

PROJECTIVE MECHANISMS SUBTENDING REAL WORLD PHENOMENA WIPE AWAY CAUSE EFFECT RELATIONSHIPS

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Causal relationships lie at the very core of our scientific description of biophysical phenomena. Nevertheless, observable facts such as chaotic dynamics, symmetry breaks, long-range collisionless neural interactions, zero-value energy singularities, particle/wave duality, ecological approaches to visual perception elude cause effect inductive explanations. We illustrate how simple topological claims, seemingly useless and far away from scientific inquiry (e.g., “given at least some wind on Earth, there must at all times be a cyclone or anticyclone somewhere”; “if one stirs to dissolve a lump of sugar in a cup of coffee, it appears there is always a point without motion”; “at any moment, there is always a pair of antipodal points on the Earth’s surface with equal temperatures and barometric pressures”) describe a real world, made of projections and mappings unsupplied with causality. Unavoidable, necessary, passive, spontaneous changes in systems’ shapes, dimensions and symmetries incarnate biophysical quantifiable counterparts of abstract mathematical concepts. Real features arising from topological mechanisms do not require causal powers to be produced, because are independent of exerted physical forces, energetic fields’ actions and thermodynamic constraints. Providing examples that shed novel interpretative light on phenomena such as double slit experiments, cellular mechanisms and brain function, we conclude as follows: countless scientific matters can be accessed through methodological weapons which not just break causality, replace temporal correlations and probabilistic a priori knowledge of previous cases, but also permit augments in available information devoid of entropy increases and energy losses.

KEYWORDS: causality; topology; Borsuk-Ulam theorem; fixed point theorem; non-Hermitian systems; Uhlenbeck theorem; dewetting transition; Kneser graphs.

Cause effect relationships can be defined as follows: “The substance S is responsible for (or contributes to) the state of affairs p’s obtaining at the subsequent time t”, where S may stand for active or passive, inanimate or living, non-sentient or intelligent, wholly active or inactive, free or constrained contributors (modified from Freddoso, 1988). For example, the evaluation of adverse drug reactions in pharmacodynamics is based on a small number of tenets (Naranjo et al., 1981; Mouton et al., 2017):

- a) Temporal correlation between the alleged cause and the reported effect.
- b) A priori knowledge of previous cases describing the same hypothetical correlation.
- c) The feasibility to repeat the chain of events, through proper experimental settings.
- d) When the cause is discontinued, the system under assessment frequently returns to its original conditions. This means that the reported symptoms disappear and bodily integrity is restored.

Causality stands for the very basic tenet of the scientific method, which dictates that theoretical claims must be empirically tested in the proper experimental setup. However, the assessment of cause effect relationships is frequently a difficult venture. Critiques to causality have been raised throughout the centuries by philosophers, theologians and theoreticians such as Pyrrho, Al-Ghazali, Nicholas of Autrecourt (1340), John of Mirecourt (Franzini 1958), William of Ockham (1974), Berkeley, Hume, Montaigne, Feyerabend, Fogelin (Popkin and Maia Neto, 2007), van Fraassen (1977). Apart from these classical concerns, it is a matter of fact that doubtful or unpredictable correlations might prevent scientific queries on cause effect relationships (Nebeker et al., 2004; Davies et al., 2011; Loke, 2012; Saedder et al., 2015). The core of causality lies in the occurrence of path-connected sets or subsets, i.e., the presence of features which can be joined together. A serious problem arises when we grasp that, in many applications, features are unknown and apparently disconnected, making it very difficult to find and recognize the proper subtending sets. Systems’ boundaries and dynamics may be irregular and indistinct, leading to a scarce knowledge which hampers feature approximation and measurement. Cause/effect relationships could be inescapably hidden from our observation, if we are unable to pin down and accurately measure systems’ components and/or events.

Lastly, sometimes causal correlations cannot even be conceived. This is the case of puzzling phenomena such as, e.g., double slit experiments, quantum entanglement, nonlinear chaotic dynamics dictated by phase parameters, long-range correlations in plasma flows and brain dynamics. We aim to show that novel topological-framed approaches allow to explain (at least some) physical and biological phenomena, without resorting to the “powers”, the thermodynamic constraints, the fields and the forces required to explain causal relationships. Topology, which studies the nearness of shapes, sets and their properties preserved through deformations, stretching and twisting, permits the investigation of very general systems’ features (Bourbaki 1966; Bredon 1997; Peters 2016). In the very last years, novel top-down, deductive, mathematical approaches provided theoretical frameworks which emphasize the role of topology in the description of real paths and dynamics. We ask whether topological-related mechanisms of projections and mappings, which stand for alternative explanations to the standard cause/effect relationships, might display physical, quantifiable counterparts. We analyze how topological changes describe physical phenomena, including the quantum ones, in which both the classical deductive logic and the recently-introduced inductive logics do not hold anymore. Further, we investigate why the very topological features of physical/biological systems give rise to unavoidable modifications that are spontaneously produced.

A FEW THEOREMS FOR NON TECHNICAL READERS

Here we describe, in plain terms, the topological weapons that will allow us in the sequel to approach biophysical phenomena escaping causal explanations.

Hairy ball theorem (HBT). In technical terms, HBT states that there is no non-vanishing continuous tangent vector field on even-dimensional n -spheres (Eisenberg and Guy R. 1979). This ensures the presence of at least one point where vectors (and/or tensors) disappear. Two naïve descriptions state that “whenever one attempts to comb a hairy ball flat, there will always be at least one tuft of hair at one point on the ball”, and “given at least some wind on Earth, there must at all times be a cyclone or anticyclone somewhere”.

Ham sandwich theorem (HST). For every positive integer n , given n measurable “objects” in n -dimensional Euclidean space, it is possible to divide all of them in half with a single $(n - 1)$ -dimensional hyperplane (Matoušek, 2003; Beyer and Zardecki, 2004). To provide an example, “given globs of ham, bread, and cheese (in any shape), placed any way you like, there exists one flat slice of a knife (a plane) that will bisect each of the ham, bread, and cheese”.

Brouwer fixed point theorem (FPT). Every continuous function from a n -sphere of every dimension to itself has at least one fixed point (Volovikov and Yu, 2008; Crabb and Jawaworski, 2013). FPT applies, e.g., to any disk-shaped area, where it guarantees the existence of a fixed point, which behaves like a whirlpool attracting moving particles. A coffee cup illustration has been provided (Su 1997): “no matter how you slosh the coffee, some point is always in the same position that it was before the sloshing began”.

Lusternik–Schnirelmann theorem (LST). If a sphere is covered by $n+1$ open sets, then one of them contains a pair of antipodal points. In other words, every time you split a sphere in three parts, one of the three must encompass an entire diameter (Dodson and Parker, 1997). In plain terms, one of the three slices must necessarily contain some antipodal surface features with matching description.

Borsuk-Ulam theorem (BUT). A general topological principle underlies the organization of physical and biological systems. It relates to a well-known and rather simple theorem, the BUT, which states that, provided the function under assessment is continuous, two points with matching description in higher dimensions map to a single point in lower dimensions (Borsuk, 1933; Matoušek 2003). In plain terms, this means that “at any moment, there is always a pair of antipodal points on the Earth’s surface with equal temperatures and barometric pressures”. In the last years, the original formulation of BUT has been modified, providing useful extensions (Borsuk 1969; Tozzi et al., 2017a). Antipodal points can be replaced by regions or shapes with matching descriptions (Tozzi and Peters, 2016a), allowing the comparison (from one dimension to another) of shapes, trajectories, functions, vectors, particle trajectories, entropies, bits (Tozzi and Peters, 2017a). The features do not need to be antipodal, but rather they must simply share no points in common (Tozzi et al., 2016a). BUT variants hold not just for convex structures such as the circumferences and spheres described by the classical theorem, but also for flat and concave ones, which better describe the intricate trajectories of real systems’ dynamics (Sengupta et al., 2016). The dimensions described by BUT may not stand just for spatial ones (as in the case of circles and spheres), but also for abstract dimensions (Tozzi et al., 2017b): the crucial issue is that matching descriptions allow commensurability between (real or abstract) entities equipped with different (real or abstract) dimensions.

Publications from far-flung scientific disciplines point towards the BUT as an universal rule for elusive physical and biological activities. For a survey of the countless applications, from pre-big bang scenarios, to quantum entanglement, emergence of life and neuroscience, see Peters et al. (2017a and 2017b); Peters and Tozzi (2016). In such topological

context, systems' operations become projections among different levels, which give rise to apparently emergent properties in higher dimensions. BUT suggests that system's properties in physical/biological spaces can be translated to abstract mathematical ones, and vice versa: this means that complete description of a wide range of phenomena can be reached just by looking at their higher levels, where the differences are easily detectable.

In sum, the above-mentioned theorems suggest that we are dealing with mathematical mappings and projections among different activity levels, instead of cause/effect relationships. Topological alterations provide by themselves physical and biological quantifiable effects. In the next paragraphs, we will tackle the crucial issue: how do topological projections work in real contexts? What are the physical or biological mechanisms leading to mappings among different dimensions in real systems' paths and trajectories? Once established that the opportunity to treat systems in terms of topological structures, how to make the leap from the simple, almost intuitive topological theorems to hugely generic events?

