THE MANIFOLD OF LIFE: THE MATH SUBTENDING LIVING BEINGS' DYNAMICS

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The dynamics of biological activities, such as cellular metabolic pathways, protein folding and brain activity, can be described in terms of curved trajectories in hyperbolic spaces, constrained by energetic requirements. Here we, starting from the theorems recently-developed by a deceased Field Medal young mathematician, show how it is feasible to find and quantify the shortest, energy-sparing functional trajectories taking place in biological systems' concave phase spaces. This allows researchers to focus their studies on the few, most prominent paths and loops able to explain, elucidate and experimentally assess rather elusive biological functions.

KEYWORDS: topology; Mirzakhani; brain; hyperbolic; manifold; polynomials

The scientific knowledge of physical dynamics is currently more advanced than their biological counterparts, the latter still lacking the required explanatory power. One of the main reasons is that, while physics has been provided with powerful mathematical tools, biology has not. Physics works much better in the description of natural features, because we have recognized its subtending manifolds. To make an example, both general relativity and quantum mechanics describe Nature using mathematical structures, such as tensors and probability theory (Yilmaz, 1982; Comte, 1996; Fre, 2013). Their subtending manifolds (i.e., the phase spaces in which the corresponding activities take place) are well-known and have been experimentally confirmed: general relativity is described on a 3+1 dimensional pseudo-Riemannian manifold with tensor fields obeying certain partial differential equations, while quantum field theory is portrayed on an R^4 projective Hilbert space, with operator-valued fields obeying certain Lorentz-invariant partial differential equations and commutation relationships (Tegmark 2008).

Concerning biology, to make an example, it is still difficult to find a definition of life. There is no unequivocal definition of biological dynamics, despite many propositions have been suggested. Apart from the intrinsic problems in describing such elusive phenomenon, the very current limit is that the most of the proposed features are just descriptive, from the concept of homeostasis to organization, from growth to adaptation, from response to stimuli and reproduction (McKay, 2004; Trifonov, 2012). In sum, we lack the corresponding manifolds, and therefore we lack objectivity. This is a huge restraint, because the sole language able to describe in quantitative terms scientific issues is the mathematical one. If we leave apart math, we do not have observables, and living dynamics are made by observables.

The aim of this paper is to make an effort to provide a mathematical, operational, quantifiable definition of the dynamics of living beings. In particular, in order to assess biological issues, we need at first to find the proper manifolds where their operations might take place. Therefore, our goal is to describe these phase spaces, by treating biological activities, and their corresponding gradient-descent Langevin equation, in terms of algebraic topology

TOWARDS THE MANIFOLDS OF LIFE

In terms of differential geometry treatments of probability measures, it is known that the manifold traced out by sufficient statistics display negative curvature, i.e., it is concave (Tanaka 2001; Sengupta et al., 2016). Moving along this hyperbolic manifold requires a measure distance that can be provided by Fisher information metric, that is able to quantify the relative entropy required for going from one point to another of the phase space. Obeying to entropic dictates, biological activities (including, for example, neural function and protein folding) tend to choose the shortest available path (Ramstead et al., 2017), i.e., to follow the steepest descent direction in order to attain their nearest free energy minimum (**Figure 1**). In operational terms, the steps of the biological system's Langevin equation (Langevin 1908) experimentally detected in our surrounding, flat, three-dimensional (plus time) Euclidean space, can be transported on a hyperbolic manifold, though, e.g., Levi-Civita or Ehresmann connections (Levi-Civita 1917; Ehresmann 1950). This means that biological dynamics can be studied on negative-curvature manifolds that mimic the real environmental phase space where such processes occur. Here the work of Maryam Mirzakhani, the recently deceased 2014 Field Medal, comes into play, allowing us to calculate the number of trajectories in a hyperbolic phase space.

