Disease as Informative Disorder*

Paolo Bellavite

Life, differentiation, and development coincide with the expression and the maintenance of a structure in the organism, with efficient storage and handling of the energy flux, while disease and death coincide with the loss of structure and of coordinated functions. In order to efficiently handle the energy flux, living systems require information. The word information refers to the special kind of energy that is required to maintain the "form"—that is, structure, order, and organization. This type of energy is present inside the organism since its embryonic beginning, both as genetic (DNA) and epigenetic information (other molecules and space-temporal structures that influence the DNA expression of specific genes), and it penetrates *from the environment* as a number of signals that are perceived by specific receptor structures.

A more detailed definition of information might be the following: *information is an intrinsic function of every spatiotemporal structure, capable of being transmitted to another spatiotemporal structure and, thus, of modifying it in a specific manner*. The term *structure* in this context defines a particular configuration (pattern) of particles, such as atoms, molecules, or ions, but there are also structures of events organized on a temporal scale as *frequencies*. The terms structure, order, and coherence may be regarded as synonyms. In the biological world, communicating information is essential for life: at the molecular level, order is expressed in the form of a given, precise association of atoms in molecules (amino acids, proteins, lipids, nucleic acids, etc.); at the cellular level, order is expressed in the regularity and reproducibility of the cell organization and of biosynthesis, transport, and movement processes.

Generally speaking, information may be to some extent assessed quantitatively. The information content is measured in *bits*, one bit being the amount of information necessary to be able to make a choice between two alternatives—that is, a binary choice (yes or no). Needless to say, the more complex the system, the more information it contains, and the more information is needed to describe it. The degree of order in a given system can be estimated by calculating how many binary choices must be made to specify its structure. For example, during the synthesis of a protein, the choice of amino acids out of 20 possible candidates requires 4.3 bits. An entire protein of 300 amino acids requires 1,300 bits, while the corresponding DNA sequence (which, for the sake of simplification, consists of 300 nucleotide triplets) requires 1,800 bits of information (Harold 1986). The genome of a human cell has approximately 3 billion bases, corresponding to about 6 x 109 bits per cell, whereas if we consider the entire organization of an individual adult, we get up to the astronomical figure of 1,028 bits.

The fact that information can be to some extent measured in bits does not entirely solve the problem in all its complexity because the quantity does not in itself comprise the *meaning* of the information. The meaning of information resides in the interaction between the information itself and the receiving system and in the result produced by this interaction. Two sequences of DNA, one of which is "normal" and the other "pathological" (for example, coding for a character that causes disease) may contain the same *quantity* of information, but the result is very different. Thus, a good musical score may contain the same amount of information (in the form of musical notes) as a very bad score. Accordingly, there is necessarily a qualitative element in information that cannot be quantified.

Life's Language

DNA, as the main data bank of the cell, has the ability to "direct" cell development and, at the same time, to incorporate and remember information: information is stored in the DNA regarding the entire evolutionary history of the species to which the individual belongs. Of course, DNA is an important information-containing material, but it is not the only one: information is contained in *every* organized structure and in every spatiotemporal event that is not casual. While the language of the gene is fairly simple, in that it is written with only a few symbols and in a linear manner, many signals use more complex languages and symbols of various kinds. Events such as changes in transmembrane electrical potential, changes in the ratios of the various phospholipid species, the alkalinization of the cytoplasm, increases in cyclic AMP, elevations on body temperature, blood pressure, the formation of a certain

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complex of factors controlling the clotting of the blood, and even the emotion experienced as a result of sudden stress are signals that act in the most disparate ways. What is more, the duration of the signal is extremely important: usually signals are short-lived, since there are many control and modulation systems. Thus, information is not merely quantitative, but essentially *spatiotemporal*. It has been shown that one of the most important intracellular signaling systems, the increase in calcium ions, performs its function by means of pulsations, or rather oscillations of concentration, which constitute a kind of "digital code" for the various sensitive systems: for a response process to be activated, what counts is the frequency of the spatiotemporal oscillations (waves) in the calcium concentration rather than the actual amount of calcium present (see, for example, Berridge & Galione 1988, Cheek 1991).

Single-cell measurements have shown that many hormones trigger a series of calcium *spikes* and that these spikes show a rise in frequency with increasing hormone concentrations. It has been suggested that many cell responses are controlled by *frequency-modulated* rather than *amplitude-modulated* signals, analogous to the transmission of information between neurons through changes in frequency of action potentials (Catt & Balla 1989). Such digitally encoded signals could more precisely regulate the cell response to changing hormone concentrations. *In vivo*, various hormones are secreted with oscillary rhythms that may have physiological importance (Matthews 1991).

Calcium waves can also propagate in tissues and organs, providing a long-range signaling system, as observed in ciliated epithelial cells, in vascular endothelial cells, in hepatocytes, and in monolayers of cultured astrocytes. This mechanism of cell-to-cell communication may contribute to the synchronization of large assemblies (Meyer 1991).

