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Constrained disorder principle-based variability is fundamental for biological processes: Beyond biological relativity and physiological regulatory networks

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ABSTRACT

The constrained disorder principle (CDP) defines systems based on their degree of disorder bounded by dynamic boundaries. The principle explains stochasticity in living and non-living systems. Denis Noble described the importance of stochasticity in biology, emphasizing stochastic processes at molecular, cellular, and higher levels in organisms as having a role beyond simple noise. The CDP and Noble's theories (NT) claim that biological systems use stochasticity. This paper presents the CDP and NT, discussing common notions and differences between the two theories. The paper presents the CDP-based concept of taking the disorder beyond its role in nature to correct malfunctions of systems and improve the efficiency of biological systems. The use of CDP-based algorithms embedded in second-generation artificial intelligence platforms is described. In summary, noise is inherent to complex systems and has a functional role. The CDP provides the option of using noise to improve functionality.

1. Introduction

In 1952 Alan Turing published a paper, "The chemical basis of morphogenesis" describing the spontaneous formation of patterns in systems undergoing reaction and diffusion of their ingredients (AM TURING, 1952). He developed a model to explain how random fluctuations drive the emergence of patterns and structures from initial uniformity impacting biology and other fields (Ball, 2015). The appearance of a form in a system functioning far from equilibrium evolves by mechanisms described by Turing's model and occurs in numerous natural processes. Multiple examples of 'Turing patterns' in biology are still being discovered (Ball, 2015). Turin recognized that the instability of a homogenous system might develop into a more complex pattern (AM TURING, 1952). Forming stable structures by competition between activating and inhibiting processes is a general mechanism for generating order from macroscopic uniformity and microscopic disorder (Ball, 2015). Pioneering work by Kupiec, followed by others, demonstrated a role for randomness in biological systems (Paldi, 2020; Kupiec, 1983; Elowitz et al., 2002). However, molecular randomness remains in doubt.

The constrained disorder principle (CDP) defines systems based on their degree of disorder bounded by dynamic boundaries (Ilan, 2022a). The principle highlights the concept of stochasticity in biological processes, also described by Denis Noble. Noble theories (NT) focused on the stochastic processes at molecular, cellular, and higher levels in organisms as having a role beyond simple noise (Noble, 2021a). This paper presents the CDP and the NT, discussing common notions and differences between the theories. It describes variability in biological systems and CDP-based algorithms for overcoming system malfunction.

1.1. The constrained disorder principle defines biological systems and differentiates them from non-living systems

The CDP implies that variability is inherent to all systems in nature at all levels (Ilan, 2022a). Per this principle, variability is mandatory for the proper function of complex systems and must be constrained within dynamic borders. Loss of variability or an increase in degree is associated with systems' malfunctions. Per the CDP, living organisms are characterized by a relatively high degree of variability constrained by dynamic borders, while non-living systems manifest a low degree of variability bounded by narrow borders (Ilan, 2022b). While the mathematical formulation of biological randomness cannot be done, the CDP is conceptually formulated using the F=B formula, where F stands for

Abbreviations: CDP, constrained disorder principle; NT, Noble's theory; AI, artificial intelligence; HRV, heart rate variability; MS, Modern Synthesis; EVs, extracellular vesicles; PRN, physiological regulatory networks; GRN, Gene Regulatory Networks.

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function and B for the dynamic borders, implying that the dynamic borders define systems' existence, function, and efficiency. The wider the borders are, the higher the degree of disorder within a system, which implies improved function. However, the borders provide a limit beyond which the system cannot further improve.

The CDP provides a platform for developing second-generation artificial intelligence systems (AI), which are based on regulating the degree of variability to improve the efficiency of systems (Ilan, 2020a, 2020b, 2021a, 2022c).

1.2. Stochasticity and chaos in biological systems

Stochasticity is an inability to predict and is inherent to biological systems. The CDP characterizes all levels of complex biological systems, from the genome to the whole organs (Ilan, 2019a, 2019b, 2019c, 2019d, 2019e, 2020c, 2020d; El-Haj et al., 2019; Ilan-Ber and Ilan, 2019; Forkosh et al., 2020; Finn and Misteli, 2019; Chiera et al., 2020; Forte et al., 2019; Mitchison and Kirschner, 1984; Kirschner and Mitchison, 1986). The CDP implies a need for a degree of stochasticity at all levels simultaneously. The stochasticity is constrained at all levels by dynamic borders that respond to internal and environmental pertubations (Ilan, 2022a).

According to NT, stochasticity is a level-dependent property, which means molecular-level stochasticity can be correlated to higher-level predictability (Noble, 2021b, 2022a, 2022b; Noble et al., 2019). At higher levels, such as thermodynamics, molecular stochasticity cancels itself out and is also used for goal-directed feedback control. (Noble and Noble, 2018). As a result, underlying stochasticity impacts a system's overall behavior depending on its ability to respond to the higher level (Noble and Noble, 2018). Per the NT, an "attractor" constrains chaotic variations. An organism's control networks cannot constrain a chaotic sequence if the "attractor" controlling it is outside their control networks (Noble and Noble, 2018).

1.3. Constrained disorder or making order from disorder

A disorder characterized by stochasticity is described as Brownian motion and was explained by Einstein as a result of the thermal jiggling of water and other molecules and particles dissolved or suspended within it (Noble, 2021c). Order characterizes the physiological control systems, and the disorder is viewed as disturbing by most biologists (Vodovotz et al., 2013; Raser and O'Shea, 2005; Schmutzer and Wagner, 2020). Schrödinger argued in his book What is Life? that living organisms derive "order from molecular level order," in contrast to physics which, through thermodynamics, is the study of "order from disorder" (Noble, 2021c). Schrödinger concluded that physics and biology differ in how the micro and macro scales relate (Ramstead et al., 2018; Khrennikov and Watanabe, 2021). Gas laws do not depend on the stochastic behavior of individual molecules (Ilan, 2020d; Ellis and Kopel, 2018; Balanovski and Beaconsfield, 1985; Chollat-Namy and Longo, 2022). Biological organizations "use" disorder under and by constraints. The random variations cancel each other out when the number of components is large (Noble, 2021a). Fine particles suspended in water show stochastic movement and are produced by random bombardment by individual water molecules (Bian et al., 2016). Like all molecules, water is also subject to quantum mechanical randomness (Ilan, 2019b; Brini et al., 2017). All objects may be subject to such randomness in quantum mechanics, although it becomes negligible at a large enough scale (Noble et al., 2019).

The CDP and NT view biological systems as living on the boundary between order and disorder. For the CDP, the disorder must occur at all levels (Ilan, 2022a); for NT, the disorder is constrained by higher levels (Noble, 2021d).

Biological constraints refer to the temporally bounded production of constraints to processes by the processes themselves, often by mediating the several levels of the interplay between the processes and the constraints (Montévil and Mossio, 2015a).

