UNUSUAL MATHEMATICAL APPROACHES TO NERVOUS DYNAMICS

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The massive amount of available neurodata suggests the existence of a mathematical backbone underlying the intricate oscillatory activity of the brain. Hidden, unexpected multidisciplinary relationships can be found when mathematics copes with neural phenomena, leading to novel answers for everlasting neuroscientific questions. We elucidate how and why underrated notions from geometry, topology, group theory/category theory are useful to describe neuronal issues and to provide a series of experimentally testable hypotheses. Once established that geometric constraints are powerful enough to define cellular distribution and drive the embryonal development of the central nervous system, we suggest that the Monge's theorem might contribute to our visual ability of depth perception and that the brain connectome can be tackled in terms of tunnelling nanotubes. Further, we contend that the human mind does not perceive the topological findings of visual images and that the multisynaptic ascending fibers connecting the peripheral receptors to the neocortical areas can be assessed in terms of mathematical approaches like knot theory and braid groups. We show how presheaves from category theory permit to tackle the nervous phase spaces in terms of the theory of infinity categories, highlighting an approach based on equivalence rather than equality. The last, but not the least, we advocate that the far-flung field of soft-matter polymers/nematic colloids might shed new light on the neurulation in mammalian embryos and hypothesize that the development of the central and peripheral nervous systems might be correlated with the occurrence of local thermal changes in embryo-fetal tissues.

Mathematics displays the curious operational feature to be able to describe and predict biophysical issues, despite our scarce knowledge of the relationships between abstract models and descriptive experimental results (Benacerraf 1965; Maddy 1988). Mathematics works in the real world, even if we do not know why (Wigner 1960; Lakoff and Nunez, 2001). It has been used as a unifying language and framework also for the description of neuroscientific issues. Different mathematical fields have been used to cope with neural matters and to tackle the cognitive functions of the brain. In particular, computational neuroscience has provided an effort to go through the intricate matters of the neural activity at different coarse-grained levels (Giusti et al., 2016; Morone et al., 2017; Kang et al., 2017; Yamazaki et al., 2021). Our approach in this paper will be slightly different. We are not going to talk about the mathematics applied to neurodata. We will not consider the areas of calculus and analysis, i.e., the mathematical branches encompassing multivariable calculus, functional analysis and numerical analysis that allow the computation of the ordinary/partial differential equations arising in many neuroscientific applications. We will not focus on the mathematics subtending the implementation of various neurotechniques such as EEG, fMRI, network reconstruction, etc. Rather, we will focus on unnoticed relationships linking mathematical abstract concepts to the neuronal activity subtending the very function on the central nervous system.

We will proceed as follows. Every chapter will be devoted to a different area of mathematics, i.e., geometry, topology, group theory and category theory. We will provide a survey of mathematical approaches and their neuroscientific counterparts that might contribute to improve our knowledge of the central nervous system. Furthermore, we will suggest next-to-come feasible mathematical developments potentially helpful in the experimental assessment of brain dynamics.

GEOMETRY

Depth perception (DP) is the visual ability to perceive the distance of an object and its three-dimensional structure (Wexler and van Boxtel, 2005). DP arises from a variety of depth cues that are typically classified into:

> a) Binocular cues. They are based on the receipt of sensory information in three dimensions from both eyes and include retinal disparity and steropsis (Chopin et al. 2019).
> b) Monocular cues. They provide depth information when viewing a scene with one eye. Monocular cues include relative size (distant objects subtend smaller visual angles than near objects), texture gradient, occlusion, perspective, contrast differences (e.g., texture gradient, lighting and shading), motion parallax, context-dependent interpretation of the size, accommodation (Harris and Wilcox, 2009).

Here we propose a novel mechanism of monocular cue that might give rise to depth perception. Our approach is based on a theorem from geometry, the Monge's theorem (MT). MT states that for any three nonoverlapping circles of distinct radii in the two-dimensional analytical plane equipped with the Euclidean metric, none of which is completely inside one of the others, the intersection points of each of the three pairs of external tangent lines are collinear (Walker 1976). See **Figure 1A** for a pictorial rendering
MT implies that the projections arising from three separated objects (i.e., two- or three-dimensional circles) give rise to a line that is external to the three objects. MT has been operationally used to calculate the correct camera position for the wearing examination of the hob's cutting edge, by calculating the inner points of the Monge cuboid and their parallel shifting (defined by the bijective Monge projections) bordered by a surface (Balajti and Dudás, 2017). Further, MT is still valid even if the plane is equipped with non-Euclidean metrics (Ermis and Gelisgen, 2021).

