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On the emergence of cognition and consciousness: from catalytic closure to neuroglial closure

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Abstract

In an analogous manner as occurred during the development of a connected metabolism that at some point reached characteristics associated with what is called 'life' —due mainly to a catalytic closure phenomenon when chemicals started to autocatalyze themselves forming a closed web of chemical reactions— it is here proposed that cognition and consciousness (or features associated with them) arose as a consequence of another type of closure within the nervous system, the brain especially. Proper brain function requires an efficient web of connections and once certain complexity is attained due to the number and coordinated activities of the brain cell networks, the emergent properties of cognition and consciousness take place. Seeking to identify main features of the nervous system organization for optimal function, it is here proposed that while catalytic closure yielded life, neuroglial closure produced cognition/consciousness.

1. Introduction

The understanding of how the integration at multiple levels —from molecules and cells to networks— of the spatio-temporal patterns of nervous system activity results in the expression of specific behaviours represents a significant challenge in neuroscience. More specifically, the emergence of consciousness and self-awareness from the activity of the nervous system remains a subject of considerable interest. In the search to identify some crucial features of nervous system organization for optimal function that may guide the emergence of conscious awareness, it may be worthwhile to compare this matter with the question about the origin of life from a set of chemical reactions, for, after all, cognition is an aspect of the living phenomena. How from the set of reacting molecules —an early metabolism— features associated with life appeared has been partly answered, at least from a global perspective which could well be the most informative level to consider these questions; the works of S. Kaufmann, F. Dyson and others

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indicate that when arrangements of various chemical reactions reached certain complexity, autocatalytic sets emerged spontaneously and metabolic closure was achieved achieved (Dyson, 1985; Kauffman, 1993). Paraphrasing this in the case of cognition/consciousness, it can be asked when from mere perception a nervous system becomes "conscious". It will be proposed in this text that another type of “closure” occurred, not of molecules in chemical reactions but of cell networks interacting with one another in the nervous system, the brain especially. The nervous system emerged in order to perceive and respond to the environment. Primitive nervous systems achieved these two functions but do not possess features associated with higher consciousness like self-awareness, although we can grant them some very basic characteristics of consciousness like perception and action. While delving into the issue of a definition of consciousness is not the purpose of this work, it should be noted that the scientific study of consciousness becomes more feasible if we do not insist on giving a precise and concise one-sentence definition of consciousness, as it can be defined by enumerating characteristics; defining phenomena by their properties is an accepted practice: think of a fundamental concept in science, linearity and nonlinearity, a linear system is defined by two main features, additivity and homogeneity (constituting the principle of superposition), thus these characteristics are used to define linearity. Similarly, life can be defined by features like self-reproduction, genetic transmission, compartmentalization etc., and consciousness can be described by memory, sensorimotor actions, self-awareness and other features that can be investigated in depth; certainly, this sort of “definition” would be very broad, but Max Velmans advised that “Definitions of consciousness need to be sufficiently broad to include all examples of conscious states and sufficiently narrow to exclude entities, events and processes that are not conscious” (Velmans, 2009). In general, definitions are inherently arbitrary and even to define the brain is proving difficult, where a certain vertebrocentric bias is evident (Pagan, 2019).

Before moving on, one consideration is important to emphasise now. For our current purposes, consciousness will be considered through the aspects of awareness and cognition in general, that is, considering crucial psychological features rather than more ethereal, or philosophical, views like the proposal of panpsychism —so popular during the 19th century— and its close relative hylopathism. From a more mechanistic perspective, it should be as well considered that cognition/consciousness is not a static property but a dynamic process, a notion proposed by many scholars (e.g. Haken, 1988), and underlying the dynamics there is a continuum. Whereas humans tend to establish (and subsequently believe in) clear demarcations between phenomena, nature works in a more graded fashion, a sort of continuum. There are reasons to believe that the emergence of consciousness followed a continuum too, was graded and took a long time to fully develop (and even the daily transition from consciousness to unconsciousness and vice versa is graded too, as anyone who has awaken from a deep sleep can attest and as C. G. Jung taught us: “We must accustom ourselves to the thought that the conscious and the unconscious have no clear demarcation, the one beginning where the other leaves off”) (Jung, 1970). Nevertheless, some aspects were more crucial than others in the development of conscious awareness, and one of these is the topic of our discussion.

This most crucial aspect is the large-scale coordinated activity among brain cell networks —the “connectivity”, as it is normally termed in the field although this may not be quite true in many instances due to the analytical methods used, an issue that has been addressed in several publications therefore we shall skip it here— and its related aspect of compartmentalization of brain cells into functionally connected networks. Hence, another important consideration follows: the level of description that may be more relevant to understand or at least characterise some aspects of consciousness. Due to the extremely large number of cells and synapses, the mesoscopic or macroscopic level of description offers some simplification, lest we become lost in the myriad of molecular and cellular mechanisms that are the bases of neuronal interactions. In our current era of biological research, where immense numbers of correlations are being sought among all sorts of quantitative measurements —and particularly in neuroscience massive sets of correlations are produced among neurophysiological magnitudes trying to decipher connectivity patterns of brain cells and their relation to behaviours— simplification is a virtue; as advised by J. W. Gibbs in a letter to the American Academy of Arts and Sciences in 1881: "One of the principal objects of theoretical research in any department of knowledge is to find the point of view from which the subject appears in its greatest simplicity". The characterization at the meso/macroscopic level may afford some simplicity, but it usually requires a few notions that are somewhat difficult to describe; one is the notion of "brain states". Brain activity is normally described from EEG (electroencephalography), MEG (magnetoencephalography) or functional neuroimaging as a superposition of dynamics at different time scales; considering what is known about how the nervous system operates during cognitive states, it is conceivable to infer that the nature of brain states consists of patterns of neuronal coordinated activity —that is, correlations of activity that can be measured as coherence or synchrony. It is already accepted that the evaluation of cell synchrony constitutes an appropriate metric to characterise nervous system dynamics —as stated by Mora and Bialek (2011) "correlations strongly determine the global state". Along these lines, Muldoon et al. (2016) classifies brain states as pairwise correlated activity. But one aspect that is sometimes forgotten in describing brain states is the behaviour —states should be related to specific behaviors— and in this regard Zagha and McCormick (2014) advocated to consider brain states as configurations of cellular activity that are stable for a behaviourally relevant time period. Normally states are dynamic, unfold continuously, and thus a careful use of this term is needed because, as J. A. S. Kelso warned: "overuse and abuse of the terminology of "states" muffles any sense of dynamics" (Kelso, 2008).

Another useful and controversial (or better yet, hard to define in a manner that satisfies everybody) notion at this macroscopic level of description is that of cell networks. In a section below some words are devoted to this matter of defining what constitutes a network. For the moment suffice to say that concepts like states or networks —functional units of activity in nervous tissue— are to some degree abstractions that help scientists communicate; considering the importance of the transient functional communication among neurons for proper information processing, perhaps a fairly adequate formulation of network could be that proposed by Sadaghiani et al. (2010) "gradual clustering according to similar activity profile". Let us now proceed to try to identify crucial features of nervous system organization for optimal function that may guide the emergence of cognition and conscious awareness, taking as a model what has been found in the study of life.

2. Conceptual parallels in the study of life and of consciousness

There are, conceivably, conceptual similarities in the basic principles that have been proposed in the study of life and those that can be advocated as fundamental features of nervous systems that give rise to consciousness. The parallel starts with the fact that it seems impossible to define either, life or consciousness, in a manner that satisfies everybody —the Introduction above proposed to define them by enumerating features, or we could follow J. Swain's advice and develop "many definitions of life [*consciousness*] some more useful than others depending on the situation in question" (Swain, 2002). It can be theorised that, as occurred during the

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development of the set of chemical reactions known as metabolism that at some point reached an organised complexity with characteristics associated with what is called life (e.g. self-replication, compartmentalization…), consciousness (or features associated with it like sensory processing, self-awareness…) arose as a consequence of certain organised "complexity" in embodied nervous systems immersed in an environment.