There is no precise cut-off point at which molecular stochasticity ceases to exist, according to the NT. According to the Central Dogma of molecular biology, molecular information determines what happens in biology at the macro-level from the micro-level (Noble, 2021a). According to NT, biology must also create order from disorder since this dogma is wrong (Noble, 2021c). According to this hypothesis, life, rather than Schrödinger's view that organisms create order from the disorder at the molecular level, is analogous to physics, especially thermodynamics, in the sense of generating order from chaos (Nicolis, 2003). As levels below them constrain each other, systems are ordered (Noble, 2021c). GWAS (gene-phenotype association studies) reveal low association scores, suggesting organisms are insensitive to molecular details (Visscher et al., 2012). Even when genes are knocked out, or inhibitory drugs are used, biological networks function well (McCloskey et al., 2018; Deutscher et al., 2008). Despite removing critical components, cardiac pacemakers continue to function (Noble, 1960; Noble et al., 1992). Under standard growth conditions, 80% of knockouts can be functionally silent (Hillenmeyer et al., 2008). Knocking out an essential gene does not affect the circadian rhythm (Debruyne et al., 2006). When a particular DNA sequence is missing, functional networks above the genome replace it with an alternative pathway. It implies that biology is similar to physics in generating macro-level order from micro-level disorder (Noble, 2021a).

Physics is based on conservation principles of symmetries. Biology follows Darwin's first principle of reproduction with a variation. It is a principle of "non-conservation" of phenotypes due also to the role of randomness, starting with the molecular level (and the interactions of all levels of an organization, "bio-resonance" (Longo and Longo, 2021; Longo, 2023).

Several theories suggest that biology is similar to physics in generating macro-level order from micro-level disorder only in a cell or an organism, a historical construction. Based on these notions, it does not happen "spontaneously" like in physics. It views physics is a particular case of biology (Longo, 2020).

Per the CDP, there is no hierarchy of the disorder. A constrained disorder is always apparent. The "creation of order" means narrowing the borders—the borders of the disorder at each level impact other levels. The CDP implies that physics, chemistry, and biology work according to the same formula, and only the disorder boundaries differentiate between them (Ilan, 2022a). Per the CDP, a constrained disorder occurs at all levels; subcellular, cellular, tissues, organs, and whole-body systems are organized where a disorder is constrained. Therefore, while they are disordered, they seem ordered (Ilan, 2022b). Multiple examples from every organ show variability as part of the normal function. A disorder characterized by dynamic instability of microtubules (MT) and heart rate variability (HRV), breathing and blood pressure variability, gate variability, and brain function variability (Ilan, 2022a; Ilan, 2022b; Chiera et al., 2020; Forte et al., 2019; Mitchison and Kirschner, 1984; Kirschner and Mitchison, 1986; van den Bosch et al., 2021; Ilan, 2023a).

1.4. Systems that are far from equilibrium: constraints of disorder or boundaries between levels

The CDP and NT define organisms as open systems operating far from equilibrium. The edges and boundaries are where non-equilibrium processes take place.

Per the CDP, internal and external boundaries are part of the areas where perturbations and triggers occur. It is vital to differentiate these boundaries from the dynamic borders of the disorder, which define the CDP (Ilan, 2022a). The CDP defines the non-equilibrium state or edge not as a physical boundary but as a measure of the degree of functionality. The boundaries per the CDP are the constraints of the disorder, which are dynamic and continuously adapt in response to external and internal perturbations, regulating the degree of the disorder in complex systems. Physical boundaries, including the skin and membranes, like all

other organs, manifest a disorder in structure and function, which is dynamic within the constraints (Ilan, 2022a). Per the CDP, the constrained disorder is a method for regulating energy (Ilan, 2022d, 2022e). Organisms' function depends on a degree of disorder at all levels.

NT and biological relativity described by Noble imply that organisms develop numerous boundaries between levels, which are not present at the single-cell level (Noble et al., 2019; Noble, 2012). A boundary like the intestine, respiratory tract, or skin depends on exchanging matter and energy through cellular membranes (Noble, 2021a). A boundary is dynamic, interactive, not passive, and cannot always be defined anatomically (Noble et al., 2019). Electrical gradients and ion concentration gradients are actively generated across cell membranes (Noble, 2021a). Phylogenetic reductionists neglect membranes' role in integrating organisms' responses to environmental challenges, assuming causation comes from the genome. Their interactions across boundaries determine an organism's function, not just their parts of composition or genome (Noble et al., 2019).

1.5. Causation: alteration of the disorder borders or boundaries between organisms' levels

The CDP and NT look into multi-directional effects. Per the CDP, continuous interactions between all levels of the organisms and between the internal and external milieus determine the disorder's borders. The dynamicity of the borders of the disorder in each system at all levels is a continuous process where all levels constantly affect all other levels in multi directions (Ilan, 2022a). There are no upward or downward forms of causation. It is different from the terminology used in physics for describing constraints (Montévil and Mossio, 2015b).

A model for a distinction between two causal regimes in biological systems: processes, which refer to the whole set of changes occurring in non-equilibrium open thermodynamic conditions, and constraints, which act upon the processes, was described. It suggested that in biological systems, constraints realize closure or mutual dependence on each other. The closure can provide an operational tool for marking the boundaries between interacting biological systems (Montévil and Mossio, 2015b).

The environment and organism function are bidirectionally causally interconnected, according to NT. Unlike molecular biology's Central Dogma, there are multiple pathways from DNA to proteins, supporting natural genetic engineering theories (Noble, 2021a; Shapiro, 2016). The NT distinguishes upward and downward causation (Noble, 2021a). In a system, upward causation is the interaction between lower and higher levels that change the system's behavior (Noble et al., 2019). Changing concentrations of ions, metabolites, and proteins trigger changes at higher levels. Heart and muscle problems can be caused by increased intracellular free calcium (Noble, 2022a; Noble et al., 2019; Noble and Noble, 2018). There is a higher level of causation when properties at the highest levels of the organism control the genome and regulate which cells from the same genome become bones or heart cells (Noble et al., 2019). A seemingly disorganized set of initial and boundary conditions represents the constraints of higher-level organizations; however, only at the higher levels is the function of genome changes apparent (Noble et al., 2019). Organizational levels provide boundaries and initial conditions for the levels below them (Noble et al., 2019). From top levels of social interactions to molecular changes, including changes in RNAs controlling gene expressions in athletic and non-athletic identical twins, downward causality exists. It supports the relevance of non-gene-dependent mechanisms on pheynotypes (Noble, 2021a). The downward forms of causation are determined by organisms' choices and their environment (Noble et al., 2019).

