

BUILDING A MINIMUM FRUSTRATION FRAMEWORK FOR BRAIN FUNCTIONS IN LONG TIMESCALES

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Running Head: from proteins folding to brain activity

Keywords: Minimum frustration principle, brain, nervous system, energy landscape, evolution, timescale

The minimum frustration principle is a computational approach which states that, in the long timescales of evolution, proteins' free-energy decreases more than expected by thermodynamical constraints as their aminoacids assume conformations progressively closer to the lowest energetic state. Here we show that this general principle, borrowed from protein folding dynamics, can be fruitfully applied to nervous function too. Highlighting the foremost role of energetic requirements, macromolecular dynamics, and, above all, intertwined timescales in brain activity, the minimum frustration principle elucidates a wide range of mental processes, from sensations to memory retrieval. Brain functions are compared to trajectories which, in long nervous timescales, are attracted towards the low-energy bottom of funnel-like structures characterized both by robustness and plasticity. We discuss how the principle, as derived explicitly from evolution and selection of a funneling structure from microdynamics of contacts, is different from other brain models equipped with energy landscapes, such as the Bayesian and free-energy principle and the Hopfield networks. In sum, we make available a novel approach to brain function cast in a biologically informed fashion, with the potential to be operationalized and assessed empirically.

SIGNIFICANCE STATEMENT

The aim of this paper is to evaluate whether the minimum frustration principle (MFP), a powerful theory developed to solve the protein-folding problem, can also provide insights into brain functioning. MFP is a computational approach based on the fact that the proteins' free-energy decreases more than expected by simple thermodynamic constraints, as they assume conformations progressively closer to the native state. We consider the neuronal background for a MFP theory of the CNS, in the attempt to achieve a proper brain phase space where mental operations might take place.

Current advances in human neurosciences shed new light on questions concerning the functional architecture of the nervous system and the status of mental and its relation to the physical. Novel innovations such as optogenetics (Deisseroth, 2014) and transcranial stimulation (Filmer et al., 2014), focus on establishing causal relations between specific aspects of neuronal activity and system-level consequences. Many people, although emphasizing the molecular basis of synaptic plasticity, accept the idea that broad methodological investigation and general theories are needed to further advance our understanding of the brain, despite the intrinsic simplifications offered by such general frameworks. Several global theories have been developed recently about the nervous system's functions, such as the role of rhythms/oscillations (Buszaki and Watson, 2012), computational models (Magosso et al., 2008; Izhikevich, 2010), connectome (Van den Heuvel and Sporns, 2011), dynamical system theories, nonlinearity and metastability (Fraiman and Chialvo, 2012; Deco and Jirsa, 2012), Bayesian approaches and the free-energy principle (Friston, 2010), information theory and multidimensional manifolds (Tononi, 2008; Sengupta et al., 2016), reductionist approaches based on atomic or molecular changes (Freeman and Vitiello, 2008) and supramolecular chemistry (Tozzi, 2015).

Based on recent findings, the aim of this paper is to evaluate whether the *minimum frustration principle* (MFP), a powerful theory developed to solve the protein-folding problem and can also provide insights into brain functioning. MFP is a computational approach based on the fact that the proteins' free-energy decreases more than expected by simple thermodynamic constraints, as they assume conformations progressively closer to the ground (native) state (Bryngelson and Wolynes, 1987; Bryngelson et al., 1995).

This paper comprises six sections. The first section elucidates the minimum frustration principle in its natural framework, namely, protein folding. MFP has an energy funnel-like structure, equipped with a transitional ridge that ensures the fastest and more efficient protein activity. To build a theory with physiological bases, section two covers the mental and functional correlates of the minimum frustration principle in the context of brain activities. To achieve a proper brain phase space where mental operations might take place, the third section considers the neuronal background for a MFP theory of the central nervous system (CNS). Section four provides a mathematical treatment for technical readers. Section five elucidates the differences between MFP and the current, most successful models of brain activity. In the final sixth section, we

speculate about the hypothetical molecular mechanisms of MFP, namely, dewetting transitions and protein “knots”.

1. THE MINIMUM FRUSTRATION PRINCIPLE FOR PROTEIN FOLDING

The concept of MFP, a statistical description of protein’s potential surface, is framed within the energy landscape theory (Ferreiro et al., 2011; Sutto et al., 2007). The most efficient physical and biological systems tend towards levels of minimum free-energy and MaxEnt, or, in other words, try to reach the deepest valleys embedded in the energy landscape. The ideal, most efficient landscape is a *smooth*, funnel-like one, where the energy trajectory rapidly converges towards the lowest energy bottom. However, in most examples this is not the case and the systems are said to be “frustrated”. The term *frustration* refers to systems where competing energy interactions occur and the energy landscape is *rough*, *i.e.*, it is not possible to reach the minimum level of energy due to the large number of peaks and asperities. The classical example is a spin glass, *i.e.*, a magnetic system in which spins are randomly arrayed in a dilute alloy. In a spin glass, the interactions between spins are equally often, with spins both at random ferromagnetic (spins tend to point in the same direction) and anti-ferromagnetic (spins tend to point in opposite directions). Hence, the two conflicting local tendencies (parallel spins versus alternating spins) cannot be satisfied completely in any arrangement of spin orientations (Bryngelson et al., 1995). Due to the intrinsic constraints given by the interactions among its components, the system is equipped with many local minima and cannot reach a single lowest possible energy level, *i.e.*, the steep funnel-like tunnel in which “minimum frustration” takes place. Thus, in most systems, the tendency towards low energy states go hand-in-hand with a residual degree of frustration (Rijito and Verkhiver, 1996). For technical readers, the next paragraph displays a mathematical treatment of frustrated systems’ dynamics.

The Minimum frustration principle for protein folding. In a spin glass, let m , x , Ω , and $m(x)$ be respectively: the magnetization, position, region occupied by the material, temperature dependent magnitude of ferromagnetic material, and potential, where $|m(x)| = f(\theta)$, $x \in \Omega$, with $f(\theta) = 0$, for $\theta \geq \theta_c$, where θ_c is the Curie point. The energy of a ferromagnetic material is assumed to have three parts, namely, exchange energy, anisotropic energy and magnetostatic energy (James and Kinderlehrer, 1990; James and Kinderlehrer, 1991). The frustration in the system results from the competition between anisotropic energy, that requires constant magnetization strength and direction, and an induced field energy that tends towards zero. The system’s energy can be written as a Lagrange functional, expressed in terms of potential u and constant applied field h_o :

$$L(m, u) = \frac{1}{2} \int_{\Omega} |\nabla_u|^2 dx + \int_{\Omega} (m \cdot (h_o - \nabla_u) - \varphi(m)) dx$$

Then, for appropriate variations of u , total system energy $E(m) = -\inf_u L(m, u)$, *i.e.*, the negative greatest lower bound of the Lagrangian $L(m, n)$ relative to varying potential u . Minimum system energy is then expressed in the following way:

$$-P^* = \inf_u E(m; h_o) = -\sup_m \inf_u L(m, u), \text{ and let}$$

$$N \subseteq \{m(x) : |m(x)| = 1, \text{ almost equal in } \Omega\}, H = H^1(\Omega^3), \text{ so that}$$

$$P_N^* = \sup_N \inf_H L(m, u), \text{ and } P_N = \inf_N \sup_H L(m, u), \text{ with}$$

$$P_N^* \leq P_N \text{ (approximate minimum energy).}$$

P_N^* represents approximate minimum system energy, provided

N is not all functions m with $|m(x)| = 1$. In general, ferromagnetic material is unstable in the single domain state. For mathematics underlying this view of system energy, see (James and Kinderlehrer, 1990). Isayev observes that there is a competition between ferromagnetic and anti-ferromagnetic spin ordering (Isayev, 2003).