We suggest to locate the line external to the three objects in the eye lens (**Figure 1B**). This line is produced by three sensed objects located in the environment. Due to MT, the projections of the three objects on the eye lens are slightly far apart one each other. The line is subsequently projected from the eye lens to the retina, giving rise to retinal objects that are slightly far apart one each other. This simple ocular mechanism, that does not involve higher mental faculties, might be the mathematical device that contributes to our three-dimensional perception of the world (**Figures 1C-D**).
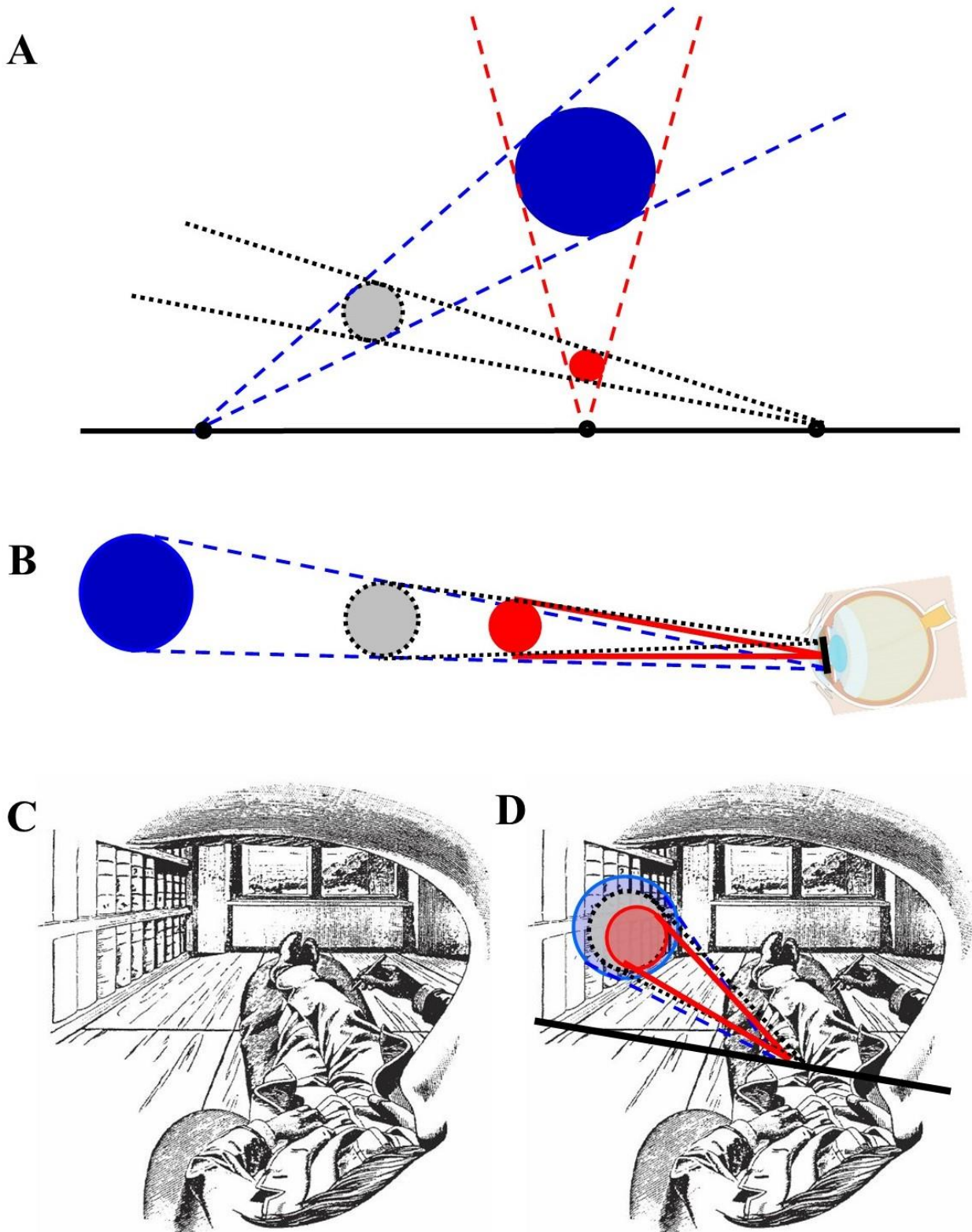
Figure 1. Monge's theorem (MT) for the evaluation of depth perception. **Figure 1A**: pictorial rendering of MT. **Figure 1B**. MT can be used to investigate the physiological mechanism of depth perception. The black line on the eye lens corresponds to the line joining the projections from the three objects embedded in the environment. **Figure 1C**. the "classical" picture of Ernst Mach lying upon his sofa with the right exe closed. "In a frame formed by the ridge of my eyebrow, by my nose and my moustache, appears a part of my body, so far as visible, with its environment" (Mach 1886). **Figure D**. An example of MT's monocular depth perception drawn from the Mach's account. Three objects with different distance from the eye are projected to a line on the eye lens, according to the MT dictates.

Tunneling nanotubes: towards a transient microconnectome? In dynamical systems, simple elements spontaneously aggregate into larger and ordered structures giving rise to different self-sustaining waves such as traveling, rotating, standing and reflected waves/spirals (Bhattacharya and Iglesias, 2019). Following Libet et al. (1983), our ability to make choices might arise from random fluctuations in the background electrical noise of the brain (Bengson et al., 2014). In non-equilibrium systems characterized by self-organization of collective active particles, input-driven local fluctuations lead to the emergence of larger-scale ordering (Chvykov et al., 2021). This is the case not just of artificial devices such as shape-changing robotic active matter, but also of biological assemblies (Linneweber et al., 2020). For example, cellular self-organization promotes follicle pattern in the avian skin (Shyer et al., 2017), while cooperative sets of firing neurons exhibit temporal complexity and emergence of criticality (Lovecchio et al., 2012). Self-organization generates many processes, such as the crystallization producing unusual self-assemblies of small and rigid organic molecules, the gathering of colloids in liquid crystals, the supramolecular assembly of metal alloys, gold nanocrystal superlattices, proteins, viruses, nucleic acids, nervus structures (Montis et al., 2021). It has been proposed that the brain is a dynamical system that moves from a subcritical regime of randomness to a critical state and then to a supercritical regime characterized by absence of complexity (Ribrault et al., 2011; Zare 2013; Wang et al., 2014; Papo 2014). Here the human connectome comes into play, i.e., the hierarchical anatomical/functional network of cortical and subcortical structures. The connectome is characterized by preferential pathways for fast communication and winner-takes-all mechanisms that obey the stochastic forces typical of dynamical systems (Sporns et al., 2005; Reese et al., 2012). A random synchronization-effect has been found inside the connectome, driven by the intrinsic hierarchy of neural timescales and by a heterogeneous, complex network topology (Pang et al., 2020). Community structures of densely interconnected brain regions of the connectome have been operationally defined in terms of a Markov process and random walks with the purpose of studying nervous multi-scale arrangements (Betzel et al., 2013).

