. Biol. 74, 395–400.
Mayr, E., 1961. Cause and effect in biology. Nature 134, 1501–1505.
Mintz, B., Ilmensee, K., 1975. Normal genetically mosaic mice produced from malignant teratocarcinoma cells. Proc. Natl. Acad. Sci. USA 72, 3585–3589.
Monod, J., 1970. Le Hasard et la Nécessité. Éditions du Seuil, Paris.
Muller, G.B., 2003. Embryonic motility: environmental influences and evolutionary innovation. Evol. Dev. 5, 56–60.
Noble, D., 2006. The Music of Life: Biology Beyond the Genome. Oxford University Press, Oxford.
Raj, A., Peskin, C.S., Tranchina, D., Vargas, D.Y., Tyagi, S., 2006. Stochastic mRNA synthesis in mammalian cells. PLoS Biol. 4, e309.
Ricoeur, P., 1975. La Métaphore Vive. Éditions du Seuil, Paris.
Rot-Nikcevic, I., Downing, K.J., Hall, B.K., Kablar, B., 2007. Development of the mouse mandibles and clavicles in the absence of skeletal myogenesis. Histol. Histopathol. 22, 51–60.
Schrödinger, E., 1945. What is Life? The Physical Aspect of the Living Cell. The University Press, Cambridge [Eng].
Shannon, C., 1948. A mathematical theory of communication. Bell Syst. Tech. J. 27, 279–423.
Sonnenschein, C., Soto, A.M., 2008. Theories of carcinogenesis: an emerging perspective. Semin. Cancer Biol. 18, 372–377.
Soto, A.M., Sonnenschein, C., 2011. The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory. BioEssays 33, 332–340.
Soto, A.M., Sonnenschein, C., Miquel, P.-A., 2008. On physicalism and downward causation in developmental and cancer biology. Acta Biotheoretica 56, 257–274.
Tang, G.H., Rabie, A.B., Hägg, U., 2004. Indian hedgehog: a mechanotransduction mediator in condylar cartilage. J. Dent. Res. 83, 434–438.
Taniguchi, Y., Choi, P.J., Li, G.W., Chen, H., Babu, M., Hearn, J., Emili, A., Xie, X.S., 2010. Quantifying E. coli proteome and transcriptome with single-molecule sensitivity in single cells. Science 329, 533–538.
Turing, A., 1936. On computable numbers with an application to the entscheidungs problem. Proc. London Math. Soc. Ser. 2, 230–265.
Tyagi, S., 2010. Genomics. E. coli, what a noisy bug. Science 329, 518–519.