CAUSE/EFFECT CORRELATIONS THROUGH THE BORSUK-ULAM THEOREM AND KNESER GRAPHS

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The assessment of hidden causal relationships, e.g., adverse drug reactions in pharmacovigilance, is currently based on rather qualitative parameters. In order to find more quantifiable parameters able to establish the validity of the alleged correlations between drug intake and onset of symptoms, we introduce the Borsuk-Ulam Theorem (BUT), which states that a single point on a circumference projects to two points on a sphere. The BUT stands for a general principle that describes issues from neuroscience, theoretical physics, nanomaterials, computational topology, chaotic systems, group theory, cosmology. Here we introduce a novel BUT variant, termed operational-BUT, that evaluates causal relationships. Further, we demonstrate that the BUT is correlated with graph theory and in particular with the so-called Kneser graphs: this means that the combinatory features of observables, such as the bodily responses to drug intake, can be described in terms of dynamical mappings and paths taking place on well-established abstract structures. Therefore, physical and biological dynamical systems (including alleged causes and their unknown effects) make predictable moves into peculiar phase spaces, giving rise to constrained trajectories that can be quantified.

INTRODUCTION

The currently available methods for the assessment of cause/effect relationships do not allow a proper qualitative analysis of doubtful or unpredictable correlations (Nebeker et al., 2004; Davies et al., 2011; Loke, 2012; Saedder et al., 2015). For example, the evaluation of adverse drug reactions in pharmacovigilance is based on four rather qualitative tenets (Naranjo et al., 1981; Mouton et al., 2017):

a) The temporal correlation between the alleged cause and the reported effect.
b) A priori knowledge of previous cases that describe the same hypothetical correlation.
c) The feasibility to repeat the chain of events, through proper experimental settings.
d) Frequently, the system comes back to its original conditions, when the cause is discontinued. In case of an adverse drug reaction, this means that the reported symptoms disappear, when drug intake is discontinued and the bodily integrity is restored.

However, in a long series of both known and unknown phenomena, the four tenets cannot be pursued, due to:

1) Our lack of knowledge of the parameters a) and/or b);
2) The unfeasibility to replicate the events described in c);
3) the possibility, in case d), that an improvement does not occur when the cause is discontinued, due to the irreversibility of the effects.

Therefore, it would be desirable to attain better methods and parameters, in particular in cases of hidden or unknown causal relationships. Here we propose a novel approach for the detection of cause/effect correlations, based on topology and graph theory. We will proceed as follows. At first, we will describe the backbone of our approach, i.e., the Borsuk-Ulam theorem (BUT) and its recently developed variants. We argue, based on the literature, that the BUT can be used in the assessment of countless physical and biological systems, because it is suitable as a very general principle. Then, we enlarge the BUT framework in order to encompass the description of cause/effect relationships. We tackle the issue by introducing a novel BUT variant, termed operational-BUT. Further, we show that the BUT is strictly correlated with, and described by, a peculiar structure, termed Kneser graph, characterized by rather constrained trajectories. This step allows us to portray the dynamics of physical and biological systems describable by the BUT (in particular the causal relationships in adverse drug reactions), in terms of predictable and conventional paths. Also, we provide examples that illustrate how the Kneser graph can be used in the assessment of causality issues.

THE BORSUK-ULAM THEOREM AND ITS NOVEL VARIANTS

The BorsukUlam theorem (BUT) has been proven useful in the description of countless physical and biological systems, from quantum entanglement to cellular homeostasis; from brain function to gauge theories. The BUT states that a single point on a circumference maps to two points on a sphere (Borsuk, 1933). In more technical terms, a point embedded in lower dimensions gives rise to two points with matching description in higher ones, provided that the function under assessment is continuous (Matoušek 2003). The original formulation of BUT displays versatile

