Advanced Tailored Randomness: A Novel Approach for Improving the Efficacy of Biological Systems

YARON ILAN

ABSTRACT

Improving the function of biological systems represents a significant task in the fight to control health conditions and slow down the aging process. Applying the laws of physics to a biological system is difficult, due to the multiple parameters that must be considered at the cellular and whole-organ levels. The second law of thermodynamics states that entropy, a measure of randomness in an isolated system, increases over time. Based on this concept, randomness has been suggested as a means by which the efficacy of isolated biological systems may be improved. While classical and quantum physics uses different definitions of randomness and complexity, biological randomness is as an essential component of the intrinsic unpredictability of life. The manifestation of biological randomness may be different for different individuals, leading to differences in patient outcomes. In this work, an approach for enhancing the effectiveness of biological systems based on a novel concept of advanced tailored randomness in patient care is presented.

Keywords: algorithm; biological systems efficacy; quantum physics; randomness.

1. INTRODUCTION

IMPROVING THE EFFICACY OF BIOLOGICAL SYSTEMS is a key requirement for managing health and controlling disease. It has been suggested that randomness, a controversial concept in science (Bera et al., 2017), may be used to improve the efficacy of these systems. Within the frameworks of classical and quantum physics, randomness is defined differently. Biological randomness is an essential component of the intrinsic unpredictability of life, and of the structural stability of biological systems, due to interactions between the various levels of organization built into their structures (Buiatti and Longo, 2013).

2. RANDOMNESS AND COMPLEXITY IN PHYSICS

The second law of thermodynamics states that entropy, a measure of randomness in a system, increases over time. The underlying concept here is that in some isolated systems, nature may prefer chaos to regularity. When moving away from equilibrium, a system organizes itself in a way that reduces the effect

Department of Medicine, Hebrew University-Hadassah Medical Center, Jerusalem, Israel.

of any applied forces (Toussaint and Schneider, 1998). In deterministic chaos theory, even for a system with few degrees of freedom, a lack of accurate knowledge of the initial conditions leads to a high uncertainty in predictions (Bricmont, 1995). This is due to the exponential divergence of the corresponding trajectories, in which small initial differences lead to significant long-term effects (Bera et al., 2017). Apparent randomness results from the lack of full knowledge as to the state of a system and any associated hidden variables (Penrose, 1979; Bera et al., 2017). On the contrary, intrinsic randomness persists, despite a full knowledge of the initial state of a system (Bera et al., 2017). Entropy is not defined in terms of stochasticity. It is related to how many microstates are compatible with the defined macrostate. Entropy is defined for the statistical description of purely deterministic model systems, as, for example, the ideal gas, without requiring any stochasticity in the dynamics (Lieb and Yngvason, 2013; Qian et al., 2016; Yamato et al., 2017).

Contrary to the case of classical mechanics, randomness is inherent to quantum physics (Hoffmann, 2016). The two types of randomness, apparent and intrinsic, may coexist in quantum mechanics (QM). Even if the state of the system is known, the predictions of QM could be intrinsically random (Messiah, 2014; Bera et al., 2017). Born's interpretation of the wave function concept suggests a probabilistic description of reality, implying that QM is inherently probabilistic. Here, randomness may originate from interactions between the system and measurement apparatus and the environment (Bera et al., 2017).

The possibility of nonlocal correlation, or quantum entanglement, was proposed by Einstein et al. (1935), who claimed that any physical theory should satisfy realism and locality. Realism implies that if the outcome of the measurement of a physical quantity can be predicted, physical quantity must have a value equal to that predicted at the time of measurement. The values of the observables are intrinsic properties of the measured system. Realism, or determinism, implies that correlations in an experiment can be decomposed into deterministic factors, where all measurements have deterministic outcomes. Locality requires that elements of reality related to one system are not affected by measurements performed on another remote system (Bera et al., 2017). The locality or no-signaling property therefore implies that infinitely fast communication is impossible. Apparent random outcomes in an experiment are consequences of ignorance as to the actual state of the system. Although each run of an experiment has a particular a priori result, only averages can be accessed (Bera et al., 2017). A possible alternative to the no-signaling principle is to allow nonlocal hidden variables while retaining system determinism, as in the case of Bohm's theory (Bohm, 1952).

Bell (1966) showed that theories that satisfy locality and realism are incompatible with QM. The local/realistic correlations between outcomes observed in two measurement devices are referred to as Bell inequalities (Bell, 1964). The unfeasibility of instantaneous communication between spatially separated systems, together with full local determinism, requires that all relationships between measurements must obey the Bell inequalities. These inequalities cannot be explained in terms of deterministic local hidden variables (Freedman and Clauser, 1972; Hensen et al., 2015; Shalm et al., 2015). Bell's experiments also indicate that measurements performed using local measurement devices are selected "freely" and cannot be predicted (Bera et al., 2017). Nonlocality is a property of correlation that violates the Bell inequalities, and is associated with intrinsic quantum randomness (Brunner et al., 2014; Bera et al., 2017). No-signaling indicates nonlocal correlations and proves the nondeterministic nature of QM reality, indicating the existence of genuine random processes (Bera et al., 2017). A small amount of nonlocality, or even entanglement, may sometimes suffice to demonstrate maximal randomness in measurements (Acin et al., 2012). However, no modeling is required in the case of device-independent solutions; here, the proof is provided by a Bell inequality violation. If such a violation is observed, the outcomes are guaranteed to be random, independent of the working principles of the adopted measurement devices (Colbeck and Renner, 2008, 2011; Bera et al., 2017).