The Mirzakhani theorem. Mirzakhani assessed the "geodesics" of hyperbolic surfaces (2008). On a negative curved surface, geodetics simply stand for the shortest paths between two points. On hyperbolic manifolds, some geodesics are infinitely long (like the straight lines in the Euclidean plane), but others close up smoothly into a loop (like the circumference on a positive-curvature sphere). There are two types of closed geodetics (**Figures 2A** and **2B**): the very rare "simple" geodetics, that never intersect themselves, and the much more frequent ones that cut across themselves several times, before closing up. The number of the latter geodetics of a given length L grows exponentially, as their length grows. Mirzakhani demonstrated that also the number of the rare simple geodesics of length L grows, as L gets larger (**Figures 2C** and **2D**). However, she showed that, as the length of these simple geodetics grows, their number grows polynomially, instead of exponentially (**Figure 2E**). The difference is subtle, but foremost. During an exponential growth, time (or space, or, in our case, the geodesics length) grows as a function K^n, where n is proportional to the size of the input and K is a constant (Wolf 1968). In turn, during a polynomial growth, time (or space, or, in our case, the geodesics length) grows as a function n^k. In the sequel, we will provide the biological counterparts of the Mirzakhani's findings, in order to operationalize her rather abstract theorem in terms of living being's dynamics.

