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FULL ARTICLE

Are Diseases the Best Possible Response of the Complex Living System to Stimuli?

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The present study examines the core concepts of the complex systems (CSs) and the relationship between our CSs and the environment and its agents. By using the concepts of modulation of behavior, reorganization, autopoiesis, and heuristic learning, it is argued that activity and response of an organism to different stimuli are its best possible outcomes. Thus, a disease is not something that befalls the body, but rather it is an active and dynamic set of processes carried out by an organism. A disease manifests as the best response to external and internal stimuli when relativizing the "best possible answer" to the following four factors: stimulus type, environment surrounding the system, system predisposition, and system state at the time of the stimulus. This vision could alter our theoretical and therapeutic approach to diseases.

Key words: Complex systems, Health, Disease, Heuristic learning, Self-organization

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INTRODUCTION

This study proposes a new systemic way to explain the organizational logic of our organism and to rationalize the ideas around the concepts of "health" and "diseases." To better understand healthy and ill living beings, we need to develop a new frame of concepts; the framework used in this paper is that of complex systems (CSs). Presently, a linear, rather than complex, logic is used for underpinning the pathophysiological processes, focusing on a singular microcompartment of the organisms at a time while ignoring the events occurring in other compartments. The problem with the approach to CSs is logical: in the linear logic for a cause, there is a consequence or an effect; to a premise *P* follows a conclusion *C*, and these two parts of the sentence constitute an argument. In a complex logic, this linearity is limited to certain subcategories and phenomena or it may even be absent. In CSs, interdependent subsystems interact, thus influencing each other. The mechanism of cause or the agent (result or action) is not always clear, and, moreover, it is not predictable but only later observable. We can locate and describe a relationship between two different phenomena, but often we cannot figure out what is the cause and what is the effect. Phenomena relate to each other in a circular, nonlinear, and recursive (repeated on itself) fashion. This is done mainly, but not only, through feedback circuits. Using this complex logic is crucial in approaching disease, diagnosis and management. This process will foster the development of new therapeutic strategies, particularly for chronic diseases.

In fact, if we search for a direct cause of disease (such as a receptor or molecular dysfunction or a gene mutation), we focus on only a singular pathophysiological aspect, not considering the other collateral cascades of events that are crucial to determine system response. Similarly, treating only a single molecular problem with the same linear approach produces only partial results. This allows one to disregard some pertinent features and the totality of processes involved will not be discovered. This can explain why, for example, a chronic disease tends to often worsen over time despite pharmacological intervention. Another example is targeted cancer therapy: if the treatments involve local mass only, later relapses are often followed. If we integrate the whole spectrum of a living system with its complex logic and chaotic behavior, we will realize that the cascade of events brought in by an administered drug is wider and deeper, and its effects on the CS are more hierarchical. It is better, therefore, to take into consideration this complexity in organizations for more efficiency and accuracy in underpinning the pathophysiological events. With respect to diseases, new systemic observations and considerations are needed to improve our theoretical and clinical frameworks. Observations that lead to reductionism should be integrated with a system-oriented inference.[1] More specifically, there is a necessity to develop multilevel research that can correlate all the observables, all the processes that generate them[2] (through the central role of the immune and nervous system), and the microscopic singularity. This approach will allow a holistic view of the living system that can integrate reductionism. It has the advantage to elevate the level and increase the precision of knowledge acquisition; however, the alternative to this vision is to render the whole integration and understanding of the observables impossible, i.e., ultrareductionism. To make an analogy, reductionism is the process by which we analyze the individual pixels that make up a letter; however, it must be accompanied by an analysis of the sentence to decode the message.

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OPERATIONAL DEFINITION OF TERMS

The organism faces a wide range of environmental or external modifiers, which determine its activity alongside the genetic codes and other internal factors (see the analysis below). The terms *agent* and *stimulus* are used here interchangeably. In this context, the word *agent* is correct and precise; for example, there is the pathological or etiological agent (without any connotation to artificial intelligence). I avoided the use of the word input because a CS is not analogous to computational, linear, mechanical, and pure algorithmic response of the type: input, algorithm, and output. An agent (or stimulus) cab be anything that the system has contact with and is influenced by; this includes every factor that can be decoded by the system and to which it can also respond. Examples of stimuli for human beings can be any microorganism, the alterations in the intracellular or extracellular electrolyte concentration, etc. A therapeutic drug is another type of environmental stimuli. Therefore, the system reacts to it actively. This means that after taking the drug, the system will recruit a new response network with new rules. If the drug-induced response network is not compatible with the framework governing the disease process, the organism will not stop the aberrant process following drug administration, but will recruit a new response network to react to it. So, we have in this case two actively competing response networks, one for the disease and one for the drug. Why are CSs so peculiar? And especially, what are the governing rules and concurrent patterns that are useful to understand weather the disease is the best response of our living CS to internal and external stimuli?

Complex System

The CS is a dynamic, organized, and ordered entity composed of many elements that interact with each other.[3] Examples of CSs are living organisms in general, ecosystems, and social and economic systems. My argument will focus on the human CS. Of all the basic characteristics of CSs,[4] the most important ones will be cited in this paper for the sake of argument and to answer the central question of interest. Understanding these characteristics is helpful to realize whether the behavior of CS in any given setting is the most efficient and effective one.

