Method article
The constrained disorder principle defines living organisms and provides a method for correcting disturbed biological systems

Yaron Ilan *
Faculty of Medicine, Hebrew University and Department of Medicine, Hadassah Medical Center, Jerusalem, Israel

1. Introduction
Numerous currently used schemes provide some actionable frameworks that allow retrieval of some properties of biological systems. However, they cannot give an entirely accurate description of biological reality. A better understanding of biological organization is needed.

Randomness is inherent to complex systems, including biological systems. Its detailed contribution to the systems' function and its potential use for correcting malfunctions were not yet described.

The constrained disorder principle (CDP) defines living organisms based on their requirement for a disorder within arbitrary boundaries, which is mandatory for their existence and proper operation. The CDP provides a way to interpret biological processes and describe them with improved accuracy providing a means for overcoming some of the challenges of the current models.

This paper presents the definition of the principle and its use for determining health and disease and correcting disturbances in biological systems.

A. The constrained disorder principle defines biological systems
i. The constrained disorder principle specifies the necessity of intrinsic randomness in biological systems.

The CDP specifies that the disorder kept within random personalized boundaries is fundamental to biological systems. The constrained disorder provides systems with the flexibility and adaptability to the continuously changing random internal and external milieus.

Randomness and variability are intrinsic to biological systems and occur in the genome, cell organelles, proteins, and whole organs[1–10]. The inherent variability of biological systems specifies a role for the disorder in living organisms. These systems possess a mixture of order and disorder and require a certain degree of disorder for proper function[5,11].

ii. The constrained disorder principle defines disorder as the differentiator and the advantage of living organisms over non-living systems
The CDP defines living organisms’ subcellular and cellular organelles and whole organs as aimless machines functioning within a degree of error. Their structure mandates disorder and operation within its arbitrary boundaries. Systems malfunctioning implies operating outside these boundaries.

The CDP is mandatory for life under variable settings. Living organisms can be viewed as purposeless machines that are inherently flexible and adaptable due to their intrinsic constrained disorder.

The CDP defines the difference and the advantage of living organisms over non-living organisms. Per this principle, living and non-living organisms operate like machines, not striving to improve or optimize.

Per the principle, living organisms comprise a disorder within arbitrary boundaries, differentiating them from non-living organisms that lack this assembly. This structure gives living organisms an advantage, enabling them to adapt to the continuously changing internal and external milieus and better respond to ongoing random stimuli.

The principle does not eliminate the importance of genetics and order, which underlie systems. Randomness is one of the aspects of living organisms, and deterministic rules are always part of systems’ backbones [12]. The complex three-dimensional organization of genomes involves chromatin domains, DNA loops, and higher-order compartments, which involve deterministic and stochasticity in transcription and higher variability of chromatin architecture in individual cells[13]. Both extrinsic and intrinsic sources of variability in genome organization were described. Similar features were defined for the transcription and translation process. The inherent combination of deterministic and stochastic components of systems has functional implications in complex systems [14,15].

iii. The constrained disorder principle implies that biological systems operate in alignment with the second law of thermodynamics

The CDP specifies that systems possess a mixture of order and disorder within arbitrary boundaries required for existence and operation. It implies that they operate under the second law of thermodynamics.

The second law determines entropy as a property of a system. Entropy cannot decrease, as isolated systems always arrive at a state of thermodynamic equilibrium, where the entropy is highest [16,17]. The second law predicts the direction of spontaneous processes and determines whether they are irreversible or impossible despite obeying the energy conservation requirement expressed by the first law of thermodynamics.

Biological systems are far from equilibrium. Self-organizing systems organize themselves and function close to the edge of instability towards chaos but never reach complete chaos [1–3]. Living organisms are not committed to eliminating their entropy production rates in the face of numerous internal and external random stimuli. Per the CDP, evolution balances order and disorder essential for proper function, and this balance is mandatory for thermodynamic energy conservation.

iv. Formulations of the constrained disorder principle.