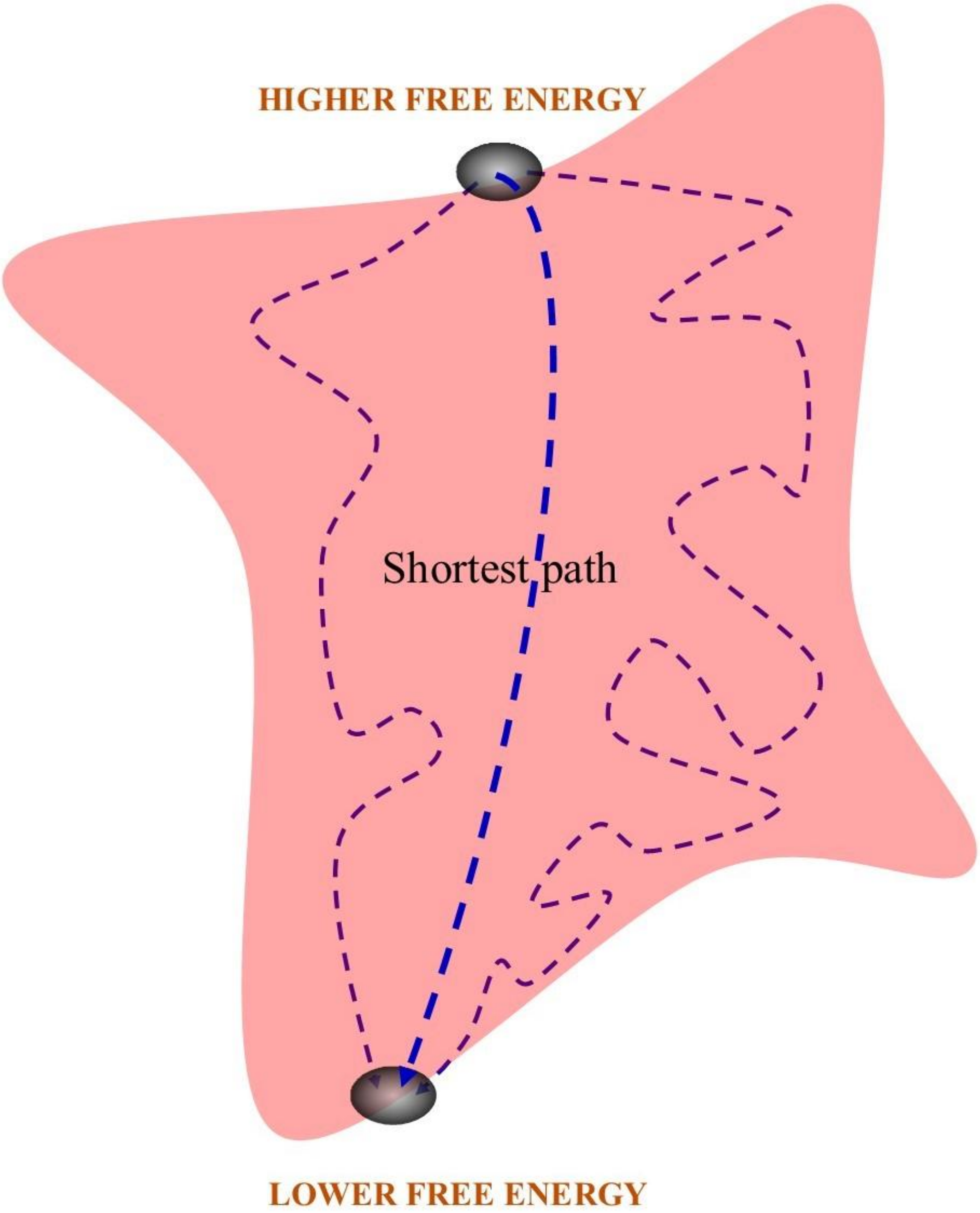

Figure 1. Biological phase spaces equipped with sufficient statistics make it possible to rigorously measure distances on a hyperbolic manifold. Therefore, dynamics transporting one distribution of system's activity to another is given by the shortest path from points to higher energetic levels to lower ones. Modified from: Tozzi et al. (2017a).