Nevertheless, recently discovered microscopic entities screw up the paradigm of random neural networks. Tunneling nanotubes (TNTs) are F-actin-based, transient tubular connections that allow active cell-to-cell transfer of vesicles, organelles and small molecules (Ariazi et al., 2017; Sartori-Rupp et al., 2019) and are involved in human diseases (Goodman et al., 2019; Tardivel et al., 2016). TNTs in primary neurons and astrocytes are possibly correlated with short-range transmission of electrical signals (Wang and Gerdes, 2012; Austefjord et al., 2014) and long-range transfer of electrical messages involving gap junctions (Abounit and Zurzolo, 2012). Developing neurons form transient TNTs that enhance electrical coupling with distant astrocytes and allow transfer of polyglutamine aggregates among neuronal cells (Costanzo et al., 2013). TNTs can be dynamically regulated, since their lengths vary as the connected cells migrate and the distance among them modifies (Austefjord et al., 2014). Their lifetime ranges from a few minutes up to several hours (Gurke et al., 2008; Seyed-Razavi et al., 2013). These features change the idea of a human connectome made of stable nodes/edges and equipped with stochastic, long-standing connexions among brain areas (Van Essen et al., 2013). TNTs might provide a multidimensional inter-cellular transient neural network with peculiar features: the nodes are not stable; the edges appear, modify themselves and vanish with time passing. TNTs can be open on both ends, challenging the dogma of a cell as detectable individual unit (Sartori-Rupp et al., 2019). The recent developments dictated by TNTs start to unveil that the nervous tissue displays a holistic behavior, acting like a system with long-range, multidimensional interactions that does not take into account stochastic issues. A non-stochastic narrative of connectome dynamics also provides an alternative explanation to the observation that some network branches of the brain modules are more visited than others.

TOPOLOGY

Topology deals with the properties of space preserved under continuous deformations, such as stretching, twisting, bending and so on. This means that two shapes of genus zero (or one, or two, and so on) are topologically invariant under homeomorphisms, i.e., they share matching topological description. Topology has been used in neuroscience with a twofold option: by one side, the network topology successfully describes the relationships between the branches and the nodes of the human connectome; by another side, the algebraic topology illustrates the mappings and projections that correlate mathematical abstractions with the biophysical world by using symmetry breaks and widespread invariances. Here we will focus on two underrated topological issues: the visual perception of topological features and the occurrence of braids in our brains.

Do we perceive the topological features of visual images? no, we don't! How do we perceive a visual image? Scholars suggest that we mammals are equipped with topological perception of the visual objects in our visual field. For example, Singh et al. (2008) cast the neural representation in the primary visual cortex in terms of the underlying persistent homology of population activity. Dabaghian et al. (2011) suggested that the hippocampal representation of space in humans and animals can be described in terms of mathematical topological spaces, concluding that the hippocampus is specialized for computing a topological representation of the environment. Chen et al. (2014) proposed the occurrence of a topological code, rather than a topographic one, underlying hippocampal pyramidal cells' spatial tuning during navigation. The use of topological coding is tempting especially in the cases of sparse sample size and fuzzy space mapping. During spatial cognition, Dabaghian et al. (2014) proved that the hippocampal place cells are concerned about the topological qualities (such as connectivity) of an environmental space, rather than its geometric properties (such as distances and angles). Taken together, these results suggest that, when we explore morphing linear tracks, our brain dissociates the geometry of the track from its topology, the latter being highlighted. If the above-mentioned authors are right, we would be able to perceive the topological findings of visual images, such as, e.g., holes, shapes, connected spaces, disjoint subsets.

However, a trivial observation points towards a different conclusion: the human mind does not perceive topological findings of visual images. Look at **Figure 2A** depicting a curtain design: how many spots can be detected? A human individual usually locates fifteen spots (**Figure 2B**). However, by a topological standpoint, the shapes located in the lower part of the picture belong to a single shape, therefore they are connected (**Figure 2C**). This means that the number of spots detected by our brain during visual perception does not correspond to the real topological number of shapes. If our perception would work according to topological rules, we could count a different number of spots, i.e., nine instead of fifteen (**Figure 2D**).

Several Authors have suggested that rules from algebraic and network topology might underlie the neuronal mechanisms, contributing to generate the functions and activities of the human brain (Babichev et al., 2019). However, our simple, rather naive experimental observation suggests that topology plays no role, at least when coping with the macroscopic level of visual perception. This implies that our brain builds internal representations of the external world independent of the topological features subtending visual images.

Figure 2. The topological features of the picture of a curtain design. The perceived spots are in higher number than the identifiable topological spots. See the main text for further details.

Braid groups, nerve fibers and somatotopic maps. Here the focus is tuned on the anatomical intertwining of nervous fibers in both central and peripheral nervous systems, introducing new mathematical players. The description of intermingling peripheral nerves and mingling grey/white matter can be appraised in terms of knot theory and braid groups (Lukyanova and Nikitin, 2018). Knots can be transformed one into another via a deformation of three-dimensional space upon itself and summed in assemblages equipped with commutative and associative properties (Cromwell, 2004). A braid is a collection of strands between two parallel planes (Artin 1947). Braids are termed isotopic when, keeping their endpoints fixed, they can be twisted into each other without cutting the strands. The operations of composition allow braids to be joined to achieve new ones. Given a set of braids with a fixed number of strands, its group structure is provided by generators and fusion rules such as, e.g., associativity, crossing, braiding/unbraiding, intertwining, composition and sequence of elementary braids, and so on. In algebraic topology, a well-established link does exist between braids and knots. Is it always possible to transform a knot into a closed braid: for example, the Alexander theorem states that every knot or link in three-dimensional Euclidean space is the closure of a braid (Alexander 1923). Nevertheless, the correspondence between knots and braids is not one-to-one, because a single knot may have many braid representations. The Markov theorem provides the moves to relate closed braids representing the same knot type (Birman 1974).