According to the NT, both forms of causation are simultaneous and do not follow a circular pattern. High-level "attractors" are not linear feedback loops that can be described as linear causation sequences (Noble et al., 2019; Noble, 2021d). Genetic and environmental factors are integrated to develop phenotypes in biological networks (Noble et al., 2019; Noble, 2021d). According to the NT principle of biological relativity, causation occurs when higher levels constrain lower levels' initial and boundary conditions (Noble et al., 2019). Most DNA changes are buffered by high-level "attractors," implying circular causality between levels of an organization. Before performing the relevant experiments, causality is not privileged (Noble, 2012). Historical and environmental factors are represented by the initial and boundary conditions. Evolutionarily conditioned for stability and robustness, the phenotype is represented by high-dimensional "attractors." In organisms, regulatory systems are more than thermostats since they vary depending on the organisms' needs (Baverstock and Rönkkö, 2014; Buiatti and Longo, 2013).

Both NT and CDP support the concept that perturbations of all components produce a change in overall behavior. For CDP, it is via an effect on borders of the disorder; for NT, it is via an effect on the boundaries between levels.

1.6. Regulating the DNA and mandatory genome variability

The CDP and NT imply that all molecules, including DNA, are subject to random variations caused by natural stochasticity in particles, atoms, and molecules, some of which may be random quantum mechanical variation, thermal noise, or a result of natural radiation (Ilan, 2022a, 2022b; Noble, 2021a).

Variability characterizes multiple processes of the genome (Finn and Misteli, 2019). When DNA is copied, random variations appear. There is a high error rate in DNA copying, around one error in every 10,000 base pairs, but accurate error-correction proteins ensure that daughter cells receive an almost error-free copy of the DNA (Noble, 2021a; Niccum et al., 2018). The mutation rate is random but varies between regions. There can be a 1000-fold difference in gene expression between cells (Noble, 2021d). Despite clonal cell populations, protein expression exhibited extensive stochasticity (Pisco et al., 2013). A population's overall distribution is determined by the landscape of its probabilities, which shifts among various stable positions (Aditya et al., 2022). In epigenetics, randomness is harnessed and canalized toward population attraction [32, 4435]. Epigenetic regulation occurs at the boundary between DNA and epigenetic control to transmit the adaptive properties of networks on which most gene knockouts have minimal impact. Due to the DNA thread-like character, it is loosened enough to be read from the condensed attachment to the histones. The sequence is not locked up in the rigid 3-dimensional structure (Mariño-Ramírez et al., 2005). The self-templating method of determinate crystals cannot be used for replication (Noble, 2021d). As a template for RNAs and proteins, DNA wraps around the chromatin proteins like a thread. According to molecular biology, DNA sequences are used to make proteins, but protein sequences are not used to make DNA (Noble, 2021d).

The CDP views this variability as mandatory for proper function under continuously changing perturbations. Per the CDP, the mutation rate is part of biological variability, and the constraints are the mechanisms that regulate it.

Per the NT, organisms can control mutation rates by harnessing mutation rates (Noble, 2021a). In changing DNA, the organism does not use template information. The organism uses natural genetic engineering when it senses stress in its environment and when it needs to use higher-level functional networks (Noble, 2021c; Shapiro, 2017). Depending on the genetic and phenotypic background, a gene deletion can have different effects (Noble et al., 2019; Zaghi et al., 2021). There is a low association between gene sequences and disease in the NT; only rare genetic diseases are clear associations. Individual genes are unlikely to play a significant role in most multifactorial diseases. Without an essential protein, functional biological networks may still function (Noble, 2021a). It is estimated that 80% of yeast gene knockouts are silent since they do not affect the phenotype (Hillenmeyer et al., 2008). According to the monogenic hypothesis, all genes contribute to the body's functions in some way (Boyle et al., 2017). In a study of 1520

athletes and 2760 controls, no genomic variants were common to elite athletes, suggesting that the organism and its lifestyle experiences regulate the genome through epigenetic mechanisms (Noble et al., 2019; Boyle et al., 2017; Rankinen et al., 2016). The statistical association implies no biological causation.

The CDP and NT describe stochasticity as a method for functionality (Ilan, 2022a). It implies canalization and harnessing of genetic variation using natural genetic engineering (Noble, 2021c). Per the CDP, all subsystems continuously affect each other (Ilan, 2022b). NT holds causal arrows are two-way since organisms are open systems nested within each other, and genotype does not cause phenotype directly.

According to the Central Dogma of molecular biology, DNA transmits genetic information unidirectionally to proteins, generating phenotypes. Transcriptional and epigenetic regulation, insertional mutagenesis by mobile DNA elements, non-protein-coding DNA, and genome reorganization under transcription are not examined (Shapiro and Noble, 2021a; Frías-Lasserre and Villagra, 2017). Genomic DNA from complex eukaryotes contains highly repetitive sequences rather than unique coding sequences (Haubold and Wiehe, 2006; López-Flores and Garrido-Ramos, 2012). Evolutionary biologists refer to non-coding DNA as "junk DNA" or "selfish DNA"[78, 79 74]. It assumes DNA is intrinsically faithful to self-replication, that genetic information is transferred one-way from nucleic acids to other cells, and that somatic and germline cells are impenetrable (Shapiro and Noble, 2021a). Most "junk DNA" is actively transcribed, indicating that it serves a purpose (Shapiro and Noble, 2021a; Doolittle and Brunet, 2017). In the evolutionary diversification of complex genomes, repetitive DNA provides signals for transcription, epigenetic modification, and chromosome mechanics (Shapiro and von Sternberg, 2005; Pappalardo and Barra, 2021; Liu et al., 2013). One of the central features of Modern Synthesis (MS) is that an impermeable barrier separates the soma and germ cells.

In the NT, RNAs and DNAs from the soma cannot be transferred to germ cells (Pittoggi et al., 2006). For example, plants get their energy from fusion processes, and new species can be created by fusing different species (Schattat et al., 2012; Hanson and Hines, 2018; Wang et al., 2004; Zhou et al., 2022). Genetic variation does not always pass vertically or only through the germline. Horizontal transfers of genome information63 can influence evolution. Bacteria acquire drug resistance through transmissible antibiotic resistance (R-factor) plasmids that evolve through transposition and site-specific recombination (Condit and Levin, 1990; Lerminiaux and Cameron, 2019). Instantaneous infectious heredity in bacteria involves the acquisition of adaptive traits by a viral infection involving host cell DNA packaged into viral particles instead of viral DNA or viral DNA integrating into the host genome and the rest of the viral genome (Fillol-Salom et al., 2019). Eukaryotes use viruses as horizontal DNA vectors (Gilbert and Cordaux, 2017). The exchange and reorganization of nucleotide sequences by living organisms are in addition to natural genetic engineering (Noble, 2022a).

1.7. Communications in biological systems: a role for variability in information transfer

The CDP and NT describe the communication of randomness and order between organisms' levels. The disorder and its control are fundamental to information communication, even at the molecular genetic level and in tissues and whole organs.

