

RANDOM WALKS ARE NOT SO RANDOM, AFTER ALL

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Physical and biological phenomena are often portrayed in terms of random walks, white noise, Markov paths, stochastic trajectories with subsequent symmetry breaks. Here we show that this approach from dynamical systems theory is not profitable when random walks occur in phase spaces of dimensions higher than two. The more the dimensions, the more the (seemingly) stochastic paths are constrained, because their trajectories cannot resume to the starting point. This means that high-dimensional tracks, ubiquitous in real world physical/biological phenomena, cannot be operationally treated in terms of closed paths, symplectic manifolds, Betti numbers, Jordan theorem, topological vortexes. This also means that memoryless events disconnected from the past such as Markov chains cannot exist in high dimensions. Once expunged the operational role of random walks in the assessment of experimental phenomena, we take aim to somewhat “redeem” stochasticity. We suggest two methodological accounts alternative to random walks that partially rescue the operational role of white noise and Markov chains. The first option is to assess multidimensional systems in lower dimensions, the second option is to establish a different role for random walks. We diffusely describe the two alternatives and provide heterogeneous examples from boosting chemistry, tunneling nanotubes, backward entropy, chaotic attractors.

KEYWORDS: noise; topology; time reversed entropy; nonlinear dynamics; memory; brain.

Random walks, noise, Brownian motion, stochasticity, Markov chains are commonly used to approach classic, relativistic and quantum systems. Applications include ecology, gambling, motion of liquids/gases, signal processing (Elowitz et al., 2002; Pontes-Filho et al., 2020). For example, the dynamical behavior of neural networks and their stochastic evolution towards criticality can be fruitfully studied through random Boolean networks equipped with noise (Kang et al., 2020). Heterogeneity in nuclear genome organization is correlated with extensive stochasticity of gene expression, with individual genes undergoing cycles of bursts and periods of inactivity (Finn and Misteli, 2019). Protein concentrations in cells fluctuate considerably because of random behavior in gene expression and variations in cellular microenvironments (Klosin et al. 2020). In biological systems, molecular stochasticity is central to understanding the stability of cellular proliferation (Kiviet et al., 2014). Phenotypical and behavioral heterogeneity does not depend just on the orthodox “Nature vs. Nurture” contraposition which emphasizes individual differences in genes, environmental interactions, epigenetic factors. In contrast, studies point towards the phenotype as shaped by another underrated actor: the nonheritable noise of developmental stochastic events. Developmental variations in individual and population fitness do not depend on epigenetic markers such as fluctuating asymmetry and global DNA methylation, rather are correlated with random, non-linear, self-reinforcing components. Stochasticity inherent in biochemical gene expression (intrinsic noise) and fluctuations in cellular structures (extrinsic noise) contribute to a broad range of phenotypic and behavioral variation in biological entities grown into near-identical rearing conditions, such as e.g., *Escherichia coli* clones (Elowitz et al., 2002), *Poecilia Formosa* genetically identical individuals (Bierbach et al., 2017), batch-mates of isogenic crayfish (Vogt et al., 2008). The intrinsic chaos during development is able to generate neural individual diversity in *Drosophila melanogaster*’s brain wiring and behavioral individuality: an anatomical set of visual neurons can be wired up in a variable stochastic manner, resulting in brain circuit asymmetry unique to each fly that confers different ability to orient to the line (Linneweber et al., 2020).

Here we question the prominence of stochasticity and noise in the assessment of dynamic systems’ affairs. Departing from the common claim that random walks follow fully stochastic paths when left undisturbed, we stress that the higher the phase space dimensions, the less the possibilities that stochastic paths return to the starting point. This means that white noise, random walks, Markov chains are restricted when weighed in multidimensions. We appraise the mathematical, physical and biological consequences of such a strong claim against randomness and propose alternative methodological frameworks to assess and quantify real-life systems dynamics.

“A DRUNK MAN WILL FIND HIS WAY HOME, BUT A DRUNK BIRD MAY GET LOST FOREVER”

When coping with random walks, an unappreciated factor must be regarded, i.e., the number of dimensions of the corresponding phase space. Consider a random walk on a lattice of dimension D^d . The probability $p^{(d)}$ that a random walk returns to the origin is: $p(1) = p(2) = 1$ (McCrea and Whipple, 1940). This means that a particle almost surely will get back to the original starting point in two-dimensional random walks. To provide an example, a person (say a drunk man) erratically walking around an infinite city arranged in a square grid will always go back home. Yet, in higher dimensions, the probability to reach the starting point decreases with the increase in number of dimensions (Domb, 1954). Indeed, $p(d) < 1$ for $d > 2$, so that, for example, $p(3) = 0.3405$, $p(5) = 0.1351$, $p(8) = 0.079$, and so on (Montroll, 1956).