Modulation of Behavior

A CS is capable of reprogramming itself, adapting its behavior to avoid errors and thus to learn from its mistakes. Learning is because of trial and errors and consequential modifications. It is a heuristic process (explained below). In this process of learning and modification, the best possible responses to unfamiliar stimuli are selected. Modulation of behavior through heuristic learning is the basis of the argument presented here. A CS, therefore, is capable of learning from the environment and its own reactions by developing the optimum responses and diverging itself from the deviant, degenerated, and ill behavior.

Interaction with the Environment

Complementary to the inner variations and optimizations of response, a CS can directly act on the environment in order to modify it.

Repair (Autopoiesis)

A CS repairs the inflicted damage. The term "autopoiesis" was first coined by Humberto Maturana.[5] An autopoietic system sustains and replaces all its components in a way that continually redefines itself. This can be represented as processes, a network of construction, transformation, and recycling of structures, which, through mutual interactions, regenerates and continuously supports the system itself.

Reorganization (Ontogeny)

A CS re-manages its internal structures to adapt to newly raised situations. This feature is typical of social, biological, and psychological systems. The ontogeny is a set of processes by which a CS accomplishes the biological development of a living organism from embryonic to adult stage: it depends both on its intrinsic sets of rules and on the environment in which the ontogenic process takes place. The environmental variations correspond to an internal restructure that occurs in accordance with the system's rules, the nomologia. The nomos of the system—*νομüς*, the laws or a set of rules—are continually updated in response to encountering an environmental agent that elicits a reaction within the organism.

Within the CS, the single parts are involved in local interactions and these cause changes in the overall organization. For example, in case of acute and chronic pain, the intense thermal, mechanical, or chemical stimuli are detected by a subpopulation of peripheral nerve fibers, the nociceptors.[6] Primary afferent nerve fibers project to the dorsal horn of the spinal cord, and then the stimulus is carried to the brain. With acute and intense activation of the nociceptor, there is a very quick response through protective reflexes, which aims to leave to the noxious agent as fast as possible. If the injury persists, there occurs great plasticity, in pain transmission pathway, within both peripheral and central nervous system.[7] In this case, a chronic pain condition may result from a state of hyperexcitability in the central nervous system and consequently enhanced processing of nociceptive signals,[8] and can lead to depression[9] and cognitive difficulties.[10]

A CS comprehends internal or intrinsic and external or extrinsic stimuli and reacts to them through its own rules of dynamic response, thereby triggering a network of processes. A stimulus produces a punctiform boundary process, with an initial small variation, that then allows responses in a diffusibility pattern, usually because of expansive processes. An example is acute inflammation. Once the pathogenic molecules are recognized by receptors, inflammatory cells undergo activation. They release inflammatory mediators; this causes clinical signs of inflammation and alteration of blood vessels, in order to permit the migration of leukocytes outside the blood vessels into the tissue.[11] At the same

time, there are several biochemical cascade systems that consist of preformed plasma proteins. They act in parallel to initiate and propagate the inflammatory response.[12] This ensemble of processes is here referred to as a system response.

From such a process arises observables. Indeed, the process involves the system reaction in its entirety: the system restructures itself and gives rise to a new network (so a new nomos). That means (1): even local small events may have repercussions at distance and (2) each little variation can amplify itself or get amplified. From one initial local event can arise a cascade of events that spreads to the whole system. In fact, the ensemble of all the system elements has the property to behave like a unitary element in relation to the environment, like it would be without internal subdivisions and compartments. This means the subunits of the system react in unison when they face an extrinsic environmental stimulus. The same may happen on encountering an internal stimulus.

Observable events are closely linked to the observer who may not be able to fully understand or capture them. It is the infinitesimal inaccuracy in the knowledge of the initial conditions and system parameters that could lead to inaccuracy in the knowledge of its future behavior. Knowing the exact initial conditions of the CSs is not feasible owing to its dynamic nature. As such, their future behavior cannot be precisely predicted. For example, two identical stimuli at two different times may elicit different responses,[13] meaning that the knowledge of stimulus is insufficient to provide the type, modality, and order of magnitude of the response. The response of a CS to a stimulus depends on its potential at that precise moment of encountering the stimulus. The precision of any predictive model is therefore directly proportional to the accuracy and completeness of the equations and related calculations we use to describe a CS.

CSs are self-organized systems. Self-organization is the appearance of regular patterns and networks, not directly imposed from the outside, but self-assigned and self-built by the system.[14,15] Organized behavior is an emergent and spontaneous property arising from the local nonlinear interactions between the subcomponents of the system.

