From AMOEBA to BRAIN: How Nature process Information*

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ABSTRACT

The paper presents a new Information Processing paradigm based on the dynamics encountered in life from organisms as different as Amoebas and the Mammalian brain.

Our thesis contemplates that life supports information processing via metabolic dynamics in self-organized enzymatic networks which have the capacity to represent functional catalytic patterns that can be instantiated by specific input stimuli. Furthermore, the information patterns can be transferred from the functional dynamics of the metabolic networks to the biochemical enzymatic activity information encoded by DNA.

The metabolic dynamics are governed by fractional dynamics that evolve in topological fractal spaces with multiscale time parameters generating complex attractors.

The complete dynamic information process is driven by the shorterm process of metabolic dynamics and the longterm process of DNA expression via epigenetic mechanisms.

"Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centres, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree."
Santiago Ramón y Cajal

CONTENTS

* New Information Processing framework

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I. INTRODUCTION.

The aim of the paper is to represent the organism as a Holo-Network formed by the integrated assemblage of neural, glial, extracellular molecular networks and the immune system that until now has always been considered in isolated compartments.

The extracellular matrix (ECM) is produced and dynamically modulated by several cell types that include neurons and glial cells. The ECM plays a role in the communication and control of the dynamics of neuroglial, intra-neural, and intra-glial networks. Also the immune system is playing a central role in the molecular dance established by these networks and the full interplay between all of them achieves the objective of the homeostasis state of the organism with its environment.

II. ORIGIN AND EVOLUTION OF THE NERVOUS SYSTEM.

A. Introduction

To understand how the most complex nervous systems works we must first understand the species evolution of these overly complex functions.

The nervous system is contingent on the development of the different eukaryotes families. We will develop in the present paper the thesis that the specialization, first of the immune system of the primordial eukaryotes in its information processing needs, and second the integration of some of the networks supporting these communication functions within the organisms, drove the development of the vertebrate nervous system.

An efficient and integrated, in dynamic terms, perception-action system linking information receptors (external and internal) to actuators, was the vital function on which evolution acted to enhance the capabilities of the nervous system. Also, the dynamics acted over the epigenetics machinery for the cell and exerted evolutionary pressures to achieve the best fitted organism according to the characteristics of the environment.

To have achieve a complete Mammalian nervous system (central and autonomous) required almost two billion years of evolution. During three-quarters of this time, roughly 540 million years ago, animal life erupted, diversifying into a kaleidoscope of forms in what is now known as the Cambrian explosion, information processing was then based on metabolic dynamics supported by the communication channels in the internal structural matrix of the individual cells. We will see these Amoeba systems in the subsection B of this section.

Subsection (II C) of this section represents the part of the evolution devoted to the mechanisms that multicellular arrangements makes to maintain signal processing coherent between the sets of cells. Also, we will look over the nervous system of the mollusc as a first step to see the evolution of the nervous system.

Subsection (II D) will present the full complexity of the Mammalians nervous system. To study these next steps in the evolutionary history of the animal kingdom, we shall consider the fertile ground of embryology. In these grounds we can see how the nervous systems emerge from a cluster of cells, the morula. We will quickly run through the fundamental discoveries of homeotic genes, thanks to experiments on the fruit fly, Drosophila, during the 1980s in which homeotic genes were discovered. They are responsible to arrange the development of the embryo and impose its final shape. We will finally get to the current complexity of the different families of specialized nervous cells (Neural and Glial) and the Extracellular matrix in which these cells are structured that sits in the core of the Mammalians nervous system.

B. Amoeba's information processing system

1. Amoeba's Immune System

Amoeba is one of the most abundant organisms in ecosystems such as pond water. Under a microscope, it is possible to see them wandering around on the slide, but it is also remarkable to see them feeding on microorganisms, like a culture of macrophages. Although It is still up for debate that the amoeba could be the earliest form of macrophage, and by an unknown evolutionary pathway, give raise to the modern macro phage. One of the clear lessons from the study of the Amoeba's behaviour is the complexity of the tasks that it accomplishes. From the feeding of Paramecium to the discrimination of food from other Amoebas it is amazing the complex dances that the simple organism develops.

One of the theories regarding the onset of innate immunity in eukaryotes is that it started in microorganism such as an amoeba to accomplish the function of discrimination between food and other Amoebas. The rationale supporting this theory is that amoebas that do not make this distinction would vanish incredibly earlier from the ecosystem. Therefore, some kind of communication system in the surface of the amoebas gets information from the outside that will makes the molecules be able to distinguish between food, that is safe to be eaten, and another amoeba, or even another part of the same amoeba. The characteristics of this communication mechanism is not yet known, but one of its basic functions is to discriminate between what is self and what is not, being extremely specific as it is the core function of the immune system.

2. Amoeba's development of the immune system

The movement of amoebas is seemingly at random, but the more evolutionary macrophages, act with an aim if they are exposed to a chemo-attractant. In that case all of themwould head in the same direction. Therefore,

under the influence of these environment signals amoebas behave like macrophages. A potential interplay with the first multicellular organisms would have happened and amoebas may have had a parasitic action. Invertebrates and vertebrates present phagocytic cells that have much in common with amoebas and fill the role of the "police" in the blood vessels and tissues, searching for aliens. One theory is that these phagocytic cells, the ancestors of macrophages, come from a population that retained an ancestral, unicellular morphology, as they are today reflected in the amoebas. One important thing to bear in mind, is that complex means of host defence were present in the genome by the time eukaryotes developed into plants and animals.

This defence system, shared by plants and animals, is the Toll receptor signalling pathway and is based on NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation of gene function. This pathway has been demonstrated in vertebrates, invertebrates and, but not conclusively, in plants.

Experiments carried out with mice demonstrated the following: Mice strains that cannot respond to bacterial lipopolysaccharide (LPS) due to a defective Toll gene cannot mount an adaptive immune response against gram-negative bacteria, which carry LPS on their surface. This is a proof that the loss of innate immunity had a discernible effect on the adaptive immune response.

More experiments have demonstrated the above role of genes involved in immunity to diseases in flies and that these genes have homologues that also operate in humans. Toll genes in flies and TLR genes in humans. Homologues of these genes have also been found in other rather different organisms like sharks, nematodes, and plants.

In summary the innate immune system provides early defence against pathogen attack, and communicates to the adaptive immune system that a pathogen invasion is happening. As we have seen a very ancient signalling pathway, the Toll pathway, is acting to support this dual function. This pathway is hundreds of million years older than the adaptive immune system and is present in practically all the superior organisms today. The other component of the innate immunity, the phagocytic cells, may have their ancestors in amoeba-like eukaryotes. One of the key points of the above discussion is that immune system bears a signalling (information processing) mechanism at its deepest roots.

3. From immune system to nervous system

One of the new paradigms that have arisen in the field of physiology is the interplay between the immune system and the nervous system. [1] The idea that neurotransmitters could serve as immunomodulators emerged with the discovery in complex organisms, that their release and diffusion from nervous tissue could lead to signalling through lymphocyte cell-surface receptors and the modulation of the immune function. [2]

The main idea is that the immune system and the nervous system, that handle thousands of neuro-immune transmitters can sense and respond to multiple environmental conditions and aggressions. Cross talk between these two systems has been reported in all the organisms and all states, and the neuro-immune interactions can operate as important immunoregulatory hubs.

In the previous section we have introduced the role of the immune system in amoebas that now we will see, can also support nervous system-like functions. In a published paper [3] it was presented the shocking behaviour of the true slime mold Physarum. When these amoebas were exposed to unfavourable conditions as three consecutive pulses at constant intervals, they reduced their locomotive speed in response to each episode. When the plasmodia was subsequently subjected to favourable conditions, they spontaneously reduced their locomotive speed at the time when the next unfavourable episode would have occurred. This implies the anticipation of impending environmental change.

Moreover, it has been also demonstrated that, Physarum Polycephalum, displays other abilities that could be initially tagged as intelligent. It can solve mazes [4] and geometrical puzzles [5], control robots [6], and in a recent paper there is presented evidence of conditioned behaviour in the organism. [7]

In our current nature's information processing paradigm this behaviour would only apply to organisms that have a nervous system. So, information processing by unicellular eukaryotes could be thought as a precursor of nervous-dependent functions in multicellular organisms. All the functions seen in the previous paragraph, no matter the way in which they are performed, have some information processing abilities that until know have remained unexplained.

We introduce here the hypothesis that these capabilities arose from the previous signalling pathways developed by the early immune system that was adapted to new information processing functionalities like the ones presented.

C. Nervous system evolution

To develop in more detail the thesis introduced at the end of the previous section we must now have a look at the evolution of the nervous system from the simple multicellular organisms to Mammalians. The idea is to tackle the complexity of mammalian models, which are comprised of highly interconnected multiple networks, studying first simpler organisms.

One of the most promising discoveries regarding early development of electrical conductance in multicellular arrangements was made by Dr. Lars Peter Nielsen [8] at the start of this century in 2009.

Dr.Nielsen introduced the concept of cable-bacteria that more recently has been complemented with

nanowire-bacteria. These bacteria are arranged in a manner that they create a cylinder of conducting wires that encases a chain of cells. The wires allow the microbes to transfer electrons involved in redox reactions that take place at spatially separated loci (centimetres in cable-bacteria and micrometres in nano-bacteria).For the cable-bacteria, the electrons are gained by oxidizing hydrogen sulphide and are then transferred to oxygen-rich sediment, where the electrons are linked to water molecules. In the nanowire-bacteria the electrons are shuttled between the oxidation side of organic compounds along the so-called protein nanowires to the electron-accepting side. There is still a lot of debate about how the bacterial nanowires conduct electrons. Dr. Derek Lovely [9] introduced the idea that chains of proteins called pilins, which consist of ring-shaped amino acids, are the key mechanism that support the electron transport creating the electric current.

Once we have seen that Nature developed the mechanisms to generate electric currents, we can make the hypothesis that similar processes were utilized by eukaryotes to be used in specialized cells to fulfil the signal transfer in multicellular arrangements.