Next, we ought to define our terminology: what does “in higher dimensions” mean? Physical and biological paths are generally described in terms of particles moving inside three-dimensional space. In this simpler case, the axes x , y and z are the three Euclidean spatial dimensions, while time passing is depicted as particles’ trajectories. Introducing further axes apart from x , y and z , the particles are allowed to move in further dimensions instead of the canonical three (plus time). This methodological step is highly profitable: the higher the dimensional number, the more information can be achieved. A higher number of parameters (everyone standing for a further dimension of the phase space) can be described in terms of scalars or vectors measured at different locations. The increased availability of big data and computational power led to multidimensional strategies to tackle problems from far-flung scientific branches, from chemical compounds to turbulent flows of plasma-like fluids (see, e.g., Dekker et al., 2017; Cardesa et al., 2017). For example, neuroscientists trace in different dimensions parameters such as spike frequencies, synchronized oscillations, color perceptual spaces and tactile qualities (Victor et al., 2017). Further, it is well known that neuronal populations encode information most efficiently when its stimulus responses are high-dimensional and uncorrelated (Stringer et al., 2019). Concerning stochastic trajectories, the more parameters we consider, the more the random walks will take place in higher dimensions. Because random walks display an extremely low probability to return by chance to the starting point, we are allowed to state that stochastic trajectories in multidimensional phase spaces are hampered and constrained.

The curse of dimensionality comes into play. The fact that random walks do not make full circles when travelling in high dimensional phase spaces is elucidated by another underrated factor too, i.e., the curse of dimensionality (Barbour 2019). Consider a n -sphere with fixed positive curvature embedded in a $n+1$ Euclidean space (Matousek, 2003): the more the n -dimensions of the sphere, the less its volume (Kůrková 2019). Paradoxically, this means that the volume of different hyperspheres with the same radius tends towards zero as their dimensionality tends to infinity (Wang 2005). In particular, the volume of a hypersphere is “squeezed” and condensed near the equator.

Therefore, random walks inside a high dimensional hypersphere are constrained by two factors:

- 1) Stochastic paths cannot come back to the starting point.
- 2) Stochastic paths tend to converge near the borders (near the equator), leaving aside the poles and traveling in a volume which becomes smaller and smaller with progressive increase in number of dimensions. Multidimensional random walks tend to be compressed in small spaces.

Once formulated a mathematical critique of stochasticity in high dimensional phase spaces, in the following chapters we will describe the procedures for the operational treatment of multidimensional stochastic trajectories in the real physical and biological world.

WIPING OUT RANDOMNESS AND ITS CORRELATES

We established on mathematical grounds that random walks in higher dimensions are not so random as believed. Here we examine the implications in the real world of physical, chemical and biological processes.

Random walks on the set of all points in the two-dimensional plane with integer coordinates are closed paths. It is noteworthy that closed paths are required for the assessment of almost every physical/biological dynamical system. For example, a closed path is mandatory to elucidate two phenomena correlated with life, i.e., autocatalysis and open thermodynamic systems (Agosta and Brooks, 2020). The cyclic (closed) pattern of autocatalytic reactions brings energy into the system, which it exports back out to the surroundings. This circular, closed configuration guarantees the evolutionary goal of indefinite persistence, i.e., transmission of information to offspring. To provide another example, it has been proposed that infinite memory with no events can be derived from a Liouville picture of the whole Universe through a process of contraction over the irrelevant degrees of freedom, while the generating aging renewal events may

imply the existence of genuine randomness (Allegrini et al., 2007; Culbreth et al., 2019). It is noteworthy that in both cases memory is described by time-convoluted structures.

Nevertheless, random walks on the set of all points in higher-dimensional planes with integer coordinates are NOT closed paths. Stochastic paths in higher dimensions are open sets, therefore they cannot produce the closed manifolds required for the quantification of natural phenomena. Because multidimensional stochastic trajectories are not closed, they cannot be described in terms of the methodologically useful two-dimensional symplectic manifolds, or in terms of the Jordan curve theorem.

How ergodicity and Markov chains disappear in higher dimensions. Our account raises concerns against the ergodic theory too. Ergodicity is a random process characterized by the fact that all the accessible microstates in a phase space are equiprobable over a long period of time (Walters, 1982; Barth, 1898). Still, random walks taking place in higher dimensions cannot be fully ergodic, because the starting points are not crossed once again with high probability. Being the “stochastic” trajectories unable to homogeneously fill the whole phase space, the ergodicity provided by random choices must disappear in multi-dimensional systems.