Biology suggests several examples of living structures standing for feasible counterparts of mathematical knots and braids. Tissue morphogenesis is produced by coordinated regional changes in cell shape driven by localized contractions of actomyosin "braids" (Bailles et al., 2019). Wire-like flow of electrons and ions along cytoskeletal elements conveying messages from the cell membrane to the nucleus has been demonstrated (Frieden and Gatenby, 2019). The three-dimensional space of neural connexions is severely constrained by physical factors, such as the anatomical overlap of neuronal arbors and the available axonal space to make synapses. The average overlap between the dendritic and axonal

arbors of different types of neurons determines neuron-type specific patterns of distance-dependent connectivity, since higher-order connexions depend on the diverse branching patterns of individual arbors of the same neuronal type (Reimann et al., 2017; Lukyanova and Nikitin, 2017).

Incorporating the mathematical/topological perspective of knot theory in neuroscience appears particularly relevant for understanding brain functions such as, e.g., how the brain represents and processes the environmental stimuli. The arrangement of nervous fibers becomes an example of isotopic braids able to describe the evolution of a multi-particle system equipped with two spatiotemporal extremes: a beginning and an end. Just like the knots are embeddings of closed lines in the three-dimensional space and cannot be reduced to simple circles by a continuous deformation (Wu, 1992), the nerves are structures that do not disentangle completely after being pulled from both ends. The nervous fibers connecting distinct structures of the peripheral and the central nervous systems are shaped as braids. For example, consider the sensory inputs from the external world detected by the peripheral nervous fibers: they follow a multisynaptic, ascending path towards the higher areas of the central nervous system. See **Figures 3A-B** for further details. This means that, if we term "braid group" the whole nervous tract between peripheral receptors and cortical areas, we are allowed to term "knots" the intermediate anatomical/functional multi-synaptic steps. **Figure 3C** tells us that also the anatomical nervous structures studied by tractography can be described in terms of braids. Our suggestion is twofold: a) simple changes in location and arrangement of nerves could explain the activity of the central nervous system; b) the external inputs follow specific nervous paths which can be described in the mathematical terms of braid groups.

The overwhelming complexity of the mammalian nervous system makes it extremely difficult to map nervous anatomical structures to mathematical manifolds equipped with knots and braids. Given the objective obstacle to find the proper group generators, why should we care to describe the nervous paths in the tricky terms of braid groups? What are the (methodological, philosophical, explanatory, medical) benefits? The occurrence of a theoretical link between the anatomical conformation of the nerves (i.e., knots and braids) and the brain activity would mean that different braiding rules might give rise to different nervous functions. Braid groups could be the key to explain the differences among different sensitive cues, since various braids conformations might lead to distinct computational processes/properties of every sensory cortex. Fully different perceptions such as olfactive, auditory, tactile, visive perceptions could be explained by diverse configurations of the braids linking the external receptors to the corresponding sensitive cortex. It is well-established that neural pathways are topographically organized, giving rise to maps that are preserved from the periphery to the cortex (Imam and Finlay, 2020). This could be explained by the occurrence of isotopic braids in nervous fibers: since the strands between the starting and the ending points (i.e., the nervous fibers between the peripheral receptor and the corresponding cortical projection) display the same intermingled conformation, they must carry the same message. This hypothesis does not require that the external message stands strictly in 1:1 relationship with the corresponding cortical area. Due to the braid rules, the relationship between the two extremities of the braids could be either injective, or surjective, bijective, and so on. Therefore, the nervous arrangement of the cortical somatotopic maps could be correlated with the arrangement of the peripheral nervous fibers. The connexions and the entanglement of their extremities give rise to reversible or irreversible topological knots, respectively standing for labile functional activities and stable anatomical tracts. This means that - at least a part of- the human brain diseases might depend on the anatomical configuration of peripheral nerve fibers. Instead of looking for alterations in the central nervous systems, it would be reasonable to look for neuropathological features in the braids and knots of the peripheral nervous fibers.
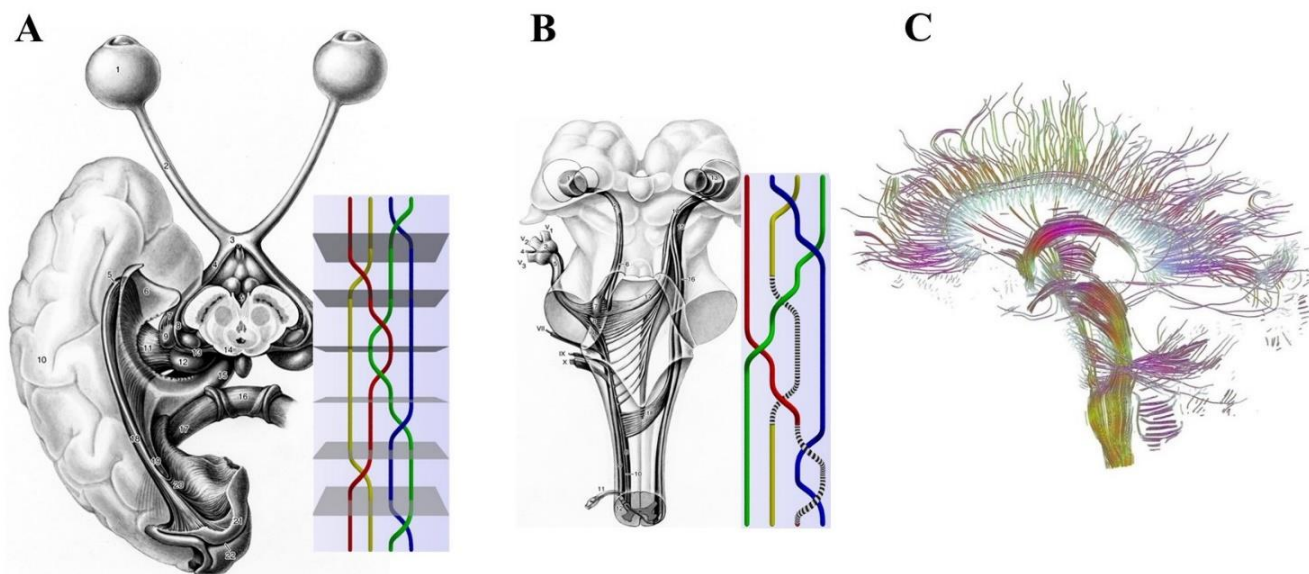
Figure 3A-B. Comparison of nervous connexions in the central/peripheral nervous systems and mathematical examples of braid groups. The Figures illustrate the retino-geniculo-cortical projection in a ventral view (**Figure 3A**), the central connections of the trigeminal nerve in a sagittal view (**Figure 3B**) and their hypothetical braid counterparts. Modified from: http://matematita.science.unitn.it/braids/summary.html and Nieuwenhuys et al. (2007). **Figure 3C**. The anatomical nervous structures detectable by tractography can be also described in terms of braids. Modified from: http://www.sci.utah.edu/~gk/DTI-data/