In the emergent process, the system exhibits properties that cannot be arisen and predicted from the behavior of its components—if observed individually. Here falls the reductionist epistemology, with emergence and chaos intervening between deterministic processes. With the emergent behavior, a new level of systemic evolution and organization is realized. To build it, two characteristics are necessary: a large quantity of interactions and their proper hierarchic and complex organization. Without a high level of efficiency and organization, the connections would generate only "noise" and no tangible evolution of systemic state. The hierarchization that optimizes the organization is a facilitating factor in the emergence. It seems that the system should achieve the right combination of organization, diversity-specificity, and connectivity before it can present the emergent behavior. This is also very important because we realize that our system is very integrated, organized, and efficient, and these characteristics are part of the explanation of the phenomena we observe. The range of hierarchic systems goes from the particle physics level to the atomic physics one to the chemical and physiological layer. The last level includes emerging and observable phenomena in systemic processes that involve the entire organism.[16] We need to verify the kind of emergence to understand how to optimize and control this dynamic multiarray system. To do this, one needs to recover the concept of complementarity. Action is built by complementary components that bind the internal environment with the external one.

A fundamental peculiarity of a CS is that its properties do not correspond to the algebraic sum of the properties of the individual components.[17] This means that we can model every part of the system by using determinism and reductionism, but we cannot calculate the sum of their actions and the related consequences. This is because the system behavior is not deterministic, but rather chaotic and with expression of the emergent properties. The gradient between the algebraic sum between the individual automata and the final realistic persona of the system is because of the regulatory and dynamic processes that coordinate the different parts and compartments.

Thermodynamic Disequilibrium

If we go further in our physical explanation and we speak about thermodynamic equilibrium, the system is far from the thermodynamic equilibrium.[18,19] As long as there is interaction with the environment and a response (through system deformation, reorganization and restructuring), there is life. If the system stops learning, reacting, and reforming itself, it dies. With death, the thermodynamic equilibrium is reached. The system tries, even during diseases, to maintain the maximum possible energy and the lowest entropy; it tries to maintain its organization and efficiency.[20]

Summarizing the concepts so far discussed, CSs respond to every stimulus through propagation of prearranged but nondeterministic (unpredictable) mechanisms, but these are relative to the system state at that moment of encountering stimulus and the characteristics of the stimulus (e.g., type and duration). The constantly changing answer always involves the entire system. Even diseases that are considered to be local such as skin eruptions are preceded by a complete renovation of the system resulting from the change in its nomos. This is a proof indicating that to understand a CS requires adopting a systematic and holistic approach to observation.

The more punctate and precise the stimulus is, the larger the systemic response to it will be. It seems a paradox, but in CSs, a punctiform agent at the boundary, placed in conditions to be influent, will trigger a broad, organized, coordinated, harmonious, and coherent response. This happens because of two reasons: first, a punctiform agent is capable of penetrating deeper into regulative structures, and second,

through deterministic chaos and continuous iterative cycles, a minimum initial variation can cause a great divergence within CSs, finally resulting in a greater shift in the system.

The system that elegantly illustrates this concept is the immune system, which, together with the nervous system, is the first responsible for the contact with the agent and the consequent reaction. For example, induction of a specific immunity after contact with a microorganism leads to the morphological change of the antigen-presenting cell, which stimulates the activation of T lymphocytes. From a boundary agent (i.e., the microorganism), there is an initial variation, which then activates the immune system processes through reaction/diffusion networks. The response is generalized, causing observable symptoms, such as chills and asthenia, and observables signs, such as fever. The response profile partially depends on the stimulus and it partially is a property of the system. This means, CSs exhibit heterogeneous spectrums of responses. Heterogeneity has two consequences: the first is increased instability, with the consequent sizable fluctuations in response to external stimuli due to positive feedback loops that amplify the cascade of events,[21] and the second is specific individualized answer patterns. This point needs to be carefully considered. In fact, all the biological systems show a high level of heterogeneity. In contemporary biological and medical research, there is the tendency to search for standard patterns and emphasize on them. There is the risk for avoiding this heterogeneity by considering it as only "noise" that disturbs the study results. It is instead worthy of further scrutiny, as diversity is a sign of flexibility and allows us to better understand all the possible, species-specific response patterns. As such, this concept encourages the development of precision, personalized medicine.[22]

It is important noting that infection is defined as the reaction of the organism to microorganisms. This implies that a given system is susceptible to a type of stimulus at any given time and that it develops a response under only certain circumstances. Its individual susceptibility determines the reaction rather than the "wicked action" of the microorganism.

This example shows a systemic nomos (aspects that regulate the immune system), which forms a network of responses and processes (activation of the acute immune cascade) and finally, in case of disease, it culminates in signs and symptoms. In general, the defense of CSs uses the following three tactics:

1. Elimination of the pathogenic agent: the system tries to kill and to eliminate it. This happens, for example, with the elimination of virus and bacteria through the flushing effect of diarrhea during enteritis.
2. Blocking the agent: the system prevents its replication, which might have unwanted districts.
3. Isolating the agent: the organism creates a closed compartment to isolate the stimulus, avoiding colonization. Examples are cystic degeneration with fibrous wall formation or granulomatous reaction.