For the CDP, the transfer of information is variability-dependent, and the communication's variability is mandatory for proper function. The micro and macro levels continuously affect each other. The order of the organism is a sum of the dynamic constraints of the disorder at all parts (Ilan, 2022b). It implies continuously adapting the degree of the disorder by changing the borders to adapt to internal and external communications (Ilan, 2022a). A change in variability borders in a way that the degree of disorder is too low or outside of the boundaries implies a loss of proper communication between biological systems. Per the CDP, communication channels between different levels of the organism are characterized by an inherent constrained variability contributing to its proper functions. Organisms function under continuous information messages delivered unexpectedly between micro and macro levels. This mechanism is independent of which structures are carrying the information.

According to the NT, communications are controlled by macro-levels. While the control is imperfect, it is close enough for only a few micro-level details to matter at the macro level. The organization of the organism itself constrains parts of the organism (Noble, 2022a). The existence of tissue-level "attractors" determines the stochastic distributions in cell populations that require intercellular communication (Noble, 2021d). Organisms balance the regulation of one variable against another because none of the variables are constant (Noble, 2022a). The germ cells receive molecules that influence gene regulation. Reverse transcription of nucleotide sequences into the genome, and long-distance transmission from the brain to the germline has been described (Noble, 2022a). Debris surrounds cells; some are found in extracellular vesicles (EVs). EVs communicate by exchanging information intercellularly (Noble, 2021d). In NT, lipid membrane structures represent quantities of structural information that can be inherited without DNA templates (Noble, 2022a). The growth rate of a bacterial film can fluctuate due to communications between cells involving intercellular potassium waves (Prindle et al., 2015).

1.8. For the immune system to function appropriately, variability needs to be restricted and not completely random

The immune system is challenged when a new antigen invades the organism and does not have the relevant DNA sequence to make an antibody with the correct structure (Nicholson, 2016). As a result, it rapidly mutates the variable part of the immunoglobulin sequence until, by chance, a cell evolves that does have the DNA sequence for an immunoglobulin with the correct shape. A feedback loop activates a massive increase in mutation rate in a highly targeted region of the immunoglobulin DNA sequence. It produces a specific gene coding region for the immunoglobulin (Galhardo et al., 2007; Odegard and Schatz, 2006a). The mutation rate is multiplied by a million-fold, and error-correction mechanisms are activated to create millions of new sequences (Saribasak and Gearhart, 2012; Blázquez, 2003). In the variable part of immunoglobulin, hypermutation increases the natural mutation rate (Noble, 2021c). Variations seem stochastic at hypermutation sites - the variable part of immunoglobulin sequences. Since the same process favors cells that produce an antigen match at the supracellular level, it is considered non-random. From the organism's perspective, harnessed randomness is not purely random because it depends on a random process at the molecular level (Noble, 2021d). In this case, stochasticity is used to generate novelty (Noble and Noble, 2018).

According to the NT, the fact that DNA does not self-replicate gives living organisms control over error-correcting mechanisms. Using it, the immune system reduces error correction in the variable part of the immunoglobulin DNA template and generates millions of new DNA sequences from which the organism selects the few that will serve as antibodies' templates (Noble, 2022a; Odegard and Schatz, 2006b).

Per the CDP, it is an example of how variability is mandatory for proper function. The CDP implies that "chance" or "random search" is a regulated disorder process. An organism fails to generate the proper antibody if the process is too random or has a lower degree of randomness.

1.9. A constrained disorder is required for the proper function of the nervous system

Stochasticity exists in all sections and levels of the nervous system: sensory, motor, and integrative (Calim et al., 2021; Guigon et al., 2008). Many types of stochasticity occur in the excitable membranes of the

nervous system. Stochasticities exist in opening and closing ion channels, integrating synaptic inputs, interneuronal connections, and interactions between organ systems (Noble, 2021a; Cannon et al., 2010; Mendonça et al., 2016).

Stochasticity in NT results in organisms making choices based on neuronal selection to fit social interactions (Noble, 2021a). To determine their behavior, nervous systems select among many variants generated by the organism (Noble, 2021a). It is from neuronal stochasticity that organisms generate unlimited forms of associative learning. Neuronal selection determines conscious, intentional behavior (Noble, 2021c). The signal can be drowned out if the noise level is too high (Noble, 2021a). For transmission along nerve axons, neurons produce all-or-nothing action potentials. The noise is minimized by amplifying minor synaptic potential changes into full-blown impulses (Faisal et al., 2008; Popovic et al., 2011). All body cells, tissues, and organs function based on this concept (Noble, 2021c).

Per the CDP, these forms of stochasticity provide the nervous system with functional advantages. Malfunctions result from too narrow borders of disorder, implying low levels or a high degree of disorder outside the borders. The "selection process" is a continuous dynamic method to respond to internal and environmental changes. It assists proper function and contributes to an intention, but the intention does not direct it (Ilan, 2022a). It does not contradict the "all or none concept," which means there is a low barrier for initiating a function but implies a dynamic level for an impulse's low and upper barriers.

1.10. Organisms must use stochasticity to function appropriately: does this mean they direct their evolution?

While Lamarck postulated that the "life force directs evolution," Darwin's theory of evolution by natural selection may suffice, even if gene variations are random (Skene, 2015). The neo-Darwinian genetic variation theory assumes that all genetic variation sources are random (Hancock et al., 2021). It is common for reductionists to promote determinism and avoid stochasticity. A better chance of survival for fitter organisms is attributed to natural selection, which is blind and does not choose which variants to generate. (Noble, 2021d; Rouzine et al., 2001). "Popper viewed natural selection" as a theory of error elimination and a filter for removing errors (Gabora and Steel, 2021; Winkler, 2016). According to Popper, indeterminism is necessary but insufficient for emergence and openness (Popper, 1988). Since organisms exchange their components, including nucleotide sequences, during evolution, the tree of life is called an extensive network (Shapiro and Noble, 2021b). An MS organism and its descendants are passive recipients of two processes outside their control: random mutations and natural selection. Randomly mutated organisms have only one evolutionary task: to reproduce more rapidly than their unmutated relatives. According to the MS, accidents in genome replication do not contribute to genetic variation (Koren et al., 2014). Microevolution gradually optimizes individual adaptations by accumulating independent localized mutations according to the observed mutation rate. During macroevolution, chromosomes or karyotypes undergo rapid punctuated evolution to generate new species (Shapiro and Noble, 2021b; Olsen and Small, 2018). Macroevolution views the organism as actively generating genetic variation and modifying its selective environment (Shapiro and Noble, 2021a).

The CDP and NT suggest that cells and organisms control and use internal, external, or environmental stochasticity.