CATEGORY THEORY AND GROUP THEORY

Once a wheat sheaf is sealed and tied up, the packed down straws display the same orientation. This trivial observation brings us into the realm of presheaves/globular sets that allowS a simple assessment of diverging and superimposing functions. A mathematically well-founded assessment of elusive nervous activities in terms of presheaves as well as the hierarchical information transmission inside globular sets provide fresh insights on different neural issues. Presheaves permit also to tackle the nervous phase spaces in terms of the theory of infinity categories, i.e., an approach founded on equivalence, rather than equality (Lurie, 2003). The key to unlocking the activity of the brain does not lie in single neurons, or single neuronal assemblies, or single neural modules, rather in its abstract functional phase spaces where equivalence, and not identity, holds. Here we will explain this time in technical terms, a novel theoretical approach to nervous paths based on infinity topoi. This permits us to introduce Lurie's theory of infinity topoi (Lurie, 2008) to describe and quantify the paths taking place inside the brain phase spaces. Because sheaf-theoretic methods are powerful and flexible enough to allow generalizations of neural paths, Lurie's theory enjoys formal properties that suggest novel functional phase spaces where brain activities might take place.

Every category of sheaves of abelian groups contains derived functors, called cohomology groups (Grothendieck, 1957), that can be defined as follows:

$$H^n (X, G),$$

where X is a topological space and G an abelian group (Lurie 2003).
This means that the cohomology group $H^n(X, G)$ can be defined in terms of sheaf cohomology:

$$H^n_{sheaf}(X, \underline{G})$$

Where $\underline{G}$ stands for the constant sheaf on X. Remind that a sheaf is a presheaf that satisfies the gluing axiom.
Lurie (2003) generalized this approach to non-abelian cohomology $H^1(X, G)$, tacking also into account the fact that the coefficient system G is not constant and may display different values. This is the case of the brain phase spaces. Specifying G is equivalent to specifying the Eilenberg-MacLane space K(G,1), together with a base point. This observation suggests that the proper coefficients G for non-abelian cohomology $H^1(X, G)$ are not groups, rather homotopy

types, i.e., purely combinatorial entities such as simplicial sets. Sheaves of homotopy types on X can be used as coefficients, achieving a theory of infinite-stacks (in groupoids) on X. Stacks, that are required to satisfy a descent condition only for covering, satisfy the Whitehead theorem: a pointed stack (E,η) can be achieved, for which $\pi_i(E, \eta)$, is a trivial sheaf for all $i>0$, such that E is not contractible. If K is a simplicial set, then the cohomology of X with coefficients K can be defined as:

$$H_{JJ}(X, K) = \pi_0(F(X))$$

Where H_{JJ} is the Joyal-Jardine homotopy theory of simplicial presheaves on X, and F is a fibrant replacement for the constant simplicial presheaf with value K on X (Lurie, 2003).

In brain terms, if X stands for the manifold where nervous oscillations take place and G stands for an operation performed by the brain (say, the oscillatory activity), the following conclusions can be drawn together with Lurie (2003):

1) if X is paracompact, H(X, K) is the set of homotopy classes from X into K.
2) if X is paracompact space of finite covering dimension, then Lurie's theory of stacks is equivalent to the Joyal-Jardine homotopy theory.

The definition of a sheaf depends just on the open sets of a topological space, rather than the individual points; this means that open sets could be replaced by other objects. The stalk F_x of a sheaf F captures the properties of a sheaf "around" a point $x \in X$, generalizing the germs of functions.