Let us consider 5 well-known principles about the origin of life (Eigen and Schuster 1982), and translate those, where possible, to the origin of consciousness.

1- Formation of polymers.
2- Competition: selection of polymers via self-replication.
3- Evolution of the quasiespecies (self-replicating molecular entities) towards optimal structures.
4- Cooperation: among competitors via catalytic hypercycles that generate new products.
5- Compartmentalization: of molecules or organelles in separate areas in order to perform their specific functions more efficiently, which in turn allows for efficient evaluation of the relevant functional properties of those new catalytic cycles and molecular structures.

Now, translated to the nervous system and brain in particular with regards to the emergence of conscious awareness, these five principles could read, more or less:

1- Formation of cell networks, via anatomical (e.g. synaptic) connections.
2- Competition: among those networks in order to entrain/engage other connected networks; as well, this leads to synaptic pruning in early development.
3- Cooperation: among those networks via synchronization.
4- Evolution of the optimal structures of anatomically and functionally connected neural ensembles.
5- Compartmentalization into functionally connected networks.

In the case of the nervous system these points could occur more simultaneously than in the case of the emergence of life; for example, it is known that cellular activity shapes the synaptic connections, thus points 1 through 3 would be simultaneously involved in the early formation of brain networks, leaving further refinement (points 4 and 5) for later stages. Note as well that most of these points are based on the —using Kelso and Engstrøm (2006) framework— "complementary pair" cooperation~competition at multiple levels of description, that along with fluctuations are the basic features for the emergence of patterns (Perez Velazquez, 2009). Many times these are two sides of the same coin; for instance, in brain cell circuits neurons *cooperate* via synchronization in order to *compete* against other cell assemblies for the dominance over the next synaptically connected neuronal network down the chain of activations. Cooperation and competition between neuronal ensembles has been addressed in numerous computational and experimental studies, there being an extensive literature on the topic (e.g. Wright and Bourke, 2016) so there is no need to delve into that now. The main interest in this narrative will be the point about compartmentalization of cells in networks and the dynamical aspects of the interactions among these compartments/networks, from where cooperation~competition arises naturally.

3. Compartmentalization in nervous tissue

Compartmentalization is a most fundamental aspect of biological phenomena. It is indeed considered the first step in biological organization and occurs spontaneously due to the drive towards equilibrium (Tanford, 1978) —although sometimes causing non-equilibrium, as for example when the phospholipids making up biological membranes aggregate striving for their own equilibrium but create at the same time a state of non-equilibrium for water-soluble molecules— that along with dissipation (of energy) gives rise to self-organization, the formation of complex structures: “Self-assembly and a process of dissipative structure formation are complementary principles of self-organization” (Amemiya et al., 2017). It is then conceivable that compartmentalization plus dissipation provide the basis for conscious awareness (Perez Velazquez et al., 2019). Moreover, compartmentalization, for reasons described below, is related to another very basic aspect of nervous system structure and function, *recurrence*, and its close relative *self-referentiality* which is one of the pillars of biological phenomena (Goldenfeld and Woese 2011) and consciousness in particular. There are more motives to pay attention to the aspect of compartmentalization of cellular structures in the functioning of the brain or nervous systems in general; a neurophysiological principle of brain function is that neuronal ensembles coordinate their activity via synchronization in a manner that is near optimal for the processing of sensorimotor transformations which result in adaptive behaviours. The coordination among cell ensembles, which can be considered functional compartments, is a subject of intense research in current neuroscience. Methods that use metrics as coherence or synchronization of neuronal activity are commonplace, and it is sort of accepted that synchrony plays a fundamental role in nervous system function, determining important aspects like information transfer (ter Wal and Tiesinga, 2017); the importance of coordinated cellular activity for brain information processing is reviewed in depth in Perez Velazquez and Frantseva, 2011.

In biological systems compartmentalization starts normally by aggregation of lipids forming micelles, then cells, and at higher levels modules of connected cells appear. In the case of nervous systems, two types of compartmentalization can be considered: the modular structure of the brain can be thought of as anatomical compartments whereas the functional compartments are given by the coordinated cellular activity (it is normally considered the neuronal activity as the important in these matters, but glial cells also have an activity and a role in establishing and modulating neuronal connectivity, hence the term that will be mostly used throughout this narrative will be ‘cellular activity’ rather than ‘neuronal activity’). Thus, a functional compartment in the brain can be thought of as a number of cell networks that are synchronous, or functionally connected.

3.1 Modular configuration of nervous systems

Let us review briefly what anatomy and neurophysiology teaches us regarding compartmentalization in the brain. It is always illuminating to consider how a particular phenomenon developed looking back at its origins and the subsequent progression. Thus we find that some of the principal molecular components of neurons occurred before neurons appeared in the biological scene, and electrical excitability emerged long before neurons or nervous systems and continues serving its purpose from sponges to mammals. But once neurons appeared and the nervous system became centralised, at the early beginning there were primitive versions composed mainly of central pattern generators (CPGs) whose basic structure has been proposed to underlie the structure of the mammalian neocortex (Yuste et al., 2005). Therefore a basic compartmental structure may have paved the road to the modern modular organization of brain anatomy.

The modular organization of invertebrate and vertebrate nervous systems has been known for many decades (Leise, 1990). Anatomical and neurophysiological studies revealed that nervous systems are designed in a modular fashion, e.g., neuronal tract tracing unveiled a modular organization consisting of connections linking regularly spaced cell clusters (Galuske et al., 2000; Perin et al., 2000). The basic module has nervous cells organised either in a columnar fashion or in other shapes. The rise of modularity in biological entities has been studied for long time and is considered to represent an advantageous organization for organisms (Lorenz et al., 2011) providing, for instance, efficient dynamics in response to fluctuating environments (Sun and Deem, 2007), thus it is not surprising its presence in the nervous system structure as brain function consists in responding to a variable environment.

In fact, neurophysiological (dynamical) indications at the macroscale level of the anatomical cellular compartments have been found. Functional consequences of the anatomical modules could be the observations obtained with invasive and noninvasive brain recordings indicating that there exist a common collection of network states that seem stable among individuals (Kramer et al., 2011; Betzel et al., 2012; Chu et al., 2012; Jamal et al., 2015; Milz et al, 2016). As well under anaesthesia, correlations in brain activity have been found which are postulated to be an intrinsic property of brain organization, perhaps helping to maintain the already set connectivity patterns (Vincent et al., 2007). Repetitions of spontaneous patterns of neuronal activity, known as synfire chains, have even been found *in vitro* (Ikegaya et al., 2004). Thus, these observations suggest that there seem to be circuits which may have already been moulded in the brain and are continuously active (Harris and Shepherd, 2015). The possibility of pre-configured neuronal functional connectivity motifs has been advanced by several scholars (Tsien, 2015). This tendency to establish functional cellular connected networks is indicated by the electrical spatiotemporal patterns recorded in cell cultures derived from cortical stem cells —termed organoids or “mini brains”— patterns that were similar to those of infants (Trujillo et al., 2018), indicating that there is a tendency to shape functional connections even without external sensory inputs. And at another level of description —the psychological— the findings that neonates can imitate facial actions like tongue protrusion (Meltzoff and Moore, 1977)—behaviours neonates had never seen themselves performing— and the experience of phantom limbs in individuals with congenitally absent limbs (Brugger et al., 2000) suggest again the presence of predetermined brain cellular circuitry.