Minimum frustration’s Hamiltonian in protein folding. Let

m_i be a coarse grain variable with values 0 or 1. The folding pathways of proteins are described with the Hamiltonian H defined by

$$H = -\varepsilon \sum_{[i,j]} m_i m_{i+1} \dots m_{j-1} m_j \text{ with the summation}$$

over native pairs $[i, j]$, $i < j$.

H is a Go-Type Hamiltonian with minimal frustration (Itoh and Sasai, 2006), used by Munoz and Eaton (1999), Henry and Eaton (2004) to analyze free energy landscapes and rates of folding many proteins. Because foldability, due to the specific energetic constraints of minimum frustration (which requires specially shaped energy landscapes resembling a funnel and a transitional ridge: Wolynes, 1996), the effect of non-native interactions and energetic frustration is strongly minimized and the energy gap between native and misfolded structures is maximized (Das and Matysiak, 2005).

However, evidence from theory and from simulation in protein folding studies indicates that the more stable proteins are “minimally” frustrated heteropolymers, *i.e.*, they are equipped with a *pure* rugged funnel-like landscape which molds the roughness underlying the detailed protein dynamics (Sutto et al., 2007; Frauenfelder et al, 1991; Hegler et al., 2008). Proteins are enriched by evolution to select amino-acidic sequences with the propensity to fold into the lowest possible energy structures, giving rise to very stable, minimally frustrated conformations. As a result, a strong energy bias towards the native basin occurs, overcoming both the asperities of the landscape and chain entropy (Onuchic et al., 1997). A positive correlation has been found between contacts with longer transition path lifetimes (the “native” contacts) and the number of residue contacts made in the native structure (the aminoacids that interact in the fully folded protein). The minimum level of energy (corresponding to the minimum frustration) is achieved when both a high number of native and residue interactions occur, leading to a faster and more efficient folding process (**Figure 1**). The “classical” funnel-like energy landscape used to describe protein folding is typically characterized by the energy, the fraction of native-like contacts and the entropy. However, in the present manuscript the x-axis displays the number of residue contacts instead of the entropy. Notice that, with a decrease in the number of residue contacts, each one quantitatively represented by numbers greater than 1, there is a corresponding decrease in entropy. For example, let 4,5,8 represent residue contacts with corresponding entropy 1.09861 and let 4,8 represent a reduction in the number of residue contact with corresponding entropy 0.693147. In the 3rd section, we construct a brain phase space corresponding to the one characterized by residual contacts (on the x-axis) and native interactions (on the z-axis). It means that in our phase

space (without the use of entropy), the energy landscape still has the shape of funnel, because the entropy or the systems' size still shrinks down towards the zero.

It has been shown that a minimally frustrated folding process (overtaking the native contacts' inhomogeneity, the non-native interactions and the residual local frustration), passes through a very fast transitional state, called "trasversal ridge", and points towards the lowest possible energy levels. Minimal frustration is very important for protein function. It is a critical prerequisite for fast kinetics and thermodynamic protein stability (Verkhiver and Rejito, 1996). Timescales enter into the picture when we consider the duration of minimized frustration: the actual value of the energy difference needed to ensure a funnelled, ridged landscape depends on the biological constraints of the folding timescale (Wolynes, 1996). In sum, in the long timescales of evolution, proteins tend towards an energy state of "minimum frustration" (Bryngelson and Wolynes, 1987; Bryngelson et al., 1995).

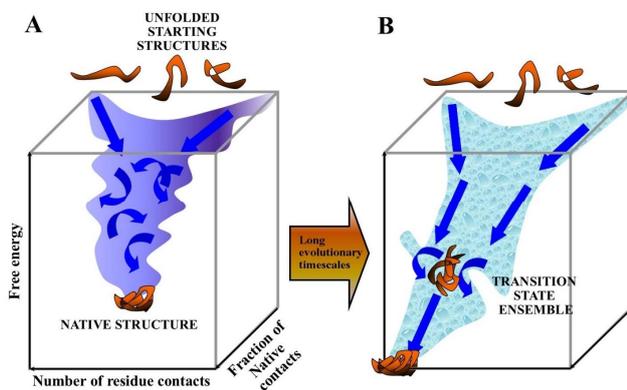


Figure 1. Protein folding (from the unfolded starting subunits to the native final structure) framed in the context of the energy landscape theory. The phase space is equipped with three parameters: the x-axis displays the number of residue contacts among the aminoacids endowed in the protein structure (e.g., the contacts among the aminoacids forming a protein). The y-axis displays the free-energy, while the z-axis the number of homogeneous "native" interactions among the aminoacids endowed in the protein structure. The arrows point towards higher values of the corresponding parameters. **Figure A** depicts a partially frustrated final conformation, while **Figure B** shows the minimum frustrated final conformation of a folded protein. Note that, when MFP taking place, the folding sequence dictated by long evolutionary timescales is pushed towards a funnel-like conformation of the energy landscape, equipped with a transitional "ridge" and with an ultimate very low level of free-energy. See the text for further details.

2. POSSIBLE FUNCTIONAL CORRELATES OF MFP FOR BRAIN ACVTIVITIES

The very general scheme of MFP might stand for a large repertoire of brain functions and activities such as sensations and perceptions, emotions, mood-state and affect, memory. For the meaning of these terms, refer to Andrews-Hanna et al. (2014). Recent data point towards the cortex as *phrenological*. That is, the cortex is comprised of extremely heterogeneous cells, with distinct regional variations, macromolecular assembly and intrinsic microcircuitry (Spruston, 2008; Yates, 2014). This suggests that every neuron (or group of neurons) embodies

different molecular information and displays different types of spiking responses (Haustein et al., 2014; Tozzi 2015), even if they retain the same broad-spectrum of energy mechanisms. This also suggests that every different brain function depends on changes in the phase space which take place in different anatomical areas or subareas.

Many brain functions can be described in terms of trajectories falling into a funnel-like attractor, which is a steep tunnel located in a functional phase space where trajectories converge as time progresses. Looking for possible mental counterparts, we may hypothesize that, when the particle falls into a partially frustrated tunnel, the correlated mental activities could be either erratic patterns of movements or thoughts, or vanishing memories, or mind wandering, or unsure perceptions, in which different ideas are not properly melted together. In turn, when the particle falls into the frustrated steep, narrow, funnel-like tunnel, the correlated psychological activities could be, for example, preserved memories, or sharp sensations of "known" objects, or accurate motor patterns, or sure perceptions due to the confluence of different sensations, or disparate, unsure thoughts which converge towards a single, fixed idea.