Using mathematics to describe biological functions and their variable processes enables a better understanding of complex systems. Using formulas for the flow of random dynamical systems is helpful for modeling time series generated by processes far from equilibrium [18].

The CDP implies entirely random systems that lack rules. Mathematically expressing the disorder and its arbitrary boundaries can improve understanding of complex biological systems. However, they cannot reach absolute accuracy, as these systems comprise numerous variables, many of which are unknown and continuously change randomly.

Formulas based on descriptive analysis of biological systems, using estimations, and means, while determining trends of systems, do not reflect biological reality with complete accuracy. The internal and external stimuli affecting systems, many of which are unknown and dynamically change, are entirely random and unpredictable—framing them within formulas assists in understanding these systems but cannot reach complete accuracy while attempting to reflect the real biological world.

B. The constrained disorder principle and ergodicity, the free-energy theory, Markov blankets, and random fluctuations in biological systems

i. The constrained disorder principle specifies a continuous balancing of complexity and surprise with information and accuracy.

The CDP accounts for entropy, surprise, and uncertainty associations. The principle implies that a degree of disorder, uncertainty, and lack of causality is mandatory for the proper operation of biological systems.

The free-energy principle (FEP) is an information theory that measures the bounds of a surprise given a generative model. The model is probabilistic of the dependencies between causes and consequences from which samples are generated [19,20]. The energy minus entropy provides free energy (F = U-TS). The energy here is the surprise about sensations and their perceived causes, and entropy is that of a system’s recognition density, an estimated probability distribution of the reasons for data [19]. Free energy is also a surprise plus a divergence term. The divergence is the difference between the recognition and posterior density, representing the prediction of actual causes. This theory suggests that free energy is an upper bound on surprise, which is the negative log probability of an outcome [19]. It measures how unlikely an observation would be by associating a system’s sensory state with an observation [20,21].

Accuracy is the surprise about sensations expected under the recognition density [19]. Free energy is also complexity minus accuracy, where complexity is the difference between recognition and a prior density of causes. It means integrating the difference between the previous density, which encodes beliefs about the world before sensory data, and posterior beliefs, the recognition density.

The free energy theory suggests that biological systems violate the second law of thermodynamics and avoid surprises within boundaries [19,22,23]. Systems resist the tendency to disorder, and natural selection limits the number of states near equilibrium and reduces entropy production [19,24]. A subtle difference in perspective to the FEP proposed that the whole is considered a primary and biological system that deconstructs information about the world rather than constructing representations [25–28].

The role of the meaning of relative or relational information is essential for the understanding of biological systems’ stability. Shannon’s notion of relative information between two physical systems enables statistical and quantum mechanics without referring to subjectivism or idealism. It allows a realistic picture of the world, providing a tool for dealing with its apparent limitations [28–30]. The concept that Meaning = Information + evolution was proposed to provide an approach for the understanding of information in complex systems [31].
The CDP defines a continuous balancing of complexity and surprise with information and accuracy within arbitrary dynamic boundaries. Systems’ function is independent of causes and consequences, and they do not violate the second law and do not resist a tendency for disorder. Per this principle, systems are machines that mandate a certain degree of disorder and surprise within the range defined by the disorder’s arbitrary boundaries for their function and do not strive toward accuracy.

ii. The constrained disorder principle defines the balance between information and surprise and between maximizing and minimizing free energy.

The CDP specifies that the system balances disorder with order and maximizing with minimizing free energy. Systems’ existence and adaptation require a degree of disorder and free energy. Per the CDP, systems mandate a degree of errors for existence under unpredictable random stimuli irrespective of the settings around them.

The free-energy theory proposes that organisms are prediction machines that model the world and minimize prediction errors [32,33]. The theory suggests that adaptive systems occupy a limited range of states to reduce the long-term surprise associated with sensory exchanges with their environments [19]. Surprise relates to the current state of systems, which cannot change, and movements between states vary. This motion is complicated when revisiting a small set of states, termed global random attractor. Attractor states that goal rather than optimization is a critical theme [34]. An attractor is a set into which a dynamic system develops with time. Points adjacent to the attractor remain close, even under small perturbations [19].