In neuroscientific words, we can state the following: even if one looks at smaller and smaller neighborhoods when single neuronal assemblies or tiny brain areas are investigated, no single neighborhood is small enough such that some limit can be taken into account (Serre, 1955). In terms of nervous issues, this means that a nervous object of investigation, e.g., either the single neurons, or the single brain modules, or an assembly of neural waves with the same frequency, stand in relation to each other in many ways. Single neural structures do not count anymore, rather the whole brain activity counts. Summarizing, an infinity topoi approach to neural dynamics suggests that nervous activities can be described in terms of sheaves and presheaves leading us into the realm of the ∞-topos, i.e., a ∞-category of ∞-stakes on a topological space that is correlated to ordinary topos. We are faced with two entirely different approaches to brain dynamics:
1) the customary concept of equality suggests the occurrence of a strict relationship between two entities (say, two neurons, or two neural waves on the brain surface);
2) Lurie's ∞-topos' concept of equivalence suggests that two entities (say, two neurons, or two neural waves on the brain surface) stand in relation to each other in many ways.
In this latter account, the relationships between the entities can be studies in terms of the different forms correlated with homotopy paths, explaining why apparently matching cortical oscillations give rise to highly different inter-individual responses.

Soft matter polymers and embryonal neurulation. The development of multicellular living beings involves morphogenetic processes that shape embryo-fetal structures through the self-organized activity of pluripotent stem cells (Veenvliet et al., 2020). The orchestrated movement of cellular groups requires genetic as well as mechanical and molecular interactions between cells and their surrounding environment (Thompson 1992; Barriga et al., 2018). Migrating cells respond to various stimuli such as cortical tension, luminal pressure and size (Chan et al., 2019), local changes in tissue architecture (Box et al. 219), as well as topographical, adhesive and chemoattractant cues (Dai et al., 2020), duplication of existing regions (Kebschull et al., 2020), topological templates (Dabaghian et al., 2014). Changes in substrate stiffness triggers collective cell migration, suggesting that tissue mechanics combines with molecular effectors to coordinate morphogenesis (Barriga et al., 2018). Here we focus on the morphogenetic dynamical processes characterized by cooperative interaction and collective cell migration of numerous cellular units (Lovecchio et al., 2012), describing an unnoticed biophysical process underlying the very structure of vertebrates' systems. The embryo-fetal development of the central/peripheral nervous system is of foremost importance in this context, since the growth of the neuronal tissue is correlated with the growth of a wide range of distinct structures (Karzbrun et al., 2021).
Brain-derived signals are involved in the regulation of the whole embryogenesis, providing long-range interactions among separate structures. During embryogenesis, unexpected interactions have been described between the nervous system and numerous craniofacial and trunk skeletal elements (Herrera-Rincon et al., 2017; Soldatov et al., 2019). Multipotent Schwann cell precursors detach from their nerve fibers commitment to become mesenchymal, chondroprogenitor and osteoprogenitor cells (Xie et al., 2019). Also, a link has been found between two apparently unrelated processes - gastrulation and neural crest migration - via changes in tissue mechanics (Barriga et al., 2018). In the sequel, our aim is to portray the embryonal neurulation in terms of liquid/crystalline phase of condensed colloidal self matter.

The cellular structures could be viewed as building blocks characterized by liquid/crystalline phases of condensed soft matter where order and fluidity coexist (Qian et al., 2017). Mechanisms for intracellular organization within distinct compartments inside the cell, known as liquid–liquid phase separation, have been recently studied in bacteria and eukaryotes (Hartmann et al., 2019; Ladouceur et al., 2020). Phase transitions drive proteins and other molecules to aggregate into cytoplasmatic and nuclear condensed fluid bodies, generating nonuniform localization patterns and subcellular compartmentalization. These biomolecular condensates include membrane protein clusters, cytoplasmic P granules (Brangwynne et al., 2009), nucleolus, histone locus body, heterochromatin domains (Strom et al., 2017), protoplasmic gelation (Nguyen et al., 2020), amyloid-like assemblies (Boke et al., 2016), intrinsically disordered mixed-charge domains (Greig et al., 2020). Liquid-phase condensates can be viewed as reaction centers where some components become enriched for processing or storage within cells. For example, Garcia Quiroz et al. (2020) found that the keratinocytes of the stratified squamous epithelium undergo a vinegar-in-oil type of liquid-liquid phase separation, crowding the cytoplasm with increasingly viscous protein droplets that drive squamous formation.

Compounds made of "liquid crystals" display properties between conventional liquids and solid crystals that can be experimentally studied in vitro. Mundoor et al. (2018) produced building blocks of a molecular–colloidal liquid crystal formed by micrometer-long inorganic silica-coated disks dispersed in a crystalline fluid host composed of molecular rods. Field-induced motion caused by magnetic fields elicited colloidal interactions between disks in nematic hosts and generated various symmetric conformations with different tangential surface orientations (**Figure 4A**). Within a range of temperature and concentration, the freely diffusing rods arranged themselves orthogonally to the solvent molecules, producing a biaxial liquid crystal. Mundoor et al. (2021) demonstrated that dispersion of isotropic charged colloidal disks in nematic host composed of molecular rods produces nematic, smectic and columnar organizations (**Figure 4A**). While regular polymeric materials respond in linear fashion to external stimuli such as high- temperature material softening, liquid crystals polymers display nonlinear and much faster macroscopic changes (Iqbal and Samiullah, 2013). Under the proper biophysical constraints, it is feasible to realize low-symmetry condensed matter phases in systems with building blocks of dissimilar shapes and sizes. During the embryo-fetal differentiation of the central nervous system, the bodily architecture recalls isotropic, nematic and smectic columnar arrangements (Chen et al., 2017). See **Figure 4B** for further details. It is noteworthy that biaxial nematics can be produced either through long inorganic nanorods and short organic molecules, or board-like molecules, or component mixtures, paving the way to future approaches focused on organic structures. Experimental clues point towards a relationship between biological elements (in our case, the nervous elements) and phase changes: for example, the assembly of the developing synaptic active zone requires the liquid phase of the scaffold molecules (McDonald, 2020).