The entropic uncertainty relationship applies in the case of quantum memory, where any two observables can be measured with arbitrary precision, and randomness in the measurements is compensated by information stored in the quantum memory (Berta, 2010; Zhang et al., 2015). Noncommuting observables are responsible for the lack of noncontextual hidden variable theories that could explain all the results of QM measurements. The presence of nonlocal and quantum correlations gives rise to the possibility of a new form of randomness (Bera et al., 2017).

Physics involves self-organizing complexity (Carlson and Doyle, 2002; Turcotte and Rundle, 2002). Highly optimized tolerance is a theory of complexity based on structured, nongeneric, self-dissimilar internal configurations, and on robust, yet fragile, external behavior. According to this theory, these are the essential features of complexity and not accidents of evolution or artifices of engineering design. In physics,

uncertainty is quantified within a given modeling paradigm. Most catastrophic events seem to be unpredictable and are “outliers” with different properties (Sornette, 2002). Taking the example of a large physical system, uncertainty and error regarding weather forecasting models are due to the fact that these are dynamical systems involving millions of variables (Smith, 2002). Threshold systems are nonlinear self-organizing systems. In the case of seismic events, the “critical point” concept for earthquakes is part of a framework of “finite-time singularities.” The singular behavior associated with accelerated seismic release results from the positive feedback of the seismic activity on its release rate (Sammis and Sornette, 2002). Self-organization in earthquake threshold systems can be analyzed at a “microscopic” scale, based on simulation results, leading to dynamical equations. On the contrary, on a “macroscopic” earthquake fault-system scale, time-dependent state vectors similar to those used in QM are used to analyze these systems.

3. CORRELATIONS BETWEEN PHYSICS AND PHILOSOPHICAL/ PSYCHOLOGICAL/SOCIAL VIEWS ON RANDOMNESS AND COMPLEXITY

The correlation between physics-based and philosophical descriptions of randomness is explored in classic deterministic theory, in which chance has an epistemic status, and allows for indeterminism in the form of a description of the world based on statistical physics. An additional type of indeterminism present in classical mechanics derives from the nonuniqueness of the solutions to Newton’s equations (Bera et al., 2017). Two forms of randomness are present in nature according to this theoretical framework. The first, epistemic randomness, belongs to a deterministic world view, in which the only way random behavior can emerge is through lack of information about the actual state of the system. The second, ontic randomness, involves a nondeterministic world view, in which randomness is an intrinsic property, independent of our exact knowledge of the system. This implies that randomness cannot be understood in terms of a deterministic “hidden variable” model. Early atomists believed the world to be deterministic and that chance is a consequence of our limited abilities. Later, it was suggested that to accommodate a real example of chance, the deterministic motion of atoms must be interrupted without cause, by “swerves.” Such indeterminacy propagates to the macroscopic scale. A characteristic feature of pure randomness and strict determinism is that there is no option to control the course of events, which is vital for free will (Bera et al., 2017). Strict determinism precludes free will, and intrinsic randomness is necessary for its existence (Gisin, 2013).

Biological processes can be described by physics laws and even as “psychological-dependent” acts. Tversky and Kahneman described the processes by which people make a judgment under uncertain conditions by looking at several types of bias (Tversky and Kahneman, 1974): representativeness, where subjects are asked to judge the probability that an event A belongs to process B; availability of instances, adopted when subjects are asked to assess the frequency of a class or the credibility of a certain development; adjustment from an anchor, used in numerical predictions when a relevant value is available. These heuristics lead to predictable errors in judgment under uncertain conditions, despite attempts to improve their accuracy (Tversky and Kahneman, 1974; Tversky and Kahneman, 1981).

Engineering imposes a structure on systems, which are therefore not self-organizing. However, some engineered systems can become complex and self-organizing by default (Turcotte and Rundle, 2002). Self-organization has also been discussed with reference to social networks (Newman et al., 2002). Concepts borrowed from management, in which change is continuous, unpredictable, and crucial for improvement, can be also applied to biology.

Organizations in our society are complex adaptive systems (CASs), characterized by complexity, emergence, interdependence, self-organization, coevolution, chaos, and self-similarity. Changes within these organizations happen incessantly, through many small steps. The punctuated equilibrium model describes organizations as evolving through long periods of stability disrupted by short periods of change. In any ordered system, the applied constraints ensure that the agent behavior is limited to the rules of the system. On the contrary, in a chaotic system, the agents are unconstrained and susceptible to statistical analysis. In a CAS, the system and the agents coevolve, interact, and affect each other. The system exerts a mild constraint on the behavior of the agent, which in turn can alter the system by interacting with it (Gupta, 2012). Each agent inside a certain environment tries to obtain a better result for itself, while the results of these efforts are influenced by the behavior of the other agents. This leads to a dynamic equilibrium that fits a power law, describing a relationship between two quantities where a relative change in one result allows

for a proportional change in the other, independent of the initial size of the two quantities. In other words, small changes in one component of the system may significantly alter the system behavior.