Heuristic Learning

Maturana and Varela state that living systems are cognitive systems, and living is a process of cognition.[23] According to this view, knowledge and learning abilities are the properties of CS that have effects on the whole system, not only on the nervous system, or the brain. For example, the immune system is delegated to knowledge, then recognition and response to pathogens, in a mechanism in which innate immunity (the most primitive) and the acquired one (more modern from an evolutionary point of view and more specific) interweave. The selection of antibodies is carried out by heuristic learning.

In fact, our system learns heuristically,[24,25] by selecting the best response through casual attempts and corrections (trial and error). As we have seen, cognition is an intrinsic phenomenon of the whole organism. Cognition is perpetrated by not only the nervous system but also the immune system, by totality of the cell receptors in the body and by the networks in between the apparently distinct systems. It can be assumed that heuristic learning involves the whole system. Heuristic learning provides the selection of the best response through random initial organization. After this first step, the next most appropriate answer is selected through trial, and eventually through error, its recognition, and a consequent new, optimized action.

In the brain, heuristic learning takes place through a first attempt in random synaptic connection, which can be flawed as accurate. After the first attempt, a second one is carried out (albeit randomly again). If this result is better than the previous one, it is reinforced. After that, the brain continues in this way. The ability to consistently learn and optimize the process of response selection results in further attempts at selection to be increasingly effective and accurate. With this dynamic and continuous modification of the learning network, the system would always guarantee the maximum efficiency at a given moment. This means that it not only learns but also improves its learning process.

Each subsystem can learn and improve its response to stimulus. For example, this happens during an infant's weaning process, when the digestive system, and especially the intestinal immune system, learns to gradually digest regular foods.[26]

To exemplify the learning that generates the selection of best response, we shall consider a brief overview of the process of maturation and selection of T and B lymphocytes. In fact, the immune system selects the lymphocytes based on their fitness to the purpose at hand; it generates a range of effector cells and then favors those that are most relevant and therefore most effective.[27,28] The lymphocytes must discriminate two classes of molecules: those of the self, belonging to our body, against which a reaction must be avoided, and nonself, external ones, against which the organism has to mount a suitable response. All lymphocytes arise as stem cells in the bone marrow, then proliferate, maturate by differentiation, and then are selected. Two types of lymphocytic populations

are deleted, those that react against self-molecules and those that do not recognize foreign antigens. In the process of positive selection, the immune system multiplies the lymphocytes that are able to react against harmful external agents. The selection of the best response to stimuli takes place also on an evolutionary basis. For our species, as well as for the others, the optimization of reaction takes place with the selection from one generation to another, depending on the encountered stimuli. In the evolutionary sense, there is a combination between chance and necessity.[29]

The Disease—A Dynamic Process

A CS organizes itself and expresses the most energetically optimum processes, by which it can maintain the lowest entropy possible.[20] The main aim of life, that is maintaining itself, together with the evolutionary processes, guide the organic activity and improve it over time. So, the system implements the best possible response based on its nomos and on the type of the inciting agent. This not only takes place during healthy states but also during diseases.

According to the Cartesian point of view, the most diffused vision is that the disease is the consequence of a mechanical rupture in the organism, which we cannot repair. We can only stop the mistake, inhibiting artificially its consequences with drugs or surgery. The current vision of the organism is still mechanistic; we think of it as a machine that reacts in a mechanical way to various stimuli and it can be affected because of molecular errors that exhibit the fallacy or frailty of human beings, or vital systems in general. To use again the Cartesian's terminology, our organism does do not work like the gears of a clock, but more like the dynamical analogical movements and instantaneous variations of life's expressions. If we use this new order and clarity, we will notice that the diseases we normally treat with drugs are dynamical processes. The diseases we treat with surgery are instead mechanical processes or material macroscopic structures. Examples of the latter pathologies are fractures, trauma, articular problems.

In the majority of cases, there is a dynamical variation of the organic response, such a deregulation of a procedure, a lack in elasticity and capability of response, a hyperactivation or at the contrary an underactivation of reactions.

Disease is currently defined as a natural phenomenon that occurs in a living system with the consequential structural and functional alteration of a cell, a tissue or an organ impacting on the general state of the organism.[30] It is also known as a dynamic state that alters the normal homeostasis, or as the absence of health.

In philosophy of medicine, there are some mainstream theories that define a state of disease.[31–40] Through the premises and concepts developed so far, disease is not a phenomenon that befalls the body, but it is rather the organism's new structure developed after processing the inciting stimulus. As we have discussed, the system—through its nomos—responds to stimuli proactively, with a sequential dynamic systemic restructuring. Moreover, the present hypothesis suggests that many diseases are caused by environmental pathological agents that can elicit indirect effects, even years after from the initial exposure. With this hypothesis in mind, we can also understand phenomena that we tend to attribute to systemic malfunctions, which we now think are intrinsic to the system. Instead, it is the coupling between the organism and the environmental agent that causes the organic response. Because of the pathogenic nature of the agent, and its persistence, the coupling with the system causes loss of efficiency, consistency, dynamism, and flexibility in the system. The system's response becomes less ordered and entropy increases. The coupling between the system and an external agent recursively interacting with it is called structural coupling.[41] Structural coupling leads to spontaneous reciprocal changements in both the CSs and the environmental agent. If the agent is harmful, the CSs integrate negative perturbations from the stimulus into its own processes. Consequently, the response and dynamic patterns worsen.