ingredients which can be modified, resulting in useful extensions of this rather simple framework (Tozzi et al., 2017a). For example, antipodal points can be replaced by antipodal regions or shapes with matching descriptions (Tozzi and Peters, 2016b). Instead of points, novel BUT variants allow the assessment (from one dimension to another) of trajectories, functions, vectors and tensors, particle trajectories in phase spaces, activities such as entropies, information, (Tozzi and Peters, 2017c). Also, the points (or features, or shapes) do not need to be perfectly antipodal: the only requirement is that they must not share points in common, but must be fully separated on the higher-dimensional manifold (Tozzi et al., 2017a). BUT variants hold not just for concave structures such as the circumferences and spheres described by the classical BUT, but also for flat, concave or more complicated structures (Tozzi 2016), such as the complex trajectories detected in several systems' dynamics (Sengupta et al., 2016). Furthermore, the dimensions described by BUT do not stand just for spatial dimensions (as in the case of a circle and a sphere), but also for abstract dimensions (such as for example, biological complexity, fractal measurements, different time-frames (Tozzi and Peters, 2016b). The crucial issue here is that matching descriptions allow commensurability between (real or abstract) entities in different (real of abstract) dimensions.

A PRINCIPLE FOR PHYSICAL AND BIOLOGICAL ACTIVITIES

Papers from far-flung scientific disciplines point towards the BUT as an universal principle for otherwise elusive biophysical activities. In such a topological context, systems operations become projections among different levels and give rise in higher dimensions to apparently emergent properties. Therefore, we are in front of a framework based on mappings and projections (other than cause/effect relationships!) among different activity levels. A complete description of a phenomenon can be reached just by looking at its higher levels, where the differences are more easily detectable. Here follows a summary of the major achievements that point towards the BUT as a general principle.

Neuroscience. A series of recent papers describe the brain activity as taking place on a multidimensional torus, so that our thoughts follow a donut-like trajectory in brain (Tozzi and Peters, 2016a). By using novel topological techniques of computational proximity, Peters et al. (2017a) detected a four-dimensional moving hypersphere, located insight the nervous connectome. Furthermore, it has been demonstrated that the Rényi entropy in primary sensory areas is lower than in associative ones: this corroborates the claim that the brain activity lies in higher dimensions than the three-dimensional (plus time) environment (Peters et al., 2017b). Tozzi and Peters (2016b) realized that a symmetry stands for two features with matching description lying in higher dimensions, while a symmetry break for a single feature lying one dimension lower. These symmetries described in terms of BUT have been correlated with neural thermodynamic activity and energy requirements/constraints during spontaneous and evoked brain activity (Tozzi and Peters, 2017b). A BUT framework allows also to understand how the brain perceives "sharp" objects and solves the Kullback-Leibler perceptual divergence (Tozzi and Peters, 2016b). Further, it has been shown how a symmetric, topological approach is able to elucidate the puzzling phenomenon of multisensory information integration in the brain (Tozzi and Peters, 2017a) and semantic cortical processing, paving the way to build four-dimensional semantic computers (Tozzi et al., 2017a).

A biophysical world of mappings. The BUT suggests that system properties in physical and biological spaces can be translated to abstract mathematical ones, and viceversa. For example, Tozzi and Peters (2016b) studied the logistic maps of chaotic activities and showed how some nonlinear dynamics can be described in purely linear terms. It has also been showed how the BUT is able to unveil the mystery of the ubiquitous (spatial) fractals and (temporal) power laws (Tozzi and Peters, 2016b). Furthermore, the typical changes in dimensions described by the BUT might help to elucidate the puzzling phenomenon of quantum entanglement: Peters and Tozzi (2016) proposed a model of quantum entanglement on a hypersphere, that requires just a further spatial dimension. This model has been recently corroborated by the finding that quantum nonlinear phenomena might occur in four-dimensional spaces (Lohse et al., 2018). BUT allows also the study of life. During evolution, living beings display an increase in complexity that is strictly correlated with increases in systems' dimensions (Tozzi et al., 2017b). In other worlds, the evolution increases the symmetries and the functional dimensions of the living beings (Tozzi and Peters, 2017c), giving rise to the overwhelming variety of species.

DETECTING UNKNOWN CAUSAL RELATIONSHIPS

Once established that the BUT stands for a universal principle, our next goal will be to correlate this theorem with the rather general issue of the cause/effect relationships. The BUT framework is based on mappings and projections among manifolds with different dimensions, rather than on causal relationships. Are we allowed to use the BUT requirements in the study of causality? In the following, we will provide an affirmative answer, introducing a novel BUT variant that we term operational-BUT.

