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Review

Overcoming randomness does not rule out the importance of inherent randomness for functionality

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Randomness is intrinsic to many natural processes. It is also clear that, under certain conditions, disorders are not associated with functionality. Several examples in which overcoming, suppressing, or combining both randomness and non-randomness is required are drawn from various fields. However, the need to suppress or overcome randomness does not negate its importance under certain conditions and its significance in valid processes and organ functions. Randomness should be acknowledged rather than ignored or suppressed; it can be viewed, at worst, as a disturbing disorder that may be treated to produce order, or, at best, as a 'beneficial disorder' that can be considered as a higher level of functionality.

Keywords. Mechanisms of disease; quantum physics; randomness; system biology

Abbreviations: ADHD, attention deficit hyperactivity disorder; AIF, antithetic integral feedback; ASD, autism spectrum disorders; CECMP, cytoskeleton and extracellular matrix-related protein; CLPA-GNR, constrained LPA with grouped nodes reallocation; CNT, carbon nanotube; DRG, dorsal root ganglia; EF, electric field; EMF, electromagnetic field; FCMs, functional connectivity matrices; GOIN, gene orientation inversion network; LPA, label propagation algorithm; LRTC, long-range temporal correlations; MCs, mast cells; MIN, microbial interaction network; MRSA, methicillin-resistant *Staphylococcus aureus*; NP, nanoparticle; PD, Parkinson's disease; PMS, Phelan-McDermid deletion syndrome; POSS, polyhedral oligomeric silsesquioxane; QSAR, quantitative structure–activity relationship; WIP, wavelet intensity patterns

1. Introduction

Randomness is intrinsic to many natural systems; however, under some conditions, disorder is not associated with functionality. In physics, chemistry, biology, medicine, and psychology, overcoming, suppressing, or combining both randomness and non-randomness is essential. Clearly, not everything is random, and randomness is not always good; this suggests that these examples do not negate the importance of randomness in processes and system functions.

1.1 *Reducing and controlling randomness in physics*

Under some conditions, reducing or controlling randomness reduces uncertainty and improves functionality.

Sensor data fusion technology is used in fault diagnosis. In a sensor data fusion system, information is described by hairiness and may be associated with partial reliability. Indeterminate information, including randomness, can be overcome by models that fuse uncertain information. This provides a rigorous measure of consistency to the sensor data, and complementary multi-sensor information reduces the uncertainty of fault recognition, thus enhancing the reliability of fault detection (Jiang *et al.* 2016). However, fuzziness may be associated with losing information. Quantitative structure–activity relationship (QSAR) modeling derives models by selecting variables from large descriptor pools and may identify random correlations. Tests for evaluating models built on random data are needed. Software that enables data preparation for y-randomization and pseudo-descriptors tests has been developed, and tests indicate the quality of QSAR models compared with chance models resulting from random data, as non-randomness is required for a good QSAR model (Lipiński and Szurmak 2017). Stochastic hill climbing with novel heuristics was used for wireless sensor network configuration learning, with a feedback-based model that reconfigures the network to optimize application. A method for launching the algorithm from a better-than-random starting point was demonstrated (Helkey and Holder 2018); however, this does not rule out equal or better functionality if a random starting point was selected. Several real-world complex systems display community structures, where individuals with

similar properties form a community. The label propagation algorithm (LPA) is a detection technique that suffers from induced randomness (Chin and Ratnavelu 2016). An improved algorithm detects the main communities using the number of mutual neighboring nodes. Improving the quality of the detected communities was performed by switching the nodes to another community or removing them from their current communities at various points of the algorithm (Chin and Ratnavelu 2016). A modified algorithm successfully handles the randomness issues in LPA. This improved CLPA-GNR updates unassigned and assigned nodes synchronously, while assigned nodes are also updated asynchronously (Hou Chin and Ratnavelu 2017). Maintaining some randomness may ensure better functionality under some conditions.

The evolution of scale-free networks under subtle changes was modeled by using competition and inner anti-preferential deletion in the growth and preferential attachment procedures. Nonlinear and dynamic control of randomness and determinacy produced prototypes that self-organize into scale-free networks with varied scaling exponents. Increased determinacy gives stricter parameter control than randomness. Small changes of randomness and determinacy may be associated with the topology universality and dissimilarity in scale-free networks (Zhang *et al.* 2016). This suggests that changes in randomness, and control rather than elimination, are required. The interaction between quenched disorder provided by a random field and network connectivity in the Blume–Capel model has been described. The replica method averages the network randomness, thus enabling an alternative route to numerical simulations and standard mean field methods, and a thermodynamic scenario with several critical points reliant on network connectivity (Erichsen *et al.* 2017). Averaging randomness does not necessarily mean eliminating it.