In pathology, the observable expressions are symptoms. Symptoms are of fundamental importance in our observation of the system, together with other objective observables expressions. In fact, usually the same agent produces similar symptoms (for example, a viral infection that causes flu with fever, chills, weakness), but we need to concentrate on the peculiar ones. These are individual unusual symptoms that characterize the answer. For example, the lack of thirst, the restlessness, or the desire to uncover during fever. With these symptoms we could formulate a precise and individualized therapy.

At this point, we have established that disease is the body's response to stimuli through the use of its rules and the structure of a new network. Therefore, it is an ensemble of active phenomena and a cascade of events that leads to external observable. This statement leads to the following question: What is the difference between physiology and disease, which brings us to the next topic.

The Disease: The Best Possible Response of Complex Living System to Stimulus

There are four factors that determine the sort of the systemic response:

1. The predisposition of the system – this involves the genetic heritage and the immune system assets.
2. The state of the system at the time (t) when it meets the stimulus. It reflects the continuous and dynamic systemic changes. The state of the immune system plays a fundamental role. With the same predisposition and genetic pool, a system that faces various stresses or in different periods will express networks and processes peculiar to those moments. This happens because of heterogeneous behavior of CSs, depending on a lot of variables.

   The sum of these two points determines the susceptibility of the system to different types of agents faced at the time t.
3. The type of the stimulus/agent.

4. The environment where the system and the stimuli are placed.

Throughout its evolutionary history, our organism has optimized its response network. Thus, through heuristic learning and deterministic chaos, it has developed numerous various, specific, precise, and efficacious response patterns. It can be said that the individual response to a stimulus is the only thing possible for the system, i.e., the best option for it. Also, it is important to point out that diseases are not extinct despite the selection of the best answers through evolution and heuristic learning. This is because the environmental conditions and the pathogenic agents are not fixed and are subject to change and evolution.

Needless to say, that the best condition is the healthy one; however, when considering the four variables we can still say that the disease is not the worst possible answer. The combinations of the four variables define the type of the body's response and bring about two options: either a reaction to the agent or not.

If the agent is incompatible with the organism's system, it will not react to it because it will not perceive it. This is the case, for example, of some animal viruses that do not infect humans. On the other hand, if the agent is recognized, the body will react. At this time, there are two possible consequences:

1. The body reacts in a healthy way: the answer is appropriate and remains in accordance with the possible desirable reactions to this specific agent. This implies that the body can overcome autonomously the external perturbation and returns to its previous condition.

   Even if the system is in good condition and reacts with its fullest potential, it will not be able to counteract the very powerful and destructive stimuli. The contact with a very pathogenic agent can inhibit and destroy the normal functions of the system or the different compartments of the body. In this case diseases imply the destruction of the body's organic functions, and they can be even life-threatening. Examples include the Ebola virus, or high-intensity radiations. In these cases, even if the system was healthy before the contact or the proximity with these agents, it would not have a chance to overcome the disease independently.
2. The organism develops a disease that can occur when the system status is not in the best of condition, in the presence of specific predispositions, and with certain pathogens. In this case, there can be a hyporesponse, a hyperresponse, or a disorderly response. This condition causes the opening of nonoptimal networks, which do not complete the processes in the most efficient, ordered, and quick way, thus leading to the emergence of other secondary symptoms and impaired functions. The organization of the system and its regulatory network worsens. The system will not be able to get back to its healthy previous functions without external help and treatment.

   However, the abnormal answer of the system is not always disadvantageous. For example, the majority of Native American Indians died after contracting viruses and bacteria of the European colonists, but small minority of them developed an out of the norm answer that led to the advantageous survival. Thus, this was an out-of-the-norm answer, but it brought an advantage to the population. This condition is the exception of normalcy: we cannot call disease the answer out of the norm of the possible reactions when it brings an advantage. In fact, the disease is just the out-of-the-norm answer that brings a disadvantage to the system.

   Population biology studies the factors that influence a population. The importance of the environment and its agents in fitness and survival of a population,[42] and in changing the genetic pool during different generations, is already known.[43] The genetic changes within a population can be responsible for disease initiation, progression, and maintenance.[44] This is consistent with the conceptual frames of CSs and structural coupling.

   This precision in the types of responses, according to the body conditions and the type of pathogen, does not detract from the central assumption that the disease is an organism's best response at a given time according to its possible reactions to a given stimuli. Without a doubt, this is an active system that tries to maintain the lowest possible entropy.

   As to the analysis of the second point, considering what happens when the body develops an illness. In the sick organism, the new state of the system after the acute phase owing to the contact with a pathogen will be a sum (not algebraic, because it is a CS and subject to nonlinear reactions) between the characteristics of the agent, the systemic state at the time of contact, the resulting reaction and the subsequent dysfunctions. A deterioration of the organic functions takes place and the disease can become chronic or terminal.