Nonetheless, the activity of these presumably pre-configured cell ensembles are perturbed by signals from environment and body (interoceptive), and the recordings of ongoing activity normally obtained from brain tissue represent the interplay between the activity determined by the anatomical structure and that imposed by outside signals, activities that are organised in diverse spatiotemporal scales (Sadaghiani et al., 2010). Therefore we encounter again the issue of the notion of neural network, ensemble or module, related terms that have been used in attempts to describe a functional unit of activity and that are, in reality, abstractions that help neuroscientists communicate. The fact is that these groupings of active cells are transient: a main feature for healthy brain processing of information (in its widest sense, see section 5.1 for clarifications of this point) is the transient functional communication among cells about which much has been written thus we will not delve now into the importance of the formation of transient neuronal connections and the pathological consequences when neurons become widespread locked in synchronous activity for long times (extensively reviewed in Perez

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Velazquez and Frantseva, 2011). Therefore a relatively adequate formulation of network in the nervous system could be that aforementioned in the introduction by Sadaghiani et al. (2010) "gradual clustering according to similar activity profile". In the following sections we will see how this transience in the functional neural communications among cellular networks leads to a concept akin to Kauffman's catalytic closure.

3.2 *Functional compartment and the notion of "neuroglial closure"*

Why the importance of discussing compartmentalization in brain activity? As mentioned above, scholars studying the origin of life have proposed that when systems with varied chemical reactions reach certain complexity, autocatalytic sets emerge spontaneously and catalytic closure is achieved in the sense that each polymer has one step in their formation catalysed by some other polymer; in short, a sort of a wide web of interrelations among all of molecular pathways in that metabolism. Apparently, Stuart Kauffman originally proposed the idea of "catalytic closure" when chemicals started to auto-catalyze themselves forming a "closed' web of chemical reactions endowed with certain complexity (Kauffman, 1993) —it should be noted that there has been some criticism to the idea that self-organised metabolic cycles were the main factor in the origin of life (Orgel, 2008).

In an analogous fashion, then, it can be conceived that (features associated with) consciousness arose as a consequence of another type of "closure", not among molecules but among the cells and networks of the nervous system, so that instead of a closed web of chemical reactions we have a closed web of cell networks connections where one can reach any neuron/network in the brain starting from any other —and to be fair, rather than calling it neural closure it could be termed neuroglial closure to include the important aspects that glial activity has on the neuronal function. The nature of the cellular activity in brain is such that cell networks coordinate their activity in order to integrate and segregate information, so the mutual activation of the networks and the fact that in the brain basically everything is connected to everything directly or indirectly suggests that a similar notion of the catalytic closure can be of help to better understand the workings of nervous systems. Here, and having in mind the previous section's comments on the arbitrariness of defining networks, a cell network can be taken as synonym of compartment, but it is more the dynamic aspect rather than the purely anatomical connectivity, it is the functional connection of cells within the networks which defines a compartment, at least for the purpose of this text. Functional compartments that form an intricate connected web may reach closure with certain implications for brain dynamics, as will be seen below. It can be postulated that when this "neuroglial closure" achieved certain complexity, the organism became self-aware, conscious. In the case of metabolism complexity is given by number and variety of molecules, but talking about nervous systems at the cellular, collective level of activity, the "complexity" can be afforded by absolute number of cells (neurons and glial cells), or perchance variety of cell properties, or even number of networks connected. The rest of the text will try to solve these questions with the aid of some high-level perspective which may help shed light on the process to uncover basic principles of brain organization responsible for cognition and consciousness in general, and ultimately to obtain at least an intuition about the necessary and sufficient condition for cognition/consciousness to emerge.

Once again, let's start from the basics, the origins. A look at a basic characteristic of essentially all nervous systems directs the attention to *recurrence* —as aforementioned in section 3 a most basic aspect of nervous system structure and function (Edelman and Gally, 2013) with fundamental physiological and psychological implications (Lamme and Roelfsema, 2000;

Orpwood, 2017)— exemplified in the organization of the central pattern generators (CPGs), structures that appeared very early in evolution. There is an extensive literature on this topic of recurrence that goes as well under other denominations that, basically, denote the same aspect of recurrent —feedback and feed-forward, but without the need for the engineering connotation of feedback as error correcting activity— activity in brain circuitries, like re-entrance, reverberating circuits, bottom-up and top-down, etc. In general recurrence is a factor in the generation of neuronal oscillations (Lewis and Rinzel, 2000) and favours the maintenance of temporally sustained patterns of activity which could underlie the aforementioned common collection of brain recordings that were found stable among individuals; this activity may be called "spontaneous" —with quotation marks because of the great difficulties differentiating spontaneous form evoked activity in the brain (Raichle, 2010)— which is of great significance as it has been shown that spontaneous fluctuations in cellular activity reverberating among ensembles shape the stimulus-evoked responses (Arieli et al., 1996). Before CPGs appeared in the scene, the considered primordial nervous systems —those of the cnidarians— present a diffuse, mesh-like system of nerve cells dispersed over the organism, with some species having two nets that are somewhat connected but the recurrent structure may not be that evident or may not have been studied in detail (Kelava et al., 2015), even though structures known as nerve rings have been identified and considered to be fused axons in which neurons show electrical coupling with gap junctions (Koizumi et al., 2015), indicating that some recurrent activity is already present in these early nervous systems.

Therefore, looking at the origins of the nervous systems one can find what probably constitutes the basis for high cognition already in the CPG, which has the structure essential for the generation of physiologic rhythms derived from the neural rhythms due to diverse synchrony patterns within the CPG cellular networks. CPGs in mammalian nervous systems are embedded in larger distributed structures, e.g. the respiratory CPG (Dhingra et al., 2019), and as mentioned above this basic structure underlies the structure of the mammalian cortex (Yuste et al., 2005). Hence, the recurrent structure of the CPGs offers an illustration of what can be conceived as the aforementioned neuroglial closure. In general in primitive nervous systems, like that of *C. elegans*, the basic structure consists on shared pathways overlapping circuits (Kunert-Graf et al., 2017). In addition, computational studies draw attention to recurrence, as reports that have reversed-engineered brain network architectures generating observed dynamics of real brains have provided evidence for reciprocally connected nets that have distinct probabilities to materialise (Steinke and Galan, 2011).

Inspecting now modern nervous systems, recurrence and overlapping circuits are again found at almost every level, basically the whole brain is a big connected system where one spike could travel from one region to any other, thus reflecting closure. While brains have what seem to be anatomically and functionally segregated regions, such segregation is not complete. It is known that the integration and segregation of sensorimotor transformations is fundamental for appropriate brain function, however, the integration aspect seems to be much better achieved than the segregation, perhaps a sign of the great interconnectedness among brain cell networks. There are numerous illustrations of this not-so-strict segregation, e.g. the visual cortex activation in blind humans during sound discrimination or the impairment in face recognition in patients with alexia after lesions to the visual word form area (VWFA) responsible for word identification, but perhaps synesthesia is the clearest manifestation of how the large brain connectivity can derive in anomalies due to the imperfect partition of sensorimotor transformations. Looks like each brain region appears to be less specialized than names might

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suggest. As well, it has been recently shown in rodents the near unfeasibility to disentangle task-evoked neuronal responses from others unrelated to the specific task (Musall et al., 2019). In sum, it is distributed cell networks rather than circumscribed centres that mediate most of sensorimotor processing. Overall, then, all nervous systems and brains in particular can be considered a functionally closed, self-sustained system of cellular networks that can conceivably be interpreted through the neuroglial closure concept; this has the additional advantage, as will be explained in section 5, of adapting analytical methods that are shedding light on the complexity needed for the origin of the connected metabolism in life's development, namely, RAF (reflexively autocatalytic and food-generated) theory.

4. Neuronal synchronization as equivalence relation: a view on integration and segregation of information in brain activity.