PHYSICAL AND BIOLOGICAL INCARNATIONS OF THE HAIRY BALL THEOREM

HBT might be used to approach biophysical systems. As stated above, the theorem ensures the presence of at least one point of the system where a function disappears. In case of living systems equipped with a continuous function, this means that there will always be a point, or a tiny area, where this function is close to zero. For example, cellular membranes must display at least a small area where surface tension disappears. Therefore, a difficulty arises: in this point, called singularity, energy gets lost, against the thermodynamic constraints. The issue is unraveled, when tackled in terms of a mathematical/topological approach. Indeed, the features modified by HBT can be restored through the mathematical device called "bubble phenomenon", borrowed from the singularity removal theorem of Uhlenbeck for four-dimensional Yang-Mills connections to higher dimensions. For technical readers, the procedure is the following: the point with vanishing continuous tangent stands for a removable singularity inside a punctured ball. Inside the singularity, uniform convergence of conformally invariant equations occurs. This means that many positive-energy solutions (instantons) on the spherical manifold are concentrated near this tiny area, where they converge towards a trivial pointwise solution. Close to the singularity dictated by HBT, a bubble-tree domain can be drawn (Uhlenbeck K. 1982a and 1982b). Provided the norm of the curvature is sufficiently small, bubble trees allow the removal of the singularity and the transformation of gauge fields to a smooth field (Tao and Tian 2004; Meyer and Rivière, 2003). In plain terms, the surface tension, apparently vanished in a tiny area of living cells' spherical surfaces, can be recovered by constructing bubbles on bubbles that restore the energy loss inside the singularity.

These theoretical singularities with vanishing surface tension in cellular membranes display a biophysical counterpart: channels cavities. Therefore, we can state that, inside channels, the surface tension gets lost and is difficult to detect and measure. The procedure suggested by Uhlenbeck permits to calculate the real surface tension of every cellular channel, even if they apparently display a zero value of such tension. One might ask: what for? Who cares of the values of surface tension inside the channels of a living cell? The issue deserves our attention, if we take into account the concept, borrowed from fluid mechanics, of dewetting transition (Sharma and Reiterb, 1996; Thompson, 2012). Dewetting transition stands for a very general mechanism of cellular functioning, because it is widespread in biophysical structures: it has been described in lipid droplets and bilayers (Thiam et al., 2013; Vargas et al., 2014), extracellular matrix and glycocalyx (Tanaka et al., 2005), protein cavities (Young et al., 2010), endothelial cells' openings (Gonzalez-Rodriguez et al., 2012), mechanosensory channels (Anishkin and Sukharev, 2004), cell adhesion (Sackmann and Bruinsma, 2002). Its peculiar mechanism is characterized by a very unusual behaviour of water's supramolecular assemblies: when water and ions are enclosed within the narrowest sub-nanometer confines of an ion channel's hydrophobic pore, a peculiar stochastic liquid-vapour water phase transition takes place near a given 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 inside the channels leads to hydrophobic gating and physiological outcomes: impaired conductance, energy barriers to ion transit and, ultimately, the closure of the channel. Because metastable dynamical states of hydrophobic gating require both very small radius and interactions with strongly hydrophobic linings (Boreyko et al., 2011; Lapiere et al., 2013), the knowledge of the surface tension inside the channels appears to be fruitful. Indeed, such knowledge might lead to the development of drugs able to modify the channel's surface tension and, therefore, to selectively interfere with the biological activities of cellular receptors.

Exceptional points in non-Hermitian biological networks. HBT dictates that dynamical systems must necessarily exhibit at least a singularity, i.e., a critical point where the behaviour of a mathematical model governing a physical system is of different nature, compared to the neighbouring points (Miri and Alù, 2019). Exceptional points are spectral singularities standing for degeneracies of non-conservative systems. Singularities in non-Hermitian systems (i.e., systems which do not obey conservation laws, because they exchange energy with the surrounding environment) are studied in quantum resonance, optics and photonics, in particular in the fields of coupled-cavity laser sources, sensors, absorbers, nonlinear resonators, spatial mode converters and isolators. Nevertheless, the ubiquitous occurrence of exceptional points in non-Hermitian systems dictated by HBT might provide fruitful applications also in revising

fundamental concepts in non-conservative BIOLOGICAL systems, such as the human brain. Non-Hermitian systems have been recently assessed in biological and neural networks too (Amir et al., 2016; Tanaka and Nelson, 2018). In particular, the brain exhibits the ingredients required by these singularities:

- a) Non-conservative elements with gain and loss are correlated with the dynamic inhibitory/excitatory balance discovered in neocortical neurons (Haider et al., 2006).
- b) The imaginary values required by non-Hamiltonian systems (able however to support entirely real eigenvalue spectra) have been recently found in the human brain of healthy subjects (Tozzi et al., 2016).
- c) The occurrence of abrupt phase transitions that dramatically alter the overall response take place both in optic/photonic dissipative systems and in neural ones (Tognoli and Kelso, 2014).
- d) In both physical and biological systems, completeness and orthogonality of the eigenbasis of the governing operators are broken and no longer diagonalized, when small perturbations are introduced.
- e) The peculiar topology of eigenvalue surfaces near exceptional points described by Gong et al. (2018) might correspond to the oscillations of sharp frequency produced by the brain activity.
- f) Non-Hermitian components can be currently extracted from neurodata, e.g., from EEG traces (Marzetti et al., 2008).

In sum, HBT dictates the constraints of biophysical systems' behaviour, independent of the exerted forces. This lead to the production of mechanisms that escape cause effect relationships, because are governed by passive topological phenomena.

TOPOLOGICAL ACCOUNTS OF LIVING CELLS AND BRAINS

Other simple theorems are useful to describe real world phenomena, being they equipped with connotations that might give rise to physical and biological consequences. In this Section, we examine HST, BFT and LST, and provide their feasible biological counterparts. We will start from life: its definition is rather qualitative, because it takes into account fuzzy concepts such as homeostasis, organization, growth, adaptation, response to stimuli (McKay, 2004; Trifonov, 2012). One of the most frequent definitions of life involves cellular duplication, i.e., the ability of living beings to produce new individual organisms (offspring), either asexually from a single parent organism, or sexually from two. Reproduction can be topologically treated, providing us with a mathematical definition of one of the foremost traits of life. Every cell gives rise to two identical "progeny": this means that, thanks to continuous mapping among manifolds, monocellular life and its primeval birth can be defined and operationalized in terms of BUT and HST. Starting from unique assemblies of macromolecules, a living cell can be topologically built and two progenitors can be achieved from an ancestral cell. In this context, life becomes the mathematical, quantifiable phenomenon standing for the continuous function required by BUT (**Figure 1, left side**). HST comes into play at the stage of cellular division, when a single cell gives rise to two indistinguishable ones. Indeed, we achieve antipodal points not due to changes in dimensions as suggested by BUT, but rather generated by a SPLIT of S^2 into two identical parts. For further details, see the **right side** of the **Figure 1**. Thanks to the ham sandwich approach, antipodal regions on a sphere are viewed as tiny balls sliced by a hyperplane, This leads to a fresh view of cell division, which becomes the result of splitting a sphere into two identical hyperspheric offspring cells.

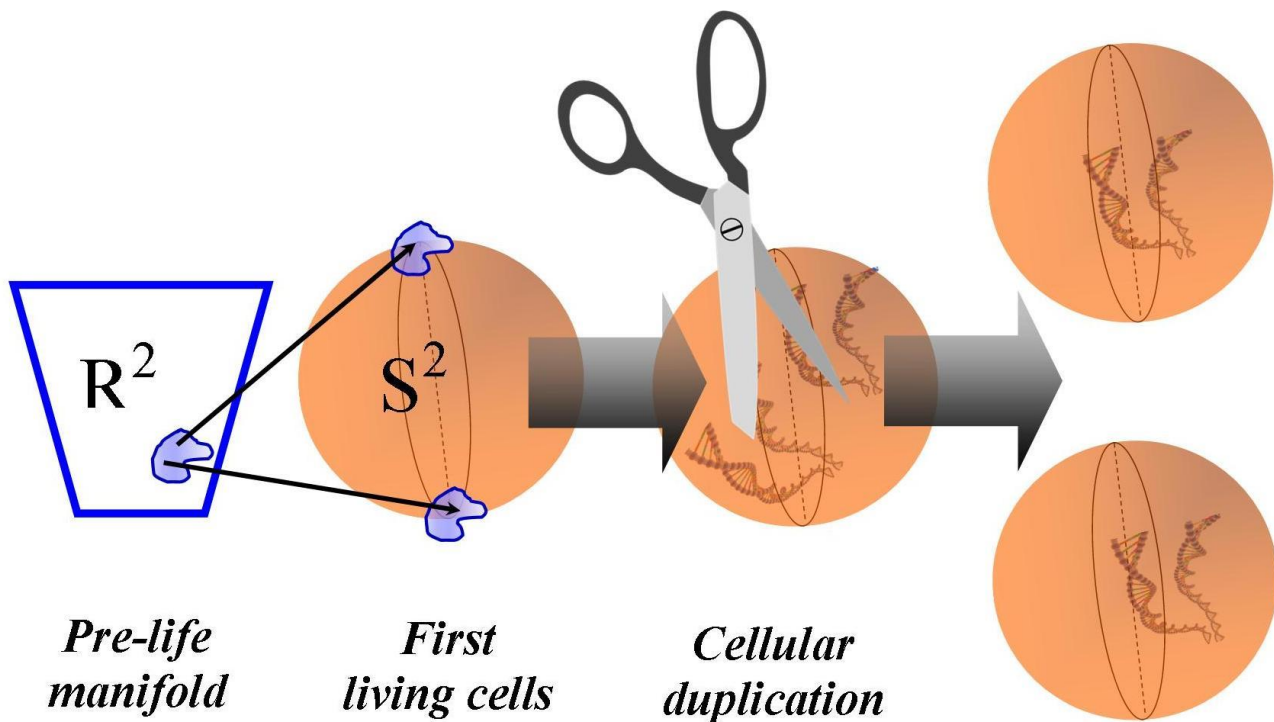


Figure 1. Topological framework for cellular duplication. The **left side** of the Figure displays a two-dimensional manifold R^2 (standing for pre-biological assemblies of macromolecules) and a three-dimensional sphere S^2 (standing for the first organization of membrane-delimited living cells). The process can be described in terms of BUT for different values of dimensions: indeed, a single feature on R^2 maps to two matching features on S^2 , and vice versa. Features stand for particularly important biological issues that are required in more than one copy to generate life: biochemical paths, nucleic acid conformation, and so on. The **right side** of the figure illustrates how, due to the ham-sandwich theorem, the three-dimensional cell with two antipodal regions can be split in two three-dimensional spheres, each one equipped with one of the antipodal features. This occurs during cellular division: a manifold separates into two manifolds with the same dimension.