The specialized cells that we commonly associate to the functions performed by the nervous systems are the neurons. We will present further on in this paper that neurons are only a part of the complex arrangement that is necessary to carry on all the functionality of the nervous system.

In any case and starting by the current paradigm, Dr. Michael Bate [10] introduced the concept that "neurons are born and differentiate in ways that are not conditioned by their future functions as elements of neural circuits" He also stated that "To understand how functions ... can emerge from these beginnings, it is worth remembering that fundamental attributes of the nervous system such as the circuitry underlying locomotion or escape behaviour are probably also present as a rather stereotyped and evolutionary conserved set of cells and connections. It is at least possible to envisage that there is a fundamental framework of circuitry just as there is a scaffolding of initial pathways".

The nervous system would then be composed of a mix of, evolutionary proven, signal pathways mechanisms, many of which were already developed in early life organisms.

The classical works to understand the basics of the nervous system has been performed in the squid giant axon. In this "simple" system main studies have been devoted to the models supporting functionality of the neuronal network of the squid. One of the approaches that we can take to get a deeper glimpse into the nervous system of these organisms regarding the biomolecules implied in the signalling paths is to get the response against anaesthetics agents that as we know now are a powerful influencers in the functionalities of the system.

One of these early works was performed by (Shrivastav et al., 1976) [11] They exposed a giant squid axon to the volatile anaesthetic halothane and recorded membrane depolarization at low anaesthetic concentrations. They observed a similar depolarizing effect with the volatile anaesthetic trichloroethylene, which also increased the threshold potential for action potential firing and reduced the amplitude of resulting action potentials. The key point of his experience was that the mechanism was acting at the level of the synapse and generated the anaesthetic effect on the neuron functionality.

More experiences were carried later by Dr. Ryden Armstrong [12]. Even if they recognized that "there remains significant uncertainty as to how and where these compounds act at the molecular and cellular levels.", regarding the anaesthetics actions over nervous systems of mollusc the results of their experiences were that "work showed that volatile general anaesthetic compounds directly interact with ion channel proteins, a potassium channel that hyperpolarized neurons, preventing neurotransmitter release. Subsequent work then showed that general anaesthetics also directly target and suppress ion movement through the excitatory acetylcholine receptor. Thus, show that some general anaesthetics target both presynaptic and postsynaptic sites on neurons. These studies also highlight the potential target sites of anaesthetic actions that include classical and peptidergic neurotransmitter synapses. Finally, the data from various studies on Lymnaea demonstrate that chronic exposure of cultured neurons to anaesthetic compounds might render neuronal growth and synaptic connectivity dysfunctional."

From these experiences we can get the point that synapses, and signal transmission in broad terms, more than cells are the key actors of the film that nature performs in the information processing representation.

D. Mammalians Nervous system

Back in 1983 Dr.Walter Gehring [13] studying drosophila, fruit fly, discovered the existence of homeobox genes responsible for a homeotic transformation where legs grow from the head instead of the expected antennae. It was the demonstration that the development of multicellular organisms is based on a program of differential expression of genetic information.

One of the subsets of homeobox genes are the Hox genes. They are the genes that determine the identity of embryonic regions along the body axis. The precursor cells of the nervous system cells arise within an epithelial field of cells made competent through the expression of one or more control genes of the bHLH type (proneural genes) mediated by the Notch-Delta interaction.

In vertebrates, the embryogenic process known as neurulation are the stages that go from the neural plate to neural tube and to the neural crest. All the cell types during this neurulation process arise from pluripotent embryonic stem cells (ESCs). The adult neural stem cells (NSCs) persist in two main areas: the ventricular-

subventricular zone, where NSCs give rise to olfactory neurons, and the hippocampus, where new neurons involved in cognitive processes are generated. In both regions, the stem cells that give rise to neurons are specialized populations of astrocytes that maintain close interactions with the brain vasculature and can be activated by behavioural and pharmacological stimuli. [14]

The important point in the previous paragraph is that the pluripotent adult cells of the nervous system derives from an astrocyte population.

If now we come back to the immune origins of the nervous system presented in (II B 3) we will see the current interrelations between the two systems in the vertebrate kingdom.

In a paper [2] Dr. Franco presented "Initially, the idea that neurotransmitters could serve as immunomodulators emerged with the discovery that their release and diffusion from nervous tissue could lead to signalling through lymphocyte cell-surface receptors and the modulation of immune function. It is now evident that neurotransmitters can also be released from leukocytes and act as autocrine or paracrine modulators". Dr. Franco finished his paper signalling that "Current and future developments in understanding the cross-talk between the immune and nervous systems will probably identify new avenues for treating immune-mediated diseases using agonists or antagonists of neurotransmitter receptors."

Last year Dra. Cristina Godinho-Silva, Dra. Filipa Cardoso, and Dr. Henrique Veiga-Fernandes in their paper [1] introduce the concept "Neuro–Immune Cell Units: A New Paradigm in Physiology". Their thesis is "The interplay between the immune and nervous systems has been acknowledged in the past, but only more recent studies have started to unravel the cellular and molecular players of such interactions. Mounting evidence indicates that environmental signals are sensed by discrete neuro–immune cell units (NICUs), which represent defined anatomical locations in which immune and neuronal cells co-localize and functionally interact to steer tissue physiology and protection. These units have now been described in multiple tissues throughout the body, including lymphoid organs, adipose tissue, and mucosal barriers. As such, NICUs are emerging as important orchestrators of multiple physiological processes, including haematopoiesis, organogenesis, inflammation, tissue repair, and thermogenesis."

This year it has been reported in [15] the regulation between Neuro-Immune Circuits mainly related to gut tissues and Organ Homeostasis. Main result of the report is "Preclinical studies targeting neuro-immune interactions upon stimulation of the vagus nerve, application of acetylcholine agonist, and b2 adrenoreceptor agonists have emerged the potential successful treatment in inflammatory diseases. Of note, the site-specific control of immune functions by the nervous system via neurotransmitters/neuropeptides suggest that the nervous system can exert a rapid and local control of immune cells".

We finalize this introduction to the Mammalian nervous system emphasizing two points;

1. the origin of the multiple cell types of the system from a unique type of "germ" that in the adult phase are the Astrocytes.

2. the full relation at the signal processing level between the immune system and the nervous systems

III. THE TETRAPARTITE SYNAPSES

A. Introduction

We could have headed this section also by the title "The nervous system: the known unknown", but we have preferred to focus on the theme that in the next section will be developed as the core of the paper. The dynamics that underscore not the individual networks that intertwined in the nervous system nor the full hyper-network which nodes are the complex synapses.

We consider that synapses are the places in which presynaptic neurons, postsynaptic neurons, astrocytes and all the molecules in the extracellular matrix make their mutual interrelations. All the actors are influenced by the results of the processing in the synapse. So, the former paradigm that the nervous system was based on the responses of the postsynaptic neurons to the signals generated by the presynaptic neurons, has now changed to a global dynamic process in which Neurons, Glial cells and Extracellular matrix composites, evolution.

We will present in the next sections several references for the subsystems implied that would aid to support the change of paradigm

B. Extracellular Matrix

From the onset of the century the role of the Extracellular Matrix (ECM) on the nervous system has started to be recognized. It was not until 1971 that was accepted the existence of the ECM initially based on the predominance of hyaluronan and chondroitin sulphate proteoglycans (CSPG). Taking in account that ECM suppose 20% of the volume of the adult brain it is shocking that its role was so diminished.

In 2008 Drs. Zimmermann in their paper [16] established that ECM is rich in hyaluronan, CSPG (aggrecan, versican, neurocan, brevican, phosphacan), link proteins and tenascins (Tn-R, Tn-C) and its role is to regulate the cellular migration and axonal growth. Thus, ECM participates actively in the development and maturation of the nervous system. ECM swift assembly and remodelling was associated with axonal guidance functions in the periphery and with the structural stabilization of myelinated fibre tracts and synaptic contacts in the maturating central nervous system.

More recently has been reported the organization of the CSPG into either diffuse or condensed ECM. Diffuse

ECM is distributed throughout the brain and fills perisynaptic spaces, whereas condensed ECM selectively surrounds parvalbumin-expressing inhibitory neurons (PV cells) in mesh-like structures called perineuronal nets (PNNs).

In [17]) is reported that "ECM not only forms physical barriers that modulate neural plasticity and axon regeneration, but also forms molecular brakes that actively controls maturation of PV cells and synapse plasticity in which sulphation patterns of CS chains play a key role. Structural remodelling of the brain ECM modulates neural function during development and pathogenesis."

The main conclusion is ECM components and the molecules they interact with, will provide new insight into the molecular networks that regulate neural plasticity

C. Glial Networks

One of the strangest things in neurophysiology studies has been for most of the time of the past century the secondary role attributed to the Glial system. Starting with the pejorative name gave to most of 50% of the total number of cells of the nervous system, glia, from the Latin and Greek for glue, and continuing for the associate role as merely "support" cells of the big kings, the neurons.

It was at the end of XIX century that the Spanish Nobel price Ramon y Cajal brought to light the potential role of these cells in two seminal articles, "Something about the physiological significance of neuroglia" (1897) and "A contribution to the understanding of neuroglia in the human brain" (1913). [18].

The posterior oblivion of these cells in the opinion of the author was due to the electrical characteristics of the neuronal system in comparison with the biochemical operation of the glial system. The measure of the activity of neurons in the century of electricity was more straightforward than the comprehension of the biomolecules implied in the functionality of glia cells.

Uniquely at the end of the century and with a big impulse from the Spanish Institute Ramon y Cajal and Dr. Alfonso Araque, Dra. Gertudris Perea and Dra. Marta Navarrete the role of glia has started to become mainstream.

One of the extraordinary ideas of Cajal in his paper of 1913 was that "The gray matter neuroglia would constitute a vast endocrine gland intertwined with neurons and nerve plexus, intended perhaps to produce hormones associated with the brain activity". Current research has demonstrated that the so-called gliotransmitters as parallel to the neuronal neurotransmitters regulate widely neuron functionality.