Before considering RAF theory, an interlude is presented related to the abovementioned closure among cell compartments that may help interpret the well-known phenomenon of neuronal synchronization and frequency locking patterns which underlie the nervous system information processing capabilities. It is thanks to the interconnectedness among cell circuits that cellular coordinated activity arises and, out of seemingly stochastic activity at small scales, coherent behaviour emerges at the macroscopic, collective scale (El Boustani and Destexhe, 2010). Talking about connectivity among cells or compartments means talking about the probabilities of connections, both structural and functional. The approaches based on the probabilistic perspective in neuroscience —either probabilities of connections between neurons and networks or as probability of transitions between brain states— has resulted in important insights in the characterization of nervous system dynamics, from the early attempts of the statistical neurodynamics of Amari et al. (1977) to the contemporary probabilistic description frameworks of Friston (2010) or Buice and Cowan (2009) and others (Perez Velazquez et al., 2019). But probabilities, especially transition probabilities, determine a relationship structure on the system's dynamical state space, a result well known in the theory of Markov processes, and therefore the related notion of equivalence classes emerges (Stroock, 2005). However, while transition probabilities between brain states defining accessibility or communication between states is an equivalence relation and thus establish a partition of the state space into equivalence classes of communicating states (interested readers can find technical explanations in chapter 3 of Stroock, 2005), other measures of correlated neural activity are not equivalence relations. For instance, 1:1 phase synchronization. Allow me now a very brief note about synchrony in brain research; we will not delve into the matter of perfect phase synchrony in neurophysiology because as everybody knows there is noise, but even in presence of noise stochastic phase locking exists (Longtin, 1995; Bahar and Moss, 2003), and in any event phase synchrony in neuroscience is understood in a statistical sense as the average phase locking over a time window. Hence, the concept of synchronization in the study of brain —or any other physiological— signals is not the exact mathematical or physical description of it, but it provides a window on the system's coordinated structure/activity.

Going back to the current matter, there are many texts where equivalence relations and the associated equivalence classes are described, being basic concepts in mathematics. For the present purposes it can be said that 1:1 phase locking is not an equivalence relation because while the properties of reflexivity and symmetry are satisfied —if a cell network A is 1:1 phase locked to another network B, then B is locked to A as well, and of course network A is always synchronous to itself— transitivity fails; for instance consider three networks, net A has a pure

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rhythm of 6 Hz and net B oscillates with two frequencies at 6 and 12 Hz, whereas net C oscillates at 12 Hz, thus A and B can be phase locked at 6 and B and C at 12, but A and C are not 1:1 synchronous (they would need the same frequency in their rhythms). On the other hand, n:m frequency locking satisfies this property because A and C will show 1:2 synchrony, hence n:m synchrony (including n=m=1 otherwise reflexivity fails) is an equivalence relation and therefore brings about equivalence classes, that is, a partition of the synchrony state space. A simple way to see it is that each equivalence class (see paragraph below) groups the signals (networks) that have the same instantaneous frequency; this instantaneous frequency may evolve over time so the signals could jump from one equivalence class to another.

What are the consequences of this sort of abstract result on the relations afforded by frequency or phase locking? As mentioned above, an equivalence relation establish a partition of the state space (more generally, of the set containing the elements that are being subjected to the relation, in our case the set is the brain composed of cell nets) into equivalence classes. An equivalence class is defined as a subset of the main set which includes all elements that are equivalent (according to the equivalence relation) to each other, and the different classes establish a partition of the set. Figure 1 depicts the concept of the partition by equivalence classes. In even simpler words, this means that to establish a partition into equivalence classes every element in the set belongs to only one of the subsets, so in the example above for 1:1 frequency locking the equivalence class of A is B, and that of C is B, hence B is in two subsets therefore there is no partition. On the other hand for n:m the class of A is composed of B and C and if there were other sets D and E synchronous (or “connected”) at another frequency then there would be another partition as the equivalence class made up of D and E, so n:m locking partitions the cell nets that are communicating into relatively independent ensembles, partition that of course is dynamically altered as the instantaneous frequencies change and new phase synchrony patterns emerge. Nonetheless, a partition it is.

The previous reasoning suggests that there is no partition of the brain synchrony state space in case of 1:1 frequency locking and thus all brain networks are sort of “connected”. On the other hand there is partition into equivalence classes for n:m locking, which physiologically means that there will be various ensembles (classes) of different interconnected nets processing specific information in each ensemble. Can this scenario be found in experimental recordings? Within the scope of a Perspective article that should not include excessive experimental data, a brief examination of this conjecture was undertaken. Inspection of the pairwise 1:1 synchronization in 4 subjects already studied in Guevara et al. 2016 (three subjects with scalp electroencephalography and one epileptic patient with intracerebral recordings), revealed that in all behavioural conditions —awake, slow wave sleep or epileptic seizures— the signals recorded in each sensor formed a synchronous “giant” cluster in which whereas not all were simultaneously synchronous (that is, there was not an all-to-all synchrony) each signal was synchronous to another which in turn was synchronous to another; the synchronization was evaluated as in Guevara et al. 2016, in brief, a threshold of the phase synchrony index taken from surrogate signals was used to determine two signals “connected” over diverse periods of times that varied between 5-10 seconds to 2-4 minutes, for each subject. For example, in one individual all signals (25 channels in total, giving 300 pairwise combinations) formed a cluster in both wakefulness state and slow wave sleep stage 3, some channels were connected to a few while other channels were connected to many others over the time period evaluated, resulting in the end in a big cluster where all signals were directly or indirectly related; in another subject only one channel (out of 25) remained unconnected, while the rest formed a cluster. In a third subject,

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3 channels (out of 19) were unconnected during wakefulness and one remained so during slow wave sleep stage 2, and the rest formed an interconnected cluster; and in the epileptic patient one channel (out of 9 intracranial sensors) was isolated during normal activity and none during the seizure. Hence with exception of the completely unconnected signals, in all conditions and all individuals the signals formed an interconnected cluster. The same trend of all signals forming a large cluster was observed in subjects recorded with 144 magnetoencephalographic channels (recordings originally reported in Garcia Dominguez et al., 2005). This brief survey of some experimental data revealed the expectation from the aforementioned considerations about 1:1 phase locking about the lack of partition of the synchrony state space, where basically all cell networks are directly or indirectly connected to others. This scenario is reminiscent of the small-world network of graph theory that has been popularised to describe brain activity, a type of mathematical graph in which most nodes are not neighbours of one another but they can be reached from every other node by a small number of steps. And there has been experimental evidence for the abovementioned ideas, to wit, the observation that densely interconnected central hubs of connectivity discriminated conscious versus unconscious states (Chennu et al., 2017).

And how about the possible partitions in case of n:m locking aforementioned? The same recordings were evaluated for 1:2, 1:3 and 1:4 locking. For time periods between 5 and 10 seconds there was a tendency to find several clusters, normally 2 to 4 (some clusters incorporating many signals and others only 3 or 4), whereas for 1:1, as reported above, there was only a giant cluster. Here the duration became important because for long durations, 2-5 minutes, the results for n:m were like those for 1:1: just one big cluster. The reason is that over a long time period the chance that signals become synchronous above the threshold value increases and therefore all signals will be related to one another directly or indirectly. In any event, analysis of short time periods of some seconds in duration is more relevant for normal brain sensorimotor transformations.

This brief survey of the clusters found in some recordings (a more in-depth study using some type of cluster analysis will be undertaken to be reported in an experimental paper) suggests that the relatively abstract perspective based on equivalence relations and classes may be relevant to address some aspects of nervous system function, particularly the segregation and integration of information, fundamental aspects of brain function (Lord et al., 2017). This high level of description indicates a possible cognitive significance of the partition afforded by various n:m frequency locking enhancing localised sensorimotor processing and the difference with the strict 1:1 locking which makes all brain "connected", so to speak, differences that suggest a view on the neurophysiology of the much talked about integration and segregation of information in the brain. In this view, 1:1 locking may benefit integration whereas n:m locking favours segregation. The partition afforded by various n:m locking favours sensorimotor processing in diverse, segregated brain circuits. The intuition behind this is easy to grasp: for 1:1 locking cells must have same frequency, say N Hz, so they would process only the input at N Hz, one input at a time (there would be one equivalence class involving the whole brain, as in a very strong and extensive epileptic seizure, or in a comatose state), whereas for n:m locking if cells have activity at N and M Hz, the cell ensembles could process two inputs simultaneously at N and M Hz. It is this simple. The schematic in Fig. 2 depicts this scenario. Conceivably, then, 1:1 locking favours integration whereas other n:m ratios favour segregation, and because these dynamic patterns occur all at the same time then the simultaneous integration and segregation in brain areas is ensured, for, after all, specialised brain regions may process specific inputs but these need to be communicated to other areas for optimal behaviour. Hence, these results are in line with the remarks in section 3.2 on the apparent functionally distinct individual brain regions that in reality are interacting with one another, because the brain is about circuits, about large-scale patterns of collective coordinated activity.