The free-energy theory suggests that adaptive systems resist a natural tendency to disorder [19,35–37]. If systems minimize free energy, they minimize surprise [19,38]. Predictive coding, where prediction error or local surprise propagates until eliminating residual error signals, happens by updating the beliefs [39–41]. For reducing free energy, systems fit their observation with complex models with lower entropy, subtracting less from their free energy [42]. Minimization of the free energy through time ensures that entropy is bounded [20]. A minimum free energy leads to minor actions for minimizing expected cost and the free energy [19,43–46].

Per the CDP, a movement between several states is mandatory for existence and proper function. The number of states is random within limits. It implies that biological systems balance maximizing with minimizing free energy and uncertainty with accuracy. They mandate a degree of free energy and uncertainty for existence and functionality. It implies that the systems do not strive to minimize actions and costs.

The CDP applies to all organs, including the brain, where structure assembly comprises a balance between information and surprise. Cell plasticity is an example of a continuously balanced system where disorder exists. Organ responses, including those of the brain, do not mandate predictions or explanations of stimuli [19,47–53]. It responds to its sensory epithelia sampling within a range of errors [19]. Organs balance information with predictability between the sensorium and their internal representation while keeping a certain level of uncertainty required for its proper function [54–61].

iii. The constrained disorder principle accounts for the concept of Markov blankets in biological systems.

The CDP is in line with the concept of Markov blankets. It defines biological organs as comprising random blankets over random blankets. The variabilities of the Markov blankets reflect the disorder in these systems. Markov blankets are dynamically random and continuously changing, and their boundaries are variable [62].

The free energy theory suggests that biological systems include Markov blankets that outline their structure [63–65]. These boundaries are flexible and are not co-extensive with an organism’s physical boundaries [20]. Markov blanket signifies a partition of states into internal states, their Markov blanket comprising sensory and active states and the external or hidden states concealed behind the blanket [38]. Internal states and their Markov blanket respond to hidden states in the environment [20,38,62]. The internal states do not affect the external states while generating active states can affect the external ones. The external states do not affect the active states [18]. The theory proposes that systems couple between internal and external states, exhibiting circular causality fundamental for self-organization, and blankets create dependencies among states [18,20,38,66–69]. Generalized synchrony is the synchronization of chaotic dynamics inside and outside the blanket. Both internal and external states are synchronized, and there is symmetry due to the Markov blanket [18]. It suggests that generalized synchronization is expressed as a principle of most minor action, minimizing free energy [68,70,71].

The CDP implies that systems respond to random stimuli irrespective of causality. Per this principle, systems have limited synchronization and symmetry, resulting from an ongoing balancing process between the different states and their Markov blankets. The CDP infers that Markov blankets manifest themselves in the short-range electrochemical and nuclear forces, where cell membranes form blankets for internal intracellular states [38]. The internal states link with the intracellular states of cells. The sensory states develop into the surface states and cell membranes overlying active states, such as the actin filaments of the cytoskeleton. The active state is the cell filaments, and sensory states are the receptors on the cells [72]. These processes are random within certain limits and manifest in the dynamic instability of the microtubules [6–9,73,74]. Each hierarchy level manifests Markov blankets comprising active and sensory states in the brain, where the active states influence lower levels not linked with predictions. The exchange of effects between the various levels keeps certain degrees of disorder and errors.

Autopoiesis is a property of living systems that enables them to maintain and renew themselves by regulating their composition and preserving their boundaries [18,20,33,38,46,75–77] Action maintains the structural and functional integrity of the Markov blanket via autopoiesis or self-assembly [20]. Per the CDP, actions and autopoiesis result from a continuous balance between the order and the disorder within arbitrary boundaries in entirely random systems. This process is mandatory for the renewing of biological systems under random settings.