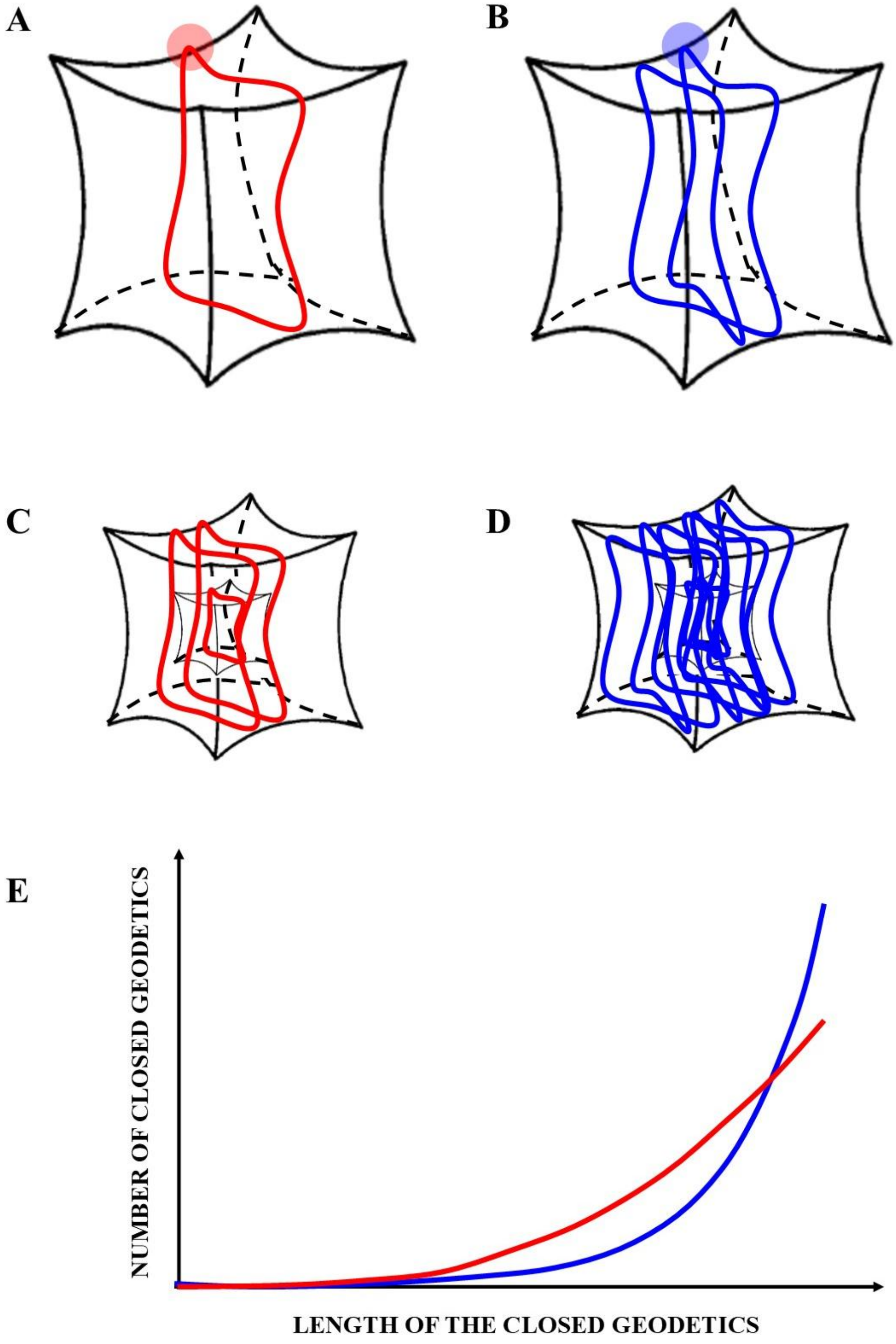

Figure 2. In this oversimplified sketch, close geodetics on negative-curved manifolds are roughly illustrated. Figure **2A** displays a rare simple geodetics, while **2B** depicts the more frequent type, the one that cuts across itself many times before closing up. The colored small circles stand for the point where the closure occurs. Figures **2C** and **2D** illustrate the increase in number and length of geodetics, that occurs when a growth in manifold size takes place. The graph in Figure **E** shows how the two types of closed trajectories display a different behavior: the rare simple geodetics (red line) follow a polynomial growth, while the frequent ones (blue line) an exponential growth.

THE MATH SUBTENDING LIVING BEINGS' DYNAMICS

The theorem by Mirzakhani allows us to extrapolate the following statement: if the size of a negative curved manifold is progressively increased, curved geodetics of increased length are achieved on its surface. This leads also to a quantifiable increase in their number. In biological terms, the increase in size of the manifold may stand for rather different systems' dynamical features: e.g., either a growth in energy, or in biological complexity, or in the neural units recruited in the brain during a mental task. Note that the Mirzakhani's very rare "simple" geodetics are of foremost importance, when translated in a biological context: indeed, they stand for the shortest paths, i.e., the steepest descent trajectory able to attain the system's nearest free energy minimum. To make an example, such kind of short and very efficient energetic paths are the ones that make the folding proteins less frustrated, therefore more efficient in performing their biochemical operations (Tozzi et al., 2016). The Mirzakhani's framework tells us that, when the available free energy increases in the phase space, the most frustrated, and therefore least-performing, proteins display an exponential growth in their number of folding paths, while the less frustrated a polynomial one.

Taking into account that the living beings' dynamics occur on hyperbolic phase spaces, two different biological activities can be assessed and carefully quantified: the first one is characterized by countless trajectories that slowly close up into loops, while the second one by less frequent trajectories that more quickly close up into loops. This faster activity, that stands for the best available trajectories from higher to lower free-energy states (according to the thermodynamic dictates), might be very important in order to explain the peculiar dynamics of, e.g., either human brain electric activity or cellular metabolic pathways. In turn, the slower activity might stand for the noisier, less efficient and more random dynamics taking place in biological systems. The Mirzakhani's approach, when transferred to the biological realm, provides the recognition and quantification of both the slower and faster activities, allowing researchers to focus efforts and experimental apparatus just on their favored one. Indeed, these mathematical devices make it possible achieve graphs that illustrate the behavior of both the geodetics occurring in the biological system under evaluation (**Figure 2E**).