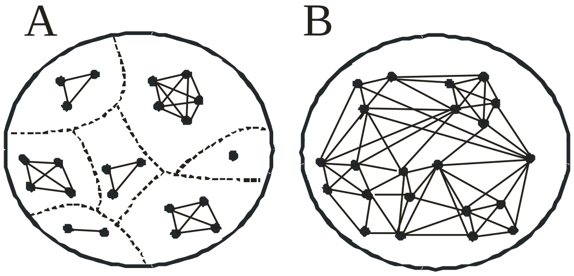

Figure 1. Graphic representation of the concept of partition of the brain state space of cell networks (black dots), some showing a relation (e.g. synchrony, solid lines) that determine the equivalence classes separated by dotted lines. In A there are 7 classes, whereas in B all nets are related (one can travel form one net to any other) thus forming one class. The scenario in A occurs for n:m frequency locking and that in B for 1:1, so that in the former specific inputs can be processed in specialised brain areas while in the latter the processed information can be shared among all necessary brain networks. As such, the simultaneous occurrence of these frequency locking patterns in brain activity favours information processing and normal cognition.

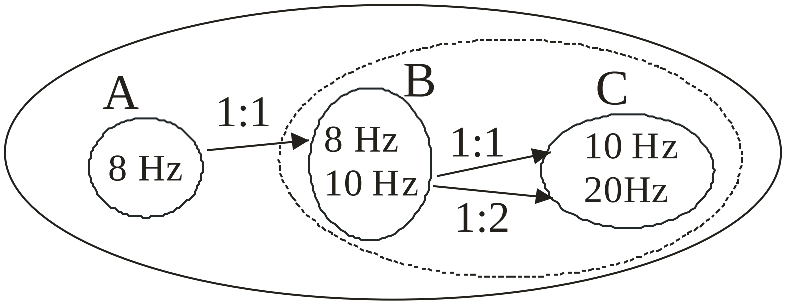

Figure 2. Simple depiction of a partition of the brain synchrony state space using phase (or frequency) locking as a possible equivalence relation, and how it may be relevant to brain information processing. Three cell networks are shown each having neurons that can have activity at the indicated frequencies. The three nets can pass information from A to C in the case of 1:1 locking, A and B oscillating at 8 Hz and B and C at 10 Hz. Thus for 1:1 locking there is only one equivalence class composed of the three nets, but for n:m only B and C can share information by synchronising in 1:2 locking patterns.

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4.1. ***Possible neurophysiological mechanisms correlates of brain synchrony equivalence classes***

While the introduced perspective from a mathematical realm may not clarify specific mechanisms by which the segregation/integration is achieved in the brain intricate circuitry, if complemented with observations at the neurophysiological level it may explain some findings. Among them, data that support the view that the inhomogeneous distribution of brain oscillations serve as a mechanism for linking sensorimotor transformations among diverse brain areas (Engel et al., 1997; Steinke and Galan, 2011). For instance, functional neuroimaging investigations of mechanisms organizing the activities in large-scale neural systems have indicated that coactivations of networks result from globally propagating neural activities (it remains to be known whether this global activity represents 1:1 frequency locking and the specific coactivations reflect other n:m locking ratios, but this is a plausible possibility), and a relationship has been found between global waves propagating across the whole neocortex and transient coactivations among specific cortical areas, observations suggesting that the spatial information of cortical networks characterized by the so-called functional connectivity is embedded in the phase of the global waves (Matsui et al., 2016; Amemiya et al., 2019).

There could be another parallel neurophysiological account which could enlighten the proposed function of the slow brain oscillations (e.g. theta waves) which "tune in" fast oscillations (gamma) —and phase locking has been reported too which led to the proposal that the transient coupling between low and high-frequency brain rhythms coordinates activity in distributed cortical areas providing mechanisms for effective communication (Canolty et al., 2006)— for the transmission of information between different brain regions; this is the relatively well-accepted view of the communication among neurons via nested rhythms, where low frequencies serve as temporal reference for information transfer at higher frequencies (Bonnefond et al., 2017). Of course being slow oscillations does not guarantee a 1:1 locking but in general slow rhythms tend to be better synchronised than faster ones. It may not be coincidence that neurons act as low-pass filters therefore responding better to low frequencies, losing this capacity under some pathological conditions like oxidative stress (Frantseva et al., 1998). As well, these ideas are related to the proposal that communications between (weakly) connected cortical oscillators employ a principle similar to that in frequency modulation, where the frequency of oscillation encodes the channel of communication and the information is transmitted via phase modulations (Hoppensteadt and Izhikevich, 1998).

On a more psychological level, the usefulness of the ideas about equivalence relations and classes describing neurodynamics has been shown in studies that proposed that cognitive macrostates emerge from partition of the space microstates (Atmanspacher, 2015). It can be envisaged that the “cells” (equivalence classes) or partitions of Fig 1 are coextensive with mental states —of course having in mind that these are two different levels of description, the psychological and the biophysical. Each of those cells in the figure could be considered a microstate, and the whole set of microstates constitute, in a specific time window, the brain macrostate; the stability of those partitions on the space of microstates depend on context, that is, the environment (Atmanspacher, 2016). Context, including not only the connection patterns of cell networks but also the environment and behaviour of the organism that contains the nervous system, is a fundamental aspect that will determine the functional relevance and stability of brain “states” (McIntosh, 2004).

In closing and by extension to other phenomena, it can be conjectured that living systems at the biological and societal/ecosystem scales share with the brain the lack of a strict partition, having occurred an evolution towards the lack of parcellation; e.g. in life it happened when a metabolism formed, and in modern societies it is clear the closure afforded by the numerous interactions among people. Perhaps then the route from a partition to global connectedness is a natural consequence followed by all systems.

5. From self-sustaining biochemistry to self-sustaining neural activity: Steps in the search for the complexity necessary and/or sufficient for the emergence of cognition

The previous digression on synchrony as an equivalence relation and the resultant partitions of the brain regions helps establish what can be called the closure principle introduced in section 3.2: all brain regions remain globally connected but at the same time allowing for partitions in which some areas are exchanging specific information. This is akin to a closed metabolic system: the whole set of chemical reactions act as a whole (it is "alive") but there are individual reactions involving a few reagents. As stated above, just think of cell networks instead of molecules.

If catalytic closure yields life, can neuroglial closure yield cognition/consciousness? Just as life started from a very complex chemical set of reactions that crystallised in other simpler giving rise to the early metabolism, brain starts complex with many cells and contacts that are pruned during development. Other scholars, like M. Eigen, have expressed some thoughts close to the present proposal of neuroglial closure: "but if there is mutual enhancement of linked neurons (forming neuronal groups), any cyclic closure may define a 'self-reproductive' firing unit". Notice he uses the words "forming neuronal groups" that have parallel to the equivalence classes aforementioned, and his "self-reproductive firing" is akin to the notion of recurrence commented in previous sections. He also admits that this cyclic closure will not lead to multiplication as occurs in metabolism/life but it will result in properties that can grow like synaptic strength (Eigen, 1994).

The idea behind the proposed neuroglial closure is schematically represented in Fig. 3 using the information flow during integration and segregation of sensorimotor transformations in the brain. It also manifests one principle of brain information processing and representation: convergence for synthesis and divergence for analysis (Fuster, 1995). Of note, the diversification, apparent in that sketch in the figure, of sensorimotor systems in vertebrate brains offers a manner for rapid integration of a diversity of internal and external information which would pose a problem if all processes were to be conscious, thus the importance that only in high level brain areas, probably the prefrontal cortex among others, does the processing enter conscious awareness.