For sake of simplicity, we describe the system under evaluation (e,g., in the case of adverse drug reactions, the human body, the drug and the adverse effect) in terms of trajectories taking place on a two-dimensional circumference. When a force is exerted (standing for the cause), a modification in trajectory takes place (standing for the effect) on the two-dimensional structure (**Figure 1A**). To assess whether the exerted force is the cause of the two-dimensional system's change in trajectory depicted in **Figure 1A**, we need to evaluate the whole system (the force plus the modified trajectory) in a dimension higher, i.e., on a three-dimensional sphere (**Figure 1B**). A transitory three-dimensional structure, where the possible cause stands for a novel functional dimension, is located between the (two-dimensional) systems before and after the applied force. In case of a true cause/effect relationship, the BUT predicts that we will find two features with matching description on the sphere. If a force is the real cause that provokes the reported effect, this means that a feature encompassed in the primitive two-dimensional system at rest must double on the transitory three-dimensional system generated by the causal operation. Indeed, if the causal correlation under investigation holds true, the function that projects between the manifolds of different dimensions must be continuous. Therefore, the higher-dimensional system must necessarily display two antipodal features with matching description, while the lower-dimensional one just a single feature.
Summarizing, the interaction between a two-dimensional system at rest and an external force (i.e., the possible cause) gives rise to a provisional structure that exhibits three coordinates instead of two, if we use the force as an added coordinate. This functional higher-dimensional construction, produced by operations performed on a system, must encompass two antipodal features. This means that something must double during a real causal interaction, compared with the system at rest before the interaction.

The operational-BUT: proofs in literature. A retrospective evaluation of previously published papers shows that there already exist scattered observations suggesting that the BUT framework holds true, at least for some causal relationships. We require the assessment of the whole system on a three-dimensional, positive-curvature manifold which encompasses both the force and the trajectory, in order to understand which parameter is repeated twice in this higher-dimensional structure. Once found a quantifiable parameter that is repeated twice, we are allowed to state that a causal correlation does exist. Note that, for the BUT dictates in the three-dimensional systems, the phrase "repeated twice" means that the two features with matching description must be disjointed, i.e., with no superpositions or points in common. The examples are countless. In case of a true cause/effect correlation, temporally disjointed repeated observations give rise to matching descriptions: the administration of the same drug provokes the same unwanted pharmacological effects in different patients, or in the same patient at different times. The possibility to repeat the chain of events and achieving the same final state of the system stands, in topological terms, for matching descriptions on abstract higher-dimensional manifolds. The BUT framework holds true also for well-established physical laws, such as: "for every action, there is an equal and opposite reaction". In this rather simple physical case, we achieve two opposite features (the force and its reaction) with matching description. Furthermore, in many biophysical phenomena, the system comes back to its initial state after cause removal. In these frequent cases, the two matching descriptions are temporally disjointed, because they stand for the system before and after the action. Other examples might be provided. In adverse drug reactions, the body and a potential harmful drug need to display something in common: they must, e.g., share the same metabolic pathways. In neuroscience, the analysis of neurodata allows to calculate pairwise entropy in different activated cortical areas after the administration of, e.g., an external stimulus (Ezaki et al., 2017): this means that we are in front of cortical areas with matching description.
According to the operational-BUT framework, during an operation on a system (e.g., a cause/effect phenomenon), something must double in the system: in the case of a living cell, the DNA interacts with transcriptional enzymes, giving rise to mRNA strands whose sequences display matching description with the primitive ones. In case of mitosis, a single cell is able, through the operations performed by its replicative machinery, to generate two cells with matching description (McKay, 2004; Trifonov, 2012). Therefore, in such a novel context, life becomes a mathematical, operational, quantifiable phenomenon, standing for the continuous function required by the BUT.
Once established the soundness of our framework, our next goal is to provide quantifiable matching descriptions of cause/effect other than the ones encompassed in the above-described four tenets. In the next section, we will go through a method from graph theory able to improve our treatment of causality issues.