4. RANDOMNESS AND COMPLEXITY IN BIOLOGICAL SYSTEMS AND EVOLUTION

Applying the laws of physics to a biological system can be difficult, due to the multiple parameters that can affect the system at both the cellular and whole-organ levels (Hoffmann, 2016). The complex dynamical behavior of structures involving a large number of interacting constituents makes prediction, even with a perfect knowledge of the initial conditions, difficult (Bera et al., 2017). Biological systems can be viewed as deterministic closed systems, operating like machines that comprised both a hierarchy and standardization, and as dynamic systems in a constantly changing state (Grobman, 2005). Complex biological systems are characterized by high levels of energy flow and cycling activity, along with great diversity and a high number of hierarchical levels (Kyriazis, 2003).

A molecular machine is a molecule or small molecular assembly that performs a task that increases free energy or performs work at the expense of chemical energy, in the presence of thermal fluctuations (Hoffmann, 2016). These machines transform one form of energy into another using random thermal motion. Models of molecular motors in biology may provide insight into statistical physics, the second law of thermodynamics, and information theory (Hoffmann, 2016). For instance, the physics of molecular machines shows that system noise may not always be a negative factor, but in fact represents an essential ingredient of functional nanoscale systems (Hoffmann, 2016). Where dynamic conditions permit, the presence of a self-organization process is expected. It is unknown whether biological randomness changes over time, in a way consistent with the second law of thermodynamics (Wang et al., 2016).

Evolution results from the dynamic instability of living systems and the “superposition” of different forms of randomness (Buiatti and Longo, 2013). It occurs in populations of individuals whose reproduction depends on a payoff strategy based on the environment, intrinsic uncertainties, and other sources of randomness (Stollmeier and Nagler, 2018). Although chaos may occur in evolution, it does not undermine its predictability (Rego-Costa et al., 2018). Chaos in evolution arises under frequency-dependent selection, caused by competitive interactions mediated by various traits (Rego-Costa et al., 2018). Environmental forces affect the outcome of evolution in systems prone to chaos (You et al., 2017). A changing environment produces fluctuations of a phenotype, interacting with the internal dynamics of a chaotic system. A strong environmental bias improves the predictability of evolution by reducing the probability of chaos and the magnitude of chaotic fluctuations, whereas weak environmental bias increases the probability of chaos (Rego-Costa et al., 2018).

The microscopic randomness of a mutation process can be amplified to produce macroscopic unpredictability by evolutionary dynamics (You et al., 2017). Replicator dynamics deterministically defines the evolution of an infinite-sized population in the presence of implementation errors and mutations, and exhibits chaos through a bifurcation sequence. This suggests that mutations have nonperturbative effects on evolutionary paths (You et al., 2017). Randomness (due to genetic drift or environmental stochasticity) and chaos (characterized by a dependence on initial conditions) are the key factors that reduce the predictability of evolution.

Organisms have evolved to cope with variations at the molecular level. They make use of physical processes in evolution to achieve functional development without the need to store all the related information in DNA sequences. This view differs from that of neo-Darwinism, which identifies “blind chance” as the origin of variation. Although “blind chance” is necessary, the source of functional difference is not at the molecular level. These notions support the concept of biological relativity, which claims that there is no privileged level of causation (Noble, 2017). Sequence randomness increases over time, consistent with the second law of thermodynamics. In the case of bacteria, the dynamics of randomness in molecular sequence evolution was investigated by examining randomness variation of coding sequences in *Escherichia coli*. It was found that core/essential genes are more ancient and random than specific/nonessential genes; moreover, an increase in sequence randomness led to an increased randomness of the GC nucleotides content and a longer sequence length (Wang et al., 2016). Chemical reactions comprise an inherent element of randomness, which appears as “noise” that interferes with cellular processes and communication (Stoeger et al., 2016). Spatial partitioning of molecular systems can remove noise while preserving regulated and

predictable differences between cells. Moreover, cellular compartmentalization can be effective without using a substantial amount of energy. Finally, passive noise filtering carried out by the eukaryotic cell nucleus was found to increase the predictability of transcriptional output (Stoeger et al., 2016).

5. APPLYING RANDOMNESS AND COMPLEXITY TO ORGAN FUNCTION

Complexity theory, chaos theory, and nonlinear mathematics are all used to describe continually changing biological systems. The classical concepts related to physiological control state that healthy systems are regulated to reduce variability and maintain steadiness. Contrary to the idea of homeostasis, the outputs of a wide variety of systems fluctuate even under resting conditions. This implies that nonlinear regulatory systems operate far from equilibrium conditions and that maintaining steadiness is not the goal of physiological control (Goldberger et al., 2002). Many healthy biological systems display randomness and fluctuations as a measure of their complexity and unpredictability. However, they are constrained by order-generating rules (Peng et al., 1994). Biological systems are dynamic networks of interactions with marked adaptive capabilities and are viewed as “complex adaptive organizations,” capable of adapting to environmental changes and coping with uncertainty. Health is perceived as a continuous adaptation, while chronic illnesses represent a rigid dysfunction (Martinez-Lavin et al., 2008).

Under basal resting conditions, most healthy physiological systems exhibit a highly irregular, complex dynamics that represents interacting regulatory processes operating over multiple timescales. The more complex the system, the higher its functionality (Lipsitz and Goldberger, 1992). These processes prime the organism for an adaptive response, preparing it to react to changes, physiological demands, and stress (Lipsitz, 2002). The notion of complexity can also be used to measure the output of physiological processes generating variable fluctuations that resemble chaos (Lipsitz and Goldberger, 1992).