Catalytic closure is considered an emergent property once certain complexity arises, this complexity given by number of polymers and polymer length (Kauffman, 1993). Indeed one straightforward manner to reach complexity is with large numbers of constituents and interactions. Interestingly, investigations on the stability and performance of biochemical cycles revealed that the performance is optimal for a certain large number of molecular constituents, dropping at smaller or larger numbers (Levine et al., 2007), which suggests that optimality may not be only a matter of numbers, rather of coordinated interactions, so we go back again to the notion of brain coordinated activity. In the case of nervous systems, the complexity could be thus given in terms of cell number, contacts and activations; obviously connections —the connectivity— constitute the fundamental aspect, such that basically when a threshold of connectedness is exceeded then the property of closure is satisfied. Because RAF theory is used to quantify the sufficient complexity to reach catalytic closure in terms of molecular size and number of reactions catalysed by any molecule (Hordijk et al., 2011), by extension it is here

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proposed that RAF theory, if it could be applied to the nervous system, could facilitate the quantification or at least the understanding of the sufficient complexity needed for cognition to arise.

RAF theory relies on autocatalytic sets, which in its original inception meant self-sustaining networks of chemical reactions that create and are catalysed by components of the system itself. In simple words, catalytic closure denotes a set of molecules involved in chemical reactions where each molecule is created by (at least) one reaction involving molecules of the set and each reaction is catalysed by at least one molecule of the set. A central notion is that of RAF, a reflexively (R) autocatalytic (A) and food-generated (F) theory which provides a mathematical framework to characterise certain properties of the system. This perspective is related to metabolic closure (Letelier et al., 2006) —already present in Robert Rosen's relational biology (Rosen, 1991)— that can be described in formal terms using RAF theory which finds applications not only to biochemical reactions but also to the study of ecosystems using evoRAFs (Cazzolla Gatti et al., 2018). Neuroscience therefore could perhaps take advantage of this mathematical background developed for the metabolic-related RAF systems.

The central concept of a RAF system in living organisms (Hordijk and Steel, 2017) applies as well to the nervous system: a self-sustaining system from its own and other resources in the environment (in terms of information acquired, sensory inputs...), but the "reactions" in this case could be "activations" of cell networks that are coordinated by units within the system. In the view of Hordjik et al., 2011: "RAF sets should be regarded very much as minimal necessary conditions for such systems, rather than in any sense sufficient". This comment already provides a clue as to the necessary and sufficient conditions we are searching to explain the emergence of cognition and consciousness, which will be addressed in section 6. Going from self-sustaining biochemistry to self-sustaining neural activity is not a great leap —recall the comments in section 3.1 about synfire chains and the relatively stable neurophysiological recordings, all suggesting self-sustaining neural activity.

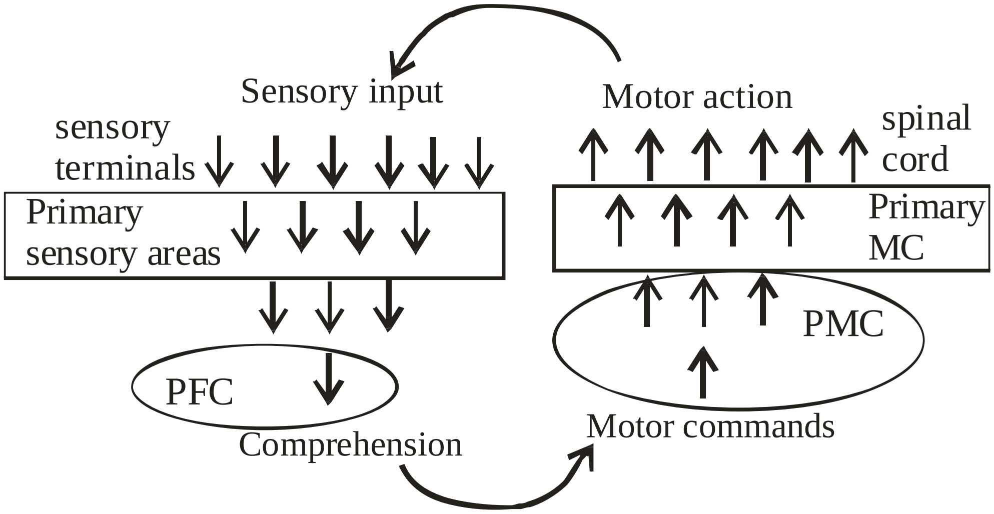

Figure 3. The notion of neuroglial closure is here represented using the integration and segregation of sensorimotor transformations in diverse brain regions, depicted in a very schematic manner where arrows denote pathways taken by information among cell networks. The loop can start anywhere, for instance, after comprehension is reached in certain brain areas (PFC, prefrontal cortex) derived

from the processing of specific sensory inputs that is becoming less and less specialised as it advances towards the PFC, an intention to commit an action starts as a relatively long-lasting high-level intention (at the psychological level) and a high-level motor command is triggered in the PMC (premotor cortex) which becomes more and more specialised running through the MC (motor cortex) until specific motor neurons innervating certain muscle cells are activated to perform the action, which in turn generates a proprioceptive input and the sensory processing stars again. Recurrence is a feature of the global processing of information and as well is present at every step, so in reality all arrows should be double arrows.

Equipped with this RAF formalism, the question of what complexity is enough for a nervous system to reach some sort of cognitive properties can conceivably be addressed. In order to set the stage about how this could be investigated, let us be a bit more precise. A RAF set is defined thus: the set of reactions R is RAF if each reaction in R is catalyzed by at least one molecule that can be produced by the set itself (starting from the food molecules), and all reactants (of all reactions in R) can also be produced by the set itself (Hordijket al., 2011).

A conceivable RAF scheme for a neural system (in parenthesis the equivalent for metabolic systems) would include the set of cells or cell networks X (molecules), the set of activations R (chemical reactions) and the set of networks that are connected to the external environment (the food set). The whole set of nets and corresponding activations would be
N = (x, r), but in the case of the nervous system one network may cause more than one activation, e.g. network A in Fig. 4, thus for this net 'A' a more appropriate expression is N = (A, r1, r3), in general then N = (x, r_i). To visualise it in a pictorial manner, a possible scheme similar to those used to address the reflexively catalytic sets in metabolism is presented in Fig. 4.

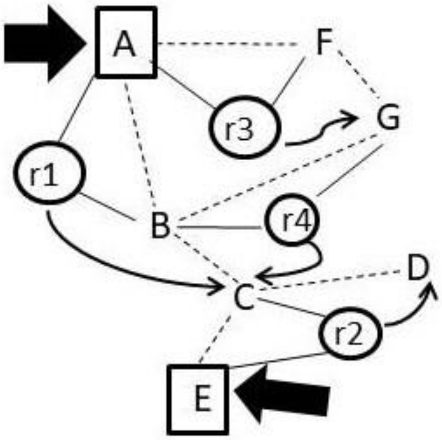

Figure 4. Simple possible scheme of a RAF-like net in the nervous system. Seven brain cell networks (capital letters) are represented. The networks A and E are the "food" nets, where inputs (e.g. sensory) are received and enter the system. The discontinuous lines represent anatomical connectivity. The "reactions", or activations in this case (see text for explanations of the translation from the metabolic RAF to the brain), are represented by circles, and the curved arrowed

lines represent the activations of the corresponding networks cause by the "reaction". Let us assume, for simplicity, that all networks have intrinsic activity and depending on the phase synchrony of the arriving inputs from other connected networks there is activation over a certain threshold that increases the amplitude of the signal (that is, the number of cells active increases) and thus activates another connected nets down the chain of anatomical connections, which results in the so-called functional connectivity. For example, when there is synchrony between the activity in A and in F (represented by r3) then network G becomes active and sends a signal to the connected network B; in this sense it can be said that synchrony between A and F "catalyses" the activation of G via r3 and possibly the synchrony between B and C via r4 and r1.