Ergodic systems and Brouwer fixed point theorem. Successful biophysical theories, such as the free-energy principle, require living activities taking place in ergodic phase spaces (Friston 2010). This means that, over long periods, the time spent by a system in a region with the same energy is proportional to the region's volume, so that all accessible microstates are equiprobable over a long period of time (Barth 1898; Walters 1982; Alaoglu and Birkhoff, 1940; Feller 1971). On the other hand, claims from neuroscience suggest that many biological systems, such as the brain, display non-ergodic behaviour. It has been suggested that brain fluctuations' properties are inconsistent with Markovian approximations (Fraiman and Chialvo 2012), that the mean-square distance travelled by brain particles displays anomalous diffusion and that some phase space region may take extremely long times to be visited (Bianco et al., 2007). A topological approach elucidates the controversial issue. Both ergodic and non-ergodic conditions can be "unified", e.g., treated in terms of algebraic topology, just by changing the dimensions of the structure under investigation. At first, we consider particles that "ergodically" travel along the whole surface a two-dimensional disk; then, we consider the corresponding three-dimensional sphere, achieved through higher-dimensional mappings. In the higher-dimensional case, our particles are constrained to move just inside the surface areas corresponding to antipodal points. This means that particles cannot meet, and, because they cannot walk across the whole surface of the three-dimensional sphere, system's ergodicity gets lost. Therefore, in the background of biosystems' topology, the discrepancy between ergodic and non-ergodic spaces stands just for a false problem: the system is ergodic in lower dimensions, while non-ergodic in higher ones. Here the FPT comes into play. In biological contexts, FPT dictates that we can always find a region containing a single feature, and every feature (for the BUT) comes together with another one, termed a "wired friend" (Tozzi et al., 2018). Every occurrence of a wired friend on a lower-dimensional structure maps to a fixed description, e.g. to another feature belonging to a manifold with higher dimensions. Therefore, every biological feature (embedded in a higher-dimensional macro-levels) is the topological description of another (embedded in a lower dimensional micro-levels), and vice versa. This means that, because of BUT, FPT and multidimensional approaches, every biological feature is the description of another, through a fully passive mechanism devoid of causality.

Sensations and Lusternik–Schnirelmann theorem. Ancient accounts of the world divide the spherical environment surrounding living observers into the four classical elements: the heaviest earth, water, air and the lightest fire (Russell 1995). In analogy with these pre-scientific claims, recent interpretations of human perception focus on the simplest and most natural standpoint: an individual (either human or animal) embedded in her environment (Gibson, 1979; Russo-Krauss, 2015). The environment stands for what surrounds living organisms who perceive and behave. In topological terms, the individual is embedded in a spatial three-dimensional ball, because her surrounding spatial environment is shaped as a sphere. In the framework of ecological approaches to visual perception (Gibson 1986), the environment perceived by the individual is not a physical one, but rather is described by the triad: “medium”, “substance” and “surfaces” (Gibson, 1950; Gibson 1986). The most stable, long-lasting perception is the ground upon which the observer stands, i.e., the horizontal surface under her feet. When the individual raises her eyes, she perceives the sky or the ceiling. The middle zone between the ground and the sky stands for the medium, where objects, e.g., something which can be handled, stand vertically. For our topological purposes, it is noteworthy that the human individual splits her surrounding environment in three components: the ground and the sky, which join together at the horizon, and the intermediate zone, the medium. Therefore, the three-dimensional ball is separated in three slices: the sky on the top, the ground on the bottom and the intermediate zone in the middle. Indeed, the brain spontaneously tends to part the environment in different closed subsets. In this context, LST might be very helpful. It states, in plain terms, that one of the three slices must necessarily contain some surface features with matching description. When an individual focuses her glance on one of the three slices of her surrounding three-dimensional sphere, her attention is driven by the slice containing antipodal points. Therefore, “attention” becomes a mental attitude that allows individuals to find, inside one of the three slices (the sky, the ground and the medium), a pair of features that share something perceivable in common. The matching features could stand for spatial objects or shapes, but also for matching movements: in the latter case, the shapes are not called objects, but events. In sum, LST provides a topological explanation of the psychological spontaneous mechanisms underlying human attention and perception.

THE BIOPHYSICAL MEANING OF THE BORSUK-ULAM THEOREM

Here we focus on BUT, that has been proven useful to describe and assess countless physical/biological systems, from quantum entanglement to cellular homeostasis, from gauge theories to multidimensional nervous activity (Tozzi and Peters 2016b, 2017b and 2017c, Tozzi 2019). Here we ask: how does BUT work in physical terms? How to come up with a plausible and meaningful understanding of how something as topologically simple as BUT could be generalized to address such a huge range of interpretations of the theorem itself? In this section, we will analyze different possibilities to build real BUT systems. Two of such possibilities concern light rays: one rests on optical reflection (gravitational lensing), another on oscillatory interference (double slit experiments). It might be objected that BUT is not much more than the observation that, if you shine a light through a clear sphere onto a plane, there will be a point in the overlapping images of the near and far side of the sphere that includes two maximally distant points. This rather qualitative suggestion leads straightly to the concept of gravitational lensing. A gravitational lens is a distribution of matter (e.g., a galactic cluster) between a distant source and an observer on the Earth. Light is bent from the source, as it travels towards the observer. The amount of bending is one of the predictions of Einstein’s general theory of relativity (Einstein 1936). The light from a distant galaxy diverges due to the gravitational effects of a foreground celestial body, which acts like a lens and makes the distant source appear either distorted or magnified. This mechanism can be explained in BUT terms: projections give rise to light rays’ deflection through a passive mechanism (**Figure 2**). In the BUT framework, a three-dimensional hidden cosmic body emits a three-dimensional oscillatory light beam that intersects a four-dimensional gravitational lens, giving rise to the two images with matching description detectable by us observers on the Earth. Note that the gravitational lens stands for a four-dimensional (and not three-dimensional) manifold, because spacetime encompasses a fourth dimension (i.e., time) apart from the three spatial ones.