Nonlinear dynamics suggests that the essence of disease is dysfunction and not necessarily structural damage. Loss of complexity leads to an impaired ability to adapt to physiological stress. Moreover, loss of complexity and inability to restore the original complex physiological status may underlie chronic diseases and aging (Kyriazis, 1991; Soloviev, 2001; Mitleton-Kelly, 2009). This interpretation views aging as a simplification of physiological dynamical complexity at the molecular, cellular, and whole-organism levels (Kyriazis, 2003). Aging is associated with a decline in the entropy of biological systems, reflecting the breakdown of regulatory systems and an impaired adaptation to external and internal changes (Lipsitz, 1995). Surviving species are those that use energy for their reproduction and for processes that increase the total dissipation of the system within a changing environment (Lipsitz and Goldberger, 1992; Toussaint and Schneider, 1998; Kyriazis, 2003). A weak system oscillates between a critical boundary and death (Bessell et al., 1991; Busciglio et al., 1998; Rubelj and Vondracek, 1999; Faure and Korn, 2001). Self-organizing, “leaky threshold” biological systems exhibit dynamic behaviors that are correlated in space and time, and display a variety of spatial and temporal scales (Rundle et al., 2002). A change in a system may be associated with improvement and normalization of its function (Belair et al., 1995; Mackey et al., 1987; Kyriazis, 2003).

Models of gene regulation show that these control systems may be chaotic. DNA and proteins can be labeled with a numerical value representing their fractal dimension, which can be calculated based on the molecular surface area and probe radius (Lewis and Rees, 1985). The fractal dimension of cells may be used to quantify both age- and pathology-related changes (Velanovich, 1996). Aging is associated with a loss of the organism’s ability to repair oxidative damage, which affects the fractal architecture of somatic DNA, whereas the fractal complexity and physiological functionality of germinal DNA remain unchanged. Age-dependent reduction of the somatic telomere length also occurs (Goyns, 2002). On aging, immune cells may be less capable of recognizing antigens due to a reduction in the complexity of their subcomponents, resulting in autoimmune diseases, chronic inflammation, cancer, and infections (Skinner et al., 1992).

Heart rate variability (HRV) is a measure of the beat-to-beat variation in heart rate and reflects the activity of the autonomic nervous system. Normal heartbeat intervals are characterized by fractional noise, and alterations in HRV can be used to predict sudden death, mortality in patients with myocardial infarction, heart failure, and for the prognostic assessment of elderly patients (Goldberger, 1996; Goldberger et al., 2002). Circulatory variations and changes in blood pressure are nonlinear and consist of nonrhythmic components (Wagner et al., 1998). Fractal organization has been observed in the physiological human

breathing cycle dynamics, along with a reduction in the complexity of respiration dynamics with aging (Peng et al., 2002). Blockage of a vascular branch re-establishes the complexity of vascularization around the affected area by generating shunts (Lipsitz, 1995). Reaction times in the brain are long and variable, as they result from a process that accumulates noisy signals over time, rising to a threshold (Genest et al., 2016). This variability persists despite the removal of all temporal noise from the stimulus, and thus arises from within the nervous system. Neurotransmitters exhibit chaotic patterns in the nervous system (Sarbadhikari and Chakrabarty, 2001).

The loss of neurons, dendrites, and some neurotransmitters is associated with loss of functional connections and compromised response capabilities (Schierwagen, 1990). With aging, the electrical activity in the brain becomes less complex (Kaplan et al., 1991; Molnar and Skinner, 1992; Skinner et al., 1992). A reduced complexity is associated with arthritis, stroke, Alzheimer's disease, and Parkinson's disease (Freeman and Tallarida, 1994; Min et al., 1998; Edwards et al., 1999). Furthermore, the secretion of many hormones oscillates in a fractal-like, power-law manner and follows the rules of chaos theory (Lipsitz, 2002); the frequency and amplitude of these oscillations are reduced with age (Topp et al., 2000; Goldberger, 2001). Fractal dynamics is also detected in the "noisy" variations observed in the stride interval of human walking. Analysis of step-to-step fluctuations revealed a self-similar pattern. These stride interval fluctuations exhibited long-range correlations with power-law decay, which disappeared during metronomically paced walking (Hausdorff et al., 1996). Moreover, the steady-state behavior of the open-loop postural control system becomes positively correlated and unstable with age, denoting a tendency to drift away from an equilibrium point over the short term (Collins et al., 1995). In contrast, the steady-state behavior of the closed-loop postural control mechanisms is negatively correlated, and is more stable in the long term (Collins et al., 1995).

Loss of stimulation reduces the complexity of the corresponding response and compromises health (Goldberger et al., 2002; Lipsitz, 2002). Multiple external stimuli increase complexity and assist in maintaining the integrity of nerve cell circuits and increasing brain complexity (Gonzalez-Lima et al., 1994; Kyriazis, 2003). This effect is associated with a higher production of neurotrophic factors and cytokines, expression of various cell survival-promoting proteins, preservation of genomic integrity by telomerase and DNA repair proteins, and the mobilization of neural stem cells necessary to replace damaged neurons and glia (Alves da Costa et al., 2002; Valero et al., 2011).