Another important consequence of our observation is related to Markov chains, widely used for the description of physical and biological events (Kirchhoff et al., 2018). As one increases the discrete-time steps in the stochastic Markov chains, there exists a probability measure at next future step that is independent of the probability distribution at the past steps (Feller, 1971). However, our framework suggests that the trajectories of Markov chains are not fully independent from the initial step, because the random possibility to come back to a single point (the starting point) is severely restricted. Therefore, when a system is evaluated in multidimensions, the memory of the previous states must exist, i.e., the same memory that prevents random walks to ergodically fulfill closed paths. This means that stochastic activities in multidimensions are incapable of producing Markov chains. Our claims are in touch with neuroscientific accounts suggesting that the properties of brain fluctuations are weakly non-ergodic, as some phase space region may take extremely long times to be visited (Bianco et al, 2007; Fraiman and Chialvo, 2012). This observation might depend on the occurrence of multidimensional nervous phase spaces (Tozzi, 2019): indeed, an increase in dimensions produces an anomalous diffusion of stochastic flows, so that seemingly stochastic trajectories are constrained in restricted zones of the phase space.

The focus on Markov blankets leads us into the realm of free additive cyclic groups and Betti numbers derived from the boundaries of holes (Don et al., 2020). A Betti number is a count of the number cyclic boundaries and of generators (= number of holes) of closed surface regions. The Betti number of a system (e.g., living beings equipped with hierarchically nested Markov blankets) grows with the increase in number of cyclic boundaries. The theory says that as the number of closed cycles increases, so does the Betti number. However, in our framework things haven't gone so well: Betti number cannot be counted when we are coping with high-dimensional stochastic dynamical systems, because cyclic boundaries do not occur in multidimensions.

Random walks can be analyzed when the system is equipped with a very low number of dimensions. In turn, physical and biological phenomena are nearly always very complex and multifactorial: this means that the scientific evaluation of real dynamics must take into account a high number of parameters (standing for different dimensions). Our mathematical arguments suggest that dynamical phenomena can be treated in term of stochasticity, white noise, topological closed manifolds, just in case scientists abridge the multifactorial system under evaluation and contemplate an extremely poor number of parameters (i.e., an extremely poor number of dimensions). When scientists include further parameters (further dimensions), phenomena can no longer be described in terms of stochastic events, because in higher dimensions the noise fades away and the systems become more and more constrained.

After a “negative” account, in the next chapter we will propose alternatives to cope with the essential impossibility of random walks and noise in multidimensional systems.

HOW TO COPE WITH WHITE NOISE IN THE ASSESSMENT OF REAL WORD AFFAIRS

In the last paragraph, we took a pragmatic turn: given an experimental apparatus, if we want to achieve manageable closed paths, we cannot cope with the genuine multidimensional fashion, rather we are required to reduce the dimensions under evaluation. In short, during the scientific assessment of the multifactorial physical/biological systems, the only way to preserve methodologically useful topological weapons (e.g., closed paths, Betti numbers and symplectic manifolds) is to make things easier, evaluating a simplified system after removal of the most of its real dimensions. Once established that random walks can be treated just in lower dimensions, we need to find viable

replacements to cope with the countless complex, high-dimensional systems surrounding us. In this chapter we aim to describe real multidimensional systems without help from noise and stochasticity. We will provide examples of anti-stochastic biological mechanisms standing for scientific explanations alternative to purely random accounts. To provide a first example, Hartmann et al. (2019) studied surface-attached biofilms of *Vibrio cholerae*, tracking cell–cell interaction inside these growing three-dimensional active liquid crystals. They found that external fluid flows control the three-dimensional morphology of biofilms suggesting that local cellular order and global biofilm architecture may arise from mechanical cell–cell interactions, instead of stochastic activity.

Boosting chemistry. Diffusion, interaction and intracellular assembly of molecules are traditionally correlated with some degree of randomness. Yet, the occurrence of random walks in the solutes bordering chemical reactions has been recently questioned. Wang et al. (2020) studied different catalyzed chemical reactions, including the click reactions occurring inside living cells. They discovered that catalyzed chemical reactions produce increases in free-energy and enthalpy which generate long-range mechanical perturbations in the surrounding medium. These perturbations speed the mobility of the Brownian diffusion of both reactants and nearby solvent. In other words, contrary to the chemistry dogma that molecular diffusion and chemical reaction are unrelated, some reactions are able to boost the surrounding reactants and solvents, increasing their speed and mobility and perturbing their stochastic behavior. The boosting mechanism is remarkable also for another reason: we speculate that, when the chemical boosts are prolonged and sustained enough, such non-random propagation might contribute to provide the energy required to start life from chemical reactions and to preserve the living organism’s efforts towards self-sustained balance at the edge of chaos.