Summarizing, we suggest to investigate the relationship between the processes of liquid crystals arrangements and the formation of the embryonic neural structures. To further scrutinize this hypothetical correlation, we provide a testable hypothesis. It is worth mentioning that the collective phenomena of colloidal interactions between disks in nematic hosts described by Mundoor et al. (2018 and 2019) are thermotropic, i.e., they are temperature-driven and temperature-dependent. Increases in temperature in such thermally reconfigurable monoclinic nematic colloidal fluids lead to unusual transitions towards more-ordered states. When temperature is lowered, symmetry-breaking phase transitions lead at first to transition from isotropic liquid to nematic phases and then to liquid-crystal smectic phase (Qian et al., 2017). In touch with classical polymer physics, Kießling et al. (2013) observed a systematic deformation of the viscous cellular matter upon temperature changes. This enables us to draw an intriguing suggestion that correlates differences in cellular temperature with developmental outcomes of the nervous system. Variations in thermal conductivity within biological cells point towards the occurrence of transient temperature spikes and heat flux for short-distance thermal signaling (Sotoma et al., 2021). These non-stationary local fluctuations of cellular temperature are worth exploring. The neocortex displays thermal gradients observed at many spatiotemporal scales (Wang et al., 2014). Tanimoto at at. (2016) quantified the temperature difference in human-derived neuronal cell lines and concluded that the temperatures in cell body and neurites are different. Membrane patch temperature impacts neuronal activity through adjustment of the opening and closing rates of ion channels (Xu et al., 2019), so that local changes in thermal properties modulate presynaptic and postsynaptic events, sensory stimuli, memory encoding and behavioral changes (Long and Fee, 2008; Kalmbach and Waters, 2012). Thermodynamic arguments point towards a relationship between changes in temperature and message content, since modifications in thermic flows are correlated with variations in thermodynamic/information entropies (Jizba and Arimitsu, 2001; Jizba, 2015). Fluctuations of thermic properties across biological regions can be absorbed into the thermodynamic frameworks of dynamical systems theory. This means that the critical slowing related to decreases in temperatures of living systems is mandated by any system which provides an effort to minimize its own energetic expenditure.

To sum up, the development of the central and peripheral nervous system could be linked with the occurrence of local thermal changes in embryo-fetal tissues. Changes in local temperature during embryogenesis might lead to anatomical modifications in the final shape of the central and peripheral nervous systems.
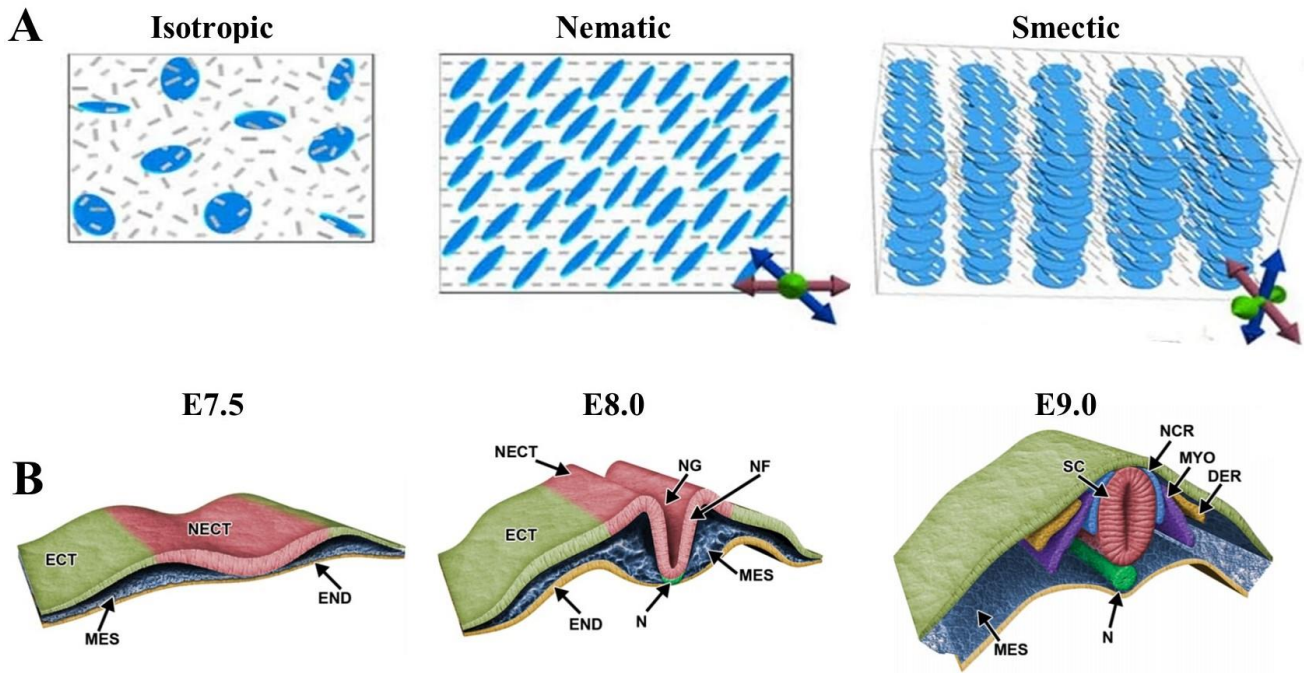
A | Isotropic | Nematic | Smectic