Distributed acoustic sensing via optical fibers uses Rayleigh backscattering to detect acoustic waves interacting with the fiber along its entire length. The randomness of Rayleigh backscattering creates nonuniform performance along the fiber. A recent study described the use of Rayleigh-based discrete reflectors with enhanced detection performance to reduce randomness in detection sensitivity, enabling enhanced detection beyond typical values and sensitivities comparable with discrete reflectors (Gabai *et al.* 2017). A mean field model of coupled phase oscillators with random heterogeneity in the coupling strength was developed. When the natural frequency of the oscillator is 'deterministically' chosen with no randomness, the system exhibits a finite-size scaling exponent. The effects of coupling-strength randomness on the finite-size scaling and dynamic fluctuation were studied (Hong 2017), with unique Anderson localization behavior found in pseudospin systems in a 1D disordered potential. There exists a critical random potential strength, beneath which the localization length declines with the random strength for a fixed incident angle. However, the localization length drops to a minimum and rises directly later. The incident angle requirement of the localization length has dissimilar asymptotic performances in the two regions of random strength. The sharp transition is caused by evanescent waves emerging in the system. For pseudospin-1/2 systems, there is a lowest localization length as the randomness increases; however, the transition from decreasing to increasing localization length at the minimum is smooth rather than rapid. In both regions, the requirement of the localization length has the same asymptotic behavior (Fang *et al.* 2017). Sound spread over the ground with a random spatially changing surface entry was studied, with the impact of randomness on the reflection coefficient amplitude and on the surface wave component wavenumbers analyzed. The mean intensity was similar to that in the non-random case, except near interferences that are smoothened out by randomness (Dragna and Blanc-Benon 2017). These examples do not rule out the possibility that randomness contributes to functionality.

1.2 *Generating less randomness in chemistry*

Si-rich W-silicide films composed of Si*n* clusters, each encapsulating W-atom clusters, were designed using a gas-phase reaction between WF_6 and SiH_4 in a hot-wall reactor. The films were amorphous semiconductors with dependence attributable to the reduced randomness in the Si network as *n* amplified, which reduced the densities of band tail states and localized states (Okada *et al.* 2016). This demonstrates the relevance of the degree of randomness, rather than suggesting a quantitative functionality parameter. A method for preparing pH-responsive superparamagnetic hybrid coassemblies with controls over the morphology and multifunctionalization was described. This overcomes the interior randomness of conventional modified inorganic NP assemblies and can be used for the controllable assembly of other NPs or polymers (Zhan *et al.* 2017). It does not, however, rule out the structural relevance of randomness.

Under certain conditions, reduced randomness has been associated with improved function. $Al_2O_3/Ag/Al_2O_3$ sandwiched thin films were placed by magnetron sputtering, generating Al_2O_3 thin films with embedded Ag NPs. The cycling stability was enhanced by the reduced randomness in the formation and rupture of conductive filaments (Gao *et al.* 2017). Regardless of the view about the randomness of carbon nanotubes (CNTs) tortuosity in CNTs, the rules of helical buckling in tubular strings are applicable to vertically aligned CNTs. A gradual increase in the total free surface energy ensures incomplete cohesion, driven by van der Waals connections, thus reducing excess surface energy. The cohesion of CNTs is convoyed by deformation and loss of straightness, leading to increased elastic strain energy in the system (Jahangiri 2017).

Other structures with reduced randomness have been described; however, their function was not compared with that for randomized cases. A cross-linked polyhedral

oligomeric silsesquioxane (POSS) nanohybrid synthesized via Schiff base chemistry using octa-amino POSS for structuring and glutaraldehyde as a dual-functional reagent gave rise to a solid-phase adsorbent, cross-linked POSS nanohybrid with selective adsorption properties for acidic dyes. The adsorption of MO is unstructured, exothermal, and associated with reduced randomness (Liu et al. 2017a, b). An oxide-based resistance memory can replace Si-based flash memory, although non-uniformity in important parameters and low strength in conventional resistance memory devices prevent its application. These obstacles could be overcome by regulating the growth direction of epitaxial brownmillerite $SrFeO_{2.5}$ thin films along the $SrTiO_3$ [111] direction. The controlled oxygen vacancy channels reduce the randomness of the conducting filament, resulting in highly uniform substituting factors for device-to-device and within-device cases (Acharya *et al.* 2017). The dynamics of large complex systems often obey an equation that captures essential information from complexities. For example, data on the thermalization of isolated many-body quantum states indicate that a detailed balance does not require coupling to baths or postulated randomness (Kim *et al.* 2018). Bound states in the continuum denote a few bound states surrounded by a continuous spectrum of extended states. A machinery to achieve a band of bound states overlapping with extended states in a class of disordered quasi-1D and -2D systems was described. The systems were partly disordered and unaffected by the randomness (Xiao *et al.* 2018).

2. More or less randomness in biological systems

Deviations from randomness underlie several genome-level processes. Direct tests of the random or non-random spreading of nucleotides were used to assess the premise of neutral, nearly-neutral, or selective evolution (Koonin 2009). The experiments were independent of functional, coding or non-coding, structural, repeated, or unique sequence properties of the DNA. The longitudinal distribution of bases in tandem repeats under the Bose–Einstein statistics showed an aberration from randomness (Valenzuela 2017). Another approach determined base dispersal within dinucleotides whose bases were separated by 0, 1, 2…K nucleotides, with differences from the random distribution again observed. The test values were periodical and included 16 dinucleotides (Valenzuela 2017).