The role of the Astrocytes releasing gliotransmitters and controlling transmission and plasticity at the synaptic level led to a new concept in synaptic physiology, the Tripartite Synapse, in which astrocytes are integral elements of the synapses and actively exchange information with the neuronal elements (Araque et al.; [19] Halassa et al.,[20] ;Perea et al. [21]).

More recently, March 2020) a Science paper written by thirty authors [22] goes further in the relation between neurons and glia establishing a powerful link between these two systems at the level of the bodies of the cells via a purinergic junction. Even if they initially stated that "Microglia perform dynamic surveillance of their microenvironment using motile microglial processes that constantly interact with neurons. However, the molecular mechanisms of bidirectional microglia–neuron communication are unclear" the results of their research are " All of these results unequivocally indicate that microglia continuously monitor neuronal status through somatic junctions, rapidly responding to neuronal changes and initiating neuroprotective actions".

Other aspect of the glia functionality that we want to take in consideration is that the most reported imaging techniques of the brain are based on the activity of the glial cells. Two of these techniques to monitor brain activity, functional Magnetic Resonance Imaging (fMRI) and Diffusion-Tensor Imaging (DTI) are not based on the electrical activity of neurons, nor the oxygen content supplied by blood capillaries (fMRI), or by anisotropic water diffusion (DTI). Oxygen consumption measured in a fMRI voxel is the result of the metabolism of different cell types in which, glial cells (astrocytes, microglia, endothelial, neutrophils, pericytes, NG2 glia, 0ligodendrocytes) are the main source with neurons and vascular as secondary. In the case of DTI is even more focused the role of the glia because DTI signal are based on the myelin-axon unit and support-providing myelin sheaths are the role of the oligodendrocytes.

So, the neuron centred brain is still today the main paradigm in the signal processing function but as we have seen glia cells have functions that clearly make this paradigm complicated to support.

The functionality of the so called "tri-partite" synapse in which Astrocytes regulate extracellular ion and transmitter homeostasis [23] as well as the role of the neuron-glia junctions is out of question and by the modulation of neuro and glia transmitters [24], and peptide hormones, fully influences the dynamics of neurons. Also, the role of the oligodendrocytes metabolically supports neuronal axons, as the base of neural circuits is clearly a powerful influence in the dynamics of these circuits.

D. Neural Networks

Hundreds of thousands of papers have been devoted to the functionalities of Neural Networks from a full range of perspectives going from computational approaches to cell biochemistry.

Taking into account that the purpose of the paper is dealing with the dynamics of the different systems implied in the information processing tasks we will focus

briefly in two aspects of the neural networks; i) the dynamics of the system isolated ii) the potential influence of external factors of the dynamic system.

The historical model for the dynamics of the neuron isolated has been the Hodgkin–Huxley and its multiple derivations. One more developed model was introduced by Eugene M. Izhikevich in 2003 [25]. The model contemplated the analyses of the dynamics using bifurcation methodologies and with only four parameters he was able to reproduce the spiking and bursting behaviour of some types of isolated neurons. In figures 1 and 2 we present a Matlab© simulation of the model using a network of one thousand randomly coupled spiking neurons. As we can see, we obtain some common features in the spike model of the neuron of the neuron 927. Figure (2).

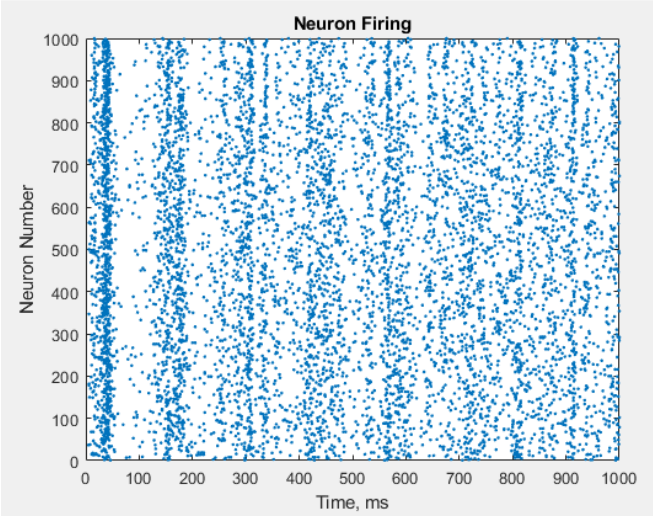

FIG. 1. 1000 Network Firing

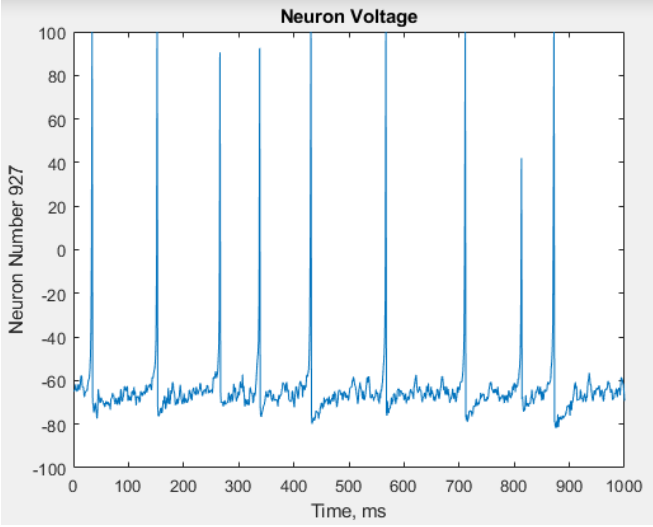

FIG. 2. Neuron 927 Spiking Pattern

Regarding models of complete neural circuits, one that contemplates high order dynamics is the Freeman model (KIV model). The model was derived from the olfactory system and presents a dynamic with chaotic evolution. To achieve this chaotic result the model is based on differential equations of second order.

The full model is presented in [26] and the summary of the model states, "We postulate that the meaning of the information exists in the interrelations of the enormous number of neurons carrying each a fragment of information, which constitutes the knowledge brains create from information. This knowledge must be stored and later mobilized in the serial processes for categorizing sensory information and then deciding on courses of action in response to the input. Mobilized knowledge has the form of bursts of oscillatory electroencephalographic (EEG) and electrocorticographic (ECoG) potentials carrying spatial patterns of amplitude modulation (AM), which emerge from chaotic oscillations of background activity through episodic bifurcations (state transitions) by which the cortex jumps from chaotic disorder into phase-locked limit cycle activity and back again."

From this model we will see in the next section, that the interrelation with the rest of the network systems implied, will get a more elaborated information processing framework.

Going to the influence of external factors in the network dynamics and with the aim to only present one of them, we focus on the effects of alcohol on the nervous system.

The complete actions of ethanol in the nervous system cannot be covered in this very brief mention and of course the effects of ethanol includes actions on glia, and extracellular matrix, but we will focus only on the actions of ethanol with the molecular signalling pathways involved. "Among the central actions stimulated by alcohol, its inhibitory gabaminergic effect, in conjunction with the inhibition of certain excitatory glutamatergic receptors, endocannabinoids, cerebellar calcium channels and hippocampal proteins which are essential for memory formation, results in sedation, loss of inhibitions, relaxation, loss of cognitive functions, attention deficit, impaired sleep-wake regulation (blackout effect), and the final state of psycho-motor depression. On the other hand, the excitatory action of alcohol on mu receptors of the opioid system and subsequent activation of the limbic system by dopamine and of 5-HT1B receptors by serotonin result in the effect of well-being and mood elevation. In addition, the down regulation of dopamine and GABA receptors explains the increase in alcohol consumption and subsequent development of chemical dependency" [27].

The key point that we want to emphasize here is that the effect of a single molecule could alter the entire dynamics of the complete neural network.

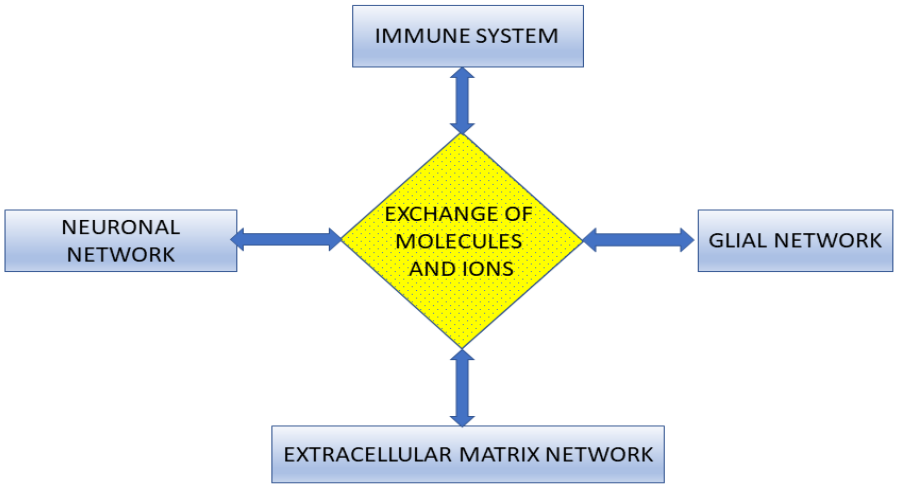

FIG. 3. Organism as a Holo-Network

E. The holo-network

In the previous subsections we have made an approach to the different networks that must be taken into account to fully grab the inner functionalities of the nervous system.

Here we will make a summary of the interrelations of these networks and the ones implicated in the immune system with the aim to delineate a common ground for the dynamics of an entire organism. Of course, the dynamics must take also into account the environment in which this organism evolves.

The objective is to demonstrate that Homeostasis of the complete system Organism plus Environment is the driver for the dynamic.

Starting with the tri-partite synapse contemplated in the glia section we can now enlarge this concept to the tetra party synapse as had been presented in (Dityatev and Rusakov [28] ; Verkhratsky and Nedergaard [29]; Smith et al. [30] Dzyubenko et al.[31]). These papers support the concept of the fully integration and interrelation of the Extracellular matrix components and the other two networks taken into account that both, neurons and astrocytes, synthesized components that become key agents at the ECM level and have a critical role in the functionality of synapses in the nervous system.

