Hierarchical structure of biological systems
A bioengineering approach

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Despite the fact that life is, in some sense, a chemical phenomenon, its distinctive character is attributed to its informatics properties as a complex system that processes information. This idea is the basis for the approach proposed in this paper.

Accordingly, this work attempts to propose a general theory of biological systems, based on its principal characteristics and hierarchical structure that apply general ideas to biological systems of different sizes using principles based on energy, information and/or mass exchange. To do this, a proposed biological system definition is explained in detail. Using this definition and some fundamental propositions, we discuss the hierarchical structure of the biological systems and their structures and fundamental functions and end with a thermodynamic analysis based on the affinity of the systems.

Results and Discussion

Definition of a biological system

A biological system is a set of self-organized, differentiated components (elements) that interact pair-wise among themselves through various networks and media, isolated from other sets by boundaries called teguments and whose relation to other systems can be described as a closed loop in a steady-state.

In agreement with this definition, a living organism can obviously be regarded as a biological system, including any individual organism within (i.e., a parasite) and the organs that constitute it, as well as their organization. So this definition considers biological systems from the living molecular structures up to the level of Gaia, including cells, tissues, organelles, organic systems, human beings, races, social aggregations, species and ecological systems.

Hierarchy of biological systems

In accordance with the above definition, a biological system is formed by subsystems depending on the physical scale of the specific system. Thus, our theory establishes that the hierarchical organization of the biological systems is an intrinsic property of nature, in contrast with the standard system theory$^{9-13}$ that considers biological systems as isolated entities. This hierarchy allows study of the connections and actual and future relations, instead of analyzing only the structure at different levels.

Proposition 1. All biological systems are formed by subsystems of various orders and are part of suprasystems of a higher order.

The hierarchy of a given biological system is formed, in turn, by subsystems of various orders, depending on the physical scale of the specific system. For instance, the system called “human being” is constituted by first order subsystems, such as the endocrine, the nerve, the circulatory, the respiratory, the digestive, the renal excretory, the thermal dissipater, the sensorial, the motor, etc. These subsystems are, in turn, formed by second order subsystems: organs and tissues, which, in turn, are formed by third order subsystems: cells. Cells, in turn, are formed by fourth order subsystems, namely organelles. This also works the other way around: systems form suprasystems of first (families), second (societies) and then higher orders. Obviously, if one decides to study a particular ecological system, the individuals would be subsystems of a given order of the original system. Independent of the chosen hierarchy, the fundamental subsystem is the nucleosome (formed by a DNA segment associated to a protein nucleus) and the higher suprasystem found all the way to Gaia, the set of all living organisms on Earth.$^{17}$

For example, if we consider a human being as our base system, represented by $S_3$, some of the subsystems can be:

- the nervous system ($S_{-3}$);
- the brain ($S_{-2}$);
- the neurons ($S_{-1}$) and
- the nucleosome ($S_{-4}$),

whereas some of the suprasystems are:

- the family ($S_{-5}$);
- the society ($S_{-6}$);
- the species ($S_1$) and
- GAIA ($S_{-7}$).

If we represent with the set inclusion (i.e., all the elements of the left set are part of the right hand one) we can write the following hierarchical relation, which establishes the order of the biological system:

Corollary 1. The order of a specific biological system depends upon which system is chosen as a reference.

For example, the human being is a subsystem of the human species and is a suprasystem of the nervous system. As another example, the family is formed by humans (subsystems) and is part of the ecological system (suprasystem). Thus, biological systems are organized one inside another, forming an order from the elemental system—the nucleosome—until the general suprasystem, Gaia.

Corollary 2. “The biological systems are organized in hierarchical, interacting networks.”

The interactions between biological systems do not depend on the size of the systems, for they can occur at any complex scale, from unicellular beings up to ecosystems. Biological systems have intersecting elements responsible for the interaction between them.

An example of an inter-system biological interaction is the biochemical communication between all the cellular organelles responsible for their metabolism. On a larger scale, different biological systems can interact pair-wise through an action-reaction circuit to establish energy or food flows (e.g., the case of predator-prey in phagocytes).

All relations between biological systems have an evolutionary origin with an adaptation objective for the optimization of resources. In all cases the biological systems have established, through specific elements, life strategies and associations to maintain their viability and to ensure their replication and multiplication.