Chaos theory may be used to challenge the traditional pharmacological practice of prescribing medications based on a regular regimen. In particular, it implies that for maximum benefit, medications should be given at irregular, pulsed, or multiple intervals, and at continually changing dosage strengths (Kyriazis, 2003). Drugs based on pluripotent molecules target several mechanisms simultaneously, forcing the system to operate in a complex state by introducing multiple interacting stimuli (Zhang and Herman, 2002a, 2002b). Similarly, humans are not designed to consume all their dietary supply at regular and fixed intervals: the intake should be nonlinear and follow the rules of chaos theory (Kyriazis, 2003).

On the contrary, it has been suggested that both increase and decrease in the complexity of a physiological system output might occur with aging. The direction of change depends on the nature of the constraints that control the system dynamics (Kirkwood, 2002). Thus, a system may be malfunctioning if it is too simple or too complex (Thaler, 2002).

6. OVERCOMING FUNCTIONAL PLATEAUS IN BIOLOGY

The theories used in biology must resemble those of physics, in that order is generated from disorder. This contrasts with Schrodinger's idea of biological processes generating order from a molecular-level order, which has inspired molecular biology. Stochasticity is connected to functionality; randomness does not necessarily imply lack of function or blind chance. The order described here originates at the higher levels, constraining the components at lower levels, the macroscale influencing the microscale. This includes the genome, which is controlled by patterns of transcription factors and various epigenetic and reorganization mechanisms. These processes occur in response to environmental stress, so that the genome becomes a sensitive organ of the cell (Noble, 2017). Increasing organization, while increasing "order," also induces growing disorder as a result of energy dispersal effects as well as by increasing variability and differentiation. The cooperation between diverse components in biological networks involves certain constraints due to the particular nature of bio-entanglement and bio-resonance (Buiatti and Longo, 2013).

Randomness can increase the efficacy of biological systems (Ilan, 2019b, 2019c). However, biological systems are multifactorial and therefore different to other systems that may be described by physics, which contain parameters that are easier to control. In medicine, variations in genotypic and phenotypic parameters necessitate the use of patient-tailored processes. Utilizing randomness in the treatment of every patient cannot be expected to produce the same effect in each case. To utilize randomness to the maximum effect, this must be tailored to the specific patient and disease. Genuine personalized randomness treatments may be designed by selecting one or more parameters in a custom-made, random-dependent manner (Ilan, 2019a, 2019b, 2019c, 2019d). In the case of each selected parameter, a randomness algorithm is applied within a predetermined personalized scale. Although apparently at odds with the concept of randomness, this approach may be viewed as an advanced level of randomness, designed for improving the efficacy of biological systems in a personalized manner.

Enhancing the effectiveness of a system by patient-tailored randomness requires increasing its complexity and carrying beneficial information that can overcome a plateau or deterioration in function. The complex and irregular dynamics of physiological systems improves individual adaptation to stress and challenges. The use of patient-tailored randomness prevents reaching a new plateau state, which would entail a new low level of functionality. Personalized randomness involves moving the system out of its “comfort zone” into the “edge of chaos,” by generating a healthier path of constant innovation and change, along with an amount of chaos (Burnes, 2004; Lewin et al., 1998). It is necessary to maintain a balance between flexibility and stability to avoid “falling off the cliff.” While this balancing point may be hard to achieve and implies some degree of instability, this path upgrades the functionality of a biological system. Systems that operate within the “edge of chaos” zone perform better than plateaued systems (Gilra and Gerstner, 2017).

7. SUMMARY

The role of randomness and complexity in several types of system, from physical to societal, is discussed here, together with a description of chaos and complexity at various length scales. Biological system complexity is reduced in the cases of disease and old age, when compared with healthy systems. It may therefore be possible to increase the efficacy of biological systems using randomness, although the effect of randomness on patient care will depend on several patient-based factors. Applying the laws of nonlinear physics and QM may enable the design of tailored randomness algorithms based on efficacy endpoints for use in patient care. These algorithms can initially be based on using true-randomness generators, to be later replaced in due course by patient-tailored QM-based random generators (Zhou et al., 2017).

AUTHOR DISCLOSURE STATEMENT

Y.I. is the founder of Oberon Sciences.

REFERENCES

- Acin, A., Massar, S., and Pironio, S. 2012. Randomness versus nonlocality and entanglement. *Phys. Rev. Lett.* 108, 100402.
- Alves da Costa, C., Paitel, E., Mattson, M.P., et al. 2002. Wild-type and mutated presenilins 2 trigger p53-dependent apoptosis and down-regulate presenilin 1 expression in HEK293 human cells and in murine neurons. *Proc. Natl. Acad. Sci. U. S. A.* 99, 4043–4048.
- Belair, J., Glass, L., An Der Heiden, U., et al. 1995. Dynamical disease: Identification, temporal aspects and treatment strategies of human illness. *Chaos* 5, 1–7.
- Bell, J.S. 1964. On the Einstein-Podolsky-Rosen paradox. *Physics* 1, 195.
- Bell, J.S. 1966. On the problem of hidden variables in quantum mechanics. *Rev. Mod. Phys.* 38, 447–452.
- Bera, M.N., Acin, A., Kus, M., et al. 2017. Randomness in quantum mechanics: Philosophy, physics and technology. *Rep. Prog. Phys.* 80, 124001.
- Berta, M., Christandl, M., Colbeck, R., et al. 2010. The uncertainty principle in the presence of quantum memory. *Nat. Phys.* 6, 659–662.