Studies of mtDNAs, prokaryote genomes, and eukaryote chromosomes showed significant non-random connections and periodicities present for up to 1000 sites of base separation, and in human chromosome 21 until separations of more than 10 million sites. Each nucleotide has its own significant distance to neutrality, leading overall to 16 hierarchical significances (Valenzuela 2017). A biophysical model implemented explicit chromosome-arm domains for the requirement of the rejoining likelihood on the initial fragment distance. The yield of 'Cluster Lesions' producing two independent chromosome fragments was tested, and the model was tested in irradiated lymphocytes and fibroblasts. The exponential and Gaussian models were employed, with good agreement observed between experimental yields and centric rings. These prototypes delivered a higher ratio of acentric to centric rings than that expected under randomness (Tello Cajiao *et al.* 2017). The spatial distribution of genes in chromosomes does not seem to be random. In humans, about 10% of genes transcribed from bidirectional promoters are organized into groups. A new network is created as the gene orientation inversion network (GOIN) encodes short- and long-range inversion patterns of the orientation of gene pairs in chromosomes. Gene orientation inversion did not follow a random pattern. Several communities in GOIN group genes encoding for proteins related to the proteome of the parasite. Machine learning models predicted the activity of proteins in the proteome (Quevedo-Tumailli *et al.* 2018). While not fully random, this does not rule out a role for randomness at the genome and transcription levels.

Electromagnetic fields (EMFs) affect the structure of protein molecules by altering amino acid residues. Electric fields (EFs) decrease the binding energy of a soliton, reducing its amplitude and modifying its waveform. The differences depend on the strength and course of the EF in the EMF. The direction impacts the effects of EMF, which decline when the angle between the direction of the EF and that of the dipole moment of amino acid residues rises; the randomness at the macroscopic level is unaffected (Pang *et al.* 2016).

Several natural systems attenuate or integrate noise, with the variability introduced defining the achievable precision across biological functions (Parag and Vinnicombe 2017). Chemical reactions comprise an intrinsic element of randomness, manifested as noise that interferes with cellular processes and communication. The ability of molecular systems to filter noise, while keeping controlled and expected differences between single living cells, was described. In contrast to filtering of active noise, cellular compartmentalization is scaled in systems without extensive use of cellular energy. Passive noise filtering used by eukaryotic cell nuclei increases the certainty of transcriptional output. It has consequences for complex multicellularity development (Stoeger *et al.* 2016). It does not rule out the need for randomness in the functionality of cells (Ilan 2019a, b, c, d).

Noise is also required for diffusion, which is important in numerous physical, chemical and biological processes (Slator *et al.* 2015; Hexner and Levine 2017). In several systems, diffusion is essential for proper function. Randomization of the swimming direction of bacteria through diffusion benefits the organism in finding nutrition and overcoming obstacles (Triller and Choquet 2003; Baker *et al.* 2007; Saragosti *et al.* 2012; Licata *et al.* 2016).

In circumstances where studying noise is vital, such as in earthquake detection randomness is unavoidable and affects the outcome (Xu and Song 2009). However it may or may

not be beneficial for the proper function of the system. Under other conditions, noise is required, and randomness is beneficial for function. This is viewed in and mutations to provide resistance against diseases or drugs (Patnaik 2007; Pohl *et al.* 2017).

The source of the noise distinguish between situations where it's possible to suppress it, such as during signal processing, from conditions in which it cannot be suppressed, such as thermal noise (McLoughlin *et al.* 2007; Weng *et al.* 2014; Lunner 2015; Chen *et al.* 2019).

Randomness is relevant in several processes. The inversion composition of homologous and nonhomologous chromosomes from Drosophila subobscura showed no deviation from H-W expectations, and no linkage disequilibrium was detected among inversions located in different chromosomes of the karyotype (Zivanovic *et al.* 2016). Peptide-expressing phage display libraries are used to interrogate antibodies. Affinity-selected peptides are used for studying epitope mimetics assuming a random representation of amino acids in the peptide library. Deviances from randomness in UAG codon over-representation and in high-G phosphoramidite abundance were shown. The UAG over-representation results from the burden imposed on the phage by the recombinant Protein 8 subunits. The excess of G is a result of the variation in synthesis-efficiency and was corrected using compensating oligonucleotide-mixtures. Improved libraries applying these correctives display random distributions of amino acids. The enriched peptides obtained in biopanning exemplify a selection event, which is necessary for applications that involve phage display (Ryvkin *et al.* 2018). Cells achieve homeostasis regardless of intrinsic noise or randomness in their dynamics. An antithetic integral feedback (AIF) motif found in natural systems enables adaptation for the dynamics of a molecular species involved in stochastic biomolecular reaction networks. This motif can lead to increased cell-to-cell heterogeneity compared with open-loop constitutive control strategies. Combining the AIF motif and a negative feedback strategy produces a trade-off among the relaxing-time of the trajectories and the stationary alteration of the controlled species, with minor variance associated with a longer settling-time (Briat *et al.* 2018).