Structure of biological systems

The definition of a biological system depends on the “boundary” (tegument) that separates the system of interest from the rest of the universe. The components...
of the system are called “elements.” Other crucial material is the one between systems, known as “medium.” The medium plays a fundamental role for the identity and separation of the elements. Thus, from the structural point of view, any biological system is characterized by its teguments, elements and its medium, both outside and inside.

**Teguments**

The tegument is the boundary of a biological system. The tegument forms a barrier that isolates, separates and preserves the biological system.

To define the biological system, it is fundamental to identify the tegument (boundary) that separates the system from the rest of the universe (exterior). This tegument determines the interaction of the system with the exterior and establishes the interchange type allowed, given its physical characteristics. Even when the tegument encloses the biological system, the system has the faculty to selectively open it to make regulated changes. The identity and autonomy of the biological system depends on the presence of the tegument.

In cellular systems the tegument is formed by the membrane (the structure responsible for all the transferring functions: breathing, digestion, excreting, heat dissipation, information transfer, etc.). The system teguments (respiratory, digestive, renal, coetaneous, muscular and sensorial) are the epithelia, specialized in certain functions. In the individual systems, the tegument is formed by all the transferring epithelia. The tegument for different biological systems corresponds, depending on the scale, to the membrane of the cellular organelles, or to the membrane of the cells, or to the epithelium of each sensorial complex, or to the meninges of the central nervous system, or to the house for the family system, or to the frontiers for the country system, or to the atmosphere for the ecosystem, etc.

**Proposition 2.** Due to the action of the teguments, the biological systems are differentiated sets isolated from the environment.

This separation occurs, for example, between two adjoining vessels, one with hot blood from the heart and another with cold blood from the limbs. It is also the case of the alveolar air and the plasma located in each side of the epithelium (in this case, the tegument), responsible for the concentration difference of the respiratory gases by the effect of the pulmonary ventilation and blood circulation.

The isolation of the biological system produced by the tegument in principle leads to a closed system, however, the system can be opened selectively to produce regulated changes. It is important to notice that the thermodynamic behavior of a biological system is strongly determined by the nature of the interaction between the system and the exterior medium. Depending on this interaction, biological systems can be classified as:

- isolated, they do not exchange energy or matter with the exterior;
- closed, they exchange energy with the exterior but not matter; or
- open, they exchange both energy and matter with the exterior.

**Proposition 3.** The transferring processes occur in an ordered pair, between the adjacent medium of a tegument (the exterior medium transferring phase and the internal medium interstitial phase).

The changes in the internal medium, occurring as a consequence of the metabolic activities (or the interactions or bio-reactions), produce transferring processes that allow recovery from losses or removal of excess energy, matter or information. The transferring processes can be: diffusion, conduction, active transport and massive transport.

Diffusion through a membrane is due to temperature, concentration, voltage or pressure gradients. For example, the capillary net of the alveolar tissue allows the gas interchange in the alveoli and the blood cells inside the capillaries by a diffusive process in which O\textsubscript{2} and CO\textsubscript{2} cross a semipermeable membrane from a high concentration region to another of lower concentration. The blood cells that cross the capillaries have smaller amounts of O\textsubscript{2} and bigger quantities of CO\textsubscript{2} and other waste gases. As a result, the CO\textsubscript{2} crosses the membrane by diffusion through the alveoli air (that has less CO\textsubscript{2}). In a similar way, the O\textsubscript{2} inside the alveoli air crosses the membrane through the blood cells.

Conduction through a channel occurs, for example, in the nervous impulse conduction from the central nervous system (spinal cord and brainstem) to the visceral and somatic effectors.

Active transport is responsible of the development of a work. For example, glucose moves through active transport from the intestines through the epithelium cells of the intestine but by diffusion from the membrane to the red blood cells. The epithelium cells need to bring the glucose obtained from the digestion to the body and forbid the inverse flux of the body glucose to the intestine. If this did not happen and the intestinal cells used the diffusion carriers of the glucose, the glucose concentration in the intestine would grow to very high levels just after eating a sugar rich food, making the glucose flow from the intestine to the rest of the body. But one hour later—with the intestine empty and the glucose concentration lower than in blood and tissues—the diffusion carriers would transport the glucose to the intestine, depleting the energy reserves of the body. This situation could be lethal, so the transferring mechanism in this case must be active transport to ensure the glucose flux is in only one direction.