Lessons from tunneling nanotubes: a transient, non-stochastic microconnectome. Stochasticity pertains also to the brain activity, if we consider that synaptic transmission involves molecular processes governed by Brownian motion (Ribault et al., 2011; Wang et al., 2014). It has been proposed that neural systems move from a subcritical regime of randomness to a critical state and then to a supercritical regime, characterized by absence of complexity (Papo 2014; Zare 2013). Following Libet et al. (1983), our ability to make choices might arise from random fluctuations in the background electrical noise of the brain (Bengson et al., 2014). Here the human connectome comes into play, i.e., the hierarchical anatomical/functional network of cortical and subcortical structures. The connectome is characterized by preferential pathways for fast communication and winner-takes-all mechanisms that obey stochastic dynamics (Sporns et al., 2005; Reese et al., 2012). A random synchronization-effect has been found inside the connectome, driven by the intrinsic hierarchy of neural timescales and by a heterogeneous, complex network topology (Pang et al., 2020). Community structures of densely interconnected brain regions of the connectome have been operationally defined in terms of a Markov process and random walks with the purpose of studying nervous multi-scale arrangements (Betzel et al., 2013).

Nevertheless, recently discovered microscopic entities screws up the paradigm of random neural networks. Tunneling nanotubes (TNTs) are F-actin-based, transient tubular connections that allow active cell-to-cell transfer of vesicles, organelles and small molecules (Ariazi et al., 2017; Sartori-Rupp et al., 2019) and are involved in human diseases (Goodman et al., 2019; Tardivel et al., 2016). TNTs in primary neurons and astrocytes are possibly correlated with short-range transmission of electrical signals (Wang and Gerdes, 2012; Abounit and Zurzolo, 2012; Austefjord et al., 2014) and long-range transfer of electrical messages involving gap junctions (Abounit and Zurzolo, 2012). Developing neurons form transient TNTs that enhance electrical coupling with distant astrocytes and allow transfer of polyglutamine aggregates among neuronal cells (Wang et al., 2012; Costanzo et al., 2013).

TNTs can be dynamically regulated because their lengths varies as the connected cells migrate and the distance among them modifies (Austefjord et al., 2014); further, their lifetime ranges from a few minutes up to several hours (Gurke et al., 2008; Seyed-Razavi et al., 2013). These two features change the idea of a human connectome made of stable nodes/edges and equipped with stochastic, long-standing connexions among brain areas (Van Essen et al., 2013). TNTs might provide a multidimensional inter-cellular transient neural network with peculiar features: the nodes are not stable; the edges appear, modify themselves and vanish with time passing. TNTs can be open on both ends, challenging the dogma of a cell as detectable individual unit (Sartori-Rupp et al., 2019). The recent developments dictated by TNTs start to unveil that the nervous tissue displays a holistic behavior, acting like a system with long-range, multidimensional interactions that does not take into account stochastic issues. A high dimensional, non-stochastic narrative of connectome dynamics also provides an alternative explanation to the observation that some network branches of the brain modules are more visited than others.

Time-reversed asymmetry and memory in random walks. Non-equilibrium steady-state systems are regulated by two directional entropies: the (forward) standard entropy per unit time and the (backward) time-reversed entropy (Gaspard, 2005). The difference between the latter and the former quantifies the entropy production in the system, according to the formula:

$$\frac{1}{\kappa_B \tau} \Delta \tau; S = h^R(P) - h(P) \geq 0$$

in which $\frac{1}{\kappa_B \tau} \Delta^\tau$; S stands for the entropy production of non-equilibrium steady state, $h^R(P)$ for the time-reversed entropy and $h(P)$ for the τ -entropy (i.e., the standard entropy per unit time τ). P is the coarse graining or partition.

The formula says that the forward entropy exhibits less randomness than the backward one: this means that the total entropy production is higher than the entropy produced by the sole standard entropy per unit time (**Figure**).

Put simply, the arrow of time has a constructive role that affects entropy production in non-equilibrium, steady state stochastic systems. This phenomenon is due to non-equilibrium steady-state constraints, together with the randomness generated by the stochastic process during system's time evolution: both the features impose stochastic boundary conditions which break the time-reversal symmetry, leading to an unexpected amount of entropy production over the course of time. It must be emphasized that the entropy production of non-equilibrium steady state is indirectly related to the thermodynamic entropy via the Boltzmann formula and to Shannon and Kolmogorov- Sinai ε -entropy via the partition P of the phase space of the system into cells ω of size ε (Cencini et al., 2000). Time-reversal asymmetry has thus two opposite effects: on the one hand, the passage of time introduces biases in the probability and influences the evolution of the system capable of memory; on the other hand, the non-equilibrium system goes towards a progressive increase of both Gibbs and Shannon entropy and, consequently, towards a lower rate of information production.