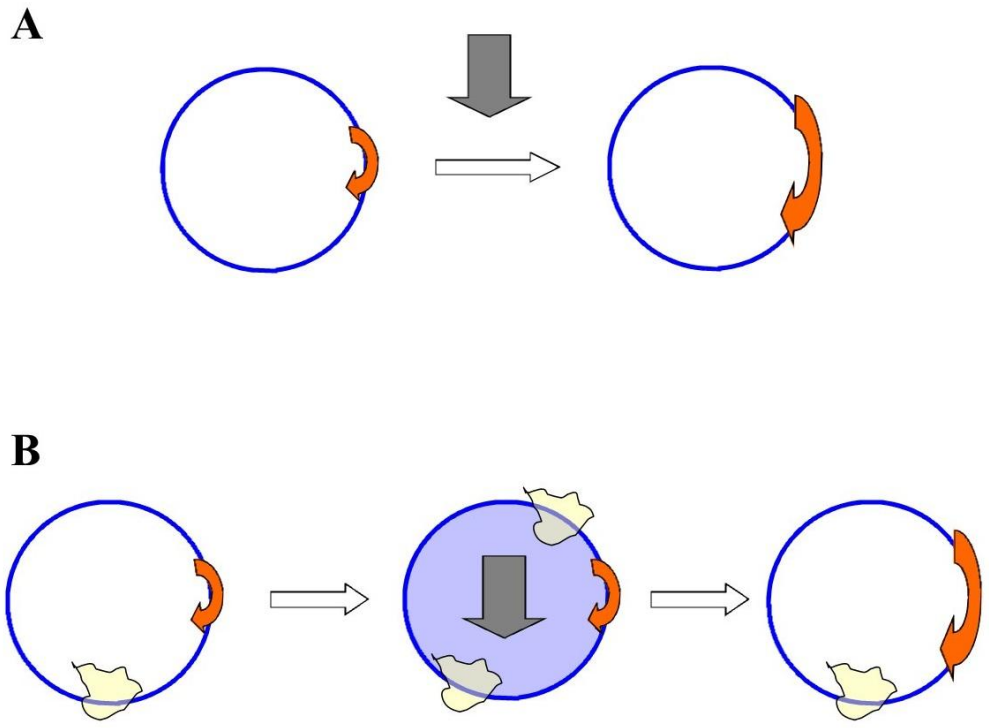


Figure 1. Cause/effect relationships mapped to an abstract two-dimensional structure. **Figure 1A**: The system is depicted in terms of a two-dimensional circle, where trajectories might take place. The changes in system's paths before and after the possible cause are displayed (red arrows). The cause is depicted by the grey arrow. **Figure 1B**. When the cause interacts with the system, a functional three-dimensional structure is temporarily produced (in this case, the sphere illustrated in the central frame). The cause stands here for a further dimension added to the original two-dimensional system. Therefore, we achieve a provisional three-dimensional system where, according to the BUT dictates, a feature in lower dimensions must display matching description in higher dimensions (yellow shapes).

GRAPH THEORY COMES INTO PLAY

Although the Borsuk-Ulam theorem seems far removed from graph theory, nevertheless it displays combinatorial significance that might give rise to fruitful applications in the detection of causal relationships. Indeed, 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. Remind that 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. This 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 allowed in a short number of moves. For example, in $KG_{5,2}$, a path that starts 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, in order 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 2B**).

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 $\frac{a}{b}$ such that the graph G can be covered by a independent sets, where each vertex occurs in at least b of them. The virtue of

coloring hypergraphs is that they display strong computational hardness, allowing the quantitative assessment a large number of operations (**Figure 2D**).
When n≥ 3k, and for for n≤ 27, all the connected Kneser graphs encompass a Hamiltonian cycle (Chen 2000), except for $KG_{5,2}$. (Shields, 2004). A Hamiltonian cycle is a traceable, circular path in an undirected or directed graph that visits each vertex exactly once (DeLeon 2000) (**Figure 2C**). 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).

How are Kneser graphs and BUT correlated? In order to demonstrate their close relationship, we need to start from a theorem linked to the BUT, i.e., the Lusternik–Schnirelmann theorem (LST). It states that, 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 them encompasses an entire diameter where the antipodal points lie. LST guarantees at least a pair of exactly opposite points on a sphere, as required by BUT (Dodson and Parker, 1997). 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 $n \geq 2k-1$, $\chi(KG_{n,k}) = n - 2k + 2$, 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's matching descriptions may 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 some trajectories and paths requiring 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 introducing the proper setting and subsets, to predict the dynamical evolution of the system under evaluation. In the next Section, we will provide an example that demonstrates the feasibility and the predictive power of a procedure that embeds adverse drug reactions on Kneser graphs.