Massive transport of a discrete quantity of material, like in phagocytoses or in exocytoses is equivalent to the relationships established for the interaction forms: paracrine, endocrine and neurocrine.

All transferences can be maintained and accelerated as a result of a gradient increase in the flow. For example, gas exchange in the capillary alveolar system is supported by both alveolar ventilation and capillary circulation. This process can be self-regulated, as a result of a closed loop.

**Elements**

The elements are the components of a biological system. Each element of a system plays a fundamental functional process to support and develop the system. Its modification or suppression causes a pathological situation in the system that, eventually, can finish it (causing the system death).

The elements are differentiated, interactive components inside a medium isolated by teguments forming closed loops. For example, the elements of the cellular...
system are the nucleus, mitochondria, endoplasmic network, Golgi apparatus, vesicles and lysosome.

**Proposition 4.** The elements of a biological system cluster, depending on the function they ought to fulfil, are divided into three groups: transfer, replication or integration. The transfer elements establish the interaction between the system and its environment carrying information. The replication elements determine and control the growth, development, regeneration, reproduction and immunity of the system. The integration elements link all the subsystem elements.

The transfer elements carry information in a thermodynamical sense. This information could be expressed, in a specific case, as a transport of matter (i.e., changes in chemical potential) or as dissipation of energy (i.e., changes in free-energy and/or entropy). For a system to be able to effectively transfer information, the receptor needs to recognize the information (encoding) by chemical and/or by physical means. In a human being, transfer elements include the respiratory, alimentary, thermal dissipation, excretory, sensorial and motor systems.

The replication elements have the task of allowing the reproduction of the individual but also of repairing and replacing the constituents of the system itself. In a human the immune and reproductive systems are the replication elements. It is known, for example, that most of the cells of the human body are replaced. There is even a term that has been proposed for this kind of function: autopoiesis.

The integration elements serve as network coordinators of unrelated systems. In terms of thermodynamics, they act as “hubs” of the biological networks inside and outside of an organism. The consequence of their integrative actions is the conservation of the steady-state of the biological system. In a human, the integration elements are formed by the nervous, hormone regulator, circulatory and vascular systems.

**Corollary 3.** All elemental processes are present in a biological system.

All biological systems breathe, eat, grow, thermally dissipate, reproduce, metabolize, organize their immunity, adapt, transform and maintain their integrity. Nevertheless, in situations such as parasite, symbiosis or ecological organizations, some functions are delegated, others are shared and others are simply reorganized.

**Proposition 5.** The elements of a biological system associate into ordered pairs.

For example, neurons are associated by pairs in order to establish synapse communication, the integrative function of the nervous system. Analogously, the breath epitheliums join the muscle through circulation in order to develop the metabolic function of contraction.

The elements are organized through arrays in parallel and series, ramifications and roots. Arrays in parallel are sets of various elements that operate simultaneously in the same direction. Their actions are an additive function. For example, parallel actions are the impulse transmission in the nerve trunk or the contractile actions in the fiber bundles of the skeletal muscle.

\[ |E_1| \to |E_2| \to |E_3| \]

Arrays in series are sets formed by a sequence or a linear linkage of elements. They are responsible of the conduction function. The elements responsible for the transport process of the respiratory gases are an example: the oxygen of the alveolar air, the diffusion of the capillary alveoli, the hemoglobin transport of erythrocytes, the capillary diffusion through the cells and the mitochondrial respiratory chain. Another example is the sequence of molecular changes developed in a metabolic chain.

\[ |E_1| \to |E_2| \to |E_3| \]

Ramifications are sets formed between a conditioning element and two or more conditional elements. Ramifications are responsible for the divergent integration, where the answers of different conditional elements can lead to various effects. Classical examples of this are the link between a pre-synaptic neuron and various post-synaptic neurons or the ramifications of the arterial tree from the ventricle exit via the artery ramifications all the way to the capillaries.