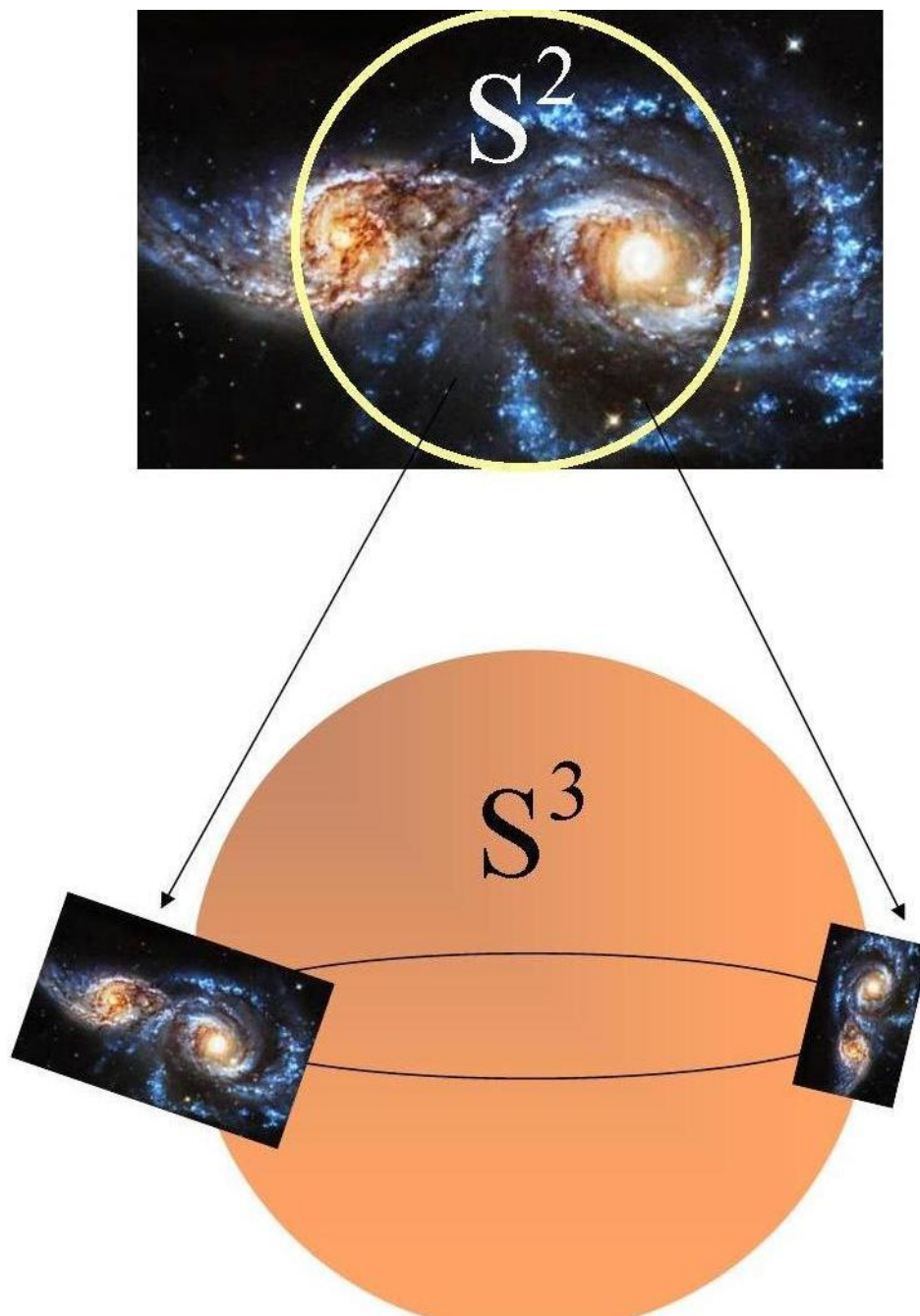


Figure 2. Relationships between gravitational lenses and BUT. Light rays from the three-dimensional galactic structure S^2 are reflected when approaching the four-dimensional gravitational lens S^3 . This leads to two matching descriptions of the galactic structure.

Physical connotations of BUT explain particle/wave duality in double slit experiment. Double-slit experiments illustrate the probabilistic nature of quantum mechanical phenomena, because they suggest that light and matter display features of both waves and particles, (Ma and Blume, 1995). A wave is split into two separate waves which later combine into a single one. The wave nature of light causes the oscillations passing through the slits to interfere (**Figure 3A**). Indeed, for the Huygens–Fresnel principle, each point on a wavefront generates a secondary wavelet, and the disturbance at any subsequent point can be found by summing the contributions of the individual wavelets at that point. When the two waves are in phase, the summed amplitude is maximum; when in anti-phase, they cancel, so that the summed intensity is zero (Ament et al., 2011). These features, known as positive and destructive interferences, produce bright and dark bands on the detection screen, a result that would not be expected if light consisted of classical particles (**Figure 3C**). Light is found to be absorbed at the screen at discrete points as individual particles (not waves), so that the interference pattern appears through the varying density of particle hits on the detection screen. Therefore, double

slit experiments proof the complementarity principle: photons behave as either particles or waves, but cannot be observed as both at the same time. As stated above, BUT-like mechanisms require a few ingredients:

- Two manifolds with different dimensions, independent of their curvature (either convex, or flat, or concave).
- A continuous function.
- A projective force which allows mappings from one dimension to another.
- Two (or more) matching features, possibly (but not necessarily) antipodal.

The double-slit experiment's setting provides every required ingredient (**Figure 3B**). The higher-dimensional manifold stands for the three-dimensional space between the double-slit barrier and the detection screen, and can be described in terms of a S^2 sphere. The lower-dimensional manifold stands for the two-dimensional detection screen R^2 . The required continuous function stands for the relative intensity of the intersecting waves, while the projective force stands for the light trajectories traveling throughout the medium. The matching features are the areas of the S^2 manifold where the relative intensities are equal. The two features with matching descriptions stand for symmetrical structures endowed in the interfering waves. Indeed, the occurrence of symmetric refraction patterns is in touch with the claims by Revelli et al. (2019), who demonstrated that interference patterns in resonant inelastic x-ray scattering disclose the symmetry of electronic excited states, in the same way as elastic scattering does for the ground state. The single feature, located on the surface of the 2D screen, stands for a single value of relative intensity. The stripes produced on the screen, caused by repeated shots of single particles, stand for the zones of high (dark stripes) and absent relative intensity (white stripes). Continuous waves, which give rise to the dark stripes on the screen, are produced when the interference is positive. In turn, when the two waves cancel and their summed intensity is zero (destructive interference), the function becomes discontinuous: therefore, the BUT does not hold anymore and the points cannot be detected (white stripes).

a BUT-framed explanation of the double-slit experiment may be drawn (**Figure 3**). When a plain wave crosses two slits of the proper size, it is split in two different waves that interfere one each other and reach the detection screen (**Figure 3A**). In a BUT account, the two interfering waves are located inside a sphere S^2 , which is endowed in the three-dimensional space between the two slits and the screen (**Figure 3B**). The interference patterns detected by Revelli et al. (2019) point towards the occurrence of intrinsic symmetries: this means that there exist interfering oscillations which display matching description in S^2 . According to quantum dictates, when the two waves reach the two-dimensional screen R^2 , they generate a single detection point. This means, in BUT terms, that two features with matching description in S^2 project to a single feature in R^2 (**Figure 3B**). Therefore, BUT-framed projections describe the counterintuitive quantum notion of light as equipped with both oscillatory and particle-like behavior in the double-slit experiment: the continuous, oscillatory components of the quantum wave are located inside the three-dimensional manifold S^2 , while the discrete particle components are located inside the two-dimensional manifold R^2 (**Figure 3C**).

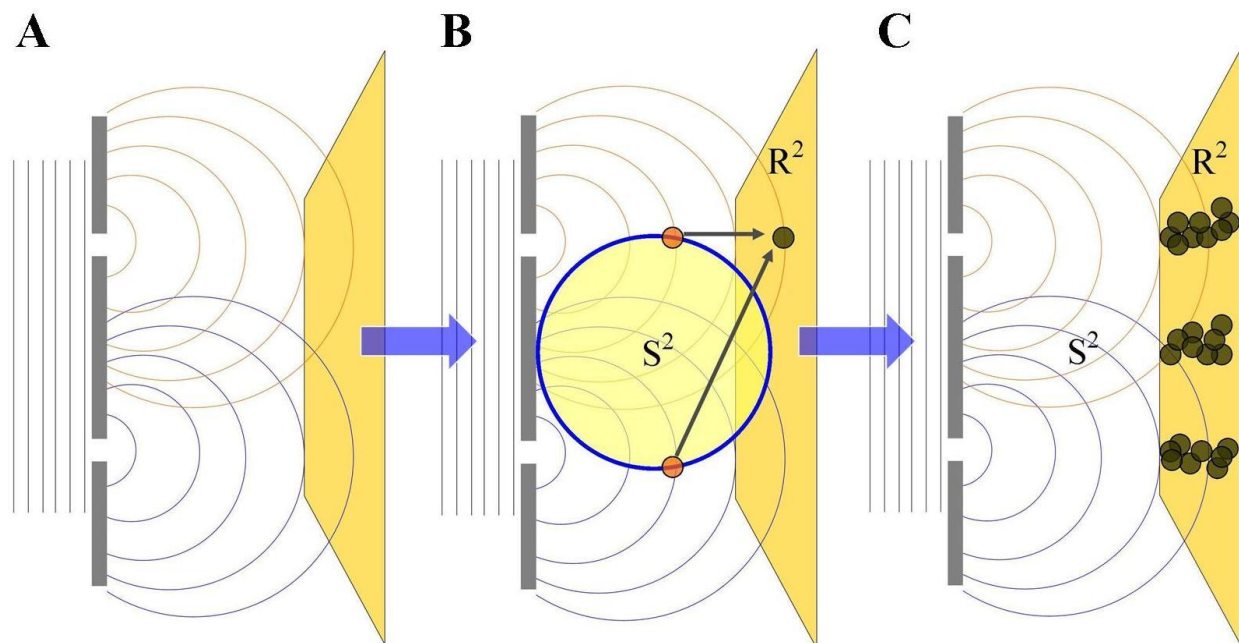


Figure 3. Topology meets double slit experiments. **3A:** A plane wave (or a laser beam) crosses two slits, giving rise to two superimposing oscillations. **Figure 3B** describes the BUT incarnation of the double slit experiment, while **3C** illustrates the interference pattern caused by bright and dark bands on the detection screen. See text for further details.

Collisionless interactions in plasma-like fluids. Plasma, i.e., the fourth state of matter at high energies, is characterized by collective movements of charged particles. Long-range correlations are required to avoid the large disruptive electromagnetic fields in presence of net charge. The collective behavior is governed by the reciprocal influences among nearby charged particles embedded in a “Debye sphere” (Sturrock, 1994; Goldston and Rutherford, 1995). A self-consistent collective electromagnetic field is produced by charged ions inside this system of interacting particles, so that time evolution of long-range interactions can be described by the Vlasov-Maxwell system of equations (Vlasov 1938). The spontaneous formation of spatial features takes place on a wide range of length scales on the boundary of a metastable state (Cheng and Gamba 2012); this means that very slight changes in just a few parameters give rise to completely different patterns. In touch with these concepts developed by high energy physics, the role of charged particles’ collective behaviors and long-range functional couplings has been evaluated also in brain dynamics, in terms of McKean-Vlasov equations of macroscopic diffusion, which are derived from the classical Vlasov ones for plasma (Tozzi et al., 2018b; Syková and Nicholson, 2008; deBuyl et al., 2011). In BUT terms, when collisionless dynamical structures modify their collective shape and reach the proper conformation, the ensuing topological changes lead to the achievement of antipodal points with matching description (**Figure 4**): this explains the spontaneous, cause-free occurrence of the long-range interactions that characterizes this type of dynamical systems.