As an example, during visual sensation, we may hypothesize that the energy is minimised in fixed point attractors, which modulate the free-energy and underwrite the perception of *known*, *unambiguous* spatial objects. When instead the trajectory falls in a rough landscape, it is not able to reach the lowest energy level, because it is trapped in the asperities of the *frustrated* funnel: it means that the perception is not *sure*, but problematic. Again, for example, recognition decision response to environmental stimuli, set in the many signalling timescales of brain function that are evolutionary constraints in protein folding, is subject to the MFP. An energy gap occurs in our fitness landscape between a well-defined global minimum state and a dynamic transitional one (the bridge), which simulates the stimuli system's behaviour before it settles into the global minimum. The sequences of stimuli are constrained: due to the continuous exposure to the same stimulus, the energy landscape becomes a funnel-like functional state. Amidst the valleys and peaks, larger variations in energy gap lead thus to deep funnels, which inexorably draw the neuronal recognition decision activities to themselves (Deco and Jirsa, 2012). In other words, the different signalling timescales occurring in brain during the processes of perception give rise to strictly constrained functional outcomes, conditioned only by long timescale statistics. The sensitive states are the possible stimuli sequences dictated by the functional constraints of the external environment and the interaction landscape. We obtain a quantifiable picture of stimuli's evolution under fitness fluctuations (Mustonen and Lassig, 2008): changes in the environmental stimuli cause effective network variations (for example, segregation in different receptors, or production of different neuronal phenotypes into the neural "niche:" we will describe them below) that modify the equilibria in an irreversible way and lead to new monomorphic decision states (distinct sensory neuron subsets). The importance of the MFP in a nervous context of sensation/perception lies in the different, robust functional brain timescales, which selection is determined by the evolution of stimuli presentation. When external stimuli reach the cortex, the corresponding perceptions become accurate just in case of trajectories on the free-energy landscape falling into funnels. MFP predicts that, overlong-term timescales, perception invariably falls in the funnels. This means that along-term exposition to the same sensation that occurs in infants and children during the first years of life, could lead to accurate perceptions.

Other mental states and operations can be hypothesized as endowed in the MFP framework. For example, stored patterns

could give rise to pattern recognition. More complex mental activities such as thinking and reasoning, might require harder work and network development on long timescales. To achieve the desired output, the time required might range from minutes (e.g., simple changes in the “software” of molecular assembly are required to achieve the goal) to months (e.g., new architecture and hardware, i.e., the genesis of new synapses or novel cells is required). In conclusion, it is important to state that the MFP, in our framework, is just one of the general mechanisms of brain function. Indeed, it is able to explain some brain activities, such as sensitization and memory retrieval, while other activities, such as sensory adaptation, mind wandering, self-generated thoughts, free thoughts, sequencing/planning, choice, judgement, creativity, might subtend other mechanisms. The alternative mechanisms are described in the sequel.

3. MFP FOR NERVOUS ACTIVITY: BUILDING THE REQUIRED BRAIN PHASE SPACE

In the attempt to build a brain theory based on MFP, one problem is obviously that we do not have an explicit model for mean interaction properties as for proteins, where we can use the well-known amino acids’ properties. We need to take into account that MFP has been developed using tools from statistical mechanics and finite systems’ phase transitions. Because the energy landscape theory is inspired by algorithms that quantify the degree of local frustration in molecules, it is equipped with a phase space. Therefore, we need at first to build a corresponding brain phase space, in which the MFP for nervous functions might take place.

Brain phase space: the free-energy on the y-axis. Concerning the parameter on the y-axis, the brain’s free-energy is the nervous counterpart of the protein free-energy in the classical MFP for protein folding (Figure 2). An issue of central relevance in this context is the *free-energy principle* (FEP: Friston, 2010). The FEP is a general theory of brain function which arises in a biologically informed fashion and has the potential to be operationalized and assessed empirically. The free-energy principle for an adaptive system such as the brain tries to provide a *unified account of action, perception and learning*. That is, any self-organizing system at nonequilibrium steady state with its environment must minimize its free-energy, thus resisting a natural tendency to disorder (non-zero entropy). This formulation, which fits nicely with MFP, reduces the physiology of biological systems to their homeostasis, namely, the maintenance of system states in the face of a constantly changing environment. The brain is regarded as an active inference machine that functions according to Bayesian principles. That is, sensory inputs constrain estimates of prior probability from past experience, to create the posterior probabilities that serve as beliefs about the causes of such inputs in the present (Barrett and Simmons, 2015). From the perspective of the MFP, one can regard this belief updating as free-energy minimisation in terms of energy gradients and information flows. The activation of the peripheral receptor leads to feedforward electric oscillations towards the cortex, in order to increase the free-energy in the connectome landscape. For example, if one considers the visual system, the best known among sensory systems in Primates (Nieuwenhuys et al., 2008), he may note that simple localized bright stimuli related to the external world evoke high frequency oscillatory firing patterns along the entire sensory pathway: from the retinal ganglion cells (Shlens et al., 2009), to the optical layers, the lateral geniculate

nucleus (Guido and Sherman, 1998; Mooney et al., 1996; Bastos et al., 2014) and the cortex.

When the energy stream crosses the cortex, the brain displays unstable dynamics (Papo, 2014). Crucially, for our argument, this neuronal activity is an example of an open-system, which, although partly stochastic due to intrinsic fluctuations, maintains an interplay between structural bottlenecks and non-equilibrium steady-state dynamics (i.e., homeostasis or allostasis), in the face of environmental fluctuations. The brain function also retains the characteristics of a complex, non-linear system, formed by a large number of interacting and inter-dependent components which exhibit emergent properties, spontaneous self-organization, circular causality (Fraiman and Chialvo, 2012), divergent susceptibility and sensitivity to initial small changes. In short, the brain operates at the edge of chaos, in a metastable state near criticality, where the maximum information function lies between randomness and regularity (Zare and Grigolini, 2013). At the cortical level, minimising entropy production corresponds to minimising “variational free-energy” at each point in time (Sengupta et al., 2013a). This approach is about trying to understand how non-equilibrium steady-state is maintained, with an apparent resistance to the natural tendency to increase entropy. In this context, the average time of variational free-energy becomes a proxy for entropy. Furthermore, because variational and thermodynamic free-energy share a common minimum, one can link information processing (i.e., Bayesian belief updating) to metabolic efficiency by noting that minimising variational free-energy is the same as maximising Bayesian model evidence, which is also the same as minimising thermodynamic free-energy (and associated entropy).

The key thrust of FEP is that energy expenditure is balanced by homeostatic mechanisms, in an effort to minimize free-energy: the interplay between neuronal structure and activity at many different spatiotemporal scales gives rise to functional attractors (Watanabe et al., 2014a). In the context of MFP, a funnel-like functional structure is required: the best candidate is the “fixed-point attractor”, a location in phase space where trajectories converge as time progresses. As we will see, the MFP framework takes into account the FEP. According to both the models, a low energy basin lies at the bottom of the free-energy brain landscape, far from the peaks and close to the lower branches. The lowest energy levels give rise to dynamical phenomena that counteract the natural dissipation that would otherwise predominate in the nervous system: attractors impose transitory constraints on the landscape and attenuate the energy loss. The time-dependent, unexpected increase of entropy production typical of random systems (Gaspard, 2005) is thus counteracted by the presence of the attractors, acting as transitory constraints for random walks.