In root sets, the conditioning actions of two or more elements match over one conditional element. In these arrays, a convergent integration takes place. Examples of this are the links between various pre-synaptic neurons and one post-synaptic, the whole set of elements of a sensorial field and the confluence of all capillaries to the veins and from them to the right atrium.

**Corollary 4.** All the activities of biological systems form closed loops.

The activity of biological systems is in receptors sensible to the action and connected through integrative hubs, closing the loop by effectors and transferring media, which go back to the initial point of activity, then producing the regulation process. Closed loops make a regulatory integration. Examples are blood circulation, the metabolic circuit, and the respiratory and cardiac cycles (Fig. 1).

The combination of all the types arrays make up a network that integrates all the links between the subsystem elements: lineal chain sequences, root convergences, ramifications divergences and closed loop recurrences. Thus, a biological network has a precise organization as a consequence of the flow that follows preferred routes imposed by the conditions of each ordered pair. This occurs, for example, in the neuronal network, a perfectly organized set formed by many loops, convergences and divergences.

**Media**

The media are the material inside the space between systems and their elements or their surroundings.

In biological systems, the media play a fundamental role for the identity and separation of the elements, and help in the development of organic processes through the interchange of matter, energy and information by establishing inter-connexion networks with the exterior and other systems. For example, the synapse space has a medium that transports the chemical activator of the post-synaptic membrane. Also, the space between cells is a transfer medium for its metabolism, and it is also the place where the cell gets rid of the resulting material of cellular activity.

In cybernetics all the elements exist in a vacuum but in real biological systems, all of the networks between different elements are established through the medium between them. This is one of the fundamental differences between cybernetics and the approach of the present paper. Here, the media plays a fundamental
role in the development of the biological processes.

The media can be a gas (such as the alveolar air), plasma (as the blood plasma), liquid (as the cerebrospinal liquid that protects the brain), gel (as the eye vitreous humor) or solid (as the bone tissue).

Proposition 6. In biological systems, the interactions are established exclusively through the media.

For example, in all sensorial modalities, stimuli act over the receptors via the transferring medium:

• The activation of the retina receptors is possible by the transparent media of the eye.
• The sound travels through a series of media: ear canal, tympanic membrane, the middle ear bones and the endolymph to reach the hair cells in the inner ear that are the receptors.
• The saliva is the medium that conducts the molecules of the flavoring materials to the ends of the flavor receptor cells.
• Mechanical agents are responsible for the activation of the touch receptors by the stratum corneum of the skin.
• Gravity acts over muscle spindles through the bones into which they are inserted.

Proposition 7. Media in biological systems comprise the following functions:

• to contain the constitutive elements of the system,
• to organize the interchange of material, energy and information and
• to establish the interaction of networks.

The inner medium is the material inside the system limited by the tegument. All the materials outside the tegument form the exterior medium. The importance of the interior medium was probably first realized by Claude Bernard through his concepts of “le milieu intérieur,” by which he described indistinctively extracellular compartments and their corresponding liquids contained within the whole organism.¹

It is important to emphasize that the medium inside a system is interior with respect to this system, but it is external for the enclosed subsystems. For example, for the cells of a multicellular organism, the interior medium is precisely inside them; its exterior medium is the interstitial liquid outside, but this liquid is an interior medium for the human self.

Proposition 8. The interior medium in biological systems is located in one of following phases: intravascular, interstitial, intersynaptic, intimate or the confined liquids.

The intravascular phase is the circulatory medium determining the reception, transport, distribution, and elimination of material, energy and information involved in the development of the system activities.

The interstitial phase is the fluid around and inside the system’s elements where the interactions are developed.

The intersynaptic phase is located in the spaces between elements and constitutes the paracrine network. It is formed by the media inside the synaptic spaces: the neuronal receptor, the neurone-neuronal and the neurone-effectors space.

The intimate phase is the fluid inside an element, like the intracellular medium.

The confined liquids are inside the spaces limited by serous like the pleura, the peritoneum, the pericardium, the synovial capsules and the meninges.

The part of the exterior medium in direct contact with the tegument of a system is called the transferring phase. An example of the transferring phase is the gas inside the breathing system (specially the alveolar air) that continuously changes its composition as a consequence of the ventilation flow and the capillary alveolus diffusion. Another example is the water or air directly in contact with the skin, responsible for the thermal dissipation, water evaporation and gas exchange.