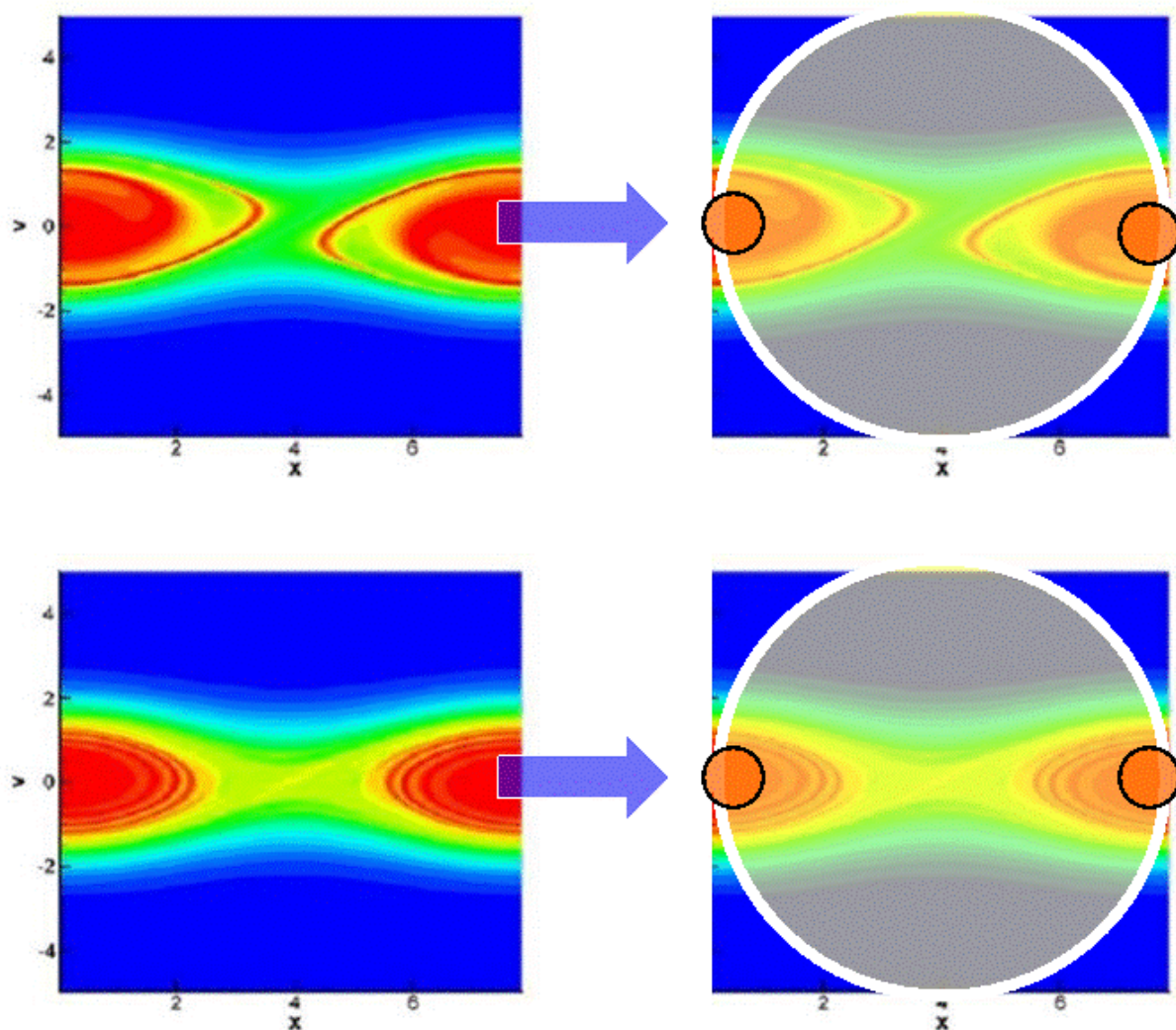


Figure 4. Left side: two examples of long-range interactions of collisionless particles’ collective movements in plasma (Modified from Cheng and Gamba 2012). A slight change in just one or two parameters gives rise to rather different patterns. **Right side:** BUT interpretation of the two examples of collisionless movements. Plasma currents are embedded in spheres equipped with antipodal features displaying matching description (red circles).

Graph theory comes into play: Kneser graphs. Although BUT seems far removed from graph theory, nevertheless it displays combinatorial significance that gives rise to fruitful applications in the assessment of causal relationships. The matching descriptions in dynamical systems that obey the BUT's dictates can be described in terms of the so-called Kneser graphs. The Kneser graph $KG_{n,k}$ is equipped with a set of n elements and subsets of k elements (Albertson and Boutin, 2007). For example, the Kneser graph $KG_{5,2}$ displays five n elements, say $\{1,2,3,4,5\}$, that can be matched in pairs of k -elements subsets, say $\{1,2\}$, $\{3,5\}$, and so on (**Figure 5A**). These subset pairs stand for matching descriptions in the BUT framework. A Kneser graph displays a number n of vertices, that are adjacent if and only they do not encompass the same elements. The graph, although vertex- and edge-transitive, is not as regular as it might appear at a first sight. If we start from a vertex and follow the allowed trajectories, we notice that the paths are constrained, so that just some dynamical configurations and steps are permitted in a short number of moves. For example, in $KG_{5,2}$, a path starting from one vertex, say $\{1,2\}$, cannot proceed towards $\{1,4\}$ in a single step. The sequence of mandatory "moves" is described by the so-called "chromatic number", that stands for the smallest number of colors needed to paint the vertices, so that no two adjacent vertices share the same color (Skiena 1990; Pemmaraju and Skiena, 2003). The chromatic number of a generic Kneser graph $KG_{n,k}$ is:

$$n - 2k + 2$$

for instance, the $KG_{5,2}$ graph requires three colors in any proper coloring (**Figure 5B**).

One of the most useful properties of the Kneser graphs is the occurrence of a large gap between the chromatic number $\chi(KG_{n,k})$ and the fractional chromatic number $\chi_f(KG_{n,k})$. The latter stand for the minimum value a/b such that the graph G can be covered by a independent sets, where each vertex occurs in at least b of them. Coloring hypergraphs display strong computational hardness, therefore allowing the quantitative assessment a large number of operations (**Figure 5D**). When $n \geq 3k$, and for for $n \leq 27$, all the connected Kneser graphs encompass a Hamiltonian cycle (Chen 2000), except for $KG_{5,2}$. A Hamiltonian cycle is a traceable, circular path in an undirected or directed graph that visits each vertex exactly once (DeLeon 2000) (**Figure 5C**). In turn, $KG_{5,2}$ displays a Hamiltonian path, but no a Hamiltonian cycle. It is called "hypohamiltonian", meaning that, although it has no Hamiltonian cycle, the deletion of any vertex makes it Hamiltonian (Albertson and Boutin, 2007).

To demonstrate the close relationship between Kneser graphs and BUT, we need to introduce once again the LST, which guarantees at least a pair of exactly opposite points on a sphere, as required by BUT. LST holds for both open and closed sets. There exists a famous conjecture that takes into account both open and closed sets: the Kneser conjecture (Kneser, 1955). It states that:

whenever the n -subsets of a $(2n + k)$ -set are divided into $k + 1$ classes, then two disjoint subsets end up in the same class.

Or, in other words:

For every $k > 0$ and $n \geq 2k$, $\chi(KG_{n,k}) = n - 2k + 2$, where χ denotes the chromatic number.

The Kneser conjecture for chromatic numbers was solved by Lovász (1978) and Bárány (1978), using the BUT. Therefore, there must exist two disjoint k -sets colored i , in touch with the BUT's requirement of two points with matching description. In sum, the dynamics of the BUT matching descriptions take place on higher-dimensional systems that display the combinatorial configuration of a Kneser graph. This means that, in a physical/biological dynamical system, just the few trajectories and paths which require the shortest number of steps are allowed. Therefore, when the antipodal points are generated in higher dimensions, they behave in a predictable fashion. This guarantees us, when the proper setting and subsets are introduced, the possibility to predict the dynamical evolution of the system under evaluation.