The funnel-like mechanism of brain activity is also suggested by a recent paper, where a novel gauge theoretic perspective of the brain provides a rigorous way of measuring distance on a manifold, such that the neuronal dynamics transporting one distribution of neuronal to another is given by the shortest path (Sengupta et al., 2016). In the context of physics, the MFP is rather close to Ising model and maximum entropy model. As described above, “frustration” was originally defined in behaviours of magnetic spins, which is well described by Ising model. This Ising model and maximum entropy model are, in addition, known to be well fitted to various empirical neural activities, ranging from neuronal spike activity and local field potential to fMRI signals (Schneidman et al., 2006). Moreover, energy landscape that was calculated by fitting Ising model to fMRI signals was shown to well account for individual difference in bistable visual perception and relevant anatomical differences (Watanabe et al., 2014b). Considering these close

relationships and accumulation of previous empirical evidence, the MFP attains solid ground.

However, it must be taken into account that countless neuronal models alternative to fixed point attractors have been proposed: for example, it has been suggested that brain function does not exhibit erratic brain dynamics nor attractors, rather a stable sequence, called transient heteroclinic channel (Afraimovich et al., 2013). According to some Authors, the neural network as an open system is not at equilibrium and may not always be described by fixed point attractors. Indeed, for example, line attractors (Seung 1996) and limit cycles (Yan et al., 2013) have been used to describe different brain functions. To make the picture also more complicated, it must be taken into account that many different functional regimes might occur in the brain: to make an example, it has been recently proposed that, at least during spontaneous brain activity, the brain might display a 4D functional Clifford torus (Tozzi and Peters, 2016). Further, crucial concepts like meta-stability and communication-through-coherence must be taken into account (Deco and Jirsa, 2012). Thus, the picture seems to be characterized by more than a single mechanism: it is possible that different functions are equipped with different kinds of attractors, or even linear and nonlinear dynamics. It is possible that the peculiar protein and macromolecular arrangements required for a nervous MFP and a subsequent funnel-like attractor are displayed just by some brain areas deputed to functions such as perception or memory storage, while other areas use other types of attractors which require - and are characterized by - other types of protein conformations. In this paper, we limit our analysis just at the building of a “pure” MFP nervous network. We will limit our treatment to a broadening of the fixed-point attractor to a simple quasi-equilibrium picture, with a constrained long timescale variance. Here will not take into account more complex attractors that could also have a mental counterpart, such as strange attractors, nor nonlinear dynamics, perimeter regimes, nor even statistical phase transitions.

The connectome subtends the presence of an energy landscape in brain, equipped with quantifiable levels of energy. How such energy levels could be correlated with the parameter we used on the y axis, i.e., the free-energy? In order to answer to this crucial question, it must be kept into account that the high metabolic brain activity is remarkably constant over time (Fox and Raichle, 2007): what consumes such large amounts of energy? For our purposes, we notice that local increases in spike frequency cause a transitory boost of energy consumption and free-energy production, with a metabolic cost of 6.5 μ mol/ATP/gr/min for each spike (Attwell and Laughlin, 2001). Thus, the increase in thermodynamic free-energy during brain activity is mostly due to spiking. In sum, the electric oscillatory activity of the extended connectome - in particular, at the spike frequency - correspond to the y-axis of our free-energy landscape.

The x- and z-axes: building the required brain networks. In the last paragraph, we stated that brain computations take place on a phase space endowed into the nervous connectome, which is equipped with a potential energy surface characterised not just by stationary points where the gradient vanishes (individual local minima), by also by transition states and basins, low-energy valleys and high-energy peaks. Starting from this energy framework, the minimum frustration comes into play as the main actor. If the MFP brain framework closely resembles the theories of protein folding in terms of free-energy landscapes for contact network interactions between amino-acids, how does it operate in the brain? How one can build a model which accommodates the overwhelming complexity of the interactions among the countless components of the nervous milieu? We need to find a nervous counterpart to residual contacts (on the x-

axis) and native interactions (on the z-axis), which are the two remnant ingredients of MFP.

The role of supra-molecular interactions is crucial in explaining how the CNS processes information and how MFP comes into play. Current theories are based on two tenets: a) information is transmitted by action potentials and b) homogeneous neuronal assemblies of cortical circuits perform operations characterized by the intrinsic connectivity among neuronal populations (Gollisch, 2009). In this view, the size and time course of any spike is stereotypic and the information is restricted to the temporal sequence of spikes (Buszaki and Watson, 2012). However, recent data point towards an alternative hypothesis: a) instead of simply passing messages, action potentials play a role in the dynamic coordination at multiple spatial and temporal scales, across several levels of a hierarchical modular architecture (Bosman et al., 2014) and b) information is processed at all levels, from macromolecules to population dynamics. For example, intra-neuronal - changes in protein conformation, concentration and synthesis (Kavalai et al., 2011) - and extra-neuronal factors - such as extracellular proteolysis, substrate patterning, myelin plasticity, microbes, metabolic status (Marcoli et al., 2015; Foster and McVey Neufeld, 2013) may have cognitive connotations by themselves. The concept of “supra-molecular chemistry” has been recently introduced (Tozzi, 2015), involving the storage of information at the molecular level and its retrieval, transfer and processing at the supra-molecular level, through transitory and labile non-covalent processes that are self-organized, self-assembled and dynamic (Lehn, 2007; Taylor and Ehenreich, 2014). Such a theory is a good starting point to evaluate a MFP for the nervous system: indeed, this operational approach, endowed in a macromolecular framework, is, formally, very close to the protein-folding problem, where native interactions and residual contacts among molecular structures are of foremost prominence.

The simplest model of the cortical layers we can think of is a network of two-dimensional functional niches, i.e., basic local compartmental units including both “neuronal decision cells” (NDC) and their own local environment (glia, extracellular space, and so on). The NDC corresponds to the native contacts (on the x-axis) in the protein folding framework (**Figure 2**). The inputs to a niche could be external, i.e. coming from other cells, or local/internal. NDC produce an activity in quasi-equilibrium with electric signalling: this timescale is slower, compared with fast speed of proteic enzymatic reactions. These signals, interacting in a multitude of neuronal synaptic pathways and compartments, regulate the functional states of both NDC and its connections, due to a quasi-static equilibrium. In robust neuronal networks as the brain, the response of signal input/output relations often displays a *sigmoidal (S-shaped) form* (Eeckman and Freeman, 1991).