Proposition 9. The transferring phase closes the loop in the organic recurrent processes when it establishes the communication between the effector and the receptor.

For example, in the hearing system, the conducting medium is formed by the air inside the external conduct, the ear drum membrane, the bone change and the endolymph. The conducting properties are under the control of the effector like the stirrup muscle, the eardrum and the vascular groove. This liquid has a large potassium concentration, responsible for the cilia sensibility under deformation.

In the case of vision, the transferring phase is formed by all of the structures of the eye transparent media. This transferring media is under the regulating influence of different parareceptors like lacrhythmal glands, extrinsic eye muscles, muscles of the ciliary process and the iris. All these effectors are capable of modifying the conducting medium, making a regulatory function. For example, the iris regulates the light entering into the eye, opening up the pupil when there is a lot of light and closing down the pupil in the opposite case.

In tactile sensibility there are various structures that correspond to the conducting media, like the stratum corneum, the hair, the nails and the vibrissae. Some of these formations are capable of conducting algogens stimuli to the sensory receptors of pain like the mast cells in such a way that, when they are activated, releases substances that work like mediators, capable of activating the free terminations.

In the muscle-skeletal system, the transferring media is the bone, which transmits the action of the gravity over the corporal mass, and the muscle responds to activate the proprioceptors (that register not only the muscle contraction over the muscle spindle but also the gravity tension).

The external medium fabricated by the social human system (society) is also a transferring media. In this category we can think of instruments, tools, weapons, dresses, rooms, furniture, etc.

Another important concept is the adjacent medium formed by the materials on both sides of the tegument, responsible for the system’s input and output.

Fundamental Functions of Biological Systems

Now, from the point of view of functionality, rather than a simple structural description, each biological system (or subsystem, depending on the reference chosen) fulfills a function, indispensable for the whole set of interacting subsystems. In spite of the enormous variety of functions that biological systems exhibit, it is possible to classify them into one of the following categories:

• reception,
• integration
• response
Interestingly, evolution is related to the differentiation of each of these groups of functions. For example, in a sponge, a single structure fulfils the three functions. In more advanced organisms, however, it could be expected that many interactions would take place, making the systems too complicated to allow a simple model.

Nevertheless, comparative evolution studies\(^1\) show that all biological systems do not only evolve through the interaction of pairs of the above categories of functions but also by simple enhancement and/or suppression of some of those categories, which are then replaced by more complicated ones—or simply disappear.

**Proposition 10.** The functions of all biological systems interact pair-wise.

The interacting pairs of the functions of biological systems are: receptor-integrator (R-I), integrator-effector (I-E) and effector-receptor (E-R). Their actions can be analyzed as matter, energy or information flows.

**Proposition 11.** The functions of all biological systems are flows (material, energy or information). Each flow is proportional to a gradient of the material, energy or information (H) under consideration, minus the medium resistance (R).

Evolution is related to the differentiation of each of these groups of functions. Nevertheless, comparative evolutionary studies\(^1\) show that all biological systems evolve by either increasing and/or suppressing some of these functions and not only through the interaction between function couples. This differentiation (evolution) replaces complex functions or eliminates essential functions. This evolution is present in ecological organizations, symbiosis and even parasites, where some functions are delegated, others are shared, and some others are reorganized. Elemental processes not necessary produce differentiated elements.

Another fundamental fact is that all interactions between biological systems occur by closed loops inside media, in contrast with the traditional approach that considers reflex arcs. The concept of a circuit was already introduced in the publications of Wiener et al.\(^1\) However, his circuits were limited to reflex arcs. The topological distinction of “closed loop” is fundamental in the biological system definition of this present work. It is also important to notice that in cybernetics theory, all of the circuits are in a vacuum, while there, they are inside a media that allows the functions to be regulated and developed and the loops to be closed.

**Thermodynamics of Biological Systems**

Every biological system is associated with an energy (U) and an affinity (A). When a system interacts with another system, the total energy remains unchanged or is conserved, according to the first law of thermodynamics; the total entropy, however, can only increase, according to the second law of thermodynamics.\(^1\)

**Proposition 12.** The thermodynamical state of a biological system is specified in terms of macroscopic state variables such as volume (V), pressure (P) and temperature (T). Other variables like gravity (g), chemical composition (mole numbers of chemical constituents, N\(_i\)), ionizing radiation (R), energy (U), and affinity (A) are functions of the state variables.