So, the actors at the synaptic level are.

(i) the presynaptic terminal

(ii) the postsynaptic element

(iii) the peri-synaptic processes of the astrocytes

(iv) the processes of neighbouring microglial cells that periodically contact the synaptic structure

(v) the extracellular matrix (ECM), which is present in the synaptic cleft and also extends extrasynaptically.

With this complex structure in mind we can make the hypothesis that tetra-partite synapses are the nodes of a kind of hyper-network (Marc) that will be the substrate for the dynamics of the nervous system. Remembering now the considerations done in subsection(II D) regarding the relations between the nervous system and the immune system we can fully expand the hyper-network presented to a Holo-Network that will also include these interactions.

We are using the prefix "holo", with the meaning of whole, entire, capturing the idea that the organism has an underlying global network that processes all the information coming from external and internal sources in order to incorporate them into an integrated framework.

The clear aim of this information process is to maintain the life of the organism and we will take life definition as the homeostatic state of the ensemble organism/environment.

IV. FRACTIONAL DYNAMICS

A. A history dependent and non-local dynamics

Newtonian calculus is based on the "Method of Fluxions", a book of Sir Isaac Newton completed in 1671 but published posthumously in 1736. This late publishing was the cause of a bitter dispute with his contemporary Gottfried Leibniz regarding the priority of the calculus invention.

In fact, Leibniz had a deeper understanding of the concept, as we will see later, due to his potential broad scope that he envisaged.

In the second half of the 17^{th} century, several mathematicians were occupied in the infinitesimal analysis introduced earlier by Barrow and the genius of Newton and Leibniz was to systematize the concept of derivative.

Newton defined the derivative **D** as the local behaviour of a function around one-point x_0 taking into account one infinitesimal δx, that would be as little as needed.

$$Df(x_0) = \frac{f(x_0 + dx)}{dx} \tag{1}$$

One of the key points in this definition is the locality of the derivative taking into account that **D** is related to the point x_0.

Also, it is important to note that this definition has in its root a kind of average around the point x_0, so if the function has a huge variation in this point, like exponential functions, the approach could be misleading.

1. Multiplicative calculus (Geometric and Bi-geometric)

Robert Katz and Michael Grossman introduced in [32] one idea that even Galileo had discussed briefly; to use ratios of the function instead of differences for the derivative definition. From this base multiplicative calculus also known as "star" calculus was born.

*a. Definition of the * derivative.*

The * derivative of the function f is given by:

$$f^\star(x) = \lim_{h\to 0}\left(\frac{f(x+h)}{f(x)}\right)^{\frac{1}{h}} \tag{2}$$

Doing some calculations (see: [32]) we can obtain the relation between the classic (prime) and * derivatives:

$$f^\star(x) = \exp^{\left(\frac{f'(x)}{f(x)}\right)} = \exp^{(\ln\circ f)'(x)} \tag{3}$$

considering that $(\ln\circ f)(x) = \ln(f(x))$. If $f(x)$ is a positive function and $f^{(n)}$ exists,

$$f^{\star(n)}(x) = \exp^{(\ln\circ f)^{(n)}(x)} \tag{4}$$

In this expression is included the case for $n = 0$ and so,

$$f(x) = \exp^{(\ln\circ f)(x)} \tag{5}$$

*b. Geometric interpretation of the * derivative.*

If we remember the geometric interpretation of the classic derivative it is the slope of the line that is tangent to the curve at a particular point.

$$y\prime(x) = \lim_{\Delta x\to 0}\frac{\Delta y}{\Delta x} \approx \frac{\Delta y}{\Delta x} \tag{6}$$

then

$$\Delta y \approx y\prime(x)\Delta x \tag{7}$$

This last relation is the change rate of the function for a change rate of the variable. Remembering the definition of the * derivative in (2) and considering $\Delta x = x_2 - x_1$ the variation of the independent variable and $\Delta^\star y = \frac{y_2}{y_1} \approx \frac{y(x_2)}{y(x_1}$ the star variation of the dependent variable. From $y^\star(x) = \lim_{\Delta x\to 0}(\Delta^\star y)^{\frac{1}{\Delta x}} \approx \Delta^\star y)^{\frac{1}{\Delta x}}$ we get finally $\Delta^\star y \approx (y^\star(x))^{\Delta x} \approx \exp^{\frac{y'(x)}{y(x)}\Delta x}$ Then we can establish that,

$$y_2 \approx y_1 \exp^{\frac{y'(x)}{y(x)}\Delta x} \tag{8}$$

Summarizing we have:
Classical derivative

$$y(x + \Delta x) \approx y(x) + y'(x)\Delta x \tag{9}$$

Star derivative

$$y(x + \Delta x) \approx y(x)\exp^{\frac{y'(x)}{y(x)}\Delta x} \tag{10}$$

c. Linear approximation versus exponential. approximation. A function $y(x)$ that is differentiable at a point $x = x_0$ has a linear approximation **L** near this point defined as follows

$$L\{y(x)\} = y(x_0) + y'(x) \times (x - x_0) \tag{11}$$

Another approximation to a function could be using exponential functions as in , $y(x) = a \times b^x$.These functions have constant star derivative and $y(x+1) = y^\star(x)\times y(x)$. The following two properties are true for all positive differential functions [33]

1. If we scale a function with a constant factor, the function and the scale one has the same star derivative that is the constant factor. This is the idea behind the *multiplicative rate of change*. So, if $Sy(x) = c \times y(x)$, then $Sy^\star(x) = y^\star(x) = c$.

2. Any positive differentiable function at a point x_0 has an exponential approximation **E** near x_0 defined by;

$$E\{y(x)\} = y(x_0) \times y^\star(x_0)^{(x-x_0)} \tag{12}$$

We can show the differences between the two approximations with next example:

$$y(x) = \frac{1}{x^2} \qquad y'(x) = -\frac{2}{x^3} \qquad y^\star(x) = \exp^{-\frac{2}{x}}$$
$$y(1) = 1 \qquad y'(1) = -2 \qquad y^\star(1) = \exp^{-2}$$

Linear approximation at $x = 1$ is

$$L\{y(x)\} = y(1) + y'(1) \times (x - 1) = 3 - 2 \times x \tag{13}$$

Exponential approximation at $x = 1$ is

$$E\{y(x)\} = y(1) \times y^\star(1)^{(x-1)} = \exp^{2\times(1-x)} \tag{14}$$

We can see the results of the approximations in the Figure (4) below

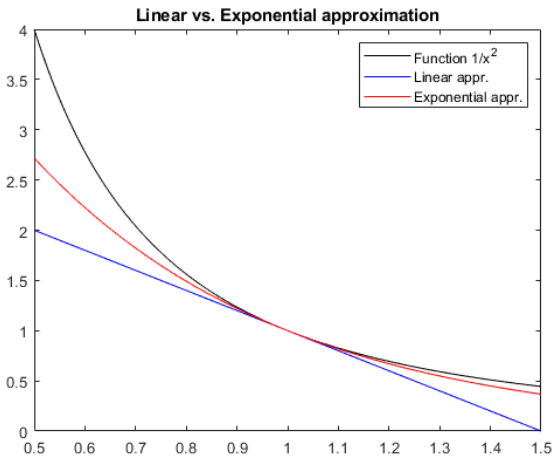

FIG. 4. Linear vs. Exponential approximation

So, for the kind of curves as the exponential, the exponential approximation has a better match than the linear.

d. Bi-geometric Calculus.

One further variation of the definition of derivative gives raise to the bigeometric calculus. In this case the bigeometric derivative is defined as being:

$$y^{\star\star}(x) = \lim_{x \to x_0} [\frac{y(x)}{y(x_0)}]^{\frac{1}{\ln x - \ln x_0}} \tag{15}$$

And the relation with the classic derivative is:

$$y^{\star\star}(x) = \exp^{\frac{x \times y'}{y}} \tag{16}$$

If we remember from the economy manuals that elasticity is the ratio between $\frac{\Delta y}{\Delta x}$ and $\frac{y}{x}$ is the relation of quantities and prices, we have with the bigeometric derivative the perfect tool to deal with the functions that arise in this domain as well as others like biology in which similar ratios, (quantities/catalysers) have a main role. (Scale law functions).

2. *Fractional Calculus*

a. Definitions. Fractional Integrals and Derivatives.

In the previous section we have seen that classic derivative gives the linear approximation of smooth functions, and multiplicative or star derivatives, allow an exponential approximation. In both cases the derivative is linked to a point of the curve and so has a purely local characteristic.

Now going further on the power laws, we will introduce the concept of Fractional Calculus that we can define as the field with objects that are characterized by power law non-locality, power law longterm memory or fractal properties by using integration and differentiation of non-integer orders.

Returning to the quarrels between Newton and Leibniz, it was this last one that invented the notation $\frac{d^n y}{d^n x}$. Perhaps it was naive play with symbols that prompted L'Hospital in 1695 to ask Leibniz, "What if n be 1/2?" Leibniz [34] replied: "You can see by that, sir, that one can express by an infinite series a quantity such as $D^{\frac{1}{2}}xy$ or $D^{1:2}xy$. Although infinite series and geometry are distant relations, infinite series admits only the use of exponents which are positive and negative integers, and does not, as yet, know the use of fractional exponents."

Later, in the same letter, Leibniz continues prophetically: "Thus it follows that $D^{\frac{1}{2}}x$ will be equal to $x\sqrt{dx} : x$. This is an apparent paradox from which, one day, useful consequences will be drawn."

Continuing with the history Euler (1730) mentioned interpolating between integral orders of a derivative. Laplace (1812) defined a fractional derivative by means of an integral, and it was Lacroix (1819) the first to write a derivative of fractional order.