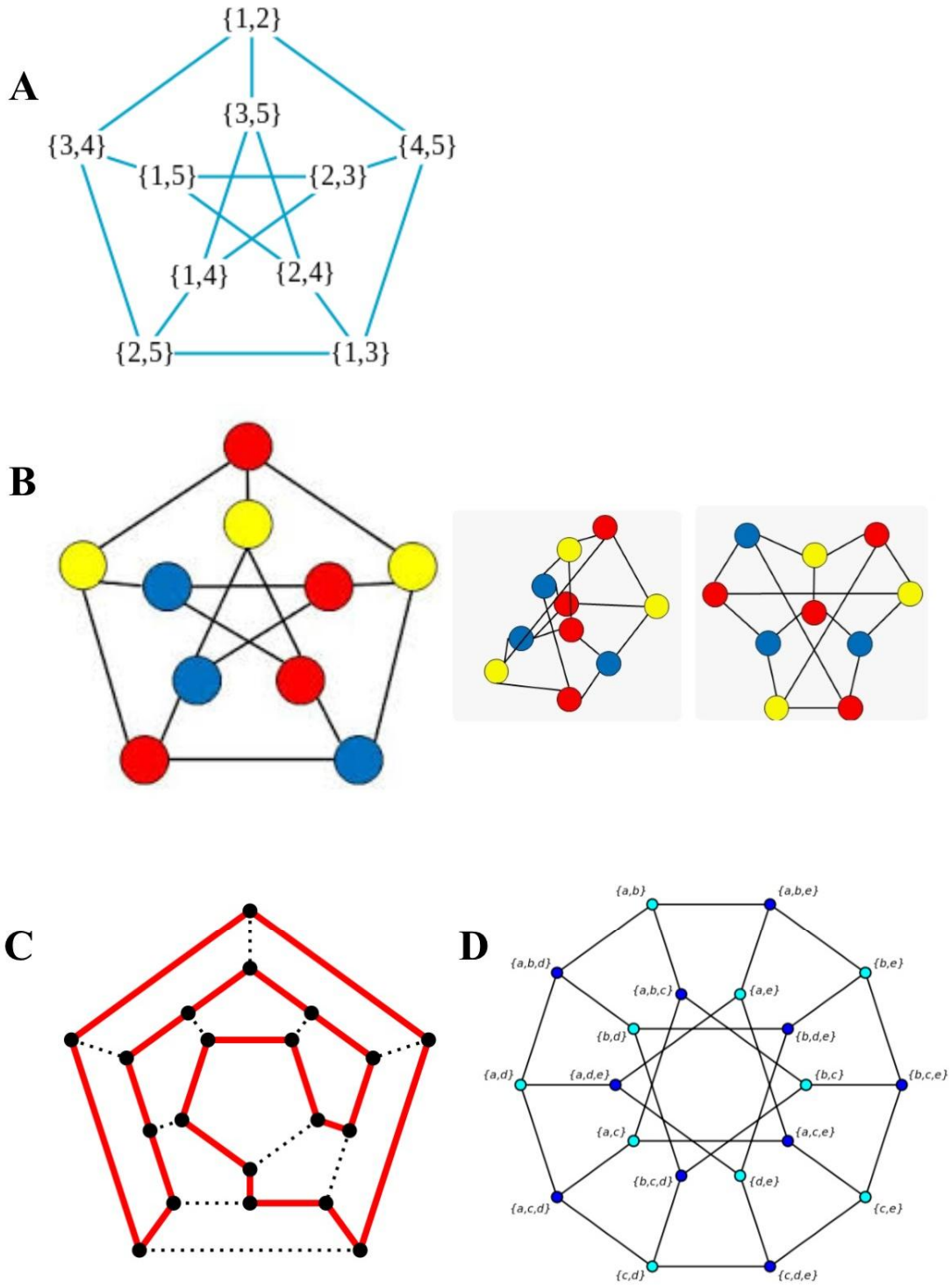


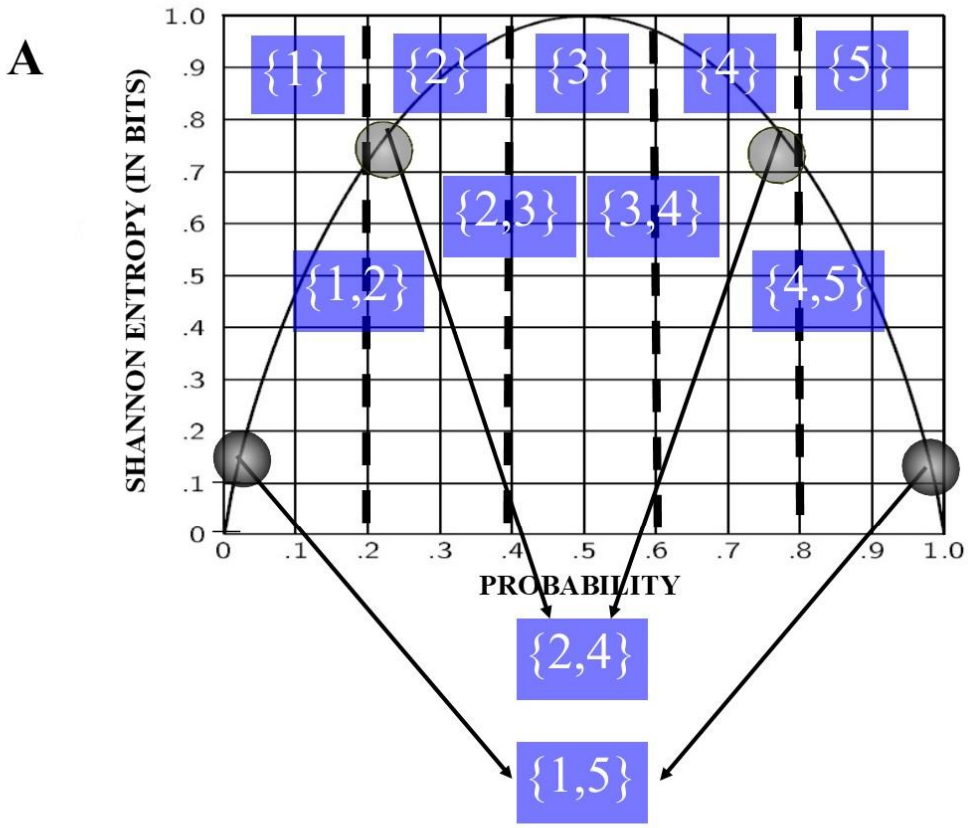
Figure 2A: The graph $KG_{5,2}$, provided as an example for Kneser graphs. **Figure 2B** illustrates the required coloring of the vertices. Note that, as shown in the central and right frames, the graph's shape does not need to be too much sharp and constrained: different vertexes' configurations are feasible, provided the relationships among the sub-set k elements are kept invariant. **Figure 2C**: a Hamiltonian cycle on a dodecahedron. **Figure 2D** illustrates 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

AN EXAMPLE OF KNESER GRAPHS IN THE ASSESSMENT OF CAUSE/EFFECT CORRELATIONS

When researchers are assessing a study population, looking for the possible causal relationship between the intake of a given drug and an unknown or unexpected adverse reaction, they have a set of possible events whose probability of occurrence are p_1, p_2, …p_n. Different studies from different researchers calculate, in many retrospective or prospective experiments, the probability value of the detection of an adverse event. Although these probabilities are known, however, that is all they know concerning which event will occur. If a long series of experiments measure the same probability, we are in front of sharp, clear case of cause/effect relationship. The things become harder when we are in front of a series of detections that give rise to controversial results, i.e., display very different probability values. In these (common) controversial cases, the description of the dynamical changes in probability frequence in terms of Kneser graphs might help to tackle the issue.

In order to demonstrate the feasibility of our approach, we could use different indexes of probability measures, such as Granger causality, pairwise entropy and so on. In this paper, we will limit ourselves to the study of the Shannon entropy (Shannon, 1948). The latter makes it possible to measure the information level in a data set. In **Figure 3A**, the entropy is plotted as a function of the random variable p, in the case of two possibilities with probabilities p and (1−p). In our specific case, the value 0 on the x axis might stand for an unfeasible correlation between drug intake and the onset of symptoms, while the value 1 for a real established correlation.