In our framework, the introduction of the unappreciated time-reverse entropy in a stochastic system has the same operational effect of increasing the number of experimentally assessable dimensions. When the dimensions of the phase space where random walks take place are increased, the stochasticity is compromised by overlapping entropic mechanisms.

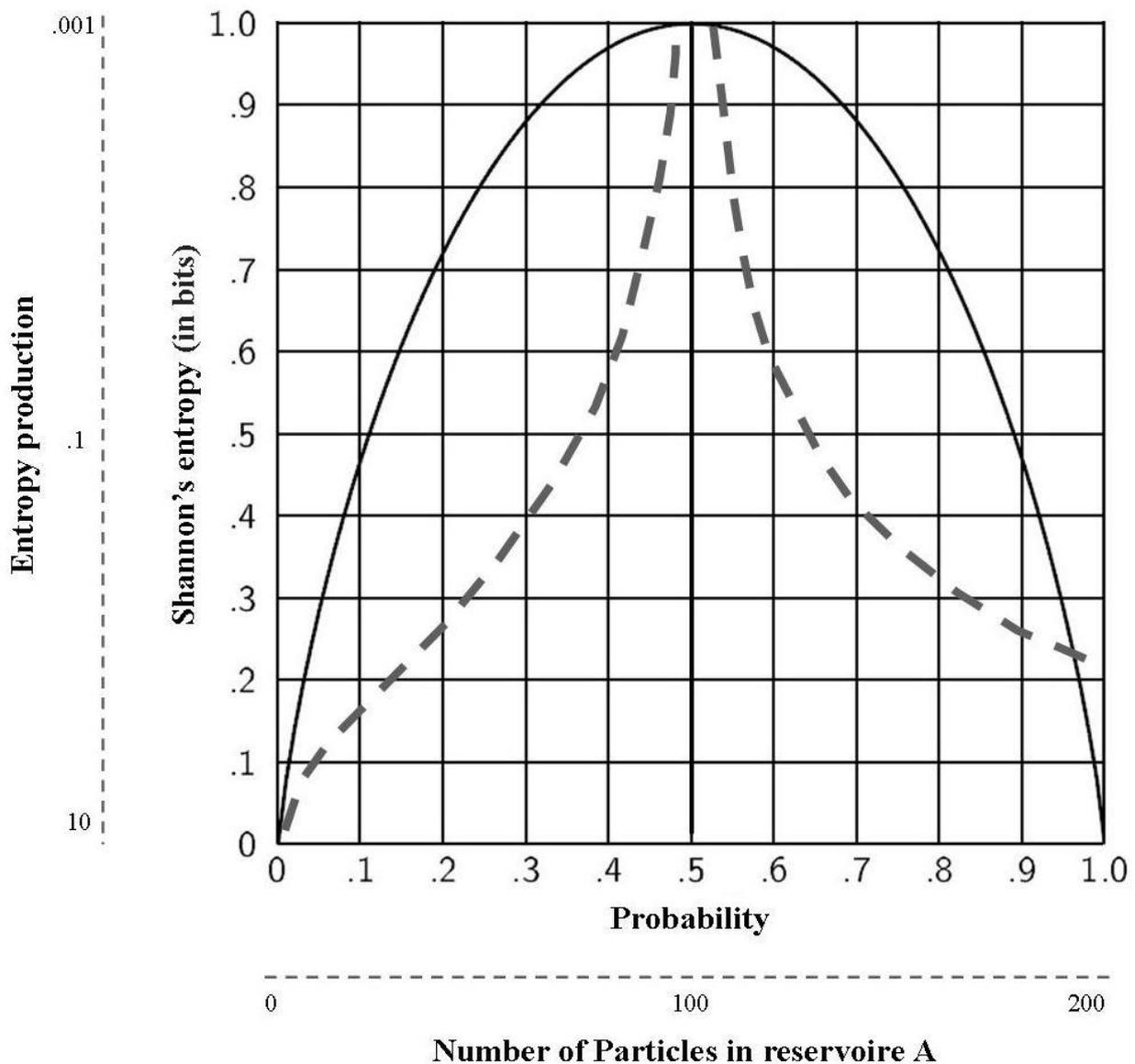


Figure. Schematic representation of Shannon entropy (solid line) and entropy production (dotted line). Shannon entropy is plotted as a function of the random variable p , in the case of two possibilities with probabilities p and $(1-p)$. The dotted line illustrates the entropy production (in a non-equilibrium steady state) versus the mean number of particles A , according to Gaspard (2005). The particles A are associated with the left-hand side reservoir for a diffusion process of Brownian particles in a pipe, while the right-hand side reservoir has its concentration fixed at $B = 100$ (see Gaspard for further details). The thermodynamic equilibrium occurs at $A = B = 100$, when entropy production vanishes. In our plot, the line A is truncated at the number of particles $A=200$. Modified from Shannon (1948) and Gaspard (2005).