It must be emphasized that the parameter t determines the shape of the sigmoidal function: it elucidates the link between minimum frustration and long timescales (Laurenbacher and Sturmfels, 2009). For example, $g(z(t))$ is a sigmoidal response function for a single neuron at time t (Benardette et al., 2008) defined by

$$g(z(t)) = \frac{1}{1 + e^t} \quad (\text{single neuron sigmoidal response function at time } t),$$

which can be typically expressed by simple logical decisions modelled by a history-dependent, bistable on-off state. This means that NDC could be in two functional states: *activated* (on) at time t and *deactivated* (off) at time $t + k, k \geq 1$. Such bistable response occurs when the sigmoidal activity is combined

with positive feedbacks. Indeed, in a bistable responsive system, there exist two states in a stimulus range, meaning that whether the system is in high- or low-activity state depends on its previous history (memory). Sometimes the on-state can also be maintained after stimulus removal, leading to an irreversible activation. Bistability and positive feedback can thus be mechanisms for noise-resistant cell-fate decisions.

Are we allowed to hypothesize an on/off mechanism of brain activity? The answer is positive: such a device has been already demonstrated in brain. A homeostatic mechanism has been revealed in the spatial distribution of synaptic strengths, by which neurons balance excitation (E) and inhibition (I), not only in time, but also in space (Xue et al., 2014). Specifically, cortical circuits appear to maintain a constant E/I ratio between the total amount of excitatory and inhibitory stimulation (Sengupta et al., 2013a; Sengupta et al., 2013b). E/I balance has been described both *in vitro* and in the spontaneously active cortex, not only for individual pyramidal neurons at a given time (Haider et al., 2006), but also across multiple cortical neurons and during neural avalanches (Lombardi et al., 2012). An optimal E/I ratio across neurons is maintained, despite fluctuating cortical activity levels, through the appropriate strengthening or weakening of inhibitory synapses (Xue et al., 2014). The relationship between the two opposing forces affects many cortical functions, such as feature selectivity and gain (Sengupta et al., 2013b), or memory of past activity (Lombardi et al., 2012), or rapid transitions between relatively stable network states (Sengupta et al., 2013b), which allow the modulation of neuronal responsiveness in a behaviourally relevant manner (Haider et al., 2006). The E/I ratio in each area can be calculated, provided that total must give zero. The E/I ratio stand for the needed parameter on the x-axis (corresponding to the residue contact in the protein folding MFP framework): the less the E/I ratio deviates from zero, the less residue contacts occur, and the lesser is the frustration.

We need now to introduce the proper neural network, where the funnel-like attractor equipped with a transitional ridge might take place. Dynamical neural networks have been widely used in brain models. For example, the recurrent artificial Hopfield networks (Hopfield, 1982) display binary threshold nodes, meaning that the unit (i.e. the node in the graph which simulates the artificial neuron) may take just one of two different values: 1 and -1. The value depends on whether or not the units' input exceeds a threshold. Pairs of nodes are linked through symmetric connections characterized by distinctive connectivity weights. Hopfield networks are equipped with an energy landscape, ruled by an effort to minimize energy. When units are repeatedly updated through learning rules such as the Hebbian one (which states that "neurons that fire together, wire together"), the energy always decreases and tends to converge towards an attractor pattern, the final stable state of minimum energy level. However, we will see in the next sections that the networks predicted by MFP are both more plastic and stable than the Hopfield ones. The MFP network is also easy to parameterize, because frustration can be extracted from just a few parameters: the microdynamics of the niches, the on/off cells ratio, the cell contact density variance and the external fluctuations, which can be parameterized by external energy variance. In touch with protein folding, in which the minimum level of energy (minimum frustration) depends on the number of residual contacts and native interactions, a free-energy brain landscape equipped with minimum frustration can be naturally designed, by taking into account just two parametrizing factors: the NDC's on/off internal/external states (on the x- axis of our brain phase space) and the NDC's cell number (on the z-axis) (**Figure 2**). The estimation of the effective population is very useful, because it allows us to perform a simple linearization. Based on these two parameters (which can be compared to residual contacts and

native interactions in the "classical MFP for protein folding), we can calculate both the mean free/energy activity in every point of the network and the gaps between the transition states (a technique called entropy pairwise fixation probabilities: Watanabe et al., 2014a). In the MFP model, thermodynamic free-energy is defined by informational entropy and pairwise probabilities - parametrized through partition function or by maximum of relative entropy - and compared with a mean entropy. The mean energy difference between on and off states accommodates an MFP lying transversal to a ridge in the joint distribution function: in other words, a transition ridge of minimum frustration, where trajectories are constrained to move, is embedded into the energy landscape (Best et al., 2013).

In short timescales, the NDC is thus allowed to decide whether to read, write, or erase memory bits, or alternatively to send out excitatory/inhibitory electric spike signals. However, in long timescales, NDC can also choose to produce different neuronal phenotypes equipped with the lowest possible degree of frustration: such a feature is of utmost importance when a long-duration of stimulus exposition occurs (which can be compared to the long evolutionary timescales in the "classical" MFP for protein folding). Also, countless environmental, epigenetic and metabolic factors might be important for the parametrization of the on-off states. We would like to stress once again that the key to understand the concept of MFP and funnelling in a neural framework lies in the well-known suggestion that the brain displays diverse timescales with diverse functions (Papo, 2015; De Pasquale and Marzetti, 2014; Gonzalez-Castillo et al., 2014; Linkaeker-Hansen et al., 2001): from the one nanosecond of side chain rotation, to the 50 nanosecond of the small loops; from the one-ten milliseconds of small protein function, to the stochastic oscillations in neuronal synapses (Kavalali et al., 2011); from the high-frequency of ultra-fast electric spikes, to the intermediate frequency of neuronal spike trains; from the low-frequency on spontaneous BOLD fluctuations (Raichle, 2010), to the ultra-slow time changes (hours or days) in protein signals (Kravchick and Jordan, 2015). In order to show how our theory can be operationalized, we provide the next section as supporting information for technical readers.

Summarizing: the ensuing brain energy landscapes - formally equivalent to the well-studied landscapes in protein folding (Morcos et al., 2014; Wales, 2012) - can be compared to a lattice. The functional assemblies of neurons, including their sensory molecular machinery, electrical interactions, extracellular fields, cortical feedbacks and also environmental stimuli, can be studied through logic models of pluri-dimensional networks, equipped with a binary interaction between neurons which is a simple two-decision state based on on/off probability distributions (stimuli-yes/stimuli-not, for example). Starting just from the quantifiable changes in free-energy due to the above mentioned connectome's electric oscillations, we achieve a functional free-energy landscape, transiently equipped with different values in diverse brain areas and with various timescales. While the minimum frustration of protein folding is dictated by the long timescales of the evolution, the minimum frustration of brain function is dictated by the long timescales of nervous activity. On longer brain timescales, we achieve the mean thermodynamic free-energy level which can be embedded in the known equations talking about free-energy difference type rate which goes into a sigmoidal function.