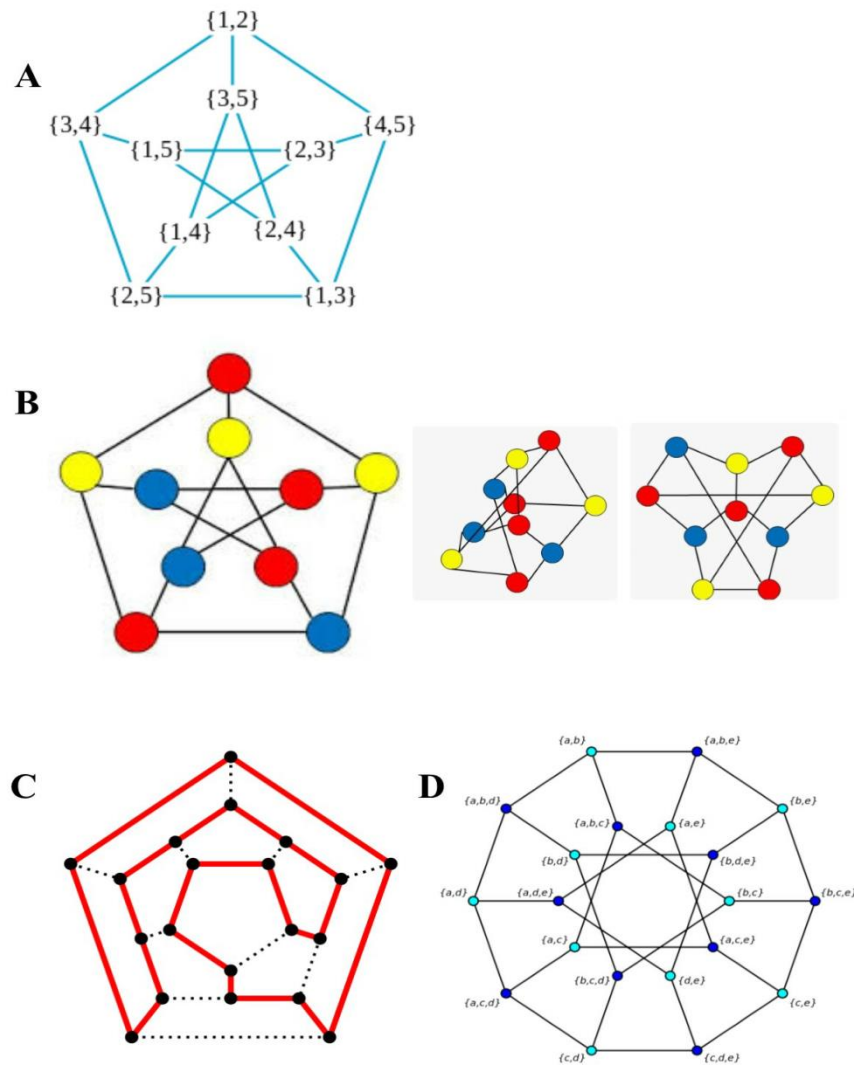


Figure 5A: The graph $KG_{5,2}$ is provided as an example for Kneser graphs. **Figure 5B** illustrates the required coloring of the vertices. Note that, as shown in the central and right frames, the graph's shape does not need to be too much constrained: different vertexes' configurations are feasible, provided the relationships among the sub-set k elements are kept invariant. **Figure 5C:** a Hamiltonian cycle on a dodecahedron. **Figure 5D** depicts a more complicated structure, termed the Bipartite Kneser Graph. This means that different possible graphs can be used, depending on the requirement of the experimental setting.

Sources: A: https://fr.wikipedia.org/wiki/Graphe_de_Kneser#/media/File:Kneser-5-2.svg; B: spring-of-mathematics.tumblr.com; C: https://en.wikipedia.org/wiki/Hamiltonian_path#/media/File:Hamiltonian_path.svg; D: <https://commons.wikimedia.org/wiki/File:BipartiteKneserGraph.svg>

CONCLUSION: WHEN CAUSALITY FADES AWAY

Taking all the above-mentioned theorems together, a conclusion can be drawn: when spatial or temporal changes occur inside dynamical systems, three phenomena are necessarily displayed, i.e., the presence of antipodal, fixed and zero-points. This means that topological-related events, such as shape and dimensions modifications, generate changes in features. They do not require causality, because no forces are needed to mediate the interactions underlying these spontaneous mechanisms. It is noteworthy that in many cases (e.g., soap bubbles, closed random walks and spontaneous activity of the brain) spatiotemporal shape modifications take place passively, without having to exert (internal or external) forces. Variations in shapes lead to real phenomena, such as the emergence of symmetries or the

occurrence of features with matching description, which are generated irrespective of energetic constraints: amazingly, free-energy, entropy and enthalpy are preserved during topological modifications.

The biophysical gist of simple topological concepts allows description of real world phenomena devoid of energetic constraints and cause effect explanations, because proper mappings and projections replace forces and fields in physical and biological dynamics, leading to causality-free scientific explanations. We described topological theorems and their recently-developed variants, highlighting the possible use in physics, biology, neuroscience. The tremendous power of BUT has been successfully used in many applications, from math to logic, from physics to biology and statistics. This allowed us to throw an operational bridge between BUT and double-slit experiments: a topology-framed explanation suggests that the continuous, oscillatory component of the quantum light wave is located inside a three-dimensional manifold, while the discrete particle component inside a two-dimensional one. This is in touch with relational formulations of quantum mechanics, which suggest relational properties among quantum systems as the most fundamental issues of the microscopic realm (Rovelli, 1996; Smerlak and Rovelli, 2007). This approach, which discards real, observer-independent quantum properties (Yang 2018), has been recently substantiated by The BIG Bell Test Collaboration's findings (2018). Experimentally detected correlations in Bell tests contradicted local realism: therefore, the claim that the physical world's properties are independent of our observation does not hold true.

Contemporary approaches to explanations in scientific theories claim primary role for causal mechanisms. Events are bound into causal chains by two relations: spatio-temporal continuity (at least in macroscopic phenomena) and statistical relevance (Van Fraassen, 1977). In contrast, a topological explanation of scientific issues does not require the two above-mentioned relationships. The dynamics of biophysical phenomena lead to obligatory modifications in shapes and features that obey to strict topological requirements, far apart from causal locality and paradigmatic statistical approaches. For example, when a soap bubble spontaneously achieves the proper spherical shape, it is mandatory for its circumference to display at least two antipodal points with matching features (such as, e.g., the same superficial tension), independent of spatio-temporal constraints and probabilistic considerations.

A topological account permits to remove energetic requirements in scientific descriptions. Indeed, topological changes have the advantage of describing energetic features which pay no heed to the second law of thermodynamics. This is due to the well-established links between thermodynamic issues and topological symmetries. Symmetry, a type of invariance occurring when an object does not change under a set of transformations, is the most general feature of countless types of systems. Symmetries, widespread at every level of organization, can be regarded as the most general feature of systems, more general than free-energy and entropy constraints too. The recent observation that, in quasi-static processes, entropy production is strictly correlated with symmetry breaks paves the way to use system invariances for the estimation of enthalpy and energy requirements in computational processing (Roldán 2014).

Symmetry break consists of sudden change in the set of available states (Roldán, 2014). In spontaneous symmetry breaking (SSB), the underlying laws are invariant under a transformation, but the system as a whole is modified. This allows a biophysical structure cast in a symmetrical state to end up in an asymmetrical one. In case of finite systems with metastable states, the confinement is not strict: the system can "jump" from a region to another (Friston 2010; Fraiman et. al., 2012). In the SSB framework, BUT is a welcome benefit, because symmetries can be assessed in terms of antipodal points on a hypersphere. Symmetries (standing for antipodal self-similar points) enclosed in the abstract spaces of n-dimensional spheres can be evaluated in terms of projections on lower-dimensional manifolds (standing for broken symmetries). "Hidden" would be a better term than "broken", because the symmetry is always there. Symmetries, hidden at a lower level, are restored at a higher level of analysis: a symmetry break occurs when symmetry is detectable at one level of observation and "hidden" at another. These steps do not obey to the second law of thermodynamics, neither to causal relationships, because the law goes unnoticed during projective topological operations. Once established that energetic issues are correlated with topology, what happens to information when proceeding from higher to lower dimensions? Information decreases, because less dimensions have less coordinates, and therefore less information (for a thorough treatment, see Tozzi and Peters, 2019).

Other theoretically feasible applications of topology can be suggested. Sociological phenomena might obey not just to cause effected relationships, but also to topological changes in temporal paths. This could lead to projection-based description of events, rather than causality-related: mappings and projections, instead of forces. In touch with this claim, the role of virus-virus interactions has been recently addressed in antiviral immunity (Domingo-Calap et al., 2019). The Authors demonstrated that viral escape from interferon (IFN)-based innate immunity is a social process, in which IFN-stimulating viruses determine the fitness and altruistic traits of neighboring ones. The link with BUT is patent, if we take into account that, in well-mixed populations, spatial structure determines whether IFN shutdown can evolve. Therefore, fundamental social evolution rules dictated by shape constraints govern viral innate immunity evasion. A recent paper published in *Nature*, which examines self-organization and symmetry breaking during intestinal organoid development, seems to fully confirm the usefulness of our topological framework in the approach to biophysical dynamics. Intestinal organoids are three-dimensional artificial structures that mimic intestinal cell-type composition and tissue organization. Serra et al. (2019) analyzed self-organizing development of organoids' cell populations derived from a single intestinal stem cell, driven by transient activation of the transcriptional regulator YAP1. When a first symmetry-breaking event occurs (in topological terms, a decrease in dimensions), a fraction of identical cells in a symmetrical sphere (in topological terms, features with matching description) differentiate into Paneth cells. The latter generate the stem-cell niche and asymmetric structures, such crypts and villi. Cell-to-cell

variability in YAP1, emerging in symmetrical spheres, leads to symmetry-breaking events and formation of the first Paneth cells. This means that single cells exposed to a uniform growth-promoting environment (in topological terms, a continuous function) display the intrinsic ability to generate emergent, self-organized behavior that results in the formation of complex multicellular asymmetric structures.

In brief, we showed how mathematical theorems work in the real world, arguing that biophysical connotations of topological modifications do not require cause effect relationships: this permits us to cope with the deep uncertainty frequently detected during the scientific assessment of real systems.