CONCLUSIONS

We argued that, from the perspective of high-dimensional phase spaces, random walks and noise are not properly stochastic, rather they are constrained. Because the world is made of stochastic paths that take place in high dimensions, we drew the conclusion that real systems can be described without help from noise and Markov blankets, closed paths, Betti number, vortexes, ergodic paths.

In this last paragraph, we want to address the issue from another, more speculative angle. Random walks can be used in an unusual setting that warrants us to provide a different meaning for stochasticity. We showed that stochastic trajectories compressed inside the small multidimensional spaces of dynamical systems cannot produce closed paths. Despite these trajectories are constrained in tiny amounts of space, they cannot meet and superimpose. This description closely reminds the definition of chaotic systems' attractors dependent on initial conditions (Strogatz 2014). Two nearby trajectories starting infinitesimally close diverge from each other, so that they can end up anywhere in the attractor. These neighboring trajectories are never exactly straight and tend to separate exponentially fast, with variations of the strength of exponential divergence (defined by the Lyapunov exponent) along the attractor. Therefore, we speculate that a correlation could exist between random walks in higher dimensions and chaotic systems equipped with positive Lyapunov exponent attractors. In this novel account, attractors become the chunks of the phase space where multidimensional fluxes are necessarily confined. This suggests that chaotic flows take place in multidimensions.

REFERENCES

- 1) Abounit S, Zurzolo C. 2012. Wiring through tunneling nanotubes--from electrical signals to organelle transfer. *J Cell Sci.* 2012 Mar 1;125(Pt 5):1089-98. doi: 10.1242/jcs.083279.
- 2) Agosta SJ, Brooks DR. 2020. Buying Time. In book: *The Major Metaphors of Evolution*. DOI: 10.1007/978-3-030-52086-1_6
- 3) Allegrini P, Barbi F, Grigolini P, Paradisi P. 2007. Aging and renewal events in sporadically modulated systems. *Chaos, Solitons & Fractals*. Volume 34, Issue 1, October 2007, Pages 11-18
- 4) Ariazi J, Benowitz A, De Biasi V, Den Boer ML, Cherqui S, et al. 2017. Tunneling Nanotubes and Gap Junctions-Their Role in Long-Range Intercellular Communication during Development, Health, and Disease Conditions. *Front Mol, Neurosci*;10:333. doi: 10.3389/fnmol.2017.00333.
- 5) Austefjord MW, Gerdes HH, Wang X. 2014. Tunneling nanotubes: Diversity in morphology and structure. *Commun Integr Biol*, 7(1):e27934. doi: 10.4161/cib.27934.
- 6) Barbour DL. 2019. Precision medicine and the cursed dimensions. *npj Digital Medicine*, 2(4).
- 7) Bartels A, Douglas CL, Henriques A. 2014. Dualizability and index of subfactors. arXiv 1110.5671v2,1-36.
- 8) Barth A. *Vorlesungen über Gastheorie*. Leipzig: 1898. OCLC 01712811. ('Ergoden' on p.89 in the 1923 reprint.)
- 9) Bengson JJ, Todd A, Kelley, Xiaoke Zhang, Jane-Ling Wang, and George R. Mangun. 2014. Spontaneous Neural Fluctuations Predict Decisions to Attend. *Journal of Cognitive Neuroscience*, doi:10.1162/jocn_a_00650.
- 10) Betzel GF, Griffa A, Avena-Koenigsberger A, Goñi J, Thiran J-P, et al. 2013. Multi-scale community organization of the human structural connectome and its relationship with resting-state functional connectivity. *Network Science*, Volume 1, Issue 3 pp. 353-373 DOI: <https://doi.org/10.1017/nws.2013.19>.
- 11) 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.
- 12) Bierbach D, Laskowski KL, Wolf M. 2017. Behavioural individuality in clonal fish arises despite near-identical rearing conditions. *Nature Communications* volume 8, Article number: 15361.
- 13) Cardesa JI, Vela-Martín A, Jiménez J. 2017. The turbulent cascade in five dimensions. *Science*. 2017 Aug 25;357(6353):782-784. doi: 10.1126/science.aan7933.
- 14) Cencini M, Falconi M, Olbrich E, Kantz H and Vulpiani A. 2000 *Phys. Rev. E* 62 427.
- 15) Costanzo M, Abounit S, Marzo L, Danckaert A, Chamoun Z, Roux P, Zurzolo C. 2013. Transfer of polyglutamine aggregates in neuronal cells occurs in tunneling nanotubes. *J Cell Sci*, 126:3678-85. DOI: 10.1242/jcs.126086.
- 16) Culbreth G, West BJ, Grigolini P. 2019. Entropic Approach to the Detection of Crucial Events. *Entropy*, 21(2), 178; <https://doi.org/10.3390/e21020178>.
- 17) Dekker J, Belmont AS, Guttman M, Leshyk VO, Lis JT, et al. 2017. The 4D nucleome project. *Nature*. 2017 Sep 13;549(7671):219-226. doi: 10.1038/nature23884.
- 18) Domb C. 1954. On Multiple Returns in the Random-Walk Problem. *Proc. Cambridge Philos. Soc.* 50, 586-591.
- 19) Don AP, Peters JF, Ramanna S, Tozzi A. 2020. Topological View of Flows inside the BOLD Spontaneous Activity of the Human Brain. *Front. Comput. Neurosci.* DOI: 10.3389/fncom.2020.00034.
- 20) Elowitz MB, Levine AJ, Siggia ED, Swain PS. 2002. Stochastic Gene Expression in a Single Cell. *Science*, Vol. 297, Issue 5584, pp. 1183-1186. DOI: 10.1126/science.1070919.