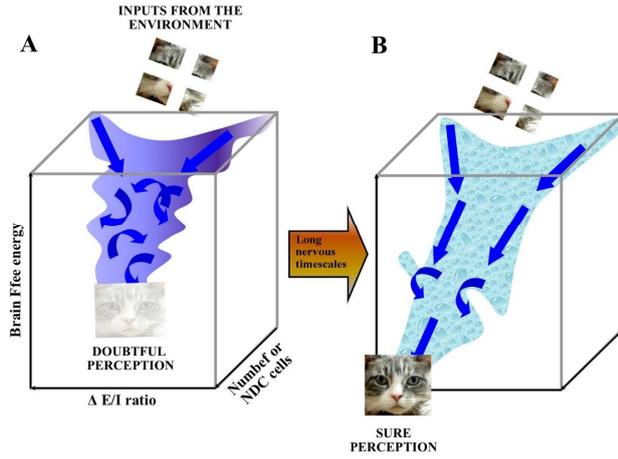


Figure 2. The nervous sensitive/perceptive counterparts of a theory of brain function based on the principle of minimum frustration. Modified from **Fig. 1**. The x-axis displays the $\Delta E/I$ ratio (the arrow points towards $E/I = 0$), while the z-axis shows the number of functionally well-adapted NDC. Note that in **Figure A** the asperities of the energy tunnel do not allow a “sure” perception of the object embedded in the external world (in this example, a cat). In turn, when the attractor is funnel-shaped and equipped with a transitional ridge (**Figure B**), the perception is sure and faster and requires lower energy expenditure. The evolutionary timescales in Figure 1 have been replaced here with long nervous timescales. Note that, after proper transversal averaging, the three parameters, according to MFP, should be globally, or even locally, related to longitudinal quantities following the ridge curve.

4. A LANDSCAPE MODEL WITH MINIMUM FRUSTRATION

As we stated in Section 3, our landscape brain model based on probabilistic and evolution fitness robustness/plasticity requires a “neuronal decision cells” (NDC) network. Here we show how a landscape model with minimum frustration can be naturally designed to populate the necessary functional/unfunctional brain states, thus leading to robust decisions that are parameterized by mean free “energy/activity” gaps between transition states. Here we show how the MFP is potentially useful in transcribing the underlying principles to experimental assessment, by describing the procedures for an estimation of the required three brain parameters (free-energy, effective NDC population and E/I ratio).

Local quasi-equilibrium for networks of regulated neuronal signals. Although a local quasi-equilibrium can be applied at all levels, from DNA to cell structure, we will focus on the level where we single out the brain memory/decision cells and their basic slow timescale. (“slow”, when compared to the speed of molecular kinetics). We will assume that the network function is gauged through the activity of NDC, embedded in their network of niches, by the lumped sigmoidal function described by a single activity measure E , which is in terms of activity at time t :

$$E_t(f, Z) : p(E_t(f, Z)) = \frac{f(E_t; \lambda)}{Z_t(\lambda)} = e^{\frac{-\beta E_t}{Z_t(\beta)}}.$$

E is a function of f and Z at time t . Then we have a means of connecting MFP and FEP relative to some timescale. Here $\lambda = \beta$ is supposed to be the inverse temperature, but we could also use other significant parameters - e.g. the total number of contacts - depending on which scaling we are using.

A clear correlation is self-evident between β and E on the one hand, and the statistical mechanics’ inverse temperature and energy level at time t on the other hand. When the average activity is measurable, the exponential model clearly leads to the MaxEnt principle. Because we have not modelled the activity in terms of decision network, a reasonable model would be to take into account the network of long-range contacts, combined with effective interaction weights symbolizing the unit states a cell can take. Many categories could be used to describe different types of division/death processes, cell states and so on: to simplify, we evaluated just a few k categorical states, i.e. an alphabet A labeled $i \in \{1, 2, \dots, k\}$.

Bilinear interactions. We now introduce the effective bilinear interactions for neuronal decision cells in long-range contacts, described by the interaction contribution M_{ij} , $i, j \in \{1, \dots, k\}$ and by the dynamic contact network (equipped as usual with nodes, positions, edges and distances) $C_{st}, s, t = 1, \dots, N$.

Here s and t stand for the positions of a cells’ sequence in given compartments, corresponding -- for active cells -- to the labelling of a nonuniform grid of niches. But s and t also stand for those activity interactions parameterized by the signal constituents (proteins, different types of RNA, small ligands such as drugs, DNA methylation, and so on). Since we are going to concentrate on NDC and their niches, we consider for simplicity the niches as equipped with a cell compartment containing different fractions of both active and quiescent neurons: the functional brain counterpart of active and quiescent neurons is the Excitatory/Inhibitory ratio (described in Section 3 of the main text). It is therefore natural to fasten together in a sole effective unit both the state variables for each niche and its closest interacting neighbours. The effective population of such units, corresponding to $N_e = \langle N^{-1} \rangle^{-1}$, can be evaluated through the spatial and/or ensemble average inverse population included in an heterogeneous NDC population.

The active cells in a network of cell niches and cell compartments $C = (C_{st})$ can be modelled through a simple bilinear interaction matrix:

$$E_t(C, M) = \sum_{s>t=1}^N C_{st} M_{i(s)k(t)} = C : Y^{(N)T} M Y^{(N)},$$

where $E_t(C, M)$ is function of the dynamic network at time t . $C : Y^{(N)}$ is a map from bilinear interactions to activity potential, given by the value $E_{(y)}$ which stands for the corresponding probability potential for decision activity. E is function of the independent variables C and M . Because it depends on neuronal activity and function, it allows us to cast a reasonable model for the distribution function of cell ensemble’s activity at time t . If we consider an approximately additive interaction model -i.e., just one neuronal cell species (normal) -, we obtain the simplest model:

$$M_{ij} = m_0 + \epsilon_0 (w_i + w_j),$$

and an effectively linear model of interactions at time t :

$$y(t) = K_{y(t)} c \cdot w^{(n)}$$

which can be parameterized in energy units for the activity cueing the decision process. Here $c = (c_s = k_s/K)$ stands for the network’s long-range contact density vector, defined as the number of contacts divided by the total number of contacts. In a simple model, the number of contacts for a given signalling channel are proportional to the compartmental cell numbers, so that:

$$k_s = K_c n_s = K_c N_e x_s$$

and

$$c = k/K = (K_c N_e / K) x^{(n)} = \rho x^{(n)},$$

where K_c stands for the effective number of signalling channels for activity $y(t)$ per cell. Because we need a fast response system for each cell, the cell function's activity is given by:

$$y(t) = y_{t_0} K_e N_e W^{(n)} \cdot x^{(n)}.$$

$$y = y_{t_0} K_c N_e W^{(n)} \cdot x^{(n)}.$$

If the compartment contains more than one cell type, we can generalize by assuming additive contribution to signals through our bilinear interaction model:

$$y(t) = \sum_{c=1}^r y_{t,c} = y_{t_0} K_e N_e \sum_{c=1}^r w_n^c \cdot x_c^{(n)} = y_{t_0} K_e N_e W^{(n)} \cdot X^{(n)}$$

For sake of simplicity, we will treat each NDC unit as a single ensemble merged into other identically distributed units, but with the extra catch that also local short-range interactions occur.

Introducing minimal frustration and deep funnels. The MFP for robust systems means that there must be a clear activity potential gap between:

- A well-defined global minimum functional state in the activity potential $E_t(y(t)_f)$ at time t , and
- A statistical dynamic network transition state, which simulates the behavior before it has settled into the global minimum.

The energy required by NDC units is proportional to a decrease of frustration at its minimal levels.