In the case of the scheme presented in the figure and under the assumption that network C needs synchronous input from B and E to become active, some activations *r* could be:

r1: A + B → C
r2: E + C = E + r1 = E + A + B → D
r3: A + F → G
r4: G + B = r3 + r1 = A + F + B → C

The system portrayed would be RA (reflexively autocatalytic) if each activation $r \in R$ is achieved by the networks involved in R: $\exists xi \in X$ such that $(xi, r) \in N$. RAF theory includes analytical methods to investigate graphs like that in the figure, and some algorithms are common to graph theory (Hordijk and Steel, 2017). Equipped with these techniques, one can address several questions. Of importance could be the analysis of the necessary and sufficient complexity of the system to support closure; for instance, given a probability of neuronal connections, the size or diversity of cellular connections to implement a closed ("autocatalytic" in the original framework) web can be investigated, or how likely it is that such a system appears. It is beyond the scope of this perspective article to probe deeper into these technicalities, rather the main aim is the exposition of the framework. Perhaps a most interesting question to resolve would be when from mere perception consciousness arise —as equivalent to the question of when from mere chemistry life arises, question which was tackled by S. Kauffman and others using the concept of autocatalytic sets and metabolic closure— but to address this question using these techniques may require a substantial extension of the framework to include, among other things, the context and environment in which those neural networks are placed because, as emphasised several times in this text, cognition and consciousness cannot be understood without reference to context and environment, all these things being tremendously interconnected.

Because RAF sets are defined in an analogous fashion to those used in graph theory, the applicability is very general. It is worth noting that the notion of closure, and RAF theory in particular, has been stretched to the origin of culture (a sort of conceptual closure) where mental representations play roles of molecules and the "reactions" are the transitions between those representations (Gabora, 1999; Gabora and Steel, 2017); and as well closure is invoked to understand dynamics of ecosystems (Cazzolla Gatti et al., 2018) or economy as a whole as a self-sustaining autocatalytic set (Hordijk and Steel, 2017). It has even been extended to non-living, robotic systems (Farnsworth, 2017).

5.1 A brief digression about information processing by nervous systems

The word information has been used many times throughout this text and this notion has not been without debate in the field (for a general account of what is conceived and assumed by brain computation and information processing see Piccinini and Scarantino, 2011), hence for the sake of clarity a comment on what is meant in our context is presented. Information processing among cell networks has been used here in its widest sense, in a sort of intuitive manner, to denote sensorimotor transformations that are carried out among nervous system's cell ensembles. The concept of information has several connotations and in general is somewhat relative: "Information is a relative concept that assumes meaning only when related to the cognitive structure of the observer of this utterance —the recipient" (von Foerster, 2003). A row of meaningless (to us) symbols has a computable Shannon information provided the probability of occurrence of each symbol is known, but it has no information for humans. But if those meaningless symbols had been written by aliens who knew the language, the message would contain information to them. So it seems that the information, more precisely the meaning, depends on the knowledge we have, and note the circularity here, saying it depends on knowledge it is saying the information depends on the information we have in our minds, so there is certain circularity; perhaps, then, trying to precisely define information in a most general manner becomes like trying to define other fundamental properties like energy: the definitions are inherently circular (chapter 12 in Nunez, 2010). Nonetheless, the various concepts of information are very useful to address questions in each specific field, the main thing needed is to specify what kind of information one studies or talks about. In case of nervous systems, and to simplify matters, information exchange (rather than information itself) can be conveniently described as the exchange of molecules or energy between cells. Normally this occurs via chemical synapses, but can occur via gap junctions (here it is more evident the direct exchange of molecules and ions) or during ephaptic transmission. Hence, in general information transmission involves a transfer of matter/energy; and because this exchange of matter/energy is what results in the coordinated activity among brain cell networks, thus the study of the brain coordination dynamics is a way to study the more elusive brain information processing. The cellular collective coordinated activity can therefore be viewed as an organised exchange of information amongst cell networks. Along these lines, it has been suggested that consciousness can be considered as an emergent property of the organization of the (embodied) nervous system, especially as a consequence of the most probable distribution of energy (information transfer) in the brain (Guevara et al. 2016; Mateos et al., 2017; Perez Velazquez et al., 2019).

6. Necessary and sufficient conditions for the emergence of cognition and consciousness

Is this RAF theory approach relevant to neuroscience? Could it provide a more formal approach allowing for specific predictions? Besides the aforesaid analytical methods to address RAF graphs, there are other aspects that need attention. According to the works of Kauffman and others, a crucial parameter for the emergence of autocatalytic sets is the probability that a molecule catalyses any given reaction (Kauffman, 1993), which in neuronal terms this could be the probability for neuronal contacts, or the probability for a safe transfer of information from one network to others connected, akin to the evaluation of spike propagation in synfire chains (Abeles, 1982). This synfire arrangement was originally proposed to account for the appearance

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of precise firing sequences because this structure can ensure a fixed level of activity in a network, something which was in fact known before the synfire concept emerged, e.g. the “complete transmission line” of Griffith (Griffith, 1963). Hence, probabilistic approaches that use the RAF framework could shed light on particular aspects, and in this regard neurodynamics has been characterised in terms of probabilistic notions in several works, as it was mentioned in section 4, efforts that started already in the 1970s (Amari et al., 1977) and continue to this day (Friston, 2010; Perez Velazquez et al., 2019).

But the scheme presented in Fig. 4, based on connectivity among cell networks, may lack an essential aspect: the functional connectivity among neuronal nets is dynamic, constantly changing, therefore the need to address the dynamics arises, which could be done using a sort of state space of cell ensembles; the elements could be groups of active cells with correlated activity and hence the dynamics of the evolution in that space can be investigated.

Nevertheless, the similarities from a high level perspective between life and cognitive phenomena prompt us to consider common study backgrounds to investigate them in the search for necessary and sufficient conditions for life and cognition/consciousness to emerge. Thus, compared with living metabolism, the emergence of cognitive properties requires mainly two similar features: exchange of energy/matter to sustain non-equilibrium in units enclosed by a “border” (compartmentalised), and collective phenomena (distributed interactions among system components) resulting in self-enhancement —autocatalysis in metabolism and re-entrance or neuronal self-sustaining activity in the nervous system. Therefore, the notions of closure and RAF theory methods could be useful to explore necessary and sufficient conditions for cognition and conscious awareness to emerge. In fact, the two aforementioned features already suggest two conditions that can be advanced, based on current neuroscientific knowledge: a necessary condition is cellular activity (energy), and a sufficient one could be the organised collective activity of those cells (that is, the energy distribution). The second condition is fundamental because we have to consider that healthy brain states are not about the total energy, or cellular activity, in the brain (e.g. there is enhanced neuronal activity during seizures, after traumatic brain injury and stroke, but the brain is dysfunctional) but rather about how that activity —or energy at another level of description— is organised; Shulman et al. already voiced this point: ”High brain activity is not consciousness; rather, it is a property that provides *necessary* but *not sufficient* support of the conscious state” (Shulman et al., 2009). As well, the second condition would entail the tendency towards the approach to equilibrium, as it is common in all natural systems: systems tend to attain the most probable state (depending on constraints and coupling to external sources of energy) which is a macrostate represented by the largest number of microstates, or equivalently maximal energy distribution. In biochemistry equilibrium means largest number of molecular configurations; in the case of nervous systems we can talk about configurations of connections. Some observations (Guevara et al. 2016; Mateos et al., 2017; Perez Velazquez et al., 2019) indicate that brain macrostates associated with conscious awareness possess more microstates (in terms of configurations of cellular connections) whose emergence and dissolution determine cognitive states.

If a sufficient complexity in the case of metabolism to produce life means large enough diversity of molecule types, in case of the nervous system to produce cognition perhaps it is a large number and diversity of cell types and network interactions: the more diverse, the more aspects of consciousness emerge; for too simple systems composed of relatively low number of cells and connections only reflex-like sensorimotor actions are possible, while adding more numbers and interaction patterns the organism can go from mere reflexes to goal-directed

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actions. But again, the tricky aspect is to address that "relatively low number of cells" mentioned above, which is not a trivial matter and the reason why this text has proposed to use the frameworks of closure and RAF systems.