For example if we use potential functions as $y = x^m$, Lacroix expressed it as,

$$\frac{d^n y}{dx^n} = \frac{m!}{(m-n)!}x^{m-n} = \frac{\Gamma(m+1)}{\Gamma(m-n+1)}x^{m-n} \tag{17}$$

Replacing $m = 1$ and $n = \frac{1}{2}$ we obtain the fractional derivative of order 0.5 of the function $y = x$

$$\frac{d^{\frac{1}{2}} y}{dx^{\frac{1}{2}}} = \frac{\Gamma(2)}{\Gamma(\frac{3}{2})}x^{\frac{1}{2}} = \frac{2}{\sqrt{\pi}}\sqrt{x} \tag{18}$$

In which we can see the result advanced by Leibniz.

To summarize a long history, we will use now on the concept of fractional derivative and integral elaborated by Liouville and reframed by Riemann:

We start with the integral presentation.

Left side:

$${}_0I_t^{\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t f(\tau)(\tau - t)^{(\alpha-1)} d\tau \tag{19}$$

Right side:

$${}_tI_b^{\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_t^b f(\tau)(\tau - t)^{(\alpha-1)} d\tau \tag{20}$$

The derivative of Riemann Liouville is defined by

$${}_a^{RL}D_x^{\alpha} f(x) = \frac{1}{\Gamma(n-\alpha)}(\frac{d}{dx})^n \int_a^x \frac{f(\tau)}{(x-\tau)^{\alpha-n+1}} d\tau$$

$$\alpha \text{ real number, } n \text{ integer, } (n-1) \leq \alpha < n \tag{21}$$

M. Caputo in 1967 made a little reformulation of the derivative

$${}_a^{C}D_x^{\alpha} f(x) = \frac{1}{\Gamma(n-\alpha)} \int_a^x \frac{f^{(n)}(\tau)}{(x-\tau)^{\alpha-n+1}} d\tau$$

$$\alpha \text{ real number, } n \text{ integer, } (n-1) \leq \alpha < n \tag{22}$$

Properties of Fractional Derivatives.

1. Linearity Fractional differentiation is a linear operation-

$$D^{\alpha}(\kappa f(x) + \lambda g(x)) = \kappa D^{\alpha} f(x) + \lambda D^{\alpha} g(x) \quad (23)$$

2. Scaling and Scale invariance

$$\frac{d^{\alpha} f(\lambda x)}{dx^{\alpha}} = \lambda^{\alpha} \frac{d^{\alpha} f(\lambda x)}{d(\lambda x)^{\alpha}} \quad (24)$$

3. Sequential Composition

$$\begin{aligned} D^{\alpha} f(x) &= D^{\alpha_1} D^{\alpha_2} ... D^{\alpha_n} f(x) \\ \alpha &= \alpha_1 + \alpha_2 + ... + \alpha_n \\ \alpha_i &< 1 \end{aligned} \quad (25)$$

b. Geometric Interpretation of fractional integration. In this section we will get the model of Dr. Igor Podlubny [35] that introduced a very visual interpretation of the fractional integration and subsequent derivation.

If we refer to equation (19)and consider the function

$$g_t(\tau) = \frac{1}{\Gamma(\alpha+1)} \{t^{\alpha} - (t-\tau)^{\alpha}\} \quad (26)$$

this function has a scaling property. So, if we take $t_1 = kt$ and $\tau_1 = k\tau$, then

$$g_{t_1}(\tau_1) = g_{kt}(k\tau) = k^{\alpha} g_t(\tau) \quad (27)$$

Now we can write the integral in the form

$${}_0I_t^{\alpha} f(t) = \int_0^t f(\tau) dg_t(\tau) \quad (28)$$

This expression can be considered as a Stieltjes integral and we will try to understand it from a representation in the axes $\tau, gandf$, for different values of t.

First we draw the curve that results of the interception of the surfaces $g_t(\tau)$ and $f(\tau)$ for (τ, g) for $0 \leq \tau \leq t$ and different values of t from $t = 10$ and intervals of $\Delta t = -1$.

Let us establish $f(\tau) = |tau + 0.5 \sin(\tau)$

Figure (5), shows in blue this curve.

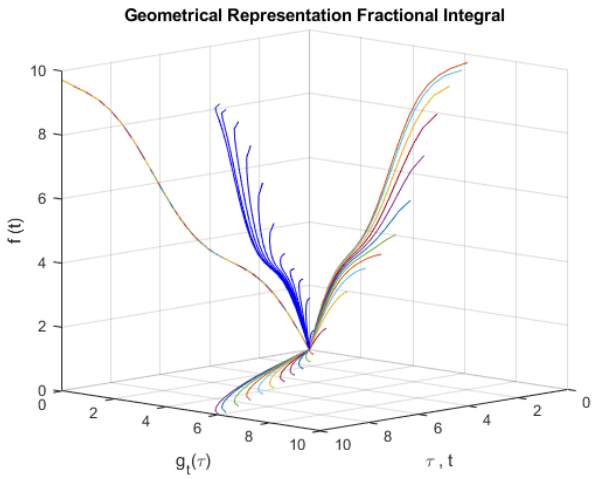

FIG. 5. Geometrical Representation of Fractional Integral

Now if we consider the projection of this curve over the three planes, projection over the plane $f(\tau), (\tau, t)$ is simply $f(t)$ and the area under the curve in this plane will represent the integral

$${}_0I_t^1(t) = \int_o^t f(\tau) d\tau \quad (29)$$

So, the integer integral.

Considering now the projection over the plane $f(\tau), g_t(\tau)$, and the area under this curve in this plane it is precisely the Stieltjes integral. The key point is that different values of t as parameter does not change the classical integral and of course changes the fractional one.

From this reflection we can point out a geometric interpretation of fractional integration, as the addition of a third dimension $g_t(\tau)$ to the classical pair $f(\tau)), \tau$. This third dimension will act as a non-lineal time scaling over the f function.

We will see later more on that with the Mellin transform that act as a kernel function defined for this geometrical explanation.

If we now consider the function f as a velocity or rate of change of a variable, the first integral of the velocity is the space travelled and if we now consider the fractional integral;

$$S_O(t) = \int_0^t v(\tau) dg_t(\tau) = {}_0I_t^{\alpha} v(t) \quad (30)$$

The "space" travelled in this case S_O is the result coming from a kind of geometrical time.

From here we can also develop a geometrical interpretation of the Rieman-Liouville derivative. Taking into account that the velocity is the derivative of the space

$$v(t) = {}_0D_t^{\alpha} S_O(t) \quad (31)$$

with ${}_0D_t^{\alpha}$, the Rieman-Liouville derivative of order α and

$0 < \alpha < 1$ is defined by

$$ {}_0D_t^\alpha f(t) = \frac{1}{\Gamma(1-\alpha)} \frac{d}{dt} \int_0^t \frac{f(\tau)d\tau}{(t-\tau)^\alpha} \tag{32} $$

Then left-sided Rieman-Liouville fractional derivative of the distance S_O is equal to the individual speed v_O (rate of change) of that object.

$$ v_O(t) = \frac{d}{dt}\ {}_0I_t^\alpha v(t) = \ {}_0D_t^{1-\alpha} v(t) \tag{33} $$

B. Network fractional dynamics

1. Algebraic considerations

In this section we must acknowledge the seminal contributions of I.C. Baianu to the algebraic approach to biology in which we have based the next paragraphs as the roots for our Holo-Network dynamics.

As we have presented in the section (III E) an organism would have a dynamic system supported through tightly coupled, biochemical subsystems, dependent upon specific, metabolic processes, information processing-linked, that we named Holo-Network.

Information processing of the kind envisaged is more a dynamic process than a digital computation as the current approach presents. If we consider the dynamic under an algebraic perspective we can make the comparison between the Boolean logic of digital computers and many-valued logic and logic algebras that is the approach that we propose here.

Robert Rosen and I. Baianu [36] presented algebraic models for "*ultra-complex*, in the sense of extreme complexity, in order to avoid any possible confusion, and clearly distinguish it from the *complicated* model systems that are routinely called *Complex Systems*", They introduced " the presence of a higher dimensional algebra and mathematical structure in categories that are representing these systems and their transformations"

Capabilities of an ultra-complex system for both metabolism, M, and repair, R, must be generated from within the system's own sufficiently complex organization; this implies also that metabolism leads naturally to repair, or Metabolism-Replacement, or (M,R), system. It is considered to be non-reducible to its components and algorithmically non-computable, in the sense of not being valuable as a function by a Turing machine. From the point of view of ultra-complex dynamics evolution is extremely complex, chaos-like.

In the paper [37] Baianu formulated the Nonlinear dynamics of non-random genetic and cell networks through categorical constructions enabled by the Łukasiewicz–Moisil Logic algebras.

This is the algebraic approach that we will also apply to the Holo-Network, In fact this approach has only certain broad similarities to the well-known method of McCulloch and Pitts.There are major differences arising from the fact that we consider the sub-networks of the Holo-Net acting in a multiple, quantum manner, and strongly coupled via signaling pathways.

The use of a Łukasiewicz–Moisil (LM) Topos expands the potential dynamics range to any sub-Network like Neural,Glial, EMC, or Genetic-Epigenetic processes.

Non-commutative and non-distributive varieties of many-valued LM-logic algebras, as applied by Baianu ([38]), open a broad field for applications both to our Holo-Networks and also to quantum systems, as we will see later on.

2. Dynamical model

Now we will develop the dynamics of our model. Based on the algebraic considerations introduced in the previous section and using the calculus tools presented in the (IV A 1 and IV A 2) sections. Holo-networks in our new framework are Categories of the Łukasiewicz–Moisil Topos, which Functors will evolve according to the multiplicative fractional calculus.