Microbes growing in animal host environments face fluctuations in both randomness and predictability. Gut fluctuations in nutrient levels are a result of the host's behavior, diet, health, and microbiota composition. Microbial cells can gain a fitness advantage by adapting their internal state in advance. A dynamic Bayesian model was used as a microbial growth strategy for molecular circuits (Katz and Springer 2016). Adding randomness into the algorithms may improve functionality. Inferring the microbial interaction networks (MINs) and modeling their dynamics provide insight for designing antibiotic and/or probiotic therapies. These models consider the measurement noise rather than uncertainties in the underlying dynamics. A stochastic model using the extended Kalman filter algorithm and a noise term to compensate for modeling uncertainties was developed to simulate randomness in measurement data from antibiotic-mediated Clostridium difficile infection. This model was found to be superior than traditional approaches (Alshawaqfeh *et al.* 2017). Phagocytosis by neutrophils is an important path in the innate immune response against entering microorganisms. Heterogeneity is present in the neutrophil potency to phagocytize bacteria. All neutrophils can phagocytize S. aureus; however, some are more powerful than others. Sequential phagocytosis of strains of the staph aureus bacteria displayed a non-random process, as bacteria strain-positive neutrophils specially phagocytized a specific strain (Hellebrekers *et al.* 2017). Assessment of bacterial diversity and dynamics was performed using 16S rRNA gene amplicon sequencing. The c-score index evaluated the randomness of the community assembly during the periods of decomposition. For all degradation times, the observed c-score was greater than the simulated c-score. During plant decomposition, bacterial communities exhibited less co-occurrence than one would expect to happen by chance. It suggests that these communities are not randomly assembled but instead are driven by species interactions (Moitinho *et al.* 2018).

Extrinsic environmental factors may intervene in natural random events. The consequence of a host's social and spatial behavior on parasite community organization was studied in the helminth communities of two hosts. While the configuration of helminth co-occurrence was similar in the two hosts, the helminth intra-communities diverged in the frequency of positive and negative pairwise species co-occurrences. The level of infection was related to non-randomness in helminth assemblages due to interactions between parasite- and host-associated factors (Spickett *et al.* 2017). The movements of a subsocial spider species, *Anelosimus studiosus*, was modeled. The spiders were found to position themselves along the edge of the web more than expected under complete randomness (Quijano *et al.* 2016). Models for the incidence of arboreal ant species in the community were developed. The co-occurrence patterns did not differ from randomness, although a segregated configuration was described for common ant species. Competition impacted the distribution patterns within a community. However, habitat attributes had no effect on the matrix-wide results and affected only a few associations (Camarota *et al.* 2016). The spatial pattern of Citrus black spot caused by *Phyllosticta citricarpa* was studied in two 'Valencia' orange groves. Cluster analyses based on nearest-neighbor distance and pairwise distances between points were used to study complete spatial randomness of infected trees. In both groves, complete spatial randomness was rejected, with short-distance movements of inoculum found to affect the spread of disease (Hendricks *et al.* 2017). Species assembly patterns of local communities are formed by an equilibrium among several abiotic/ biotic filters. However, for cold/ drought tolerance-related beta niche properties, aberration from randomness was described. Non-random clustering

occurred in higher latitudes with harsh climates. Thus, both randomness and non-randomness result from the alpha and beta niches. Dispersal procedures and/or species equalization via trait similarities in producing randomness was proposed (Kubota *et al.* 2018). Spatial randomness and heterogeneous Poisson process prototypes were used for studying spatial distribution of tree species. The main pattern in forests was an aggregated distribution; reduced percentage and intensity with growing spatial scale, abundance, and diameter at breast height. Rare species were more aggregated than other species. Topographic variables such as elevation, slope, aspect, and convexity significantly influenced the species distributions (Du *et al.* 2017). Intraspecific trait inconsistency is relevant to the spatial distribution of trees types. Intraspecific trait dispersions underlying specific paths diverge more from null model expectations in species with aggregated rather than random distributions. The nearest-neighbor distance analysis showed that 14 of 45 species were distributed randomly and the other 31 were distributed in aggregation, with no species distributed uniformly. Niche processes lead to a spatial structure of species with aggregated distributions, whereas stochastic processes drive those with random distributions (Yan *et al.* 2018).

In the environment, stochastic models provide quantitative evaluations of earthquake occurrence. Ambient seismic noise is described by randomness acquired by the place and power of the noise sources and heterogeneous properties of the propagating medium. Noise data documented prior to the 1996 Gjalp eruption in Iceland show that a decrease of noise randomness is a temporary precursor to volcanic activity. Randomness reduction began eight days before the earthquake and ten days before the onset of the eruption. Randomness amplified to its previous levels 160 min following the earthquake. The decrease of randomness was due to the lack of higher frequencies (>1 Hz) in the noise wavefield caused by high absorption losses as hot magma soared in the upper crust (Glynn and Konstantinou 2016). This example shows that randomness can be used to predict earthquakes. Search systems such as simulated annealing and batch training solve nonconvex optimization problems. These methods can search over wider ranges when the randomness added to the standard gradient descent method is decreased. This explains why large batch training degrades generalization performance (Takase *et al.* 2018); however, it cannot overcome the resulting loss of data. A fuzzy-stochastic programming method was developed to optimize water resources systems under uncertainties. A water resources management problem with random features demonstrated the ability of this approach to optimize water resources allocation under fuzziness and randomness (Wang et al. 2016a, b, c). A cloud model for simulating debris-flow hazard assessment was shown to be useful for the analysis of hazards in debris-flows. This prediction approach avoids the randomness and fuzziness of uncertainty problems and produces reasonable prediction results (Cao *et al.* 2016). The transition from fail-safe to safe-to-fail makes resilience examination popular in urban drainage systems. The severity of flooding can be evaluated outside of uncertainties regarding climate change and urbanization. A recent model considered functional variety, topological complexity, and disturbance randomness based on the social severity of urban flooding, environmental severity of sewer overflow, and technological severity of influences on downstream facilities (Dong *et al.* 2017). Stability against random perturbations is of great importance in the Earth's climate system. In modeling the Amazonian vegetation system, very slight threats to the forest state stability represent Levy noise with large, low-intensity jumps, such as fires in non-drought years. During droughts, high-intensity fires accelerate the transition among forest and savanna states (Serdukova *et al.* 2017). Overall, these data support the need to consider randomness under certain conditions.