REFERENCES

- 1) Alaoglu L, Birkhoff G. 1940. General ergodic theorems. *The Annals of Mathematics*, 41(2), 293-309.
- 2) Albertson MO, Boutin DL. (2007), "Using determining sets to distinguish Kneser graphs", *Electronic Journal of Combinatorics*, 14 (1): R20, MR 2285824.
- 3) Ament LJP, van Veenendaal M, Devereaux TP, Hill JP, van den Brink J. 2011, Resonant inelastic x-ray scattering studies of elementary excitations. *Rev. Mod. Phys.* 83, 705.
- 4) Amir A, Hatano N, Nelson DR. 2016. Non-Hermitian localization in biological networks. *Phys. Rev. E* 93, 042310. doi:https://doi.org/10.1103/PhysRevE.93.042310.
- 5) Anishkin A, Sukharev S. 2004. Water dynamics and dewetting transitions in the small mechanosensitive channel MscS. *Biophys J* 86:2883-2895.
- 6) Aryal P, Sansom MS, Tucker SJ. 2015. Hydrophobic gating in ion channels. *J Mol Biol* 427:121-30.
- 7) Autrecourt, Nicholas of. About 1340. *The Universal Treatise*. Marquette University Press, Milwaukee, Wisconsin, 1971.
- 8) Barth A. *Vorlesungen über Gastheorie*. Leipzig: 1898. OCLC 01712811. ('Ergoden' on p.89 in the 1923 reprint.)
- 9) Beyer WA, Zardecki A. 2004. The early history of the ham sandwich theorem. *American Mathematical Monthly*, 111(1): 58-61.
- 10) Bianco S, Ignaccolo M, Rider MS, Ross MJ, Winsor P, Grigolini P. 2007. Brain, music, and non-Poisson renewal processes. *Phys. Rev. E* 75, 061911.
- 11) Boreyko JB, Baker CH, Poley CR, Chen CH. 2011. Wetting and Dewetting Transitions on Hierarchical Superhydrophobic Surface. *Langmuir*, 27:7502-7509.
- 12) Borsuk K. 1933. Drei sätze über die n-dimensionale euklidische sphäre, *Fundamenta Mathematicae* XX, 177–190.
- 13) Borsuk K. 1969. Fundamental retracts and extensions of fundamental sequences, 64(1): 55–85.
- 14) Bourbaki N. 1966. *Elements of Mathematics. General Topology* 1, Chapters 1–4. Translated from the French. Reprint of the 1966 edition. *Springer-Verlag, Berlin*, 1989. viii+437 pp. ISBN: 3-540-19374-X, MR0979294.
- 15) Bredon GE. 1997. *Topology and Geometry*, corrected 3rd printing of the 1993 original. *Graduate Texts in Mathematics*, Springer-Verlag, NY, xiv + 557 pp., MR 1700700.
- 16) Cheng Y, Gamba IM. 2012. Numerical study of one-dimensional Vlasov–Poisson equations for infinite homogeneous stellar systems. *Commun Nonlinear Sci Numer Simulat* 17 (2012) 2052–2061
- 17) Davies EC, Rowe PH, James S, et al. (2011). "An Investigation of Disagreement in Causality Assessment of Adverse Drug Reactions". *Pharm Med.* 25 (1): 17–24. doi:10.2165/11539800-000000000-00000.
- 18) de Buyl P, Mukamel D Ruffo S. 2011. Statistical mechanics of collisionless relaxation in a non-interacting system. *Phil. Trans. R. Soc. A* 2011 369, 439-452. doi: 10.1098/rsta.2010.0251
- 19) Dodson CTJ, Parker PE. 1997. *A user's guide to algebraic topology*, Kluwer, Dordrecht, Netherlands, 1997, xii+405 pp. ISBN: 0-7923-4292-5, MR1430097.
- 20) Domingo-Calap P, Segredo-Otero E, Durán-Moreno M, Sanjuán R. 2019. Social evolution of innate immunity evasion in a virus. *Nature Microbiology*
- 21) Copeland EJ, Kibble TWB. 2010. Cosmic strings and superstrings. *Proc. Math. Phys. and Engg. Sciences* 466, no. 2115, 623-657.
- 22) Crabb, M.C., Jawaworski, J. 2013. Aspects of the Borsuk-Ulam theorem. *J. of Fixed Point Theory and Applications* 13, 459-488, DOI 10.1007/s11784-013-0130-7, MR3122336.
- 23) Davis A-E, Brax P, van de Bruck, C. 2008. Brane inflation and defect formation. *Philos. Trans.: Mathematics, Physical and Engineering Sciences* 366, no 1877, *Cosmology Meets Condensed Matter*, 2833-2842.
- 24) DeWitt BS. 1967. Quantum Theory of Gravity II. The Manifestly Covariant Theory. *Phys. Rev.* 160, 1195-1239

- 25) Einstein A. 1936. Lens-like Action of a Star by the Deviation of Light in the Gravitational Field. *Science*. 84 (2188): 506–7.
- 26) Eisenberg M, Guy R. 1979. A Proof of the Hairy Ball Theorem. *The American Mathematical Monthly*, 86 (7): 571–574. doi:10.2307/2320587.
- 27) Feller W. 1971 *An introduction to probability theory and its applications*, vol. 2, Wiley
- 28) Fraiman D, Chialvo DR. 2012. What kind of noise is brain noise: anomalous scaling behavior of the resting brain activity fluctuations. *Frontiers in Physiology*, 3:307.
- 29) Franzinelli A. 1958. Questioni inedite di Giovanni de Mirecourt sulla conoscenza (Sent. I, q. 2–6). In *I Sent.*, qq. 2–6, ed. A. Franzinelli. *Rivista Critica di Storia della Filosofia* 13/3: 319–40.
- 30) Freddoso AJ. 1988. Medieval Aristotelianism and the Case against Secondary Causation in Nature, pp. 74–118 in Morris TV, ed., *Divine and Human Action: Essays in the Metaphysics of Theism*. Ithaca, NY: Cornell University Press.
- 31) Friston K. 2010. The free-energy principle: a unified brain theory? *Nat Rev Neurosci* 11(2):127-138.
- 32) Gibson JJ. 1950. *The Perception of the Visual World*. Greenwood Press, Westport, Conn.
- 33) Gibson JJ. 1979. *The theory of affordance in the ecological approach to visual perception*. Hillsdale, Erlbaum.
- 34) Gibson JJ. 1986. *The ecological approach to visual perception*. Boston: Houghton-Mifflin.
- 35) Goldston RJ, Rutherford PH. 1995. *Introduction to Plasma Physics*. CRC Press, Plasma Physics Series.
- 36) Gong Z, Ashida Y, Kawabata K, Takasan K, Higashikawa S, Ueda M. 2018. Topological phases of non-Hermitian systems. *Phys. Rev. X* 8, 031079.
- 37) Gonzalez-Rodriguez D, Maddugoda MP, Stefani C, Janel S, Lafont F, Cuvelier D, Lemichez E, Brochard-Wyart F. 2012. Cellular dewetting: opening of macroapertures in endothelial cells. *Phys Rev Lett* 25, 108(21):218105
- 38) Haider B, Duque A, Hasenstaub AR, McCormick DA. 2006. Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. *J. Neurosci.* 26, 4535-45. doi: 10.1523/JNEUROSCI.5297-05.2006.
- 39) Kneser, M. Aufgabe 300. *Jahresber. Deutsch. Math.-Verein* 58, 1955.
- 40) Lapierre F, Coffinier J, Boukherroub R, Thomy V. 2013. Electro- (de)wetting on Superhydrophobic surfaces. *Langmuir*, 29: 13346-13351.
- 41) Loke YK. 2012. Adverse drug reactions. *Br J ClinPharmacol.* 2012 Jun;73(6):908-11. doi: 10.1111/j.1365-2125.2012.04235.x.
- 42) Lovász, L. Kneser's Conjecture, Chromatic Numbers and Homotopy. *J. Comb. Th. A* 25, 319-324, 1978.
- 43) Ma Y, Blume M. 1995. Interference of fluorescence x rays and coherent excitation of core levels. *Rev. Sci. Instr.* 66, 1543.
- 44) Marzetti L, Del Gratta C, Nolte G. 2008. Understanding brain connectivity from EEG data by identifying systems composed of interacting sources. *Neuroimage* 42, 87-98 (2008). doi: 10.1016/j.neuroimage.2008.04.250.
- 45) Matoušek, J. 2003. *Using the Borsuk-Ulam Theorem. Lectures on topological methods in combinatorics and geometry*. Written in cooperation with Anders Björner and Günter M. Ziegler, Springer-Verlag, Berlin, 2003. xii+196 pp. ISBN: 3-540-00362-2, MR1988723.
- 46) McKay, Chris P. 2004. What Is Life—and How Do We Search for It in Other Worlds? *PLoS Biology*. 2 (2(9)): 302. doi:10.1371/journal.pbio.0020302.
- 47) Meyer Y, Rivière T. 2003. Partial regularity results for a class of stationary Yang-Mills fields in high dimension, *Rev. Mat. Iberoamericana*, 19, 195-219.
- 48) Miri M-A, Alù A. 2019. Exceptional points in optics and photonics. *Science*, 363 (6422), eaar7709. DOI: 10.1126/science.aar7709.
- 49) Mouton JP, Mehta U, Rossiter DP, Maartens G, Cohen K. 2017. Interrater agreement of two adverse drug reaction causality assessment methods: A randomised comparison of the Liverpool Adverse Drug Reaction Causality Assessment Tool and the World Health Organization-Uppsala Monitoring Centre system. *PLoS One*. 2017 Feb 24;12(2):e0172830. doi: 10.1371/journal.pone.0172830. eCollection 2017.
- 50) Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, et al. 1981. A method for estimating the probability of adverse drug reactions. *ClinPharmacolTher.* 1981 Aug;30(2):239-45.
- 51) Nebeker JR, Barach P, Samore MH (2004). Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann. Intern. Med.* 140 (10): 795–801. doi:10.7326/0003-4819-140-10-200405180-00017. PMID 15148066.
- 52) Ockham of W. 1974. *Opera philosophica*, ed. Philotheus Boehner, Gedeon Gál, et al.; vol. I. St. Bonaventure, NY, Franciscan Institute.
- 53) Pemmaraju S, Skiena S. 2003. *Computational Discrete Mathematics: Combinatorics and Graph Theory in Mathematica*. Cambridge, England: Cambridge University Press.
- 54) Peters JF. 2016. *Computational Proximity. Excursions in the Topology of Digital Images*. Edited by Intelligent Systems Reference Library. Berlin: Springer-Verlag. doi:10.1007/978-3-319-30262-1.