Consequent malfunctions can occur at the following two levels:

1. The ability of self-regulation and optimization of the body's response is undermined. In this case the dysfunction is systemic and deep, and it covers the regulative subsystem. This is a systemic control network, which works with physical, chemical, and energetic rules. It is at the same time global and punctate, precise and ordered; it underlies the processes we observe. This network has smaller orders of magnitude than those normally observed in the study of physiology and pathophysiology, and it is deeper.
2. A malfunction of a specific trait, or of a "local", compartmentalized function. This happens when the local structure is not able to do what the regulative subsystem orders it to do. In this case, the problem is more localized, and it can also secondarily influence the subregulatory system, which will try to compensate for this functional deficit.

According to these evaluations of malfunction, we note that there is another element that allows us to talk about the best answer: even if the system is sick, the functions that still work correctly and remain intact compensate those defi-

ciency. In this way, the system is able to continue with its vital processes. The damage due to the deficits diminishes and remains more silent for a longer period.

The hypothesis is that there are more pathologies caused by environmental or extrinsic stimuli than is now known, even in chronic cases. An immunological agent—like a virus or bacterium—can be the first trigger of a chronic disease, or rather a contributory cause of it.[45]

The following question could arise: If—according with the pathogen/stimulus type—the disease is the best possible response of complex living system, does the system never commit mistakes?

There is one condition in which the disease is an error of the system: genetic pathologies or genetic mutations. The system makes mistakes in cases of spontaneous genetic mutations. Spontaneous mutations are mutations that are not produced by known mutagens; these are due to errors in the molecular processes of DNA or RNA. Usually they alter one or a few pairs of bases of a nucleotide sequence. They are very rare and occur, on average, once every 10^6 or 10^8 nucleotides.[46] This means at least 50,000 molecular lesions every cell every day.[47] If they happen in somatic cells, some of these mutations can make the cells malignant, and therefore, cause cancer. If they relate to cells of the gametes or germ lines can cause heritable genetic diseases.

Once there has been a mutation, different DNA repair mechanisms intervene. If these are ineffective, and/or mutations accumulate, the cell becomes dangerous. Then another defense system takes place: the apoptosis, which is the programmed death of defective and dangerous cells. However, if one of the mutations affects a system that controls DNA repair, or induces apoptosis, the cell becomes more susceptible; we observe substantial acceleration of genomic instability and increases the risk that it becomes cancerous.[48]

At this point, there is another "gate" (the third after repair and apoptosis)—the defense of the immune system. The NK cells (natural killer), which are part of the innate immunity, recognize as nonself cells with low expression of MHC-I such as cancer cells, inducing their lysis.[49] If NKs do not find in target cells the normal self-receptors, they can cause cell death by apoptosis. This mechanism is sometimes impaired by some tumors, like melanoma.

In conclusion, the tumor can be considered an error of organism in reconfiguring its complex, interrelated system. But is it always the case? Or is it possible that some tumors are the best answer for a given system at a given time, according to a set of pathogenic environmental agent? We can answer affirmatively to this second question.

In a research published in 2016 where algorithmic models were used, combined with a genetic approach and statistical data,[50] the authors concluded that 70%–90% of the risk for major cancer types are due to external environmental factors, like smoking, carcinogenic foods, environmental pollution, or solar radiation. Only 10%–30% of major tumors derive from multiple spontaneous mutations that are not repaired and not followed by NK reaction. This means, the intrinsic risk contributes from only 10% up to 30% of major cancers.

According to these models and data analysis, the accumulation of internal mutations would not be enough to justify the risk of cancer observed. Thus, we are facing a case where even if the system is not particularly "ill" or predisposed, environmental conditions prove dangerous for it, from which it cannot always defend itself effectively.

The pathogens (to which the body is usually exposed in a chronic way, as they are environmental factors) are too strong, too mutagenic for the organism. The system does what it can to defend itself, but require just a small change of health, physical, emotional, and mental status, to lower the activity of the immune system and to decrease the overall efficiency of the systemic response. Also in this case, it has been shown that environmental conditions are widely involved than was thought before.[51–56]

At this point, a new question arises: How can we distinguish between physiology and pathology? So, for example, where is the difference between chills after cold exposure (that are considered physiological), and chills, fever, and weakness after streptococcal infection (that are considered pathological)? Among others, there are two differences between a physiological and a pathological pattern:

- The severity/pathogenicity of the environmental agent (following the example, streptococcal infection is more dangerous than a short cold exposure).
- The consequences: in most cases, the cold exposure will not cause a durable and lasting response, so the symptoms will disappear relatively soon together with the temporary discomfort. The pathogenicity of *Streptococcus*, instead, will cause a response network with symptoms that cause discomfort and malfunction of some traits (as explained before). The malfunction can be temporary, lasting only some days, or could last longer, causing chronic symptoms and signs. In the example of *Streptococcus* are well-known poststreptococcal nephritis and arthritis. So, the consequences of a pathological response are more severe, durable. They imply lasting discomfort and malfunction.