3. More or less randomness in health and disease

The connectivity theory assumes that the brain contains developmentally pre-programmed cell assemblies known as the functional connectivity motif, which is associated with relational patterns and generalized knowledge. This is in contrast to the presumed randomness within mature with naive cell assemblies. Pre-configured canonical computations may be conserved across many circuits, going from those encoding memory engrams and imagination to decision-making and motor control (Li *et al.* 2016). Pre-programing in some networks does not rule out the relevance of randomness to other processes. Indeed, both random and non-random functions appear in different brain areas. Dorsal root ganglia (DRG) contain the cell bodies of joining primary sensory neurons. The configuration of neuronal cell bodies at the widest point of DRG is clearly non-random, showing a radial tendency in density that increases toward the outside (Ostrowski *et al.* 2017). The theory of connectivity suggests that intelligence is imbedded in a power-of-two-based permutation logic. Dopaminergic neurons use a simpler logic. The specific-to-general permutation logic remains intact, although receptors are erased during adulthood, signifying that logic is pre-configured. Computational logic is implemented in the cortex over a random-connectivity strategy in superficial layers 2/3 combined with non-random structures in deep layers 5/6. The randomness of layers 2/3 is ideal for maximizing cross-modality novel pattern-extraction, -discrimination, and -categorization using sparse code. The non-randomness in layers 5/6 contains a higher proportion of general circles projecting mostly to subcortical systems, associated with feedback-control of motivation, emotion, consciousness, and behaviors (Xie *et al.* 2016). Brain connectomics in healthy and diseased states are determined by functional connectivity density mapping. Functional connectivity hubs in visual and posterior parietal cortices are associated with alterations in cortical gray matter hubs. Randomness cannot account for the

probability distribution, and the Shannon entropy increases in proportion to the power of the hubs, signifying a high information flow per unit time, particularly in medial occipito-parietal regions (Tomasi *et al.* 2016). Thus, randomness may have different effects in different brain areas.

A mathematical outline for analyzing randomness from functional connectivity assessments was described. Random matrix theory is applied to the examination of functional connectivity matrices (FCMs). The resulting randomness measure comprises probability density functions and statistical testing methods. This approach confirms that whole-brain FCMs are not random. Rather, randomness is an indicator of non-random arrangements within a non-random FCM (Vergara *et al.* 2018). Host factors affect the degree of randomness. Connectivity in the brain can be assessed from functional magnetic resonance imaging (fMRI) signals determining the blood oxygen level. These signals can be contaminated by noise that is distinct to the brain's intrinsic activity. A mathematical framework designed to test the randomness of connectivity configurations suggests that specific parts of the brain show decreasing randomness with age and gender (Vergara and Calhoun 2016).

The natural world is unconstrained and contains intrinsic uncertainty. The brain deals with randomness in the surrounding environment, having the capability to analyze our acoustic environment by extracting regularities from surrounding sounds. Natural sound environments are rarely completely predictable. However, the brain successfully deduces its surroundings by mining valuable information from stochastic sounds. The brain is sensitive to higher-order statistics, detecting temporal dependences among sound events was shown in studies in which listeners were asked to notice changes in randomness in the pitch of tone sequences. Thus, listeners collect statistical estimates to process received sounds (Skerritt-Davis and Elhilali 2018). Similarly, the brain adapts for color vision. Failures of color vision may be a result of ambiguity. Using images of vegetated and non-vegetated outdoor scenes indicate that color offers a variable guide to surface identity. Failures to match relations between colors were defined by a measure of the randomness of the colors in scenes, the Shannon entropy (Foster 2018). In voluntary movement, an essential measure is the reaction time between the onset of a visual stimulus and a saccade toward it. The reaction time establishes high variability. Oculomotor activity gradually builds up once a visual target appears, until a dangerous level is reached, at which point a saccade is activated. The rise-to-threshold course begins from a dynamic state that comprises other incipient, internally driven motor plans, which contest with the target-driven activity. The resultant conflict-resolution course is shown in elusive differences between baseline activity, build-up rate, and threshold, and entails deterministic interactions. This explains the detected reaction time spreading while invoking a relatively minor amount of intrinsic randomness (Hauser *et al.* 2018).