- 21) Feller W. 1971 An introduction to probability theory and its applications. Wiley.
- 22) Finn EH, Misteli T. 2019. Molecular basis and biological function of variability in spatial genome organization. *Science*. Vol. 365, Issue 6457. DOI: 10.1126/science.aaw9498.
- 23) 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.
- 24) Gaspard P. 2005. Brownian motion, dynamical randomness and irreversibility. *New J. Phys.* 7 77. doi:10.1088/1367-2630/7/1/077.
- 25) Goodman S, Naphade S, Khan M, Sharma J, Cherqui S. 2019. Macrophage polarization impacts tunneling nanotube formation and intercellular organelle trafficking. *Scientific Reports*, 9: 14529.
- 26) Gurke S, Barroso JF, Gerdes HH. 2008. The art of cellular communication: tunneling nanotubes bridge the divide. *Histochemistry and Cell Biology*. 129 (5): 539–50. doi:10.1007/s00418-008-0412-0.
- 27) Hartmann R, Singh PK, Pearce P, Mok R, Song B, et al. 2019. Emergence of three-dimensional order and structure in growing biofilms. *Nature Physics* volume 15, pages251–256.
- 28) Henriques, A. and Penneys, D. 2016. Bicommutant categories from fusion categories. arXiv 1511.05226v2,1-35.
- 29) Kang Y, Liu R, Mao X. 2020. Aperiodic stochastic resonance in neural information processing with Gaussian colored noise. *Cognitive Neurodynamics*.
- 30) Kirchhoff M, Parr T, Palacios E, Friston K, Kiverstein J. 2018. The Markov blankets of life: autonomy, active inference and the free energy principle. *The Royal Society Interface*. <https://doi.org/10.1098/rsif.2017.0792>.
- 31) Kiviet DJ, Nghe P, Walker N, Boulineau S, Sunderlikova V, Tans SJ. 2014. Stochasticity of metabolism and growth at the single-cell level. *Nature* 514, 376–379. doi:10.1038/nature13582.
- 32) Klosin A, Oltsch F, Harmon T, Honigmann A, Jülicher F. 2020. Phase separation provides a mechanism to reduce noise in cells. *Science*. Vol. 367, Issue 6476, pp. 464-468. DOI: 10.1126/science.aav6691.
- 33) Kůrková V. 2019. Some insights from high-dimensional spheres: Comment on “The unreasonable effectiveness of small neural ensembles in high-dimensional brain” by Alexander N. Gorban et al. *Phys Life Rev*. <https://doi.org/10.1016/j.pprev.2019.03.014>.
- 34) Libet B, Gleason CA, Wright EW, Pearl DK. 1983. Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential). The unconscious initiation of a freely voluntary act. *Brain*. 106 (Pt 3):623-42.
- 35) Linneweber Ga, Andriatsilavo M, Dutta SB, Bengochea M, Hellbruegge L, et al. 2020. A neurodevelopmental origin of behavioral individuality in the *Drosophila* visual system. *Science*. Vol. 367, Issue 6482, pp. 1112-1119. DOI: 10.1126/science.aaw7182.
- 36) Matoušek J. 2003. Using the Borsuk–Ulam Theorem. *Lectures on Topological Methods in Combinatorics and Geometry*. Berlin Heidelberg: Springer-Verlag.
- 37) McCrea WH, Whipple FJW. 1940. Random Paths in Two and Three Dimensions. *Proc. Roy. Soc. Edinburgh* 60, 281-298.
- 38) Montroll EW. 1956. Random Walks in Multidimensional Spaces, Especially on Periodic Lattices. *J. SIAM* 4, 241-260.
- 39) Pang JC, Gollo LL, Roberts JA. 2020. Stochastic synchronization of dynamics on the human connectome. *BioRxiv*. doi: <https://doi.org/10.1101/2020.02.09.940817>.
- 40) Papo D. 2014. Functional significance of complex fluctuations in brain activity: from resting state to cognitive neuroscience. *Frontiers in Systems Neuroscience*, 8, 112. doi: 10.3389/fnsys.2014.00112.
- 41) Peters JF, Tozzi A, Deli E. 2017. Towards Equations for Brain Dynamics and the Concept of Extended Connectome. *SF J Neuro Sci* 1:1.
- 42) Pontes-Filho S, Lind P, Yazidi A, Zhang J, Hammer H, et al. 2020. A neuro-inspired general framework for the evolution of stochastic dynamical systems: Cellular automata, random Boolean networks and echo state networks towards criticality. *Cognitive Neurodynamics* volume 14, pages 657–674.
- 43) Reese TM, Brzoska A, Yott DT, Kelleher DJ. 2012 Analyzing Self-Similar and Fractal Properties of the *C. elegans* Neural Network. *PLoS ONE* 7,(10): e40483. doi:10.1371/journal.pone.0040483.
- 44) Ribault C, Sekimoto K, Triller A. 2011. From the stochasticity of molecular processes to the variability of synaptic transmission. *Nat.Rev.Neurosci.* 12, 375–387. doi:10.1038/nrn3025.
- 45) Sartori-Rupp A, Cordero Cervantes D, Pepe A, Gousset K, Delage E, et al. 2019. Correlative cryo-electron microscopy reveals the structure of TNTs in neuronal cells. *Nat Commun*;10(1):342. doi: 10.1038/s41467-018-08178-7.
- 46) Seyed-Razavi Y, Hickey MJ, Kuffová L, McMenamin PG, Chinnery HR. 2013. Membrane nanotubes in myeloid cells in the adult mouse cornea represent a novel mode of immune cell interaction. *Immunol Cell Biol*; 91:89-95; Doi: 10.1038/icb.2012.52.
- 47) Sporns O, Tononi G, Kötter R. 2005. The human connectome: A structural description of the human brain. *PLoS Computational Biology*. 1 (4): e42. doi:10.1371/journal.pcbi.0010042.
- 48) Stringer C, Pachitariu M, Steinmetz N, Carandini M, Harris KD. 2019. High-dimensional geometry of population responses in visual cortex. *Nature* volume 571, pages361–365.