Biological significance. Here we provide a few examples of the effectiveness of these kinds of purely mathematical approaches in the evaluation of biological issues. During a given brain activity (say during perception), some neural assemblies are recruited and start to fire. Interactions occur among the members of the assembly (the neurons), giving rise to electric paths that take place in a functional hyperbolic phase space. For technical readers, such space can be built and quantitatively assessed through the authoritative tools of differential geometry, parallel transport and dynamics on manifolds described by Sengupta et al. (2016). Some of these trajectories are closed, others are not. In both real and artificial neural networks, these functional loops may follow linear, sigmoid, exponential or logarithmic responses (Zeiler et al., 2013; Tozzi et al., 2016). While the most of the closed trajectories follow random walks, a few obey to the dictates of energy optimization, taking the shortest available paths (Sporns, 2011). Despite the random walks of neural ensembles have been proven to be able to encode input stimulus without any specific training (George et al., 2018), nevertheless, the faster, nonrandom, more efficient, polynomial paths of activation described by us are of foremost importance in the brain, because they allow better responses and energy sparing. It is not easy to detect such rare and peculiar polynomial activities among the others. When, an increase of the given brain activity takes place (e.g., an increase in perceptive task load) and more neural assemblies are recruited, the closed trajectories on the negative curved manifold grow in number with exponential or polynomial behavior. The feasible operational procedure is the following, provided just as one of the countless examples and possibilities. During a visual perceptual task, BOLD brain activity is detected through fMRI techniques. At first, we will notice the activation of the visual primary sensory areas, then of the ventral/dorsal visual pathways and frontal areas. The next step is to project such three-dimensional BOLD dynamics on a hyperbolic manifold, looking for the closed loops of this brain activity. Our experimental prevision is that, when more neuronal areas will be progressively recruited, we will observe a generalized exponential increase in BOLD loops. Furthermore, we will detect the simultaneous presence of a few loops displaying polynomial growth. The latter stand for the most efficient and powerful activities related to the visual task under investigation. Therefore, due to the Mirzakhani's results, it becomes easier for neuroresearchers to detect and separate the two different types of closed trajectories: the less useful grow exponentially, the more efficient ones grow polynomially. This allows scientists, when assessing the "mare magnum" of brain oscillations, to "erase" from their analysis all the useless closed trajectories, and to focus just on the more interesting ones.

The same approach holds for biological systems, such as living cells. During evolution, an increase in cellular complexity takes place from prokaryotes to eukaryotes (Tozzi et al., 2017b). In Mirzakhani's terms, this means that the size of the subtending concave manifold expands from prokaryotes to eukaryotes. Therefore, with increases in evolutionary complexity, different, novel metabolic paths can be assessed: some of them display an exponential growth, others a polynomial one, and both can be detected and quantified.

CONCLUSIONS

We made an effort to provide a feasible manifold where the activities of living beings might take place, taking into account that physics is very successful in coping with the complexity of our world, while biology still lacks the required mathematical tools. For this reason, instead of inductively analyze the currently available empirical data, we preferred to start from a very abstract mathematical framework, in order to formulate top-down previsions that can be experimentally tested.

Based on the recent literature, we introduced a negative curvature, concave, hyperbolic phase space where the functional trajectories of biological dynamics might take place. Such kind of manifold gave us the possibility to use the theorems developed by Maryam Mirzakhani, the first female mathematician honored with the prestigious Fields Medal Award (corresponding to the Nobel Prize for math), died in 2017 at just 40 years. Her approach allowed us to isolate and rigorously quantify the evolution of two different kinds of biological responses: the exponential and the polynomial ones. It is noteworthy that, during a dynamical process taking place on a negative curvature manifold, at first the increase in polynomial growth is higher, when compared with the exponential one. In turn, when the dynamical process recruits more systems' units, the exponential growth prevails. Our approach also suggests that, when assessing the dynamical activity of artificial or real biological networks, it would be preferable to focus the research on the more efficient and significant polynomial responses, rather than the linear, sigmoid or exponential ones. Indeed, polynomial functions exhibit many desirable theoretical properties that make them best-suited for the study of biological issues.

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