Alterations in the magnitude of randomness signify disease activity. Brain oscillations display long-range temporal correlations (LRTCs), reflecting the orderliness of their fluctuations. This supports the notion that the brain functions near criticality – a state where neuronal activities are stable between order and randomness. Using closed-loop brain training neuro-feedback increases the spontaneous post-training LRTCs. This outcome was observed in patients with post-traumatic stress disorder, in whom abnormally random dynamics were overturned. Regions displaying abnormally little LRTCs, i.e., excessive randomness, normalized toward healthy levels. When exposed to appropriate training, spontaneous cortical activity can 'self-tune' its own temporal complexity, despite manifesting the abnormal dynamics observed in some psychiatric disorders (Ros *et al.* 2017). A shift toward randomness in the topological organization of the cortical thickness network is noted in depressed patients. Altered nodal centrality in some areas of the brain affects machineries within the default mode, salience, and central executive networks. Disturbed nodes attached in the default mode and executive networks may be related to depression severity (Wang et al. 2016a, b, c).

A statistical platform for peripheral activity determined the cognitive control of visuomotor actions in schizophrenia, with the stochastic signatures of minute fluctuations in motor performance differing between patients and controls. Velocity-dependent signatures show that schizophrenics have extra noise and randomness in their moment-by-moment hand micro-motions. The normative geometric-dependent signatures of deliberateness are lacking from the goal-directed reach in patients. They can be found in their natural hand retractions to rest. The unremitting flow of micro-motions contributes to inside sensed feedback from self-produced actions. This suggests that sensory-motor integration with outwardly apparent inputs is impaired (Nguyen *et al.* 2016). The fMRI-derived functional connectomes are more disconnected in schizophrenics than in healthy subjects, displaying a lower edge density and greater number of (dis)connected components. Topological randomization in schizophrenia may be a result of the 'non-significant' edges added when studying connectomes based on correlations. Probabilistically, threshold connectomes show decreased randomness and increased consistency across participants (Váša *et al.* 2018). Alterations in EEG complexity among deficit (DS) and nondeficit (NDS) schizophrenia reflects cognitive processing capacities. Cognitive processing in the frontal networks in DS is less complex than in patients with NDS, as reflected by EEG measures (Cerquera *et al.* 2017). The adaptability of the brain to continually shifting environment is reduced in psychotic disorders. Resting-state brain signal complexity is also changed, and this is linked with cognitive impairment. Patients with mental disorders exhibit either decreased complexity toward regularity or toward randomness. In schizophrenia, decreased complexity toward regular signals has been observed in the hypothalamus; in psychotic bipolar

disorder, a decrease was noted in the left inferior occipital, right precentral, and left superior parietal regions. No brain region with reduced complexity toward regularity was shown in schizoaffective disorder patients. All patients showed increased brain signal randomness in dorsal and ventral prefrontal cortex. Unaffected relatives did not manifest complexity differences. Bipolar and schizoaffective patients showed increased brain signal randomness in some brain areas, as did probands (Hager *et al.* 2017).

Parkinson's disease (PD) is characterized by a breakdown in the configuration of stride duration variability. Activating the upper body during walking improves the spatiotemporal parameters of gait in PD, acting against the randomness of PD gait and the characteristic gait hypokinesia. This improvement may be due to upper body recurrent movements acting as rhythmical external cues to circumvent their imperfect basal ganglia circuitries (Warlop *et al.* 2017). Attention deficit hyperactivity disorder (ADHD) patients have augmented undirected functional connectivity, suggesting a higher degree of dependency among regions, and amplified directed functional connectivity. These support a stronger connection and transmission of information among brain regions. In ADHD, the undirected functional network is more arranged than in normal subjects, indicating an irregular increase in undirected functional connectivity. In contrast, the directed functional networks are more random, which means greater disorder in causation and more chaotic information transfer between brain regions (Wang et al. 2016a, b, c). The micro-scale head motions in patients with ASD exhibit excess noise and randomness, suggesting an uncertain motor-feedback signal. Deleterious configurations of noise are worsened by the existence of secondary neuropsychiatric diagnoses, lower verbal and presentation intelligence, and degree of severity of autism (Torres and Denisova 2016). Phelan-McDermid deletion syndrome (PMS) has a high penetrance of ASD. Characteristic walking signatures are lacking in children with PMS and with idiopathic-ASD, with unusual leg rotational acceleration signatures that render PMS unstable. The median values of the estimated Gamma parameters separated children from adolescents with PMS, with the former showing more randomness and more noise. Variations in arm gestures during walking also have uncharacteristic statistics that are distinct for males and for females in PMS. They manifest higher rates of noise accumulation in idiopathic ASD (iASD) children (Torres *et al.* 2016). EMGs of vastii muscles in runners were recorded using a bipolar current amplifier generating wavelet intensity patterns (WIP). The clusters designed by random surrogate WIPs were used to analyze whether the groups were likely to be non-random. The steps were divided into groups displaying similar WIPs, and the correlations between the vastii muscles noted during similar steps were greater than those of WIPs noted during successive steps, indicating the non-randomness of the WIPs (von Tscharner *et al.* 2018).