Biological communication is so important that nature has gone out of its way to find the most differentiated forms of communication (languages). To those we have already mentioned may be added others, the foremost and most obvious of which are the sense organs endowed with photoreceptors, chemoreceptors, baroreceptors, and others. This appears only too self-evident, and there is no point in dwelling on this aspect. More pertinent perhaps to our case is the problem of communication via electromagnetic waves. Light is a basic means not only of transmitting energy (sun-earth) but also of communicating. Many fish communicate with light messages, and some cells in mammals also produce light (chemiluminescence), while an infinite amount of luminous information is received by the organs of sight. Light would also appear to be important for establishing many biorhythms. Light, however, constitutes only a small part of the electromagnetic spectrum, and it may seem strange that nature has not learned how to handle other types of electromagnetic fields.

In a nutshell, then, *every biochemical or biophysical system endowed with a certain degree of order acts as a vehicle for information*, which, when suitably decoded by receptor and transduction systems, may have biological consequences. The information molecules *par excellence* are the nucleic acids because they are characterized by a very substantial degree of order (consider the arrangement of the nucleotides in very long sequences), by a major degree of complexity (consider all the mechanisms controlling the expression of the genetic code and also its continual transformation), and by great physicochemical stability (given its particular double-helix structure, DNA is one of the most resistant molecules, and, in addition, many systems exist for repairing and remedying possible errors). Many other molecules, however, contain and transmit information. Proteins, peptides, sugars, lipids, and even mineral salts and protons (H^+) serve nature as transmitters of information and thus as regulators of biological systems. Leaving aside the molecular field, we also find information transmitted by frequencies, such as sound and electromagnetic waves and rhythmic, oscillatory chemical events. The more complex a system is, the more complex will be its communications strategy, which may be made up of many elements arranged in sequences and networks.

The "Logic" of Disease

At the opposite extreme to the organization of life is death, which therefore represents the maximum disorder, dissipation of information, and increase in entropy, tending toward thermodynamic equilibrium. Disease lies somewhere between the two, consisting in partial disorder of systems of information, energy, and matter, localized in space and time.

Disease is thus essentially an information disorder. Genetic diseases are the most striking examples of this: the *order* of the genetic code sequence is changed, and the disorder lies in the very information store itself. Genetic disease can also be caused by a very minor transcription error in the basic cell library. Even acquired diseases or diseases in which genetic and environmental factors are mixed (these are by far the majority) are disorders of information at a more complex level: what is altered is not just the molecular order of DNA, but also the information order governing the supramolecular systems. In most diseases we can identify an imbalance of the homeostatic biological systems at various levels. The molecular, cellular, tissue, organic, and neuroimmunohematological systems tend in themselves to function according to deterministically correct parameters.

For example, in inflammation, thrombosis, atherosclerosis, hyperplasia, and endocrine disorders, it often proves possible to identify not a primary defect of the system itself but a defect in the system's regulation. Thus, the platelet, even when it causes a thrombus, is doing its job, as are thrombin and fibrin. The macrophage, when it engulfs oxidized lipoproteins, is doing its job (scavaging), even if this then causes an accumulation of foam cells in the tunica intima of the artery. It is true that a particular genetic defect may cause the pathological event (for example, a lack of C/S proteins in thrombosis or lack of LDL receptors in atherosclerosis), but more often than not, in practice, such genetic defects are neither marked nor decisive. Furthermore, every disease, even if primarily genetic, depends to a large extent in its clinical course on the occurrence of regulatory imbalances, inasmuch as the system would tend to counteract every defect with an adequate compensation mechanism.

When reflecting on the question of disease, one problem that immediately springs to mind is understanding which of the various events observed are primary and which secondary: not everything in the disease process is pathological, in the sense that it is damaging. Disease is disorder, but it nevertheless obeys certain laws and thus embodies some measure of order, though this is conditioned by chance events. The homeostatic biological systems that govern health are the same that cause most pathological phenomena when activated inadequately, excessively, or unsuitably in relation to the circumstances. On the other hand, it is also true to say that many phenomena that are called pathological are biologically useful (even if they cause pain), representing a stage of transition to a state of greater vitality, energy, and resistance to pathogens (= information gain). For instance, we need only mention inflammation and immunity, both of which are pathophysiological processes which, though carrying a certain price to be paid in terms of subjective symptoms and possible organ damage, in actual fact serve the purposes of repairing, defending, and inducing a state of enhanced resistance. This enhanced resistance derives from the biological memory of past experiences.