According to the NT, stochasticity must be harnessed since if simply a chance is experienced rather than used functionally; then a choice cannot be made (Noble, 2021c). As a result of natural selection, blind nature selects between fit and unfit individuals. Evolution is not entirely blind. To protect the organism from the detrimental effects of genomic change, cells maintain their integrity through regulatory networks that buffer molecular-level random variations (Noble, 2021c). "Active Darwinism" suggests that organisms can, at least partly, direct their evolution. (Noble, 2021d; McClintock, 1984). Organisms can harness the chance to direct genetic and epigenetic changes.

In contrast to the slow accumulation of point mutations, mutation loci and rates of genome reorganization produce functional reorganizations (Noble, 2021d). Organisms react and construct their way forward under stress, employing hypermutation and other mechanisms. Disorders in living systems, such as random mutations, serve regulatory ordering processes (Noble, 2022a). NT posits that proteins evolve by accumulating minor mutations that alter amino acids one by one on their polypeptide chains. When domains are shuffled, evolution occurs faster than when amino acids are substituted one by one (Shapiro and Noble, 2021a). A physiological control system involves physiological regulatory networks (PRN) or gene regulatory networks (GRN), implying that a physiological control system is multigenic in nature (Noble, 2021d). According to the NT, natural selection is not artificial; it achieves 'blindly' what artificial selection achieves by humans actively intervening in breeding animals, plants, and other species. It implies a distinction between upward and downward causation and a mathematical requirement for both if there are levels higher than physics and chemistry. Organisms would be automata without it (Noble, 2022a). New cell types emerge due to spontaneous variation followed by selective stabilization (Noble, 2021a, 2021d). Biology cannot be reduced to physics and chemistry (Noble, 2021a).

Per the CDP, stochasticity is fundamental for biology, physics, and chemistry. The difference between them relies on the borders' range, which determines the degree of the disorder in a system. The fact that it seems to be a not entirely blind process implies constrained disorder but not necessarily a high-level control (Ilan, 2022a). The CDP supports the importance of variability for coping with internal and external perturbations. The inherent variability at all levels is fundamental for adaptability and flexibility. Improving functionality and effectiveness and a mechanism for coping with perturbation may present itself in evolutionary processes. It does not mandate affecting evolution but is reflected by evolution. The CDP views systems as purposeless machines which are indifferent to their destination. They work better using variability, but this does not necessarily mean they were directly impacted by their predecessors or affect their successors. The brain's inherent variability is part of its adaptability and flexibility and characterizes its function. The CDP does not account for a "higher level" of control or consciousness (Ilan, 2022a).

CDP and NT support the importance of flexible rules to govern organisms' functions (Noble, 2022a). Stochasticity cannot be used to generate behavior using fixed algorithms. NT views this process as moving along the arrow of evolution, and though specific outcomes are necessarily unpredictable, they may be explicable in retrospect (Noble, 2022a). By preserving an organism's internal coherence and its relationships to its ecosystem, organisms travel along an evolutionary path that is mainly unpredictable. As a result of random effects at each level and bio-resonances between them, it is unpredictable (Noble et al., 2019).

Per the CDP, flexibility is inherent to function and is independent of an overall direction. The CDP looks at complex systems as aimless. The dynamic character of disorder, determined by its ever-changing boundaries, is mandatory for function. It may have implications for the long-term evolutionary process but does not mean an organism is directed toward a target (Ilan, 2022a).

1.11. Changes in variability or the presence of new species within the tissue characterize a tumor

According to NT, cancer develops inside the host as a new somatic species. As tumors develop, stochasticity may play a vital role (Noble, 2021d). A late-stage metastatic cancer is characterized by a rapid generation of new genomic forms, which explains why aggressive chemotherapy can lead to further mutations. (Noble, 2021c). There are more processes involved in the evolution of tumors than the gradual

accumulation of point mutations. At levels above the genome, mutations follow the development of new "attractor" states. It is necessary to develop successful therapeutic strategies to identify the processes that control tissue heterogeneity (Heng and Heng, 2022). According to NT, drug resistance in cancer does not result from Darwinian evolution with random mutations. As a result of network dynamics, "attractor" transitions are misdirected by molecular signaling pathways into the wrong "attractor" (Noble, 2021d).

Per the CDP, tumor development results from a loss of genome variability or increased variability beyond the borders. No higher control regulates processes. Overcoming drug resistance requires regulation of the degree of variability (Ilan and Spigelman, 2020).

1.12. There is an identically or similarity between quantum mechanics and biology

In nature, the material is fundamentally stochastic, either by random kinetic energy producing Brownian motion of molecules or by quantum mechanical behavior at the particle level (Noble and Noble, 2018).

According to NT, multilevel causality is interpreted by Biological Relativity in the same way as quantum wave theories. In interpreting electrons circling a nucleus, they are called clouds because they cannot be identified by location. The cloud is a quantum mechanical state described by quantum mechanical wave equations (Sahni, 2022). The state of a multilevel biological system matters, not where any particular electron may be, implying that the system's state matters more than its break into separate causal sequences (Noble et al., 2019). Quantum mechanics refers to entangled causation as conditional causation (Vecchi et al., 2018). The causal states involved cannot be separated, and the entanglement resembles that of quantum mechanical states. Similar to quantum mechanics, it is fuzzy (Noble et al., 2019). Due to entangled causation, there is no biological reason to assume that a single causal factor regulates every switch point. Multiple simultaneous difference-making causes regulate a threshold mechanism at every switch point in an interactive manner (Noble et al., 2019). As organisms resist changes in phenotype caused by molecular changes, including DNA sequence changes, downward causation has a high strength.

Per the CDP, quantum states in physics are similar to biological systems; both are characterized by constrained randomness contributing to functionality. Conservation principles are maybe sufficient to explain this in physics. A spin-up or down may have pre-given border conditions, which per some theories, are not constraints (Montévil and Mossio, 2015a). Numerous phenomena in biological systems are hard to explain based on current rules and are explainable by quantum effects (Melkikh and Khrennikov, 2015). The CDP accounts for quantum effects that underlie biological processes, describing quantum randomness and entanglement in biological systems in a way that there is no single causal factor that regulates every switch point (Ilan, 2022a, 2022b; Shabat and Ilan, 2021). However, it is not downward versus upwards forces but continuous multi-directional forces.

1.13. An error-based process or a decision by a higher authority in a constrained disorder trial

According to NT, higher-level guidance can be active or passive. Hypermutation results in a higher-level choice within the immune system. Lymph nodes and germinal spleen centers trigger the process of somatic hypermutation in activated B cells (Noble, 2021d). Photosynthetic processes are examples of passive guidance. Passive absorption of photons by plants and cyanobacteria does not result in random energy storage - it is the canalization of radiation energy without active selection (Pisciotta et al., 2010; Kanazawa et al., 2021; Yamori, 2016; Kramer and Evans, 2011). To achieve better outcomes, active physiological control must allow for flexibility. PRNs, or genetic regulatory networks, imply that gene regulation occurs at a "higher level" rather than at the cellular level. Genes themselves are regulated. Despite random molecular noise, gene loci are not independently active but globally coordinated, resulting in stable recurrent gene expression patterns (Noble, 2021d). A higher-level decision is dictated by the organism's aspirations, according to the NT (Noble et al., 2019). A closure of constraints in biological systems distinguishes them from other natural systems (Noble et al., 2019).