Immunology contains several examples of how the microenvironment affects the degree of randomness. Neutrophil recruitment in the hepatic sinusoid occurs in nearly all liver diseases and assists in pathogen clearance or tissue damage. Neutrophil rolling is unlikely to appear in liver sinusoids. LFA-1 dominated the static or shear resistant adhesion of neutrophils, while Mac-1 decelerated neutrophil crawling. The presence of Kupffer cells affected the randomness of neutrophil crawling (Yang *et al.* 2017). HLA yields a large variety of alloreactive donor T-cell responses, which may explain the randomness in the development of alloimmune reactions. The subsequent simulated organ-specific alloreactive T-cell clonal growth showed marked variability, with the T-cell count alterations spanning orders of magnitude (Koparde *et al.* 2017). Young subjects with type-1 diabetes mellitus have autonomic nervous system behavior that leans toward randomness compared with healthy subjects. This finding is associated with reduced sympathetic and parasympathetic activity of the autonomic nervous system in these patients. Nonlinear indices including recurrence rate, determinism, Shannon entropy, and indices in the frequency and time domains showed reduced values in type-1 diabetes mellitus patients (Souza *et al.* 2016). HIV-1 manifests changes in its genome resulting from both recombination and mutation during the progression of an infection. A single cell needs to be infected by two HIV strains for a recombination to occur. The coinfections are more common than would be expected for independent infection events and do not follow a random distribution. Alterations in target cell vulnerability explain the non-randomness, both for direct cell-to-cell transmission and for free virus transmission. A model that considers the heterogeneity of target cells exhibited that the number of infection events per cell during cell-free HIV-1 infection follows a negative-binomial distribution (Ito *et al.* 2017). Typical survival analyses with time-dependent covariates do not usually consider random fluctuations or contamination of variables by measurement errors. A model that overcomes this limitation was used to analyze spatial-clustered survival data with a fraction of long-term survivors alongside repeated measurements of CD4(+) T lymphocytes for HIV individuals. The model comprises a flexible method to determine nonlinear behavior in different CD4 profiles over time and a spatial cure method for analyzing data of long-term survivors. This model outperformed traditional survival approaches (Martins *et al.* 2017). A stochastic epidemic model for the transmission dynamics of a tick-borne disease in a single population showed significant differences in predictions from those of deterministic models. The likelihood of an outbreak is higher if the disease is introduced by infected deer as opposed to infected ticks (Maliyoni *et al.* 2017). Methicillin-resistant Staphylococcus aureus (MRSA) transmission in hospital areas is characteristically stochastic, and the randomness is further emphasized by the small population sizes involved. A stochastic model describing the MRSA transmission process considered the associated

microbiological environmental contamination. It suggested that the optimal intervention varied, and was subject to the outcome measure. Certain consequences required a minor subset of targeted interventions to control the outcome measure (Lee *et al.* 2017).

The role of randomness, environment, and genetics in cancer development has long been debated (Stensrud *et al.* 2017). Cancer can be viewed as an evolutionary process where random mutations and the selection process shape the mutational pattern and phenotype of cancer cells. Clustering algorithms that involve randomness produce diverse results on different executions with the same dataset. The non-deterministic nature of K-means-type algorithms is due to the random selection of data points as initial centroids. An upgraded model selects data points from dense regions as the initial centroids. Using datasets comprising ten cancer gene expression datasets, this algorithm provided good predictions of cancer subtypes from gene expression data (Nidheesh *et al.* 2017). Using a CRISPR/Cas9 system, the translational initial site in the GATA1 gene in K562 cells was studied. Significant heterogeneity was detected among alleles in the same clonally expanded cell, and between alleles from additional clonal expansions. This suggests randomness plays a role in the resection indorsed by nonhomologous end joining after CRISPR/Cas9 cleavage in cells experiencing genetic reengineering. This heterogeneity predicted altered functionality inside target tissues. (Bloh *et al.* 2017) Cytoskeleton and extracellular matrix-related proteins (CECMPs) Bioinformatics was used to measure the effect of amino acid substitutions on the sensitivity of CECMPs to proteases applicable to melanoma and on the binding affinities for HLA class I. CECMP peptides with amino acid substitutions exhibited increased sensitivity to proteases implicated in melanoma development (Callahan *et al.* 2018). The polyoma BK virus was observed with clonal integration and breakpoints randomly dispersed across the human and viral genomes in polyoma T-antigen-expressing carcinomas. The randomness of viral insertion sites remains functionally unclear (Sirohi *et al.* 2018). The notion of randomness in some cancer-associated mutations was challenged by showing that molecular mechanisms of stress-mediated biogenesis of mRNA-derived small RNAs can target and increase the local mutation rate of the genomic loci they originate from. The probability of mutations at specific loci could increase in a stress-specific and RNA-dependent manner, increasing the probability of generating mutations that alleviate stress situations. This mechanism is likely because tumor- and anticancer drug-associated stress situations trigger cellular reprogramming and inflammation, leading cancer cells to express molecular tools that 'attack' and mutate their own genome in an RNA-directed manner (Auboeuf 2016). Mammographic tissue areas related to density fluctuations are predominant in tumorous breasts. The causal physical developments are random, lack spatial correlation, and offer free diffusion. This signature is related to tissue disruption and loss of tissue homeostasis (Marin *et al.* 2017). The location of tumors inside an organ is viewed as a random event, though statistics suggest otherwise. More than half of invasive breast cancers start in the upper outer quadrant of the breast, although only 35–40% of breast tissue is in this quadrant. Tumors may form in healthy tissue where there is an increase of microvessels and high blood flow. The fractional probability is that at least one microvascular hot spot in each region of the breast assumes a Poisson distribution of microvessels in two-dimensional cross-sections of breast tissue. The microvessel density in numerous areas of the breast was determined by near-infrared diffuse optical spectroscopy in diverse areas of the breast. Thus, the spatial location of tumors is not entirely random (Yu and Mitchell 2017).