These considerations lead us to our first conclusion: judging what is useful and what is damaging, on every occasion and in every aspect of disease, is by no means easy, in that it presupposes a knowledge of the "logic" of disease and normality, a knowledge of the languages of complex systems (some of these systems are inflammation, immunity, neuroendocrine organizations, subtle metabolic regulatory mechanisms) rather than of the language of molecules. Disease is a problem of molecules but, also in a different dimension, it is a problem of cells, of physiological systems, and of the human being as a whole: if the molecular disorder is not compensated for by supramolecular systems, it is the latter that are responsible for the disease, and not the molecule. Disease is a problem of the individual, but it is also a problem of the environment: the individual is often the victim of a disease greater than him- or herself (for example, violence, pollution, epidemics, misinformation by the mass media, social alienation, loneliness), and whoever reflects on the real nature of diseases can hardly be satisfied with a reductionist explanation that fails to go beyond the latest biochemical consequences of these problems.

If disease is an information disorder of complex systems, then to get to the heart of the matter, the molecular approach, which analyzes only one aspect of information, is necessary but not enough. New approaches, new models, and new concepts are beginning to be introduced in biology in order to overcome this hurdle. It is not enough to understand the individual elements and try to put them together according to a computer-aided or cybernetic model: no one believes any longer that the formulation of a precise, predictive model, capable of taking account of all the variables involved in a single cell, is remotely feasible, not to mention the even unlikelier construction of exact models for the functioning of organs or systems.

If we want to capture in a single image the whole crux of the problem of information regulation in vital processes, and thus also of its pathological aspects, it may be illuminating to refer to the model of an orchestra. The orchestra is the body, and the music is its life. In the orchestra there is a material, "molecular" part, composed of instruments with precise structure and of musicians with their receptive, elaborative, and motor capabilities. What matters most, however, is that the orchestra plays in harmony according to a program provided by the score and at a pace dictated by the conductor. A performance may prove unsuccessful because one of its material parts breaks (the strings of a violin, or the stool of one of the musicians), but it may also fail because the various musicians are in discord. The quality of music the orchestra produces depends on conditions such as the

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quality of the instruments, the quality of the score, the skill of the conductor, and above all else, the degree of union and harmony between the members. If there should be interference due to some outside noise or disturbance, or if an orchestra is tired or distracted, there is a risk that the orchestra will play out of tune, and this risk is all the more serious the less able the conductor is to keep the orchestra under control. If the music is seriously out of tune, or the conductor is weak, the flaw may involve the entire orchestra to the distinct detriment of the work as a whole.

This example shows us that an information disorder can also arise as a result of subtle and not immediately perceivable deviations from the norm, which are then amplified and/or stabilized by adaptation and positive feedback mechanisms. In the healthy body this orchestra plays continuously in a coordinated manner. It is difficult to say whether there is a "conductor" because all parts, including the brain, function properly, influencing one another reciprocally. If, however, the coordination is lost—that is, the *connectivity* of a system as a whole and in relation to the rest of the body—certain subcomponents may oscillate in an excessive, unpredictable and pointless manner, thus generating localized disorders that may, however, be amplified. Oscillation thus becomes disorder and takes on the aspect of disease, in that it causes the emergence of substantial symptoms and damage. In a complex system, loss of communication and of connections means pathology. Thus, the major goal of the medical intervention is to reestablish proper communications, helping the self-organization process (healing) of the organism.

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From Mach's Principle to Human Health: A Multiscale Model of Homeostasis

Michael Conrad

Given the question on the floor—the meaning and role of energy and information in the context of biology and medicine—it is perhaps useful to recall that the post-Galilean development of physics witnessed a long-running dispute about the proper measure of "quantity of motion." One school advocated mv, now known as momentum. A second supported $mv^2/2$, now known as kinetic energy. Eventually it was recognized that conservation of momentum is associated with symmetry of spatial translations, while conservation of total energy (potential as well as kinetic) is associated with symmetry of time translation. Later, with the advent of relativity, energy and momentum could be seen as aspects of a broader energy-momentum tensor. Concepts as seemingly diverse and independent as inertia and heat could be subsumed under a single principle.

On the surface it might appear that the current debates over the proper definition of information foreshadow a similar development of useful distinctions and eventual unification. The situation is different in a basic respect, however. When systems reach a certain level of complexity, complete and precise description becomes impossible. Abstractions and frameworks that capture different aspects of the territory are inevitable. It is not so easy for the sociologist, the biologist, the thermodynamicist, and the semiotician to transform to each other's shoes.

Shannon's concept of information as the difference between initial and final uncertainty is quite commonly criticized as not doing this or that job. Nevertheless, it robustly retains its status as the most commonly used definition of information. The reason, I believe, is that its alleged vice is its virtue: it is a naked definition, unbound to any particular framework. Its content derives from the procedure for binding it.

I will here resist further comment on these conventions and procedures (discussed at length in my book on biological adaptability [Conrad 1983]). Instead, I will give some indication of the framework in which I cast these technicalities

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