- Bessell, E.M., Punt, J., Firth, J., et al. 1991. Primary non-Hodgkin's lymphoma of the central nervous system: Phase II study of chemotherapy (BVAM) prior to radiotherapy. *Clin. Oncol. (R. Coll. Radiol.)* 3, 193–198.
- Bohm, D. 1952. A suggested interpretation of the quantum theory in terms of “hidden” variables. *Phys. Rev.* 85, 166–179.
- Bricmont, J. 1995. Science of chaos or chaos in science. *Ann. N. Y. Acad. Sci.* 775, 131–175.
- Brunner, N., Cavalcanti, D., Pironio, S., et al. 2014. Bell nonlocality. *Rev. Mod. Phys.* 86, 419–478.
- Buiatti, M., and Longo, G. 2013. Randomness and multilevel interactions in biology. *Theory Biosci.* 132, 139–158.
- Burnes, B. 2004. Kurt Lewin and complexity theories: Back to the future. *J. of Change Management.* 4, 309–325.
- Busciglio, J., Andersen, J.K., Schipper, H.M., et al. 1998. Stress, aging, and neurodegenerative disorders. Molecular mechanisms. *Ann. N. Y. Acad. Sci.* 851, 429–443.
- Carlson, J.M., and Doyle, J. 2002. Complexity and robustness. *Proc. Natl. Acad. Sci. U. S. A.* 99 Suppl 1, 2538–2545.
- Colbeck, R., and Renner, R. 2008. Hidden variable models for quantum theory cannot have any local part. *Phys. Rev. Lett.* 101, 050403.
- Colbeck, R., and Renner, R. 2011. No extension of quantum theory can have improved predictive power. *Nat. Commun.* 2, 411.
- Collins, J.J., De Luca, C.J., Burrows, A., et al. 1995. Age-related changes in open-loop and closed-loop postural control mechanisms. *Exp. Brain Res.* 104, 480–492.
- Edwards, R., Beuter, A., and Glass, L. 1999. Parkinsonian tremor and simplification in network dynamics. *Bull. Math. Biol.* 61, 157–177.
- Einstein, A., Podolsky, B., and Rosen, N. 1935. Can quantummechanical description of physical reality be considered complete? *Phys. Rev.* 47, 777–780.
- Faure, P., and Korn, H. 2001. Is there chaos in the brain? I. Concepts of nonlinear dynamics and methods of investigation. *C. R. Acad. Sci. III* 324, 773–793.
- Freedman, S.J., and Clauser, J.F. 1972. Experimental test of local hidden-variable theories. *Phys. Rev. Lett.* 28, 938–941.
- Freeman, K.A., and Tallarida, R.J. 1994. A quantitative study of dopamine control in the rat striatum. *J. Pharmacol. Exp. Ther.* 268, 629–638.
- Genest, W., Hammond, R., and Carpenter, R.H. 2016. The random dot tachistogram: A novel task that elucidates the functional architecture of decision. *Sci. Rep.* 6, 30787.
- Gilra, A., and Gerstner, W. 2017. Predicting non-linear dynamics by stable local learning in a recurrent spiking neural network. *eLife* 6, e28295.
- Gisin, N. 2013. Are There quantum effects coming from outside space–time? Nonlocality, free will and “no many worlds”, Chapter 3, 23–40. In *Is Science Compatible with Free Will? Exploring Free Will and Consciousness in the Light of Quantum Physics and Neuroscience*. Ed: L. Vaidman. Springer, New York.
- Goldberger, A.L. 1996. Non-linear dynamics for clinicians: Chaos theory, fractals, and complexity at the bedside. *Lancet* 347, 1312–1314.
- Goldberger, A.L. 2001. Heartbeats, hormones, and health: Is variability the spice of life? *Am. J. Respir. Crit. Care Med.* 163, 1289–1290.
- Goldberger, A.L., Amaral, L.A., Hausdorff, J.M., et al. 2002. Fractal dynamics in physiology: Alterations with disease and aging. *Proc. Natl. Acad. Sci. U. S. A.* 99 Suppl 1, 2466–2472.
- Gonzalez-Lima, F., Ferchmin, P.A., Eterovic, V.A., et al. 1994. Metabolic activation of the brain of young rats after exposure to environmental complexity. *Dev. Psychobiol.* 27, 343–351.
- Goyens, M.H. 2002. Genes, telomeres and mammalian ageing. *Mech. Ageing Dev.* 123, 791–799.
- Grobman, G. 2005. Complexity theory: A new way to look at organizational change. *Public Administration Quarterly*.
- Gupta, A. 2012. Insights from complexity theory: Understanding organisations better. IIM Bangalore. Retrieved June 1, 2012.
- Hausdorff, J.M., Purdon, P.L., Peng, C.K., et al. 1996. Fractal dynamics of human gait: Stability of long-range correlations in stride interval fluctuations. *J. Appl. Physiol.* (1985) 80, 1448–1457.
- Hensen, B., Bernien, H., Dreau, A.E., et al. 2015. Loophole-free Bell inequality violation using electron spins separated by 1.3 kilometres. *Nature* 526, 682–686.
- Hoffmann, P.M. 2016. How molecular motors extract order from chaos (a key issues review). *Rep. Prog. Phys.* 79, 032601.
- Ilan, Y. 2019a. Beta-glycosphingolipids as mediators of both inflammation and immune tolerance: A manifestation of randomness in biological systems. *Front. Immunol.* 10, 1143.
- Ilan, Y. 2019b. Generating randomness: Making the most out of disordering a false order into a real one. *J. Transl. Med.* 17, 49.
- Ilan, Y. 2019c. Randomness in microtubule dynamics: An error that requires correction or an inherent plasticity required for normal cellular function? *Cell Biol. Int.* 43, 739–748.
- Ilan, Y. 2019d. Why targeting the microbiome is not so successful: Can randomness overcome the adaptation that occurs following gut manipulation? *Clin. Exp. Gastroenterol.* 12, 209–217.
- Kaplan, D.T., Furman, M.I., Pincus, S.M., et al. 1991. Aging and the complexity of cardiovascular dynamics. *Biophys. J.* 59, 945–949.