EPILOGUE

This paper presents a coherent theory to explain the nature and dynamics of the living body as a CS and its interaction at the boundary and with external stimuli. The theory, first, explains the body as a unified dynamic structure continuously in response, until death. The entire system restructures and reorganizes itself, creating each time a new network. Second, it clarifies what a disease is. Third, it shows that the body always offers the best possible answer through evolution, complexity rules, and heuristic learning. Compatibly

with the four factors analyzed (predisposition, system status at a given time, agent type and environmental characteristics), the organism always produces the best possible reaction. This means that the disease is the best possible response for that individual organism at that time with that agent.

This approach will provide a theoretical background for more holistic therapeutic strategies. The consequence would be to administer therapy to optimize a regulatory subsystem that determines the response network, without focusing on single molecular problems.

We are now blocking one malfunctional aspect of the systemic response at time. But if the disease is the best possible response of our complex living systems, we would need to stimulate and regulate the entire system rather than blocking its malfunctions. Through new types of medicaments and therapies, we would encourage heuristic learning, to stimulate self-healing. Systemic efficiency preservation after illness and resolution of the totality of the symptoms should be the first target in the treatment of a disease. If this model is analyzed in depth and carefully, it could lead to a deep, thorough, and overall change in medicine and in the actual method of curing.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Anderson PW. More Is Different. **Science** 1972; 177(4047): 393–96.
2. Barabási A-L, Gulbahce N, Loscalzo J. Network Medicine: A Network-Based Approach to Human Disease. **Nat Rev Genet** 2011; 12(1): 56–68.
3. Bodenschatz E. *Complex Systems*. Available from: URL: https://www.mpg.de/36885/cpt08_ComplexSystems-basetext.pdf. Accessed 2009.
4. Bettelli O. *Modelli per Sistemi Complessi*. Brescia, Italy: Starrylink, 2004.
5. Maturana H, Varela F. *Autopoiesis and Cognition: The Realization of the Living*. *Dordrecht, Holland; Boston: D*. Reidel Publishing Company, 1980.
6. Basbaum AI, Jessell T. *The Perception of Pain*. In: *Kandel ER, Schwartz J, Jessell T (Ed.). Principles of Neuroscience*. New York, Appleton and Lange; 2000: 472–491.
7. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and Molecular Mechanisms of Pain. **Cell** 2009; 139(2): 267–284.
8. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. **Nature** 1983; 306: 686–688.
9. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. **Neural Plast** 2017;2017:9724371.
10. Mazza S, Frot M, Rey AE. A comprehensive literature review of chronic pain and memory. **Prog Neuropsychopharmacol Biol Psychiatry** 2017. Available online 8 August.
11. Kumar R, Clermont G, Vodovotz Y, Chow CC. "The dynamics of acute inflammation". **J Theor Biol** 230(2): 145–55, 2004 Sep 21.
12. Cotran RS, Kumar V, Collins T. *Robbins Pathologic Basis of Disease*. Philadelphia, W.B Saunders Company, 1998.
13. Mosmann TR, Coffman RL. TH1 and TH2 Cells: Different Patterns of Lymphokine Secretion Lead to Different Functional Properties. **Annu Rev Immunol** 1989; 7(1): 145–173.
14. Bennett CH. Dissipation, Information, Computational Complexity and the Definition of Organization. Santa Fe: Proceedings of the Founding Workshops of the Santa Fe Institute: PINES, D Ed, 1985.
15. Kelso JAS. *Dynamic patterns: the self-organization of brain and behavior*. Cambridge, MA: MIT Press, 1995.
16. Barabási AL, et al. Scale-Free and Hierarchical Structures in Complex Networks. In AIP Conference Proceedings, 2003; 661: 1–16. AIP Publishing.
17. Kane EA, Higham TE. Complex Systems Are More than the Sum of Their Parts: Using Integration to Understand Performance, Biomechanics, and Diversity. **Integr Comp Biol** 2015; 55: 146–65.
18. Prigogine I. Time, Structure, and Fluctuations. Science 201 (September):777–785, 1978.
19. Prigogine I, Stengers I. *La Nouvelle Alliance: Métamorphose de La Science*. Paris, France: Gallimard Editor, 1979.
20. Prigogine I. **Bull Acad Roy Belg Cl Sci** 1945; 31: 600.
21. Miller JH, Scott E. *Complex Adaptive Systems: an Introduction to computational models of social life*. Princeton, Princeton University Press, 2007.
22. Hillger JM, Lieuw WL, Heitman LH, IJzerman AP. Label-free technology and patient cells: from early drug development to precision medicine. **Drug Discov Today** 2017; S1359–6446(17)30153-8.
23. Maturana H, Varela F. *The Tree of Knowledge: The Biological Roots of Human Understanding*. Boston: Shambala, 1987.
24. Fukuda T, Kohno T, Shibata T. Heuristic Learning by Genetic Algorithm for Recurrent Neural Network. Proceedings of IEEE 2nd International Workshop on Emerging Technologies and Factory Automation 1993; 71–77.
25. Satinover J. *The Quantum Brain: The Search for Freedom and the Next Generation of Man*. New York: John Wiley & Sons Inc, 2002.
26. Mermiri DT, Lappa T, Papadopoulou AL. Review suggests that the immunoregulatory and anti-inflammatory properties of allergenic foods can provoke oral tolerance if introduced early to infants' diets. **Acta Paediatr** 2017; 106(5): 721–726.
27. Ribatti D. Sir Frank Macfarlane Burnet and the clonal selection theory of antibody formation. **Clin Exp Med** 2009; Dec 9(4): 253–258.
28. Smith KA. The quantal theory of how the immune system discriminates between "self and non-self". **Med Immunol** 2004; Dec: 17;3(1):3.
29. Monod J. *Chance and Necessity: An Essay on the Natural Philosophy of Modern Biology*. London: Penguin, 1997.
30. Definition of Disease. Available from: URL: http://www.biology-online.org/dictionary/Disease. Accessed September 29, 2008.
31. Saborido C, Moreno A. Biological Pathology from an Organizational Perspective. **Theor Med Bioeth** 2015; 36(1): 83–95.
32. Wachbroit R. Normality as a Biological Concept. **Philosophy of Science** 1994; 61(4): 579–591.
33. Sedgwick P. *Psycho Politics: Laing, Foucault, Goffman, Szasz, and the Future of Mass Psychiatry*. New York: Harper & Row, 1982.
34. Margolis J. The Concept of Disease. **J Med Philos** 1976; 1(3): 238–255.
35. Engelhardt T. *The Foundations of Bioethics*. New York: Oxford University Press, 1986.
36. Goosens WK. Values, Health, and Medicine. **Philosophy of Science** 1980; 47(1): 100–115.
37. Reznek L. *The Nature of Disease*. London: Routledge and Kegan Paul, 1987.