Some examples of a reduction or loss of randomness are association with malignancy. Mast cells (MCs) gather in the stroma surrounding tumors, where they secrete angiogenic cytokines and proteases. In endometrial cancer, the spatial distribution of MCs deviates significantly from randomness. MCs augment tumor angiogenesis and preferentially localize along areas of new vessel formation, supporting their role in angiogenesis (Guidolin et al. 2017a, b). In human gastric cancer, both chymase-positive MC and vessels exhibit deviations from randomness with respect to their spatial relationship with gastric parenchyma (Guidolin et al. 2017a, b).

Quantitative analysis of randomness was developed for prediction of clinical situations (Ilan 2019a, b, c, d). Quantitative analysis of randomness in heartbeat patterns distinguished healthy human and humans subject to heart failure (Costa *et al.* 2002; Goldberger *et al.* 2002). Magnitude of randomness, defined the extent of correlation in human walking rhythm distinguished healthy human and humans subject to neurological (Hausdorff *et al.* 1997).

4. Reducing randomness in human behavior psychology

Mainstream psychology and psychiatry use linear correlation-based data analysis techniques. However, tools capable of managing the stochastic complexity of complex biopsychosocial systems are required. These systems exhibit intrinsic randomness, non-Gaussian probability distributions, non-stationarity, contextuality, and non-Kolmogorov probabilities, and are absent of mean and/or variance and conditional probabilities. Process algebra is capable of generating non-Kolmogorov probabilities for use in fundamental problems in quantum mechanics and developing psychosocial systems (Sulis 2017). The importance of alternatives captures the uncertainty noted by decision makers. Thus, interval number judgments are associated with limited rationality, which can be tested by introducing interval multiplicative reciprocal comparison matrices showing whether interval number judgments are inconsistent. A method of determining the interval weight vector

considers randomness in comparing alternatives, allowing a trajectory of interval weights to be determined (Liu et al. 2017a, b). Subjective randomness may result from a statistical inference assessing whether an event was produced by a random generating process. Observing randomness as statistical inference allows us to consider regularities created by computing machines and to restrict the set of probability distributions that illustrate regularity. Models of human randomness judgments typically apply non-binary sequences, binary matrices, and spatial clustering (Griffiths *et al.* 2018). Surprise can be hypothesized as related to improbability, and may specify a breakdown in models used to quantify probability. People can be surprised when they recognize patterns where their model suggests there should only be random noise. A model that formalizes this notion of surprise has been described. People may use randomness deficiencies to change their beliefs about the underlying origins of events (Maguire *et al.* 2018).

Studying human behavior is challenging. A game-based approach to determine non-randomness and the effect of memory on human exploration was proposed, and a simple memory model with a depth of 6–8 steps was adequate to estimate a 'human-like' level of exploration efficiency (Viswanathan *et al.* 2016). Free-choice tasks produce slower responses than forced-choice tasks. The randomness of the free-choice replies is influenced by the working memory load. An increase in working memory load caused a decrease in randomness and response speed. Thus, free-choice tasks are similar to random generation tasks (Naefgen and Janczyk 2018). In the case of expert disputes, people with low education are most likely to attribute arguments to expert incompetence, whereas people with higher self-reported knowledge attribute disputes to expert bias. The more highly educated attribute disputes to natural factors, including the irreducible complexity and randomness of the phenomenon (Dieckmann *et al.* 2017).

Planning evacuations and ensuring safety at mass gatherings involve many complex interactions. Experimental modeling has revealed a surprising degree of resemblance between the two contexts, producing similar prediction probabilities of peoples' escape strategies without observing them in action (Haghani *et al.* 2016). Studies of subsets of mass killings that have a common trait, such as family killings or public killings, show them to have a memoryless feature, suggesting that mass killing events within each category are random. This means that one mass killing occasion does not indicate whether another killing event is pending. This memoryless feature of these events is not detected when all mass killings are joined into a single analysis, consistent with evidence of a contagion effect. Because of the temporal randomness of public mass killings, the data suggest that systemic infrastructure-based interventions are the best way to deter such events (King and Jacobson 2017).

In summary, living and non-living objects in nature are subject to intrinsic random fluctuations such as thermal variabilities and others. Various physical, chemical and biological processes are driven by random fluctuations: collisions between the reactant molecules during chemical reactions; appearance of nuclei and their growth associated with phase transition; conformational fluctuations during protein's enzymatic activity, and others. The assumption that there is a need to suppress or overcome randomness under certain conditions does not rule out the importance of randomness in specific situations and its necessity for the valid functioning of processes and organs. There are clearly conditions in which overcoming randomness is associated with functionality. In some cases, the associated type of function may not necessarily be better. Thus, randomness should be considered rather than ignored or simply suppressed (Ilan 2019a, b, c, d). Looking at randomness as a disturbing disorder that can be 'corrected' into order, it is suggested that a superior level, or 'beneficial disorder', exists, and this can be viewed as a higher level of functionality.

Disclosure

YI is the founder of Oberon Sciences and a consultant for Teva; ENZO; Protalix; Betalin Therapeutics; Immuron; SciM; Natural Shield; Tiziana Pharma; Plantylight; Exalenz Bioscience.

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