- 49) Strogatz S. 2014. *Nonlinear Dynamics and Chaos*, 2nd Edition. Westview Press. ISBN-13 : 978-0813349107.
- 50) Tardivel, M., Begard, S., Bousset, L., Dujardin, S., Coens, A., Melki, R., et al. 2016. Tunneling nanotube (TNT)-mediated neuron-to neuron transfer of pathological Tau protein assemblies. *Acta Neuropathol. Commun.* 4:117. doi: 10.1186/s40478-016-0386-4.
- 51) Tozzi A. 2019. The multidimensional brain. *Physics of Life Reviews*, 31: 86-103. doi: <https://doi.org/10.1016/j.plrev.2018.12.004>.
- 52) Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K. 2013. The WU-Minn Human Connectome Project: an overview. *NeuroImage*. 80: 62–79. doi:10.1016/j.neuroimage.2013.05.041.
- 53) Victor JD, Rizvi SM, Conte MM. 2017. Two representations of a high-dimensional perceptual space. *Vision Res.*, 137:1-23. doi: 10.1016/j.visres.2017.05.003.
- 54) Vogt G, Huber M, Thiemann M, van den Boogaart G, Schmitz OJ, Schubart CD. 2008. Production of different phenotypes from the same genotype in the same environment by developmental variation. *Journal of Experimental Biology* 2008 211: 510-523; doi: 10.1242/jeb.008755.
- 55) Walters P. 1982. *An Introduction to Ergodic Theory*, Springer, ISBN 0-387-95152-0.
- 56) Wang X. 2005. Volumes of Generalized Unit Balls. *Mathematics Magazine*, 8(5):390–395.
- 57) Wang H, Wang B, Normoyle KP, Jackson K, Spitler K, et al. 2014. Brain temperature and its fundamental properties: a review for clinical neuroscientists. *Front. Neurosci.* doi: 10.3389/fnins.2014.00307.
- 58) Wang H, Park M, Dong R, Kim J, Cho Y-K, et al. 2020. Boosted molecular mobility during common chemical reactions. *Science*, 369, 6503:537-541. DOI: 10.1126/science.aba8425.
- 59) Zare M, Grigolini P. 2013. Criticality and avalanches in neural network. *Chaos Solitons & Fractals* 55, 80–94. DOI: 10.1016/j.chaos.2013.05.009.