In examining these questions it should always be kept in mind that cognition/consciousness developed in a graded, continuous fashion. In fact, microorganisms, without any nervous system, have primordial features of consciousness, for instance, they respond to changes in their environment. Continuing with the similarities with the study of life, same thing can be said about the concept of being alive: basic aspects of life are exchange of energy, compartmentalization and self-reproduction, therefore some inorganic materials that have these properties could be considered at least "half alive" (Li et al., 2014; Monnard and Walde, 2015). One should never forget either that these notions we have created, life, consciousness, intelligence etc. are nothing but our inventions and that similar principles of organization apply to the living and the nonliving (Perez Velazquez, 2009). Out there in nature there is a continuum and trying to impose clear demarcations in these concepts may lead to misunderstandings.

Can we then conceive that as more cells and networks are added to those primitive nervous systems, the characteristics of consciousness emerge in a graded fashion? Let us review some basic facts. Recurrent connectivity is a fundamental aspect of brains, and the brain features that may explain the differences in cognitive powers amongst species do not seem to be the absolute or relative brain size, rather the number of cortical neurons and the connections among them (Roth and Dicke, 2005), and especially connectivity patterns are viewed as essential in the emergence of cognitive powers (Manrique de Lara, 2017). It is thus conceivable that the addition of recurrent neural ensembles between the sensory (perception) and motor (action) systems will result in features of conscious awareness emerging. An illustration may be offered by considering the withdrawal reflex in worms. These animals respond to cutaneous touch but not to self-induced touch (such as during crawling); they therefore differentiate between information about the outside world and the self-produced sensory input thanks to the corollary discharge, which consists in the transmission of a copy of motor commands to sensory cortex where the expected sensation is generated. This phenomenon —once termed Feinberg theory (Feinberg, 1978)— allows for a primordial distinction of self and non-self, and it is present in humans too, being associated with disorders like schizophrenia. The few cell numbers and connected networks in worms do not allow them, presumably, for a self-conscious determination of the withdrawal, being just a reflex. Other ancient animals like bees have emotion-like reactions (Baracchi et al., 2017) that while may go under names like "appetitive motivation", in the final analysis these behaviours represent the continuum in cognition alluded above; the essentials are already present in these primordial nervous system Therefore, whereas we can endow these creatures —and even microorganisms as commented in the previous paragraph— some cognitive faculties as they possess some features of consciousness, the many cells and networks with the appropriate connectivity allow humans and probably other animals to go beyond the pure reflex, to display self-awareness and to have all the properties one can think of when enumerating the features of consciousness, and of course one can try to set up a hierarchy in which self-awareness could be at the top, but again, that hierarchy would be our invention.

Hence, while a necessary condition for the emergence of "higher" cognition is the number of nerve cells (neurons and glial cells) and of course their activity, the functional connectivity —or the collective coordinated activity— is the other crucial aspect, perhaps the sufficient condition. Numerous observations, that cannot possibly be reviewed here, indicate the crucial role of the distributed and fluctuating neuronal connections. Just one very illustrative example, the information processing during slow wave sleep (SWS): sensory inputs arriving at these SWS stages activate local primary sensory cortex but there is no conscious awareness, whereas during awake states there is global activation where sensory information is widely distributed, resulting in awareness of that input. This suggests that distributed connections are fundamental. Those connections —the functional connectivity— have to be organised, though. Certain organization of the neuronal activity patterns is necessary for the brain to execute proper sensorimotor transformations. But, as W.R. Ashby reminded us, "Organization is partly in the eye of the beholder […] There is no property of an organization that is good in any absolute sense; all are relative to some given environment" (Ashby, 1962). And herein lies the problem, to resolve the intertwined nature of the environment plus the body that contains a nervous system with a brain. Three components: body, brain and surroundings, and the relations among them result in the neural organised activity leading to adaptive behaviours. A complete understanding of nervous system dynamics necessitates consideration of the interaction with the environment because adaptive behaviours emerge from this interaction dynamics under its boundary conditions/constraints (Warren, 2006). At the risk of belabouring the point, I will emphasise again, using H. Haken words, that it is through the environmental conditions that the collective activity acquires "meaning" (Haken, 1988). Therefore one more necessary condition for the evolution of consciousness can be added to that of enough cellular activity: the presence of an environment. Notwithstanding the very complex nature of these relations, some simplifications can be made in order to start advancing towards a general principle of organization. Some hints about how to move forward have been given by observations suggesting that some aspects of the collective organization of cellular activity in brains may mimic what is found out there in nature, especially considering critical phenomena (Chialvo, 2010) or statistical dependencies (Yufik and Friston, 2016).

7. Conclusions

The notion of neuroglial closure has been introduced as an aspect in the emergence of cognition, building on the proposal of catalytic closure in the metabolism that resulted in the emergence of what we term life. It has been proposed that similarly as it occurred during the development of a connected metabolism, that at some point reached characteristics associated with what is called 'life' due to a catalytic closure phenomenon when chemicals started to auto-catalyze themselves forming a closed web of chemical reactions, features associated with cognition and consciousness arose as a consequence of a closed web of brain cell network interactions where all brain regions remain globally connected but at the same time there are partitions in which some areas process specific sensorimotor information. The global connectivity of all brain areas and the existence of relatively (never strict) independent modules found support by considering neural synchrony as an equivalence relation, from where global and local —integration and segregation— sensorimotor processing emerged as equivalence classes.

Upon some reflection, what this type of closure —after so much talking about closure it is time to point out that scholars in other fields like computer science or philosophy have also other concepts of closure— implies is a fundamental aspect for survival, be it ecosystems, societies, neurons or life all together, for in the same manner that an isolated chemical reaction within a connected metabolism will disappear as soon as its reactants/energy fade, isolated neurons will perish too (recall the abundant observations on the trophic effects of neural communication) or an isolated individual in a society/ecosystem will become extinct. Closure or reflexivity seems to be present at all levels, from the molecular to the societal. Particularly for nervous systems it is reasonable to say that all, including the most primitive, seem to be closed in this sense, as commented upon in section 3. But there could be moments when this closure, this interconnectedness, disappears transiently; for instance, during a localised epileptic seizure. A typical example could be absence seizures, where thalamus and cortex are highly synchronous and sort of detached from other brain areas; as a result the brain loses its global closure, having these 2 networks —considering the cortex and thalamus as networks— as one equivalence class (recall the previous comments in section 4 on synchrony as an equivalence relation) and the rest of brain areas as other classes whose connectedness may have been altered as well by the thalamic-cortical synchrony. The result of this partition is loss of conscious awareness. One could say that a strict parcellation of activity is deleterious for brain function and results in lack of awareness, idea supported by observations demonstrating that disrupted brain modularity in disease leads to dysregulation of dynamical interactions among brain cell ensembles (Alexander-Bloch et al., 2010; Breakspear et al 2003); there are many observations showing the functional reorganization of brain networks in pathological states, reviewed in Castellanos et al., 2011. Overall, the importance of this kind of closure to reach a self-sustaining system is expressed in the words of Hordijk and Steel: “A ubiquitous feature of all living systems is their ability to sustain a biochemistry in which all reactions are coordinated by catalysts, and all reactants (along with the catalysts) are either produced by the system itself or are available from the environment” (Hordijk and Steel, 2017), and this “ubiquitous feature” for a successful self-sustaining system can be found at all levels of description as remarked in this paragraph.

This text has presented a high, global perspective on cognition/consciousness and its relation to the study of life, and the justification for choosing this level of description being that there are questions which are best addressed in a global framework, specially when seeking general principles of organization. The idea that life evolved from very complex chemical sets of reactions that crystallised in other simpler, and the fact that brains start complex with many cells and contacts which are pruned during development already provides food for thought and suggest a possible path towards finding a general principle of brain organization, which the present study has tried to address. In closing, it has been proposed that while catalytic closure yielded life, neuroglial closure produced cognition/consciousness.

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