Moreover, if we want to achieve a robust functional behavior of the unit, we should appeal not just to the MFP, but also to other opportunities, in order to achieve a plastic global network where a certain degree of fragility/disorder is helpful in order to improve performance.

Let:

$$\Delta E_t(y(t)) = E(y_{lm}(t)) - E(y_f(t)),$$

$$\Delta E(y | y_{lm}) = E(y_{lm}) - E(y_f),$$

where $y_{lm}(t)$ at time t is defined by

$$y_{lm}(t) = F_{lm}(t) = E_{lm}(t) - TS, \text{ with } E_{lm}(t) = E_{lm}(t) + \frac{\Gamma^2}{T},$$

and

$$S = -\frac{\left(\frac{\Gamma^2}{T^2}\right)^2}{2} + S_0,$$

which stands for the mean free potential activity gap between:

- the average potential activity in the functional state y_f with minimum activity potential, and
- the statistical liquid-like transition ensembles occurring just above the functional minimum activity state.

A larger ΔE_t at time t gives rise to a deeper funnel, which is essential to achieve an operating mean activity (function). The liquid activity ensemble is thermodynamically stabilized either by a larger configurational entropy of the disordered phase (S_0), or by a larger ruggedness of its activity landscape, modulated by the activity potential mapping. The evolution of NDC and signalling and decision circuitry will try to avoid:

- either dysfunctional locally trapped minimal activity states occurring in a disordered regime of negative entropy (where $T < T_g$),

- or unstable equilibria (where $T > T_i$), which occur, for example, in potential activity maxima regime of negative free-activity potential energy differences.

Advantages of neural MFP. The MFP, as derived from evolution in the monomorphic fitness limit, gives a robust ridge approximation of the decision sigmoidal function/rates, in such a way that the mean free (activity) energy gap can be monitored and directly related to the contact density, multiplied by the activity weight factors derived from the activity matrix. This is because, at the very slow evolutionary time scales, the evolutionary equilibrium distribution can be expressed as a MaxEnt principle for the selection of the functional constraints. The mean free-energy gap should be larger than zero (stable functional equilibrium in the lab frame) and the frustration should be small or (if you want the the inverse frustration) large. We define the non-dimensional quantities:

- The mesoscopic frustration : $\kappa = \Delta E / T$ []
- The nondimensional energy standard deviation: $\gamma = \Gamma / T$
- The mean (free) energy gap : $e = \Delta E / T, f = \Delta F / T$

In terms of these variables, we find - by marginalizing the joint exponential distribution for the mean free-energy gap and the inverse frustration - that the problem in the (κ, γ) plane (or in any pair of the four nondimensional quantities above) has a ridge following a path: $\kappa = h(\gamma)$ which in principle can be linearized around any fixed point κ_0, γ_0 , in order to give the relations $\delta \kappa = h'(\gamma_0) \delta \gamma$.

At the same time, the minimization of the proper mixture of NDC is ensured by the stable homeostasis in line equilibria, which guarantees that, if the number can be robustly controlled, the total energy is located in a ridge distribution, where several NDC distributions can be easily checked towards insults. It can be achieved in the Grand Canonical liquid activity ensemble, by optimizing the number of contacts through a mixture of chemical potential constraints together with an extra term. Again, we have to constrain the mean free potential activity difference and minimize both its frustration and each of the contacts' frustration. We expect, from the transversal minimization of the frustration parameter, an equilibrium ridge which now contains a variance contribution for each contact/cell type. Evolution therefore benefits from the natural stable equilibria occurring in the multispecies interacting neuronal cells' potential activity. Our model suggests a mean probability for a NDC to have activated function F , given a signal y_f :

$$p_F(y_f(t) | E_t, Z_F) = \frac{e^{-\lambda \Delta E_t(y_f(t) | y_{lm}(t))}}{Z_F},$$

$p_F(y_f(t) | E_t, Z_F)$ is a conditional probability that depends on E_t, Z_F .

for each cell function affecting both the active cells' net growth and their interaction with other compartments. In the simplest case, when y_{lm} is fixed, the active state's probability into the active local cell's mean ensemble (which is embedded in a cell niche compartment interacting with other cell compartments) is:

$$p_F(y_f(t) | E_t, Z_F) = \frac{e^{-\lambda E_t(y_{fm}(t))}}{Z_F}.$$

In this case, y_{lm} suggests that the ensemble means over local niche compartments give rise to effective population scale and effective average weight factors for cell signalling.

Other possible models. In this section we just discussed the mean decision rates as a microscopic background for the commonly used Integrate and Fire (IF) neuronal model. Nevertheless, the model could also be applied to:

- a) Brain/neuronal cells' networks casted as a Markov model for global states of networks in an open environment, and/or:
- b) Commonly used network approximations as, for example, the simplest case of a set of interacting decision hubs modelled as kernels *in time and space* for correlated decision hubs.

We believe that our essay is a starting point to evaluate brain decision-activity functions in terms of energy costs landscape. The state of minimum frustration described above is a novel theoretical framework available for both evolution and biological network signals (such as the brain), either in stochastic or mean models of decision activity rates over time.

5. MINIMUM FRUSTRATION PRINCIPLE: WHAT FOR IN BRAIN STUDIES?

The question now is: what does MFP theory bring into play in the evaluation of brain activity? How do predictions from the MFP approach differ from predictions from current dynamical models, such as FEP or Hopfield Networks?

As in the FEP, MFP too considers free-energy as a statistical average quantity including temperature, entropy and transition state mean energy. The perceived inputs will be thus averaged over transition states. However, MFP states that, if there is a large enough timescale, the perceived inputs will be also averaged, because the brain perceptual machinery is tuned by evolution to ensure precisely that. In MFP, what is very significant is that the perception/decision apparatus is constrained to recognize just in "long" timescales. Friston's prior probability becomes, in MFP terms, the rugged funnel-like landscape in which the predictions signals are conveyed by *long-standing* past experiences. If in Friston's model the input sequence of coded signals leads to increases or decreases of free-energy which is dissipated as the coding sequence has passed, such a concept does not matter in MFP: the entropy might decrease or increase after a single sensation to get higher order - which could mean both higher or lower free-energy - but, on average, after numerous sensations on long timescales, the outcome leads inexorably to a decrease of free-energy, otherwise it would not be a stable recognition process. MFP thus stresses that the outcome must lead to a more ordered structure at recognition, not necessarily through immediate changes in free-energy. Further, while FEP emphasizes macro-phenotype dynamics and scarcely takes into account micro-anatomy and neuronal milieu, the MFP, at least its protein counterpart, is clearly grounded on micro-dynamics and macromolecular interactions.

In touch with the Hopfield networks, also MFP describes the brain in terms of dynamical energy landscapes, which activity is ruled by an effort to minimize free-energy. Nevertheless, MFP displays important differences also with respect to Hopfield networks. Hopfield uses McCullough-Pitts' dynamical rules, in order to make the retrieval possible: activations of multiple neurons map onto the activation of a new neuron's firing rate and their weights strengthen the synaptic connections between the new activated neurons. However, in the original formulation of Hopfield networks, this process occurs in a repetitious fashion:

an attractor pattern is a final stable state and, under updating, is not able to modify any value within it. In the Hopfield network, contrary to MFP, the dynamical rule will always modify the values of the state vector in the direction of one of the "fixed" stored patterns. Both MFP and Hopfield Network are able to change the minima: however, Hopfield Network achieves this result by changing the weights, while in MFP the change of minima is both more plastic and more stable, because it depends on the duration of non-zero Hamiltonian. Therefore, while the Hopfield networks retain a "rough", more "frustrated" landscape, the MFP tends sharply towards a smooth, more efficient funnelled trajectory.