The state of a biological system evolves irreversibly toward a time-invariant state in which we see no further physical or chemical changes in the system. This is the state of thermodynamic equilibrium called death. All biological changes drive the system to a state of thermodynamic equilibrium in which the affinities of the reactions vanish.

As motion is explained by the Newtonian concept of force, chemical changes are driven by the force of “affinity.”\(^1\) Here, we will use affinity to describe changes in biological systems.

Let us consider a closed system, where a chemical reaction of the form takes place: \(X + Y \rightarrow 2Z\).

The changes in the mole numbers \(dN\), \(dN\), and \(dN\) of the components X, Y and Z are related by stoichiometry as:

\[
\frac{dN_X}{-1} = \frac{dN_Y}{-1} = \frac{dN_Z}{2} = \frac{di}{1}
\]

where \(di\) is the change in the extent of reaction. In this case, it is defined by the state variable called affinity, \(A\):

\[
A = i_1 + i_2 - 2i
\]

This affinity is the driving force for chemical reactions. A nonzero affinity implies that the system is not in thermodynamic equilibrium (this is the case for all living biological systems) and that chemical reactions will continue to occur, driving the system toward equilibrium (death).

In terms of affinity (A), the rate of increase of entropy is written as:

\[
\frac{dS}{dt} = A/T \times \frac{di}{dt} \geq 0 \quad (1)
\]

Thus, the entropy production due to a chemical reaction is the product of a thermodynamic force, and a thermodynamic flow. The reaction rate is given by the flow that is a measure of the conversion of reactants to products (or vice versa) which is caused by the thermodynamic force.

Notice that, although a nonzero affinity means there is a driving force for chemical reactions, the velocity at which this chemical reaction will occur is not specified by the affinity value. The rates of chemical reactions are usually empirically determined, and they depend on different mechanisms. Also, at equilibrium the thermodynamic flows, and hence the entropy production, must vanish. This implies that in the state of equilibrium, the affinity is null.

If several simultaneous reactions occur in a closed system, an affinity \(A\) and a velocity of reaction can be defined for each reaction, and the change of entropy can be written as:

\[
\frac{dS}{dt} = \Sigma (A/T) \times \frac{di}{dt} \geq 0
\]

For this inequality to be satisfied, it is not necessary that each term be positive. One can be negative provided it is compensated by a positive one. Coupled reactions are common in biological systems and the decrease in entropy due to one reaction is compensated by the increase in entropy to the other. The affinity of a reaction is driven away from zero at the expense of another reaction whose affinity tends to zero.

The concept of affinity not only describes chemical reactions but also the flow of matter from one region of space to another (diffusion). When the chemical potentials of adjacent parts of a system are unequal, diffusion of matter takes place until the chemical potentials of the two parts become equal. The process is similar to the flow of heat that occurs due to a difference in temperature.

For simplicity, let us consider a system consisting of two parts of equal
temperature $T$, one with chemical potential and mole number $N_1$ and the other with $N_2$. The flow of particles from one part to another can also be associated with an “extent of reaction,” though no real chemical reaction is taking place here:

$$-dN_1 = dN_2 = d\alpha$$

The transport of particles results in the change of entropy given by equation 1 with $A = \alpha_1 - \alpha_2$. The positive sign of this equality, required by the second law of thermodynamics, implies that particle transport is from a region of high chemical potential to a region of low chemical potential. This is the process of diffusion of particles from a region of higher concentration to a region of lower concentration.

Conclusions

The propositions outlined above are rather general, in terms of the biological systems to which they can be applied. As opposed to the standard systems theory, which regards a given system as an isolated entity, the present approach considers the hierarchical organization of systems, subsystems and suprasystems, not only as a structure that can be accommodated to all possible cases, but also as an intrinsic property of nature. In this way, one cannot only study the structure at different levels of resolution within a given system but also the actual and potential connection and relations among systems which are apparently uncorrelated. This model also allows accounting for the thermodynamics of the specific system by considering the same hierarchical structure as part of a statistical mechanics-type of theory.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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