- Kirkwood, T.B. 2002. Changing complexity in aging: A metric not an hypothesis. *Neurobiol. Aging* 23, 21–22.
- Kyriazis, M. 1991. Applications of chaos theory to the molecular biology of aging. *Exp. Gerontol.* 26, 569–572.
- Kyriazis, M. 2003. Practical applications of chaos theory to the modulation of human ageing: Nature prefers chaos to regularity. *Biogerontology* 4, 75–90.
- Lewin, R., Parker, T., and Regine, B. 1998. Complexity theory and the organization: Beyond the metaphor. *Complexity* 3, 36–40.
- Lewis, M., and Rees, D.C. 1985. Fractal surfaces of proteins. *Science* 230, 1163–1165.
- Lieb, E.H., and Yngvason, J. 2013. The entropy concept for non-equilibrium states. *Proc. Math. Phys. Eng. Sci.* 469, 20130408.
- Lipsitz, L.A. 1995. Age-related changes in the “complexity” of cardiovascular dynamics: A potential marker of vulnerability to disease. *Chaos* 5, 102–109.
- Lipsitz, L.A. 2002. Dynamics of stability: The physiologic basis of functional health and frailty. *J. Gerontol. A Biol. Sci. Med. Sci.* 57, B115–B125.
- Lipsitz, L.A., and Goldberger, A.L. 1992. Loss of ‘complexity’ and aging. Potential applications of fractals and chaos theory to senescence. *JAMA* 267, 1806–1809.
- Mackey, J.K., Alexieva-Jackson, B., Fellers, D.V., et al. 1987. Bone and gallium scan findings in malignant fibrous histiocytoma. Case report with radiographic and pathologic correlation. *Clin. Nucl. Med.* 12, 17–21.
- Martinez-Lavin, M., Infante, O., and Lerma, C. 2008. Hypothesis: The chaos and complexity theory may help our understanding of fibromyalgia and similar maladies. *Semin. Arthritis Rheum.* 37, 260–264.
- Messiah, A. 2014. *Quantum Mechanics*. Dover Publications, Mineola, New York.
- Min, B.H., Jeong, S.Y., Kang, S.W., et al. 1998. Transient expression of clusterin (sulfated glycoprotein-2) during development of rat pancreas. *J. Endocrinol.* 158, 43–52.
- Mitleton-Kelly, E. 2009. Ten principles of complexity & enabling infrastructures. London school of economics. Archived from the original (PDF) on December 29, 2009.
- Molnar, M., and Skinner, J.E. 1992. Low-dimensional chaos in event-related brain potentials. *Int. J. Neurosci.* 66, 263–276.
- Newman, M.E., Watts, D.J., and Strogatz, S.H. 2002. Random graph models of social networks. *Proc. Natl. Acad. Sci. U. S. A.* 99 Suppl 1, 2566–2572.
- Noble, D. 2017. Evolution viewed from physics, physiology and medicine. *Interface Focus* 7, 20160159.
- Peng, C., Hausdorff, S.V., Havlin, J.M., et al. 1994. Non-equilibrium dynamics as an indispensable characteristic of a healthy biological system. *Integr. Physiol. Behav. Sci.* 29, 283–293.
- Peng, C.K., Mietus, J.E., Liu, Y., et al. 2002. Quantifying fractal dynamics of human respiration: Age and gender effects. *Ann. Biomed. Eng.* 30, 683–692.
- Penrose, O. 1979. Foundations of statistical mechanics. *Rep. Prog. Phys.* 42, 1937.
- Qian, H., Kjelstrup, S., Kolomeisky, A.B., et al. 2016. Entropy production in mesoscopic stochastic thermodynamics: Nonequilibrium kinetic cycles driven by chemical potentials, temperatures, and mechanical forces. *J. Phys. Condens. Matter* 28, 153004.
- Rego-Costa, A., Debarre, F., and Chevin, L.M. 2018. Chaos and the (un)predictability of evolution in a changing environment. *Evolution* 72, 375–385.
- Rubelj, I., and Vondracek, Z. 1999. Stochastic mechanism of cellular aging—Abrupt telomere shortening as a model for stochastic nature of cellular aging. *J. Theor. Biol.* 197, 425–438.
- Rundle, J.B., Tiampo, K.F., Klein, W., et al. 2002. Self-organization in leaky threshold systems: The influence of near-mean field dynamics and its implications for earthquakes, neurobiology, and forecasting. *Proc. Natl. Acad. Sci. U. S. A.* 99 Suppl 1, 2514–2521.
- Sammis, C.G., and Sornette, D. 2002. Positive feedback, memory, and the predictability of earthquakes. *Proc. Natl. Acad. Sci. U. S. A.* 99 Suppl 1, 2501–2508.
- Sarbadhikari, S.N., and Chakrabarty, K. 2001. Chaos in the brain: A short review alluding to epilepsy, depression, exercise and lateralization. *Med. Eng. Phys.* 23, 445–455.
- Schierwagen, A.K. 1990. Growth, structure and dynamics of real neurons: Model studies and experimental results. *Biomed. Biochim. Acta* 49, 709–722.
- Shalm, L.K., Meyer-Scott, E., Christensen, B.G., et al. 2015. Strong loophole-free test of local realism. *Phys. Rev. Lett.* 115, 250402.
- Skinner, J.E., Molnar, M., Vybiral, T., et al. 1992. Application of chaos theory to biology and medicine. *Integr. Physiol. Behav. Sci.* 27, 39–53.
- Smith, L.A. 2002. What might we learn from climate forecasts? *Proc. Natl. Acad. Sci. U. S. A.* 99 Suppl 1, 2487–2492.
- Soloviev, M.V. 2001. [On possible role of chaotic behavior of the gene regulation system in aging]. *Adv. Gerontol.* 8, 27–33.
- Sornette, D. 2002. Predictability of catastrophic events: Material rupture, earthquakes, turbulence, financial crashes, and human birth. *Proc. Natl. Acad. Sci. U. S. A.* 99 Suppl 1, 2522–2529.