38. Caplan AL. *If Gene Therapy Is the Cure, What Is the Disease?* In: *Gene Mapping (pp. 128–141), G. Annas and S. Elias (eds.)*. Oxford: Oxford University Press, 1992.
39. Wakefield JC. The Concept of Mental Disorder. On the Boundary between Biological Facts and Social Values. **Am Psychol** 1992; 47(3): 373–88.
40. Ereshefsky M. Defining 'Health' and 'Disease.' Stud. **Hist Philos Biol Biomed** 2009; 40(3): 221–27.
41. Maturana HR. Autopoiesis, structural coupling and cognition: A history of these and other notions in the biology of cognition. **C&HK** 2002; 9(3–4): 5–34.
42. Méndez V, Campos D. Population extinction and survival in a hostile environment. Phys Rev E Stat Nonlin Soft Matter Phys. 2008; Feb;77(2 Pt 1):022901.
43. Orr HA. Fitness and its role in evolutionary genetics. **Nat Rev Genet** 2009; 10(8): 531–9.
44. Mones AA. Microarrays Need Phylogenetics. Sci Signal. 2008; Dec 23: 1(51): eg11.
45. Diani S. A new model for chronic diseases. **Med Hypotheses.** 113:30–39, 2018; Apr.
46. Nachman MW, Crowell SL. Estimate of the mutation rate per nucleotide in humans. **Genetics** 2000; 156(1): 297–304.
47. Harvey L, et al. *Molecular Cell Biology*. 5th ed. New York: W. H. Freeman, 2000.
48. Torgovnick A, Schumacher B. DNA repair mechanisms in cancer development and therapy. **Front Genet** 2015; 6: 157.
49. Marcus A, Gowen BG, Thompson TW, Iannello A, Ardolino M, Deng W, et al. Recognition of tumors by the innate immune system and natural killer cells. **Adv Immunol** 2014; 122: 91–128.
50. Wu S, Powers S, Zhu W, Hannun YA. Substantial Contribution of Extrinsic Risk Factors to Cancer Development. **Nature** 2016; 529(7584): 43–47.
51. Singer AC, Shaw H, Rhodes H, Hart A. Review of Antimicrobial Resistance in the Environment and Its Relevance to Environmental Regulators. **Front Microbiol** 2016; 7: 1728.
52. Zhang S, Wei Z, Liu W, Yao L, Suo W, Xing J, et al. Indicators for Environment Health Risk Assessment in the Jiangsu Province of China. **Int J Environ Res Public Health** 2015 Sep; 12(9): 11012–11024.
53. Villanueva K, Pereira G, Knuiman M, Bull F, Wood L, Christian H, et al. The impact of the built environment on health across the life course: design of a cross-sectional data linkage study. **BMJ** 2013; 3(1): e002482.
54. Mmari K, Lantos H, Brahmbhatt H, Delany-Moretlwe S, Lou C, Acharya R, et al. How adolescents perceive their communities: a qualitative study that explores the relationship between health and the physical environment. **BMC Public Health** 2014; 14: 349.
55. Perna L, Bolte G, Mayrhofer H, Spies G, Mielck A. The impact of the social environment on children's mental health in a prosperous city: an analysis with data from the city of Munich. **BMC Public Health** 2010; 10: 199.
56. Ashbolt NJ, Amézquita A, Backhaus T, Borriello P, Brandt KK, Collignon P, et al. Human Health Risk Assessment (HHRA) for Environmental Development and Transfer of Antibiotic Resistance. **Environ Health Perspect** 2013 Sep; 121(9): 993–1001.