The CDP implies that all systems have a certain degree of disorder, such as hypermutations of photons in photosynthesis; no "virtual higher level" decides. It is never completely random and is reflected by a "trial and error" process at the end of which a "selection" occurs. A "selection" is a state which results from the ongoing constrained random process. Internal and external environments characterize stochasticity, and the final result continuously changes (Ilan, 2022a). It means a continuous process where the disorder's border changes through internal and external perturbations. A gene or a cell does not "think": pure chemistry dictates the result. The CDP views all systems in nature as functioning under identical rules. The constraints on the disorder exist in chemistry, physics, and biology. The difference is the degree of variability determined by the borders. The range can be narrower in chemistry and wider for some biological systems (Ilan, 2022a).

The CDP supports the fact that systems can improve, but this is part of an ongoing change of the borders of the disorder, according to the current conditions. It may seem to someone looking from above that there is an arrow of progress, but in reality, it is an ongoing trial-and-error process that entirely changes under altered conditions (Ilan, 2022a). It is not a vector of progression but a response reflected by a change in the degree of disorder (Ilan, 2022a).

1.14. Balance of random pressures or choices or a "good-enough" match of choices

Per the CDP, living and non-living systems are aimless and differ by their degree of disorder (Ilan, 2022b). It accounts for defective engineering, where a disorder in non-living objects affects their functionality (Attariani et al., 2017; Zhang et al., 2019). The degree of disorder is mandatory for accommodating changing conditions and determines their phenotype and behavior. Stochasticity is an inherent process not associated with making choices (Ilan, 2022a). Organisms do not "make choices" to survive in changing environments. The changing conditions lead to changes in variability, an adaptability process. Choices are inherent to a condition; they are not generated. A molecule does not "think" and does not "generate" conditions. The random behavior of molecules is inherent and characterizes biological and non-biological systems. It is always unpredictable, and randomness never stops. While it may seem, in retrospect, that the final result evolves from a regulated process, in reality, the changing conditions determine what develops at every moment in responding to the ongoing changes.

Per the CDP, stochasticity is inherent to systems and is not "used" by organisms. It may seem that biological systems generate novelty from stochasticity, directed by the "higher level," nevertheless, this is an ongoing process "regulated" by responses at a specific point. Randomness does not stop. What seems to be a "selection of behavior that lead to novelty" is a method nature has for adaptability and flexibility to ever-changing conditions (Ilan, 2022a). The CDP removes intentions and making choices from the process. Living and non-living systems are machines designed to react; they do not act. The method inherent to all systems is changing borders reflected by their degrees of disorder in reactions to triggers.

Stochastic and chaotic processes are seen as part of an organism's ability to make choices by NT (Noble and Noble, 2018). It is natural for living organisms to have a purpose. To survive, they engage in anticipatory and creative behavior (Noble, 2022a). A biological system targets an environmental challenge, and organisms devise multiple solutions using stochasticity. A situation that seems unpredictable can be understood in the future. Organisms act and not just react when interacting socially with other organisms to choose particular behaviors in response

to challenges. Intentionality and causal independence are required (Noble and Noble, 2018). When NT specifies an unpredictable process, it provides rational justification once it has occurred (Noble and Noble, 2018). An organism's state is determined by its environment, but its reactions and solutions do not determine it. The organism searches for possible fits to the problem template instead of an automatic response (Noble and Noble, 2018). According to the NT, a DNA sequence is needed to determine the correct immunoglobulin shape. In the absence of such a solution, hypermutation occurs. To generate novel solutions, organisms activate stochastic processes within themselves. The organism triggers stochasticity but is no longer controlled by it (Noble and Noble, 2018).

It is known that neural processes are stochastic, manifested by the opening and closing of ion channels via action potential generation, spontaneously or through synaptic transmission. The organism controls cognitive functions, according to NT (Noble and Noble, 2018). By comparing what is generated by the stochastic process with the template of the problem, the nervous system determines whether it fits. An organism "knows" when it has found a solution. It is commonly assumed that animals behave as though they are calculating probabilities. It is possible that animals are not calculating, and the Rational Choice Theory may not be accurate (Ilan, 2019e). Decisions are influenced by whether they involve gains or losses, according to NT (Noble and Noble, 2018). A rational outcome is not guaranteed in a stochastic process, as human choices are often irrational. It is common to expect partial success; a "good enough" template matches (Noble, 2021c; Santos and Rosati, 2015). Short-term memory defects in Drosophila affect choice behavior (Tang and Guo, 2001). In organisms capable of choice, associative learning is unlimited, implying consciousness and anticipatory action on the part of the organism (Ginsburg and Jablonka, 2019). Exercising influences gene expression in muscles and lungs, changing the initial conditions under which all muscles in the body function. The athlete's lifestyle has a physical effect at the molecular level (Noble et al., 2019); due to choice processes in organisms, organs are altered, including neuronal circuits subject to selection (Noble, 2022a).

CDP does not view retrospect as a means for making conclusions. What seems to be "justified" is a method nature uses to adapt. Organisms do not activate a process of stochasticity. The stochasticity characterizes them, and the borders determine their degree of change in response to perturbations. It is an "automatic" response; solutions are not "generated," and there is no library to select a solution. Randomness characterizes systems, and the pressures in the environment determine its degree. A balance among the multiple triggers determines the degree of variability. For the immune system, the hypermutation process is ongoing and stops for a specific antigen when the pressure created by the antigen is relieved by having the proper antibody structure (Ilan, 2022a).

For the nervous system, the CDP implies that stochastic processes are inherent to all levels; the occurrence of this process does not necessarily explain cognition. There is no "control" over the process by the organism. The process is regulated by balancing the numerous environmental pressures that reduce or increase the degree of stochasticity. The "choice-making" process results from a balance of pressures exerted by dynamic environments on a system; no "free will" is involved. There is no "decision process," no predictability or free will at the level of the molecules, tissues, and organs; they respond to changing triggers. Per CDP, the "choice process" is a compromise between ongoing pressures; the solution is never final. There is no subjective knowledge of "logic decision-making," which impacts behavior (Ilan, 2022a).

Per the CDP, stochasticity is inherent to biology but does not explain human behavior and decision-making and does not account for cognition. Systems respond to triggers and lack memory. A system change can be viewed as its "memory" or a new initial condition for the next trigger, but this is not a memory inherent to systems. Stochasticity that characterizes genes, molecules, tissues, and organs is not consciousness. The fact that there are changes in gene expression and organs following a subject's decision does not imply causality. The CDP differentiates between decisions made by animals and humans and the chemistry of their molecules and organs. Connecting cognition with the body's stochasticity is an extrapolation for which the CDP does not account (Ilan, 2022a).