B | E7.5 | E8.0 | E9.0

Figure 4. Comparison of two seemingly uncorrelated phenomena. i.e., liquid crystal phases and embryonic development of the nervous system. **Figure 4A**. Mixtures of molecular/colloidal rods and disks of fluid condensed matter give rise to temperature-dependent columnar chains that display different uniaxial symmetries. Depending on the structural arrangement, we achieve isotropic, nematic and smectic liquid crystals. Modified from Mundoor et al. (2021). **Figure 4B**. Schematic transverse sections of neurulation in the mouse embryo at different stages of development. While the primitive confined neuroectoderm at E.75 recalls isotropic liquid crystals (**left picture**), the converging neural folds at E8.0 remind the arrangement of nematic liquid crystals (**middle picture**). In turn, the spinal cord at E.9.0 evokes the typical arrangement of smectic liquid crystals (**right picture**). Legenda: E: embryonic age in day; DER: dermatome, ECT: ectoderm, END: endoderm, MES: mesoderm, MYO: myotome, N: notochord, NECT: neuroectoderm, NF: neural folds, SC: spinal cord. Modified from Chen et al. (2017).

CONCLUSIONS

Our account emphasizes the value of the mathematic-framed mechanisms shaping the structure and the activity of biological entities. Simple changes in the arrangement of the anatomical and functional nervous structures might elucidate (at least partially) the activity of the central nervous system. In touch with the old claims of D'Arcy Thompson (1992), we conclude that the arrangement and the pattern make the function in countless biological instances. Geometric constraints are powerful factors able to define shape, size and cell distributions, drive crucial biological phenomena and give rise to deterministic patterns that are predictable and reproducible. For example, methods to develop spatial and temporal control of stem cell–derived epithelial organoids have been described, thereby rendering a stochastic process more deterministic (Gjorevski et al., 2022). Showing that natural three-dimensional natural rock fragments reproduce the Plato's cube, Domokos et al. (2020) demonstrated that distinct fragment patterns tend towards a ubiquitous, standard shape. Geometric constraints stand for overarching design principles for icosahedral and octahedral architectures that can be formulated in terms of Archimedean lattices (Twarock and Luque, 2019). The spontaneous occurrence of peculiar self-assembled artificial structures suggests a comparison with the design of natural organic crystalline materials such as the nervous structures. In particular, a fullerenic-like geometry is widespread in our universe (Palotás et al., 2020). Both artificial and natural quasicrystal structures can generate fullerenic-like self-assemblies grounded on simple geometric rules (Montis et al. 2021). The same fullerenic structures have been recently proposed to explain some features of the cortical microanatomy (Tozzi et al., 2017a). The tubular cortical microcolumn, i.e., the embryological, anatomical and functional basic unit of the brain, can be flattened to form fullerene-like two-dimensional lattices equipped with about 80 nodes corresponding to pyramidal neurons.

A mathematical-framed approach to scientific matters such as the neuroscientific ones provides a metatheoretic starting point that might be termed "testable rationalism": sharp experimental previsions arising from top-down, deductive mathematical approaches. Technical devices such as group structure and generator operations point towards a novel approach to long-standing questions concerning human sensation and perception, leading to the suggestion that the very structure and intermingling of nervous structures might contribute to the cortical brain activity. Since the dynamical processes of living systems are characterized by the cooperative interaction of many units, we are allowed to portray the development of the central and peripheral nervous systems in terms of assemblies of building blocks dictated by mathematical constraints.

We want to give a further, last suggestion, this time drawn from algebra and number theory. Are there elliptic curves in the brain? Elliptic curves, generated through cubic equations, are characterized by two-dimensional paths devoid of either cusps or intersections (Young 2006). These curves are embedded in algebraic two-dimensional finite fields defined in terms of points and integer/rational numbers (Gebel et al., 1994; Heath-Brown 2004). Both classical neurotechniques such as EEG and fMRI patterns and novel one such as Diffusion Tensor Imaging and Diffusion Tensor Tractography describe neural wavefronts and projections that roughly resemble elliptic curves (Alizadeh et al., 2019). Therefore, a mathematical account suggests the possibility to examine the brain anatomy/activity from afar, looking for the possible presence of abstract subtending structures. The obvious question is: what elliptic curves bring on the table in the assessment of the nervous activities? Elliptic curves might stand for the abstract counterpart of the anatomical neural projections lying inside the finite field of the brain. Operationally, a brain including elliptic curves could be partitioned in numbered zones characterized by integer and rational numbers. These zones could be assessed through number theory, complex analysis, algebraic geometry and representation theory. Since elliptic curves are abelian (Kühne 2021), they are equipped with symmetries apparently hidden at first sight. The occurrence of these hidden symmetries would allow the matching and simultaneous activation of neuronal tissue located in far-flung brain areas. It is noteworthy that half of the elliptic curves displays a finite number of rational numbers, while the other half displays an infinite number of rational numbers (Smith 2017). In operational terms, this means that half of the nervous patterns are continuous, while half are discontinuous and arranged in spatiotemporally quantized steps. The last, but not the least, elliptic curve is a type of cubic curve whose solutions are confined to a region of space that is topologically equivalent to a torus. This means that anatomical and functional nervous trajectories could be assessed in the easily manageable terms of trajectories occurring inside a torus, as suggested by Tozzi et al. (2017b).

As a final remark, we would like to emphasize that our experimental suggestions are technically achievable with the current technology. Concerning, for example, our novel approaches to the mechanisms of nervous growth correlated with the liquid crystals and embryonic development of the nervous system, it is noteworthy that the recent availability of artificial embryonic trunk-like structures from mouse stem cells' aggregates (Telley et al., 2019) provides the exciting possibility to study in vitro complex developmental processes.

STATEMENT

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