The key point is that dynamics get the non-locality and historical properties from fractional dynamics and power law "additivity" via the multiplicative geometric and bigeometric calculus.

a. Info-Mechanics [39]

The above framework could be nominated Info-Mechanics as a new dynamic framework related to the classical mechanics and quantum mechanics. To briefly remember the basics for these systems: Classical Mechanics:

1. Dynamic evolution in a spacetime that is 3D Euclidean and 1D time independent.
2. Galileo relativity principia. All the nature laws are the same for all the Inertial systems (Systems that move straight and uniformly)
3. Newton determination principia. All the movements are fully determined by the initial position and velocity

Hamiltonian Mechanics:

1. Dynamics is described in the Phase-Space that has the structure of a sympletic variety and the Poisson Integral as the Invariant.
2. A new relativity principium (Einstein's special relativity) could be introduced in the framework.
3. Hamiltonian Function. Each uniparametric group of symplectic diffeomorphisms of the phase space that keeps constant the Hamiltonian are associated to a prime integral of the movement.

Info Mechanics

1. Dynamic evolution over a Łukasiewicz–Moisil Topos.

2. Nature is structured in Categories which inner morphisms are based on holo-networks.

3. Functors between Categories evolution according to multiplicative fractional calculus.

We introduce the hypothesis that the different models of mechanics that apply to Nature are related to the spatial-temporal scale in which we make the analysis.

With this approach Quantum Mechanics (a Hamiltonian quantized mechanics) and its broad application Quantum Field Theory (QFT) are applied to Nature in the microworld., from Plank distance to micrometre. Info-Mechanics will appear as the necessary framework for the mesoscale, to planet wide scale, and finally General Relativity (GR) as the frame for the Universe scale.

The inconsistencies between QFT and GR could now be contemplated as a scale factor in a wide theory Info related. Considering Mellin transform as the convolution model for the RL Integral with kernel t^s with respect to the Haar measure $\frac{dt}{t}$ (multiplicative invariant), some nice relations have been developed by Dr. Liam Fitzpatrick, showing that Mellin space serves the Info role in the context of the AdS/CFT correspondence. [40].

b. Toy Model

In this section we will develop one simplest model based on the previous statements.

The model takes in account the evolution of the Functors between a simple Category on Info, a virus, and the three subcategories, Neural Nets, Glial Nets, and Immune Nets, of a Superior Organism Category (Holo-net).

For the dynamic equations we will use the Chua system that initially contemplates an electronic circuit that achieves chaotic dynamics (Figure 6). The system was implemented in Matlab© , Simulink©. This circuit has a memristor component that according with [41] introduces the current according to the parameters shown in the circuit,

$$I_M(t) = W(\phi(t))V_1(t) \tag{34}$$

where $W(\phi(t))$ is the incremental memductance defined as

$$W(\phi(t)) = \frac{dq(\phi)}{d\phi} \tag{35}$$

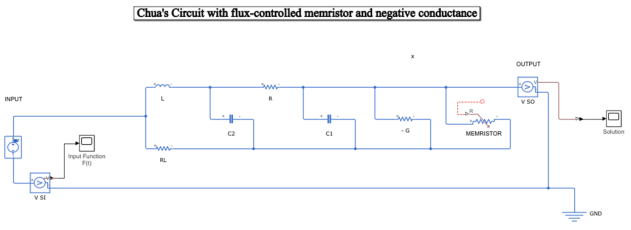

FIG. 6. Chua's circuit with Memristor

The dynamics of this circuit with a passive memristor (flux-controlled memristor and negative conductance) are given by the ODE (Ordinary Differential Equations) system

$$\begin{aligned}
\frac{dV_1(t)}{dt} &= \frac{1}{C_1}[\frac{V_2(t) - V_1(t)}{R} + GV_1(t) - W(\phi)V_1(t)] \\
\frac{dV_2(t)}{dt} &= \frac{1}{C_2}[\frac{V_1(t) - V_2(t)}{R} + I_L(t)] \\
\frac{dI_L(t)}{dt} &= \frac{1}{L}[-V_2(t) - R_L I_L(t)] \\
\frac{d\phi(t)}{dt} &= V_1(t)
\end{aligned} \tag{36}$$

If we translate these variables to the Info space:

$V_1 = Immune_{Net}.Info$
$V_2 = Glia_{Net}.Info$
$I_L = Neural_{Net}.Info$
$\phi = Virus.Info$

That reflects the action of the virus (Memristor component in the Chua system) over the three sub-networks, Immune system, Neural system and Glial System.

If we now transform the variables in dimensionless parameters according to [42]

$$\begin{aligned}
x = V_1 \quad & y = V_2 \quad z = I_L \quad w = \phi, \\
C_2 = 1 \quad & R = 1 \\
\alpha = \frac{1}{C_1} \quad & \beta = \frac{1}{L} \quad \gamma = \frac{R_L}{L} \quad \epsilon = G
\end{aligned} \tag{37}$$

The system (36) is transformed to

$$\begin{aligned}
\frac{dx(t)}{dt} &= \alpha(y(t) - x(t) + \epsilon x(t) - W(w)x(t) \\
\frac{dy(t)}{dt} &= x(t) - y(t) + z(t) \\
\frac{dz(t)}{dt} &= -\beta y(t) - \gamma z(t) \\
\frac{dw(t)}{dt} &= x(t)
\end{aligned} \tag{38}$$

where piecewise-linear function $W(w)$ is defined by

$$\begin{aligned}
W(w) &= a \quad for \quad |w| < 1 \\
&= b \quad for \quad |w| > 1
\end{aligned} \tag{39}$$

Now, to obtain our system dynamics, we will change the first derivative by fractional ones.

$$\begin{aligned}
{}_0D_t^{q_1} x(t) &= \alpha(y(t) - x(t) + \epsilon x(t) - W(w)x(t) \\
{}_0D_t^{q_2} y(t) &= x(t) - y(t) + z(t) \\
{}_0D_t^{q_3} z(t) &= -\beta y(t) - \gamma z(t) \\
{}_0D_t^{q_4} w(t) &= x(t)
\end{aligned} \tag{40}$$

To solve numerically the system of fractional derivatives equations we will use a method described by Petras

[43]. It is a time domain method that leads to equations described by

$$
\begin{aligned}
x(t_k) &= (\alpha(y(t_{k-1}) - x(t_{k-1}) + \epsilon x(t_{k-1}) \\
&\quad - W(w(t_{k-1})x(t_{k-1}))) \, h^{q_1} - \sum_{j=\nu}^{k} c_j^{(q_1)} x(t_{k-j}) \\
y(t_k) &= (x(t_k) - y(t_{k-1}) + z(t_{k-1})) \, h^{q_2} \\
&\quad - \sum_{j=\nu}^{k} c_j^{(q_2)} y(t_{k-j}) \qquad (41) \\
z(t_k) &= (-\beta y(t_k) - \gamma z(t_{k-1})) \, h^{q_3} - \sum_{j=\nu}^{k} c_j^{(q_3)} z(t_{k-j}) \\
w(t_k) &= x(t_k) \, h^{q_4} - \sum_{j=\nu}^{k} c_j^{(q_4)} w(t_{k-j})
\end{aligned}
$$

Where

$$
\begin{aligned}
W(w(t_{k-1})) &= a \quad for \quad |w(t_{k-1})| < 1 \\
&= b \quad for \quad |w(t_{k-1})| > 1
\end{aligned} \qquad (42)
$$

The total time for simulation that we will use is 200 seconds and h is the interval of calculation that is 0.005 seconds. So, total number of points per curve for each calculation is forty thousand.

The coefficients $c_j^{(q_i)} j = 0.1....)$ are binomials $(-1)^j (\frac{q_i}{j}$ that we will calculate according to the expression [44]

$$
c_0^{(q)} = 1, \quad c_j^{(q)} = (1 - \frac{1+q}{j}) \, c_{j-1}^{(q)} \qquad (43)
$$

Value of the parameters for calculation are:
$\alpha = 10, \quad \beta = 13 \quad \gamma 0.1 \quad \epsilon = 1.5 \quad a = 0.3 \quad b = 0.8$
$q_1 = 0.97 \quad q_2 = 0.97 \quad q_3 = 0.97 \quad q_4 = 0.97$
$x(0) = 0.8 \quad y(0) = 0.05 \quad z(0) = 0.007 \quad w(0) = 0.6$
The results are presented in the Figures (7, 8, 9, 10).

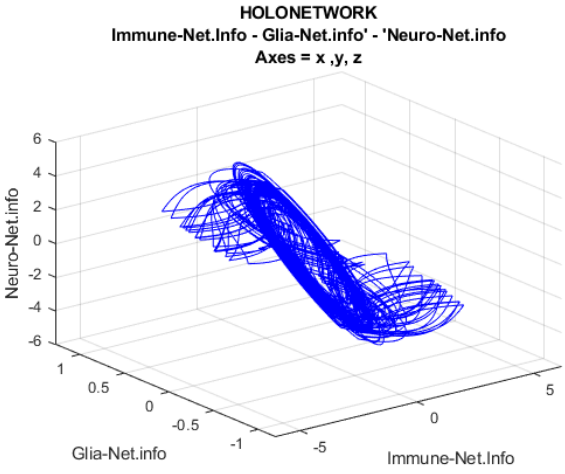

FIG. 7. Holo-Network Axes (x, y, z)

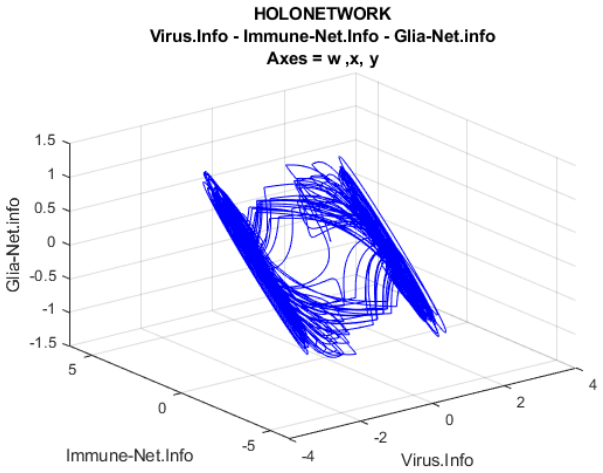

FIG. 8. Holo-Network Axes (w, x, y)