The BUT says that the Shannon entropy can be assessed in terms of matching descriptions (**Figure 3A**). Indeed, the same levels of entropy on the y axis correspond to two points sharing matching description on the curved line: for example, the value 0.7 bit of Shannon entropy on the y axis stands for the probabilities 0.2 and 0.8 on the x axis. Therefore, the entropy value on the axis y is the same in both the cases. We are allowed to treat such matching description in terms of a Kneser graph. How to proceed? If we take into account, as an example, the $KG_{5,2}$ graph, we can arbitrarily split the curve in five rectangles, each one standing for one of the five elements of the required set (**Figure 3A**). Almost every detected value of Shannon entropy in every single experiment stands for a subset that might be described bya pair of elements with matching description on a Kneser graph. Indeed, when we draw the events on a $KG_{5,2}$ graph, it is easy to see that just particular sequences of pairs are allowed in a small number of steps (**Figure 3B**). If the path described by different experiments does not follow the trajectories imposed by the Kneser graph's structure, this means that, in the specific case under assessment, the cause/effect relationship is unfeasible. In sum, this simple method allows the investigation od cause/effect correlations also in the debatable cases that cannot be solved by the above-mentioned four tenets of causality.



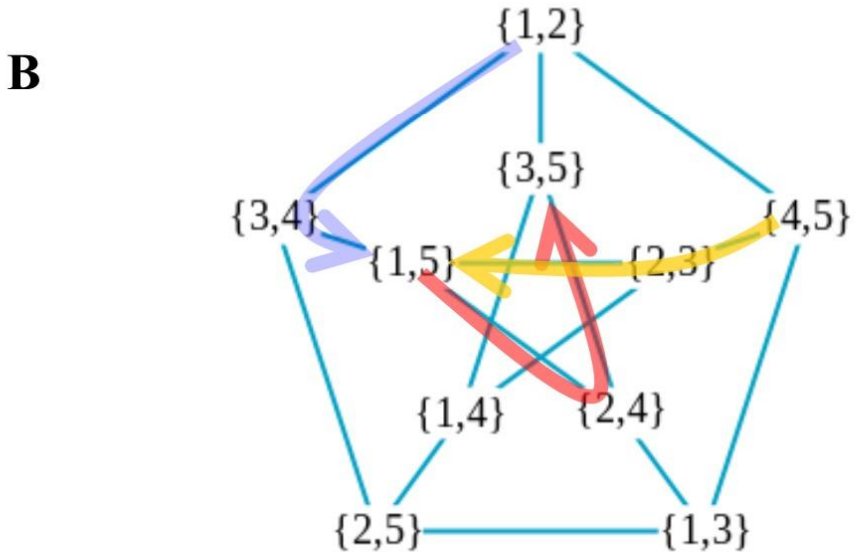


Figure 3A. Shannon entropy for a probability distribution $P = (p, 1-p)$ under ergodic conditions (from the original Shannon's graph). **Figure 3B**: possible paths on $KG_{5,2}$. The study of the trajectories says that, if a researcher performs experimental observations, just a few patters are feasible in case of a true cause/effect relationships. For example, if the causal relationship is real, the detection of a pair {1,2} cannot be followed by a pair {2,4} in a single step.

CONCLUSIONS

Once attained that the BUT is a useful principle able to assess countless physical and biological systems, we described its novel variants that allows a feature (e.g., a shape, a trajectory or an energy) located in the environment to be translated to an abstract space, and vice versa. Due to its versatility, we suspected that the BUT mechanism could be also useful in the description of a very important issue, i.e., the causality effect in pharmacodynamics. Our model, retrospectively substantiated by widespread, scattered findings from far-flung disciplines, predicts that a causal event gives rise to a transitory, functional increase in system's dimensions. In particular, we showed that, when a force (e.g., a causal operation) is exerted, the system's trajectories at rest must be perturbed in a way that is quantifiable: otherwise, a real causal relationship does not occur and cannot be determined. Furthermore, we showed that Knesner's conjecture and graphs are correlated with BUT. This means that known and unknown causes can be quantitatively described in terms of topological operations performed on physical and biological systems. Indeed, our approach points towards a single description of the dynamics of unknown cause/effect correlations, expressed in terms of antipodal features on Kneser graphs.

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