- Stoeger, T., Battich, N., and Pelkmans, L. 2016. Passive noise filtering by cellular compartmentalization. *Cell* 164, 1151–1161.
- Stollmeier, F., and Nagler, J. 2018. Unfair and anomalous evolutionary dynamics from fluctuating payoffs. *Phys. Rev. Lett.* 120, 058101.
- Thaler, D.S. 2002. Design for an aging brain. *Neurobiol. Aging* 23, 13–15.
- Topp, B., Promislow, K., deVries, G., et al. 2000. A model of beta-cell mass, insulin, and glucose kinetics: Pathways to diabetes. *J. Theor. Biol.* 206, 605–619.
- Toussaint, O., and Schneider, E.D. 1998. The thermodynamics and evolution of complexity in biological systems. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* 120, 3–9.
- Turcotte, D.L., and Rundle, J.B. 2002. Self-organized complexity in the physical, biological, and social sciences. *Proc. Natl. Acad. Sci. U. S. A.* 99 Suppl 1, 2463–2465.
- Tversky, A., and Kahneman, D. 1974. Judgment under Uncertainty: Heuristics and Biases. *Science* 185, 1124–1131.
- Tversky, A., and Kahneman, D. 1981. The framing of decisions and the psychology of choice. *Science* 211, 453–458.
- Valero, J., Espana, J., Parra-Damas, A., et al. 2011. Short-term environmental enrichment rescues adult neurogenesis and memory deficits in APP(Sw,Ind) transgenic mice. *PLoS One* 6, e16832.
- Velanovich, V. 1996. The spectrum of *Helicobacter pylori* in upper gastrointestinal disease. *Am. Surg.* 62, 60–63.
- Wagner, C.D., Stauss, H.M., Persson, P.B., et al. 1998. Correlation integral of blood pressure as a marker for exercise intensities. *Am. J. Physiol.* 275, R1661–R1666.
- Wang, G., Sun, S., and Zhang, Z. 2016. Randomness in Sequence Evolution Increases over Time. *PLoS One* 11, e0155935.
- Yamato, I., Murata, T., and Khrennikov, A. 2017. Energy and information flows in biological systems: Bioenergy transduction of V1-ATPase rotary motor and dynamics of thermodynamic entropy in information flows. *Prog. Biophys. Mol. Biol.* 130, 33–38.
- You, T., Kwon, M., Jo, H.H., et al. 2017. Chaos and unpredictability in evolution of cooperation in continuous time. *Phys. Rev. E* 96, 062310.
- Zhang, J., Zhang, Y., and Yu, C.S. 2015. Entropic Uncertainty Relation and Information Exclusion Relation for multiple measurements in the presence of quantum memory. *Sci. Rep.* 5, 11701.
- Zhang, Y., and Herman, B. 2002a. Ageing and apoptosis. *Mech. Ageing Dev.* 123, 245–260.
- Zhang, Y., and Herman, B. 2002b. Apoptosis and successful aging. *Mech. Ageing Dev.* 123, 563–565.
- Zhou, H., Li, J., Pan, D., et al. 2017. Quantum random number generator based on quantum tunneling effect. Available at: <https://arxiv.org/pdf/1711.01752.pdf> Last viewed November, 2018.

Address correspondence to:

Dr. Yaron Ilan

Department of Medicine

Hebrew University-Hadassah Medical Center

P.O.B 12000

Jerusalem IL-91120

Israel

E-mail: ilan@hadassah.org.il