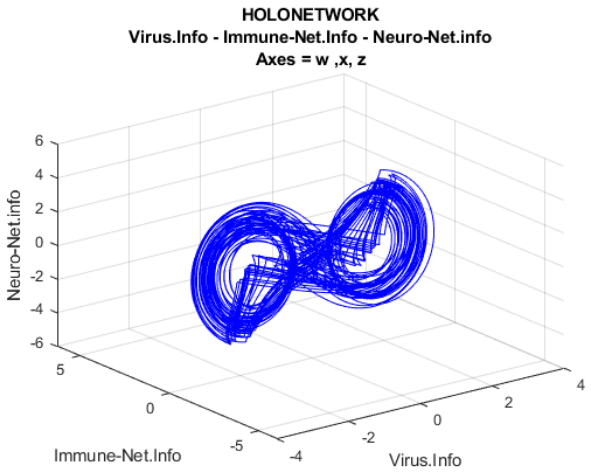

FIG. 9. Holo-Network Axes (w, x, z)

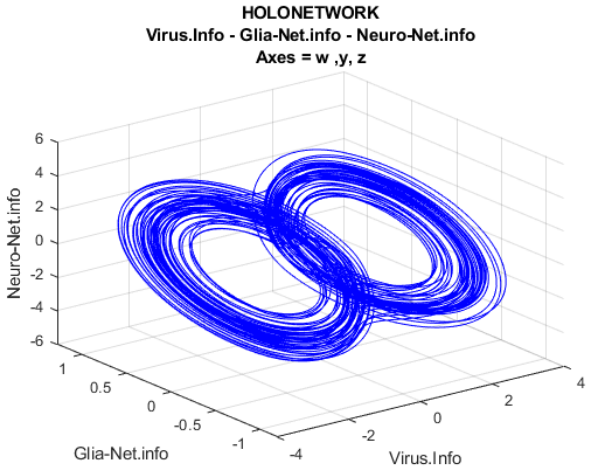

FIG. 10. Holo-Network Axes (w, y, z)

In the complementing materials([45], [46], and [47]) you will find three videos that contain the graphics presented related to "Virus.Info" variable interactions, with a variation of the α parameter.

C. Shorterm vs. longterm information processing

In the previous sections we have focused on the mathematical approach to the Info space, here we will present briefly how the short and long time scales of the space are processed.

If we start considering organism's biomolecular processes, they would be the substrate that could allow to implement one of the instantiations of the Info Functor previously described.

Anther clear instantiation of the Info Functor is the structure of DNA/RNA as we have used in our Toy model with the Virus role.

As we have seen in the dynamics graphics (Virus.Info), figures (8, 9, and 10) introduces two separate regions on the phase space. The permanence of the system in one of the regions is abruptly broken with a transfer to the other region that takes place after a usual long time, compared with the time of the transfer.

We can speculate that dynamics that happen within the regions are short term processes based on the biomolecular mechanisms while the transfer region corresponds to DNA/RNA processes. These last plastic processes could be genetic or epigenetic.

In our toy example Virus.Info, DNA/RNA instantiation gets the system from its initial state to one of the regions. From this moment metabolic processes in the three networks (Holo-Net) lead the dynamics of the system until a new DNA/RNA process happens, usually replication of the Virus.Info, but could also be DNA/RNA processes on the Holo-Net. From this moment a totally different dynamic of the system takes place. It is not highly speculative to associate these dynamical changes to the different states that organisms suffer under virus stress.

We will not go any further in this part of the analysis because a more detailed mathematical model beyond the toy model presented is necessary.

Only as a matter of quantification of the different time scales for the different Nets.Info, we see that for the biomolecular/metabolic processes it takes times from microseconds to seconds, while plastic processes take place during hours (circadian) or several days.

V. PRACTICAL DEVICE IMPLEMENTATION

A. Light and sound correlated as an input stimuli to the network

The device that we have developed profiting from the concepts presented in the previous sections, is mainly a Light and sound generators that focus the visual and ear channels of the patient in the two signals that we can advance are highly correlated.

The current prototype is shown in the picture of the Figure (11)

FIG. 11. Device Sound & Light (Prototype)

showing the light matrix and the earphones for the sound.

For the first implementation of the device we are working in an Info related open loop, with the meaning that the light and sound signals generated are independent of the state in which that the holo-net system is taken.

The evaluation in this initial approach is more focused on the demonstration of the reaction of the Holo-Net system, more than the optimization of the actions and potential improvements on the health (dynamics) of the patient. As we will see in the next section, there are health conditions, such as Epilepsy, in which an immediate change in the dynamics of the system entered after the Epileptic seizure is more than enough to prevent major damages.

Of course, a subsequent close-loop device will be devel-

oped after we obtain the results of the tests with the current prototype. Unfortunately for this second device the current status of the technique will not allow us to have an on-line feedback from Immune-Net.Info and even will be difficult (Imaging techniques) from Glia-Net.Info, but we hope that a full set of interfaces with these systems will be developed in the near future. Even the interfaces with Neural-Net.Info are in the first stages but the news coming from this front are very exciting (see: Neuralink presentation [48]).

The characteristics of the sound and light waveforms as well as the times and protocols for its implementation are at the time being under industrial secrecy and we are not able to fully disclose them in the present paper.

An example of a treatment with one of the devices is shown in the picture of the figure (12.

FIG. 12. Treatment with the Device Sound & Light

B. Potential effects in Epilepsy and other neurological diseases

As we have advanced in the previous section the initial tests of the device are being made with patients suffering from Epilepsy.

Epilepsy is a grave central nervous system illness that is normally related to other complex neurological disorders, resulting frequently in the development of recurrent seizures. These seizures can potentially result in the death of the patient as they usually occur without previous warning.

The WHO (World Health Organization) estimates that epilepsy affects more than 50 million people worldwide. Taking into account that the total world population is about 7 billion there are 7 people out of 1000 suffering epilepsy in the world. Epilepsy has an enormous influence on the quality of life of the patient with collateral effects such as body lesions related to seizures and in the case of treatment with antiepileptic drugs, depression, anxiety and other adverse neurological disorders induced by the treatments.

An epileptic disorder can be classified as partial, generalized, or unclassified nature depending on the diverse types of seizures suffered. The most damaging is the status epilepticus (SE) in which the seizure is sustained for prolonged time. SE has been defined as a prolonged generalized tonic-clonic seizure persisting for more than 5 minutes (or 10 minutes for focal seizures with or without impairment of consciousness), or more than one seizure within a period of 5 minutes without recovery of consciousness in between.[49].

Incidence of SE, according to different estimates, varies from 6.8 to 41 cases per 100.000. Taking into account that 60% of the total cases are refractory to drug treatment and death is common between the SE patients there is so far a dim future for these patients.

We have focussed our tests on the use of the device immediately after the first symptoms of the seizure are present.

For the current experiments of light stimuli methods in the Holo-Net.Info system we introduce the work made with mice by Kristie M. Garza, Lu Zhang, Ben Borron, Levi B. Wood, and Annabelle C. Singer. [50]. The results are summarized; “Many neurodegenerative and neurological diseases are rooted in dysfunction of the neuroimmune system; therefore, manipulating this system has strong therapeutic potential. Prior work has shown that exposing mice to flickering lights at 40 Hz drives gamma frequency (40 Hz) neural activity and recruits microglia, the primary immune cells of the brain, revealing a novel method to manipulate the neuroimmune system. However, the biochemical signalling mechanisms between 40 Hz neural activity and immune recruitment remain unknown.”

Other remarkably interesting experiment was made in this case with zebra fish by Carmen Diaz Verdugo, Sverre Myren-Svelstad and several collaborators. They studied [51] Glia-neuron interactions that underlie state transitions to generalized seizures. The briefly conclusion of the work was “The transition from a preictal state to a generalized seizure is an abrupt process accompanied by strong alteration of the functional connectivity between

glial and neural networks".

Even if the subjects of the experiments were mice and zebrafish and not humans the results for our thesis are appealing and induce a high positive potential for the results of the device.

Other tests related to other neurodegenerative diseases, like Alzheimer disease, will be carried on in the near future even as in this case the positive effects of the treatment could take more time to be acknowledged.

C. Potential effects on COVID-19 patients

As a supplementary material due to the current dismal situation caused by the COVID-19 we have been committed to start without any delay a battery of tests with special waveforms of sound and light in the device to test in COVID-19 newly confirmed patients.

One of the most characteristic symptoms of the disease is the acknowledgement that patients cannot smell the food nor taste that they are eating. Normally these early symptoms are the first indicators of the virus SARS-Cov-2 in action in the human body.

Therefore, this action links, as in our toy model, the action, information processing of a virus with the networks of the nervous system. Several papers of the thousands edited during the last months regarding SARS-Cov-2, take into account the potential short term and long term problems caused by the disease in the nervous system but for the moment only general treatments aimed at known therapy paths are being tested.

One of the points that we want to raise in this noticeably short justification for the ongoing tests of the device in COVID-19 patients is the cytokine release syndrome (CRS)–induced ARDS and secondary hemophagocytic lymphohistiocytosis (sHLH). This cytokine "storm" was observed in patients with SARS-CoV and MERS-CoV in 2008 as well as in leukaemia patients receiving engineered T-cell therapy. The suppression of the storm was the base for the first treatments in March and April this year 2020, based on therapeutics suppressing CRS, such as tocilizumab, that entered clinical trials with some positive effects but with a severe and grave secondary ones.

Our current approach will try to change the dynamics of the virus via the effects that we will induce in the nervous system (neural, glial, and potentially affecting the extracellular matrix), with the Sound and Light device therapy.

The first essays will be done in a way patients newly diagnosed with COVID-19 will be subject, with their total and positive consent, to a session of 15-30 minutes interaction with the device before their sleeping period.

The next morning, they will be checked again for the virus absence or presence ideally quantitatively and qualitatively.