Table 1 summarizes some common concepts and differences between the CDP and the NT.

1.15. Using noise to correct malfunctions using CDP-based artificial intelligence

Biological systems use noise for better adaptation and environmental challenges. CDP and NT support the importance of noise and its use by organisms.

In biology, phenotypes' variability stems from stochastic gene expression and intrinsic and extrinsic fluctuations primarily based on the contingency of evolutionary and developmental paths and ecosystemic changes. Both forms of randomness contribute to biological robustness. It differs from conventional computable dynamics, where elaboration and transmission of information are robust when they resist noise. Based on some theories, symmetry breaking is particularly relevant in biology in contrast to physical conservation properties, thus symmetries; it provides another critical component of biological historicity and randomness as a source of diversity-supporting stability and organization based on variation and adaptability (Bravi and Longo, 2015).

A key question raised by NT is whether a biological variation is random or whether organisms can somehow direct their development and evolution (Noble, 2021a). According to NT, using noise entails selecting and targeting disorders at the molecular and cellular levels (Noble, 2021d). Cells with different gene expression profiles are selected by stochasticity, and the immune system selects cells with different outcomes of hypermutation (Noble, 2021d). The existing genetic variability permits rapid genetic assimilating if a rapid mutation is already occurring as a reaction to stress (Noble, 2021d; Kiviet et al., 2014). Several generations of epigenetic changes enable genetic assimilation. A clear endpoint and a higher direction are involved in NT.

The CDP broadens the concept and implies that biological systems' flexibility evolves from their inherent variability. Variability is dynamic, and the restrictions for adaptability are continuously changing. It is an automatic neverending mechanism of responding to perturbations and pressures. It is a sophisticated mechanism for making use of noise by biological systems.

The CDP defines malfunction as getting out of the borders of the disorder; having a low level or too high a degree of disorder leads to a system's lack of efficiency. Using the CDP enabled the establishment of a method for regulating noise to correct malfunctions and improved the functionality of systems (Ilan, 2022a).

An example is the development of resistance and drug tolerance in chronic diseases (Ilan, 2019e, 2019f, 2021b, 2022c, 2023b; Ilan and Spigelman, 2020; Kessler et al., 2020; Ishay et al., 2021a, 2021b; Kolben et al., 2021, 2023; Kenig et al., 2021; Azmanov et al., 2021, 2022; Potruch et al., 2020; Isahy and Ilan, 2021; Khoury and Ilan, 2019, 2021; Kenig and Ilan, 2019; Gelman et al., 2020, 2022, 2023; Hurvitz et al., 2021, 2022; Rotnemer-Golinkin and Ilan, 2022). For multiple drugs, chronic use leads to tolerance and partial or complete loss of response (Ilan, 2020a). A CDP-based second-generation artificial intelligence (AI) system implements variability into therapeutic measures to improve the response to therapies (Ilan, 2020a, 2020b, 2021a, 2022c). The algorithms involve using noise in a regulated, personalized way to improve the efficiency of interventions in disease conditions. Organisms are aqueous 'computers' with a degree of stochasticity at the molecular and organ levels (Noble, 2022a). However, they are not computers in the sense of direct input and output devices. They are always active unities

Table 1
A comparison of the constrained disorder principle (CDP) and some of Denis Noble's theories (NT) on stochasticity in biology.

	CDP	NT
Stochasticity	Characterizes all levels of systems in biology, from the genome to whole organs.	There is a level-dependent relationship between molecular-level stochasticity and higher-level predictability.
The need for stochasticity	There is a need for a degree of stochasticity at all levels simultaneously.	In goal-directed feedback control processes, molecular stochasticity cancels itself out at higher levels.
Using stochasticity	Stochasticity is required for proper function at all levels.	The higher level of the organization determines whether the underlying molecular stochasticity impacts a system's overall behavior.
Constraints of stochasticity	The stochasticity is constrained at all levels by dynamic borders that respond to environmental perturbations.	An attractor constrains chaotic variations. The variations will be random if the attractor that constrains a chaotic sequence is not part of the organism's control network.
The central dogma of molecular biology	Biology involves constrained disorder. Order is about narrowing the border of the disorder under the appropriate conditions.	The Central Dogma of molecular biology is wrong; biology must create order from disorder.
Physics and biology	Biology and physics are similar. "Creating order" is about altering the disorder borders, as there is always a degree of disorder.	Life resembles physics, particularly thermodynamics, in creating order from disorder.
Organisms are open systems operating far from equilibrium. Hierarchy of the disorder	Molecular and higher levels have degrees of disorder that impact each other. There is no hierarchy.	Constraints exerted on levels below cause systems to be ordered. Macro-level actions ensure order at the molecular level.
Systems exist on the boundary between order and disorder; The edges and boundaries are where non-equilibrium processes occur	Internal and external boundaries are part of the areas where perturbations and triggers occur and need to be differentiated from the dynamic borders of the disorder, which define the CDP. The edge is not a physical boundary but a measure of the degree of disorder. The boundaries are the constraints of the disorder, which are dynamic and continuously adapt. Physical boundaries are similar to all organs and are characterized by a degree of disorder in structure and function.	Anatomic boundaries are between levels: the intestine, respiratory tract, and skin exchange matter and energy through cellular membranes. Boundaries are dynamic and do not always have a precise anatomical location. It is not the parts of the composition, nor the genome, that determines an organism's function, but their interactions across these boundaries that determine it.
The degree of organism flexibility; perturbations produce a change in overall behavior	The dynamicity of the borders of the disorder at all levels is a continuous process. All levels constantly affect each other in multiple directions. The constraints determine functionality.	The state of the boundaries between higher and lower levels determines phenotypes. The effect is on the boundaries between levels.
Causation	Causation is a dynamic process that occurs continuously between all levels and is multi-directional. It manifests in continuously changing the borders of the disorder.	There are upward and downward forms of causation. In a system, upward causation refers to the interaction between the lower and higher levels of the system. In downward causation, higher levels constrain the dynamics of lower-level elements by imposing constraints on them.
Phenotype	The phenotype is a sum of the disorders at all levels. It changes based on the constraints which determine the degree of disorder.	Biological networks integrate genetic and environmental factors in developing phenotypes that are regulated at a higher level.
System's organization	There is no hierarchy. The lower and upper levels continuously affect each other. The organization's state is a disorder at each level determined by the disorder's border range.	Based on biological relativity, causation is the constraint higher levels exert on the initial and boundary conditions that govern lower-level dynamics.
Organisms buffer themselves from genomic variation	The mutation rate reflects biological variability, and the constraints are the mechanisms that regulate it.	In response to environmental challenges, an organism can control mutation rates.
Communication between organism levels	The micro and macro levels continuously affect each other. The order of the organism is a sum of the dynamic constraints of all the disorders.	Communication is controlled at the macro level. An organism's organization constrains its parts, not the other way around.
Data transfer	An inherent constrained variability characterizes communication channels between different levels of the organism. Organisms function under continuous information messages delivered between the micro and macro levels independent of which structures carry the information.	Germ cells receive molecules that influence gene regulation. Structures of lipid membranes that are not dependent on DNA templates represent quantities of structural information inherited in addition to DNA.
Using variability by the immune system	Variability is mandatory for proper function. A "chance" or "random search" is a constrained disorder process. An organism fails to generate the proper antibody if the process is too random or has a lower degree of randomness.	The selection process at the cellular level is random, but at the supra-cellular level, the same process is viewed as non-random because it favors cells that produce a match for the antigen. At the molecular level, those cells depend on a random process.
Stochasticity in the nervous system: is it intentional?	Stochasticity provides the nervous system with functional advantages. Malfunctions result from too narrow borders of disorder, implying low levels or wide borders implying a high degree of disorder. It is a continuous method to respond to changes. An intention does not direct it.	As a result of stochasticity, organisms make behavior choices that best suit social interactions. Intentional, conscious behavior depends on neuronal selection.
An all-or-none effect	Variability has a range; too low or too high levels of variability are associated with malfunction. It does not contradict the "all or none concept," which implies a low barrier for initiating a function and a dynamic level for the low	Transmission along nerve axons is all-or-nothing. If the noise level in the nervous system is too high, the signal can be drowned out. The interfering noise is minimized by amplifying minor synaptic potential