The MFP network is less rigid: its niches are able to produce, after a long-duration of stimulus exposition, different neuronal phenotypes, equipped with the lowest possible degree of frustration. This means that MFP networks are allowed to modify their energy features in long timescales, dynamically changing either their function, or structure, or even morphology. It gives rise to a system equipped with robustness and plasticity: accordingly, the active populations' stability limits towards dysfunction or misfunction are better guaranteed, compared with Hopfield networks.

The MFP solves also a problem raised by Rabinovich: he hypothesizes a neural processing model based on transient dynamics as in "liquid state machines", with no need for classical attractors (Rabinovich et al., 2008). He emphasizes that, because neural phenomena occur on very short timescales, classical attractor states (i.e., fixed points) cannot be realistically reached. However, the very fast mechanisms of a funnel-like MFP attractor overtake this objection, in order that an attractor state can be reached in brain easier and faster than previously expected.

As we stated above, MFP requires a specially shaped energy landscape resembling a funnel. Because the funnel depends on the biological constraint of the evolution, timescales enter into the picture when we consider the duration of minimized frustration. The overwhelming role of timescales in the MFP context is once again emphasized: the standpoint here is the presence of long-lasting external environmental inputs which act on the organism's internal milieu. In sum, the MFP-based brain model is simply different from the others, as derived explicitly from evolution and selection of a funneling structure in a constrained free-energy valley, equipped with contacts' microdynamics (which allows the lowest possible energy level) and a transversal ridge path. Minimal frustration is a critical prerequisite for fast kinetics and thermodynamic protein stability; it means that a brain model based on minimal frustration gives rise to more stable, efficient and fast mechanisms of nervous activity.

6. POSSIBLE MOLECULAR CANDIDATES

An interesting question then arises, which can be approached speculatively, because of our current lack of knowledge: are there micro-molecular candidates for the MFP theory? We propose a hypothetical mechanism for many classes of brain receptors, including the well-studied mechanosensory channels (Anishkin and Sukharev, 2004); namely, a state of dewetting transition: a concept borrowed from fluid mechanics (Sharma and Reiterb, 1996; Thompson, 2012). When water and ions are enclosed within the narrowest sub-nanometer confines of an ion channel's hydrophobic pore, they exhibit an odd behaviour: in such a peculiar context, a stochastic liquid-vapour water phase transition occurs, near a critical point (Aryal et al., 2015). These transient vapour states are "dewetted", i.e. effectively devoid of

water molecules within all or part of the pore. The decreased amount of water molecules in liquid state leads to impaired conductance, energy barriers to ion transit and closure of the channel (corresponding to an increase of inhibition in the E/I ratio), in a process termed “hydrophobic gating”. The principles underlying the metastable dynamical state of hydrophobic gating require a very small radius of the tube and interactions with a strongly hydrophobic lining (Boreyko et al., 2011; Lapiere et al., 2013). Dewetting transitions, characterized by such an unusual behaviour of water’s supramolecular assembly, represent an increasingly important general principle that has been applied to countless morphological and/or functional biological structures, ranging from protein cavities (Young et al., 2010) to lipid droplets (Thiam et al., 2013) and opening of macroapertures in endothelial cells (Gonzalez-Rodriguez et al., 2012), from extracellular matrix and glycocalyx (Tanaka et al., 2005), to cell adhesion (Sackmann and Bruinsma, 2002) and lipid bilayers (Vargas et al., 2014). We speculate that dewetting transition might have a role as physical/chemical, supramolecular and functional substrate for the mechanisms of E/I ratio decreases, leading to augmented neuronal inhibition and subsequent changes in MFP networks.

A possible molecular role for prefrontal methyltransferases in working memory, emotion and cognition has been recently suggested (Jakovcevski et al., 2015). Such an interesting observation throws an unexpected bridge between topology, molecular assemblies and brain function. Methyltransferases are among the rare enzymes exhibiting the weird property of “knot” in their backbone. In other words, they are proteins with structures that do not disentangle completely after being pulled from both ends (Virnau et al., 2011). A knot is indeed the embedding of a closed line in the 3-D space and cannot be reduced to a simple circle by a continuous deformation (Wu, 1992). The knot theory arises from topology and provides tools for cataloguing different types of knots, for possibly transforming one into another via a deformation of 3-D space upon itself and for summing different knots in assemblages equipped with commutative and associative properties (Cromwell, 2004). In turn, the “supramolecular chemistry” suggests that complex chemical entities can be reversibly constructed from molecular components bound together by labile non-covalent interactions (Lehn, 2007). Incorporating such different perspectives appears particularly relevant for understanding how the brain does represent the stimuli coming from the environment. Nevertheless, recent findings suggest that nervous structures could process information through topological, other than spatial, mechanisms: for example, it has been suggested that hippocampal place cells create a topological template to represent spatial information (Dabaghian et al., 2014). Further, structures quite different from spikes, such as macromolecular assemblies, may play a role in information processing in nervous system: we do not yet understand to what extent the diffusion and biophysical cues, such as the mechanical properties of the extracellular matrix (Sur et al., 2013), have to be taken into account when talking about the brain function. Thoughts could be metaphorically compared with open strings made of proteins and/or supramolecular assemblies, a sort of random walks wandering around in the viscous fluid of the nervous milieu, until they reach a steady attractor. The entanglement of their extremities may give rise to reversible or irreversible topological knots, respectively standing for labile or enduring perceptions and memories. The link with MFP becomes clearer when we consider that topology is another key factor governing folding reactions. Indeed, structures of transition state ensembles (Clementi et al., 2000; Koga and

Takada, 2001), folding rates (Chavez et al., 2004), the existence of folding intermediates (Ferreiro et al., 2005) and dimerization mechanisms (Levy et al., 2004) are well-predicted in models where frustration has been removed and topological information of the native state is the sole input.

7. CONCLUSIONS

Every mental state is a result of an evolutionary self-preservative processes, a biological functional phenotype trying to maintain invariance or steady state. The ideal point about which the nervous activities of the organism moves in constant oscillations has a logical-mathematical significance when framed in MFP theory. The concept of energy landscape for bio-networks, combined with the evolutionary fitness and selection principles of minimum frustration, promises to shed new light on our understanding of brain function. In conclusion, this paper is an effort to unify current perspectives on brain function in a coherent framework that retains their most important tenets. We have emphasized that nervous system activity is characterized by peculiar energy requirements and constraints, based on its countless spatio-temporal levels. We have suggested a role of MFP, a concept borrowed from protein folding, to further advance our understanding of the self-organised brain.

ACKNOWLEDGEMENTS

The Authors would like to thank Karl Friston for commenting upon an earlier version of this manuscript.

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