- 55) Peters JF, Tozzi A. 2016. Quantum Entanglement on a Hypersphere. *Int J Theoret Phys*, 1–8. Doi:10.1007/s10773-016-2998-7.
- 56) Peters JF, Tozzi A, Ramanna S, Inan E. 2017. The human brain from above: an increase in complexity from environmental stimuli to abstractions. *Cognitive Neurodynamics*,11(4), 391–394. DOI: 10.1007/s11571-0-17-9428-2.
- 57) Popkin RH, Maia Neto JR (Editors). 2007. *Skepticism: An Anthology*. Prometheus Books. ISBN 1591024749 (ISBN13: 9781591024743).
- 58) Revelli A, Moretti Sala M, Monaco G, Becker P, Bohatý L, et al. 2019. Resonant inelastic x-ray incarnation of Young's double-slit experiment. *Science Advances*, 5(1): eaav4020. DOI: 10.1126/sciadv.aav4020
- 59) Roldán E, Martínez IA, Parrondo JMR, Petrov D. Universal features in the energetics of symmetry breaking. *Nature Physics* 10, 457–461 (2014) doi:10.1038/nphys2940.
- 60) Rovelli, C. Relational Quantum Mechanics. *Int. J. Theor. Phys.*1996, 35, 1637–1678.
- 61) Russell B. 1995. *History of Western Philosophy*, Routledge, ISBN 0-415-07854-7.
- 62) Russo Krauss C. 2015. L'empiriocriticismo di Richard Avenarius tra psicofisiologia e teoria della consocenza, in R. Avenarius, *Il concetto umano di mondo*, Morcelliana, Brescia.
- 63) Sackmann E, Bruinsma RF. 2002. Cell adhesion as wetting transition? *Chemphyschem*. 12:262-269.
- 64) Saedder EA, Lisby M, Nielsen LP, Bonnerup DK, Brock B. 2015. Number of drugs most frequently found to be independent risk factors for serious adverse reactions: a systematic literature review. *Br J Clin Pharmacol*. 2015 Oct; 80(4): 808–817. doi: 10.1111/bcp.12600 PMID: PMC4594723.
- 65) Sengupta, Biswa, Arturo Tozzi, Gerald K. Cooray, Pamela K. Douglas, and Karl J. Friston. 2016. "Towards a Neuronal Gauge Theory." *PLOS Biology* 14 (3): e1002400. doi:10.1371/journal.pbio.1002400.
- 66) Serra D, Mayr U, Boni A, Lukonin I, Rempfler M, et al. 2019. Self-organization and symmetry breaking in intestinal organoid development. *Nature* 569: 66–72. Doi: <https://doi.org/10.1038/s41586-019-1146-y>.
- 67) Sharma A, Reiter G. 1996. Instability of Thin Polymer Films on Coated Substrates: Rupture, Dewetting, and Drop Formation. *JColloid Interface Sci*178: 383-399.
- 68) Skiena, S. *Implementing Discrete Mathematics: Combinatorics and Graph Theory with Mathematica*. Reading, MA: Addison-Wesley, 1990.
- 69) Smerlak, M.; Rovelli, C. Relational EPR. *Found. Phys.*2007, 37, 427–445.
- 70) Sturrock PA. 1994. *Plasma Physics: An Introduction to the Theory of Astrophysical, Geophysical & Laboratory Plasmas*. Cambridge University Press. ISBN 978-0-521-44810-9.
- 71) Su FE. 1997. Borsuk-Ulam implies Brouwer: A direct construction. *Amer. Math. Monthly* 104 (9): 855–859, MR1479992.
- 72) Syková E, Nicholson C. 2008. Diffusion in brain extracellular space. *Physiol Rev*. 88(4):1277-340. doi: 10.1152/physrev.00027.2007.
- 73) Tanaka M, Rehfeldt F, Schneider MF, Mathe G, Albersdorfer A, Neumaier KR, Purrucker O, Sackmann E. 2005. Wetting and dewetting of extracellular matrix and glycocalyx models. *Journal of Physics: Condensed Matter* 17, 9.
- 74) Tanaka H, Nelson DR. 2018. Non-Hermitian Quasi-Localization and Ring Attractor Neural Networks. arXiv:1811.07433.
- 75) Tao T; Tian, G. 2004. A singularity removal theorem for Yang-Mills fields in higher dimensions. *J. Amer. Math. Soc.* 17 (3): 557–593.
- 76) The BIG Bell Test Collaboration. Challenging local realism with human choices. *Nature* 2018, 557, 212–216.
- 77) Thiam AR, Farese Jr RV, Walther TC. 2013. The biophysics and cell biology of lipid droplets. *Nat RevMolecular Cell Biol*14: 775- 786.
- 78) Thompson CV. 2012. Solid-State Dewetting of Thin Films. *Ann RevMaterials Res* 42: 399-434.
- 79) Tognoli E, Kelso JAS, 2014. Enlarging the scope: grasping brain complexity. *Front. Syst. Neurosci.* doi: 10.3389/fnsys.2014.00122.
- 80) Tozzi A, Peters JF. 2016a. A Topological Approach Unveils System Invariances and Broken Symmetries in the Brain. *Journal of Neuroscience Research* 94 (5): 351–65. doi:10.1002/jnr.23720.
- 81) Tozzi A, Peters JF. 2016b. Towards a Fourth Spatial Dimension of Brain Activity. *Cognitive Neurodynamics* 10 (3): 189–99. doi:10.1007/s11571-016-9379-z.
- 82) Tozzi A, Peters JF, Jausovec N. 2016. A repetitive modular oscillation underlies human brain electric activity. *Neurosci. Lett.* 653, 234-238. 10.1016/j.neulet.2017.05.051.
- 83) Tozzi A, Peters JF. 2017a. From abstract topology to real thermodynamic brain activity. *Cognitive Neurodynamics*, 11(3) 283–292. Doi:10.1007/s11571-017-9431-7.
- 84) Tozzi A, Peters JF. 2017b. Towards Topological Mechanisms Underlying Experience Acquisition and Transmission in the Human Brain. *Integr Psychol Behav Sci.* 51(2), 303–323. doi: 10.1007/s12124-017-9380-z.
- 85) Tozzi A, Peters JF, Fingelkurts AA, Fingelkurts AA, Marijuán PC. 2017. Topodynamics of metastable brains. *Physics of Life Reviews*, 21, 1-20. <http://dx.doi.org/10.1016/j.plrev.2017.03.001>.
- 86) Tozzi A, Peters JF, Fingelkurts A, Fingelkurts A, Perlovsky L. 2018a. Syntax meets semantics during brain logical computations. *ProgrBiophys Mol Biol*, 140: 133-141. <https://doi.org/10.1016/j.pbiomolbio.2018.05.010>.

- 87) Tozzi A, Peters JF, Deli E. 2018b. Towards plasma-like collisionless trajectories in the brain. *Neurosci Lett.*662:105-109. <https://doi.org/10.1016/j.neulet.2017.10.016>.
- 88) Tozzi A. 2019. The multidimensional brain. *Physics of Life Reviews.* doi: <https://doi.org/10.1016/j.plrev.2018.12.004>.
- 89) Tozzi A, Peters JF. 2019. The Borsuk-Ulam theorem solves the curse of dimensionality: Comment on “the unreasonable effectiveness of small neural ensembles in high-dimensional brain” by Alexander N. Gorban et al. *Physics of Life Reviews.* <https://doi.org/10.1016/j.plrev.2019.04.008>.
- 90) Trifonov EN. 2012. Definition of Life: Navigation through Uncertainties. *Journal of Biomolecular Structure & Dynamics.* Adenine Press. 29 (4): 647–50. doi:10.1080/073911012010525017.
- 91) Uhlenbeck K. 1982a. Connections with L^p bounds on curvature. *Comm. Math. Phys.* 83 (1): 31–42.
- 92) Uhlenbeck K. 1982b. Removing singularities in Yang-Mills fields, *Commun. Math. Phys.* 83, 11-29.
- 93) Van Fraassen BC. 1977. The pragmatics of explanation. *American Philosophical Quarterly* 14 (2):143-150.
- 94) Vargas JN, Seemannab R, Fleury JB. 2014. Fast membrane hemifusion via dewetting between lipid bilayers. *Soft Matter* 10: 9293-9299.
- 95) Vlasov AA. 1938. On Vibration Properties of Electron Gas. *J. Exp. Theor. Phys.* 8 (3): 291.
- 96) Volovikov, Yu A. 2008. Borsuk-Ulam Implies Brouwer: A Direct Construction Revisited. *American Mathematical Monthly* 115 (6): 553–56. doi:10.2307/2975293.
- 97) Yang, J.M. A Relational Formulation of Quantum Mechanics. *Sci. Rep.* 2018, 8, 13305.
- 98) Young T, Hua L, Huang X, Abel R, Friesner R, Berne BJ. 2010. Dewetting transitions in protein cavities. *Proteins* 78:1856-1869.
- 99) Walters P. 1982. *An Introduction to Ergodic Theory*, Springer, ISBN 0-387-95152-0