(*continued on next page*)

Table 1 (*continued*)

	CDP	NT
	and upper barriers. There is no "interfering noise" in a proper function system.	changes into full-blown impulses.
Evolution	Stochasticity is fundamental for all processes in biology, physics, and chemistry. The difference relies on the borders, which determine the range of the disorder. The fact that it seems to be a not entirely blind process means a constrained disorder. It does not imply high-level control.	The evolutionary process is not entirely blind. Regulatory networks protect organisms from the deleterious effects of genomic change by buffering "higher levels" against molecular-level random variations. A distinction between upward and downward causation is implied at levels higher than physics and chemistry.
Directing evolution and higher levels	Variability is mandatory for coping with environments for adaptability. Improving functionality and a mechanism for coping with perturbation may present itself in evolutionary processes. It does not mandate affecting evolution but instead is reflected in the evolution. Systems are purposeless machines and are indifferent to their destination. They perform better when implementing variability, which does not imply a direct effect on their predecessors or affect their successors.	Organisms can direct evolution. Evolution cannot be completely blind. Stress causes organisms to employ hypermutation and other genetic processes to find their way forward. Disorder, such as random mutations, serves regulatory order. Higher levels regulate the process.
Importance of flexible rules to govern organisms' functions: is there an arrow?	Flexibility is inherent to function and is independent of an overall direction—complex systems as aimless. The dynamic degree of disorder, determined by the ever-changing boundaries, is mandatory for function. It may have implications for the long-term evolutionary process, but it is not that an organism is directed toward a target when functioning.	Evolution moves along an arrow, and while specific outcomes are unpredictable, they may be explainable in retrospect. Organisms preserve internal coherence. Random effects at each level and bio-resonance effects between levels make it unpredictable.
Cancer development	Tumor development results from a loss of variability or increased variability beyond the borders. Overcoming drug resistance requires regulation of the degree of variability. No higher control regulates processes.	In cancer, new species develop stochastically within the organism's tissues. The development of new attractor states above the genome leads to mutations. Developing successful therapeutic strategies requires identifying the processes that control tissue heterogeneity at that level.
Higher level control	Systems have a certain degree of disorder; however, no "higher level" decides. It is never completely random and is always constrained as part of a "trial and error" process at the end of which a selection occurs. A gene or a cell does not "think."	Physiological control leads to better outcomes. Regulation is at a higher level and notby genes. "Higher-level" decisions are made based on what an organism wishes.

Table 1 (*continued*)

	CDP	NT
Improving systems	Systems can improve as part of an ongoing change of the borders of the disorder. It seems like there is an arrow of progress, but in reality, it is a trial-and-error process at each point, which changes when conditions change. There is no arrow of progress but a response reflected by a change in the degree of disorder.	Each dynamic element's initial conditions are its opening values at lower levels. The history of the development of the system, including stochastic variation and previous states of the system, determines them.
Systems' aims	Living and non-living systems are aimless. Their degree of disorder determines their phenotype and behavior. The changing conditions determine the result at every moment. Choices are inherent to a condition; they are not generated. What seems to be a selection of behavior that lead to novelty is a method for adaptability to changing conditions.	Living organisms are purposive. Biological systems aim to target. As a result of stochasticity, organisms can generate multiple possible solutions to environmental challenges. Consequently, what seems unpredictable in the present can become understandable in the future.
Act or react	There are no intentions in making choices. Living and non-living systems are machines designed to react; they do not act.	Organisms act and not just react. They select particular forms of behavior in response to challenges.
Retrospect justification	The organism does not look at retrospect for making conclusions. What seems to be "justified" is a method nature uses to adapt.	Once a system has been implemented, there is an unpredictable process with a rational explanation.
Making choices	The process balances pressures exerted on the system by a dynamic environment. There is no decision process; molecules, tissues, and organs respond to triggers. There is no predictability or "free will" at the level of the organs.	Decisions are influenced by whether they involve losses or gains. Stochastic processes do not guarantee that a rational solution will emerge from human choice. Most of the time, partial success is expected, a "good enough" template match.
Cognition	CDP does not account for cognition and differentiates between decisions made by organisms and the chemistry of their molecules and organs.	Gene expression, muscles, and other organs are affected by a subject's decision. The processes of choice in organisms lead to selection.
Biological systems use noise for adaptation	The CDP provides a method for regulating noise to correct malfunctions and improves functionality. CDP-based second-generation algorithms are used to correct malfunctions.	

constrained by bodily, material, and ecosystemic continually reconstructed constraints (Soto et al., 2016; Longo and Montévil, 2013).

The CDP-based algorithms use personalized noise to improve the effectiveness of drugs[18-35154]. Similarly, using variability-based algorithms can improve sports training (Gelman et al., 2022).

The current AI systems do not produce conscious-decision making or generate criteria for the equivalent of agency in living organisms. The closed-loop personalized algorithms are based on pre-defined endpoints, which the system does not decide to select (Ilan, 2020b, 2021a, 2022c). Nevertheless, using second-generation AI algorithms that use noise is a

step forward in that direction.

In summary, NT and CDP are theories that underlie the fundamentals of the importance of noise in nature. The difference between them supports the importance of continuing the studies of variability at all levels of biological systems. These studies, as shown above, provide options for improving interventions for correcting malfunctions and improving the performance of complex systems.

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YI is the founder of Oberon Sciences.

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