VI. CONCLUSIONS AND FURTHER WORK

A. Summary

Further work must be done with the aim to:

1. Develop more complex models of Holo-Nets and evaluate the fitting with natural occurring cases.

2. Evaluate potential implementations of more advanced devices according with the results obtained from complex models.

3. Study advanced artificial implementations for the dynamic models going beyond electronic circuits.

4. Make deeper studies in the relation Quantum Mechanics and Info Mechanics, that could help to establish a bridge between quantum computation and Holo-Network dynamics. At this point a potential implementation of quantum algorithms over Holo-Networks is the most appealing result envisaged.

B. Disclaimer

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Appendix A: Biological papers

This Appendix will present the Biological literature related to the paper. One of the most complete bibliographic references is contemplate in the article [52]. Other Books are [53], [54], [55], [56], [57], [58], [59],

Appendix B: Mathematical Papers

This Appendix will present the Mathematical literature that gives support to the Calculus and Algebraic methods used in the paper. Different articles related to fractional Calculus are in the books [60] and [61]. Seminal book for non-Newtonian calculus is [62].

[1] F. C.Godinho-Silva, Neuro–immune cell units: A new paradigm in physiology, Annu. Rev. Immunol. **37**, 19 46 (2019).

[2] P. R. Franco R, The emergence of neurotransmitters as immune modulators, Annu. Rev. Immunol. **28(9)**, 400 407 (2007).

[3] T. T.Saigusa, Amoebae anticipate periodic events, Phys.Rev. Lett. **100**, 018101 (2008).

[4] H. T.Nakagaki, Maze-solving by an amoeboid organism, Nature **407**, 470 (2000).

[5] R. T.Nakagaki, Obtaining multiple separate food sources: behavioural intelligence in the physarum plasmodium, Proc. R. Soc. B **271**, 2305 –2310 (2004).

[6] K. S.Tsuda, Robot control: From silicon circuitry to cells, BioSystems **87**, 215 (2007).

[7] I. M. D. la Fuente et al., Evidence of conditioned behavior in amoebae, Nature Communications **10**, 3690 (2019).

[8] L. P. Nielsen, On the evolution and physiology of cable bacteria, PNAS **116**, 38 (2019).

[9] D. E. H. Derek R. Lovely, Protein nanowires: The electrification of the microbial world and maybe our own, Journal of Bacteriology **JB.00331**, 20 (2020).

[10] B. M., Making sense of behaviour, Int. J. Dev. Biol. **42**, 507 509 (1998).

[11] S. et al., Mode of action of trichloroethylene on squid axon membranes, J. Pharmacol. Exp. Ther **199**, 179 188 (1976).

[12] R. S. Armstrong R, Mechanisms of anaesthetic action and neurotoxicity: Lessons from molluscs, Front. Physiol. **8**, 1138 (2018).

[13] W. J. G. et al., Genomic and cdna clones of the homeotic locus antennapedia in drosophila, EMBO J **2(11)**, 2027–2036 (1983).

[14] C. E. Henderson, Stem cells in the nervous system, Am J Phys Med Rehabil. **93**, 11 0 3 (2014).

[15] M. S. Jakob M. and Klose, Neuro-immune circuits regulate immune responses in tissues and organ homeostasis, Front. Immunol. **11**, 308 (2020).

[16] M.-Z. D.R.Zimmermann, Extracellular matrix of the central nervous system: from neglect to challenge, Histochem Cell Biol. **130**, 635 653 (2008).

[17] H. K. Shinji Miyataa, Formation and remodelling of the brain extracellular matrix in neural plasticity: Roles of chondroitin sulphate and hyaluronan, BBA - General Subjects **1861**, 2420 2434 (2017).

[18] M. N. Alfonso Araque, The cajal school and the physiological role of astrocytes: A way of thinking (2014).

[19] A. A. et al.n, Tripartite synapses: glia, the unacknowledged partner, Trends Neurosci. **22**, 208 215 (1999).

[20] F. T. Halassa M.M., Tripartite synapses: roles for astrocytic purines in the control of synaptic physiology and behaviour, Neuropharmacology **57**, 343 346 (2009).

[21] N. M. Perea G, Tripartite synapses: astrocytes process and control synaptic information, Trends Neurosci. **32**, 421 431 (2009).

[22] C. et al., Microglia monitor and protect neuronal function through specialized somatic purinergic junctions, Science **367**, 528 537 (2020).

[23] P. et al., Activity-dependent switch of gabaergic inhibition into glutamatergic excitation in astrocyte-neuron networks, eLife **5**, e20362 (2016).

[24] M. N. et al., Extracellular calcium acts as a mediator of communication from neurons to glia, Science Signalling **5**, 208 (2012).

[25] E. M. Izhikevich, Simple model of spiking neurons, IEEE Transactions on Neural Networks **14**, 6 (2003).

[26] W. J. Freeman, *Chaos, CNN, Memristors and Beyond* (World Scientific, 2013) Chap. 22.

[27] S. V. P. Malheiros, A review on alcohol: from the central action mechanism to chemical dependency, Rev. Assoc. Med. Bras. **61(4)**, 381 387 (2015).

[28] R. D. Dityatev A, Molecular signals of plasticity at the tetrapartite synapse, Curr Opin Neurobiol **21(2)**, 353 359 (2011).

[29] N. M. Verkhratsky A, Astroglial cradle in the life of the synapse, Philos Trans R Soc Lond B Biol Sci **369**, 1654 (2014).

[30] S. M. Smith ACW, The tetrapartite synapse: extracellular matrix remodelling contributes to cortico accumbens plasticity underlying drug addiction, Brain Res **1628**, 29 39 (2015).

[31] G. C. Dzyubenko E, Neuron-glia interactions in neural plasticity: contributions of neural extracellular matrix and perineuronal nets, Neural Plast **5214961** (2016).

[32] M. Grossman and R. Katz, *Non-Newtonian Calculus* (Lee Press, 1972).

[33] D. Stanley, A multiplicative calculus, Primus **9(4)**, 310 326 (1999).

[34] G. W. Leibniz, G w 1695a letter from hanover, germany to g.f.a. l'hopital, september 30, 1695, Mathematische Schriften 1849, reprinted 1962, Hildesheim, Germany **2**, 301 302 (1849).

[35] I. Podlubny, Geometric and physical interpretation of fractional integration and fractional differentiation, Arxiv.math **arXiv:math/0110241 [math.CA]** (2001).

[36] I. C. B. et al., Robert rosen's work and complex systems biology, Axiomathes **16**, 25 34 (2006).

[37] I. C. B. et al., Complex non-linear biodynamics in categories, higher dimensional algebra and lukasiewicz–moisil topos: transformations of neuronal, genetic and neoplastic networks, Axiomathes **16**, 65 122 (2006).

[38] I. C. B. et al., A lukasiewicz-moisil many-valued logic algebra of highly-complex systems, BRAIN. Broad Research in Artificial Intelligence and Neuroscience **1**

(2010).
[39] We will maintain the word Info and not Information to discriminate the concept Info, that is a dynamic concept, from the concept Information that is a static concept.
[40] A. L. F. et al., A natural language for ads/cft correlators, Arxiv.hep-th **arXiv:1107.1499v2 [hep-th]** (2011).
[41] C. L.O., Memristor - the missing circuit element, IEEE Transaction on Circuit Theory **CT-18**, 507 519 (1977).
[42] C. L. Ito H., Memristor oscillation, International Journal of Bifurcation and Chaos **18**, 3183 3206 (2008).
[43] P. I., A note on the fractional-order chua's system, Chaos, Solitons and Fractals **38**, 140 147 (2008).
[44] D. L., Numerical models for the simulation of the fractional-order control systems, The Academy of Sciences. Inst. of Experimental Physic, Kosice, Slovakia **UEF-04-94** (1994).
[45] I. Ozcariz, "https://youtu.be/1uqe0ih7yuk" (2020).
[46] I. Ozcariz, "https://youtu.be/uf64qmkq2n4" (2020).
[47] I. Ozcariz, "https://youtu.be/bdjep2dntfa" (2020).
[48] NEURALINK, "https://www.neuralink.com/" (2020).
[49] B. E. et al., *An Introduction to Epilepsy* (West Hartford (CT): Am Epilepsy Soc., 2006).
[50] e. a. Kristie M. Garza, Gamma visual stimulation induces a neuroimmune signalling profile distinct from acute neuroinflammation, The Journal of Neuroscience **40(6)**, 1211 1225 (2020).
[51] S. M.-S. Carmen Diaz Verdugo, Glia-neuron interactions underlie state transitions to generalized seizures, Nature Communications **10**, 10.1038/s41467-019-11739-z (2019).
[52] D. L. et al., Systems protobiology: origin of life in lipid catalytic networks, J. R. Soc. Interface 10.1098/rsif.2018.0159 (2018).
[53] C. HERRICK, *Brain of Rats and Men* (University of Chicago Press, Chicago, 1926).
[54] H. KUHLENBECK, *The central nervous system of vertebrates* (S. Karger, Basel, 1975).
[55] R. NÄÄTÄNEN, *Attention and brain function* (Erlbaum, Hillsdale (New- Jersey, USA)., 1992).
[56] C. Adami, *Introduction to Artificial Life* (Springer- Verlag Inc., New York, 1998).
[57] M. Eigen, *The Hypercycle. A Principle of Natural Self-Organization* (. Springer, Berlin, 1979).
[58] M. Eigen, *Steps Towards Life* (Oxford University Press, Oxford., 1992).
[59] M. Eigen, *From Strange Simplicity to Complex Familiarity.* (Oxford University Press, Oxford., 2013).
[60] C. Catani, *Fractional Dynamics* (De Gruyter Opn Ltd., Varsaw, Berlin, 2015).
[61] M. Eigen, *The craft of fractional modelling in science and engineering* (MDPI, Basel, 2013).
[62] M. Grossman and R. Katz, *Non-Newtonian Calculus* (Lee Press, Pigeon Cove, Mass. USA, 1972).
[63] M. M. Luigi F. Agnati, The brain as a "hyper-network": the key role of neural networks as main producers of the integrated brain actions especially via the "broadcasted" neuroconnectomics, Journal of Neural Transmission 10.1007/s00702-018-1855-7 (2018).