The FEP, Markov blankets, and other models are approaches with limitations that do not provide an entirely accurate description of biological reality. They describe actionable frameworks that allow retrieving some properties of the biological systems but are insufficient for complete accuracy. The CDP provides a method to interpret biological processes with better accuracy.

iv. The constrained disorder principle implies that biological systems are ergodic.

Multiple examples of ergodicity inherent to biological systems align with the principle of constrained disorder. Ergodicity underlies cyclin activity levels during the cell cycle, where stochastic external signals induce continuous oscillating motion [78]. Ergodicity explains each phase of the budding yeast. Diffusion in cell membranes displays anomalous dynamics and a high rate of fluctuations. The potassium channels’ machinery comprises ergodic
and nonergodic processes in membranes [79,80]. The macromolecular assembling reflects an ergodic process, and the binding to the actin cytoskeleton is a nonergodic process [80].

The free-energy theory suggests that ergodicity is the time average of a measurable function of a system that converges over an appropriate period [38,81]. Entropy is a measure of uncertainty and is the average self-information or surprise of outcomes sampled from a probability distribution or density [19]. Low entropy means that the result is relatively predictable. Per this theory, ergodic systems converge to an invariant set of states [82–87]. The ergodic sets are groups of states from which the system, once entering, does not leave when subject to internal noise [88,89].

Entropic dynamics is an outline in which dynamical laws are derived as an application of entropic methods of inference [90]. It implies a lack of an underlying action principle and that dynamics is driven by entropy subject to the constraints appropriate to the problem. A standard diffusion process is an example of the nature of time, and imposing the additional constraint that the dynamics are non-dissipative leads to Hamiltonian dynamics. Using concepts from information geometry led to the type of Hamiltonian that describes quantum theory [90].

The geometric information approach to the chaos framework suggests that when identifying a complex system's microscopic degrees of freedom, it is mandatory to obtain data and select essential information constraints on the system [91]. A statistical model describes the system in probability distributions characterized by macro variables determined by the data and the specific functional expression of the information constraints used to implement statistical inferences. When a system changes, the corresponding statistical model evolves from its initial to final configurations in a manner specified by entropic dynamics, the elements of which are probability distributions [91]. A change in probability distributions is a principle of entropic inference. Entropic dynamics specifies the expected rather than the actual dynamical paths of the system [92].

In physical systems, forces change according to Newtonian laws and are redefined by the methods of Lagrange and Hamilton using an identification of the governing action principle as a general framework for dynamics. Living systems' structure generates informational metrics and course configurations for the required action dynamics [93]. The experiential process of acquiring and translating information into actionable meaning for adaptive responses is the driving change in biological systems. It involves an innate action principle that determines the system's directional changes. An entropically driven trajectory minimizes the information gradient differences and is an inference procedure for directional change considered an action functional for the living system [93].

The CDP implies that entropy, a measure of a system's disorder and randomness, is obligatory for proper operation. Systems mandate a degree of uncertainty and are not striving to eliminate unpredictability. Per this principle, systems maintain numerous states to keep their flexibility under dynamic random settings. Modeling systems can provide a tool for determining the trends of biological systems, but per the CDP, they may not reach complete accuracy.

The constrained disorder principle defines the self-organization and non-equilibrium steady states of biological systems

The thermodynamics and information theories explain the self-organization of far-from-equilibrium systems [94]. The CDP implies that the non-equilibrium steady state is mandatory for the systems' proper operation. It specifies that non-equilibrium steady-state systems comprise a dynamic balance between continuously changing and opposing random forces. Random dynamical systems exhibit stochastic chaos and involve a degree of independencies at non-equilibrium steady-states [18].

Self-organization in biology is a property of ergodic random dynamical systems [18,38,95–98]. Systems' self-organization to non-equilibrium forms underlies their structures [99]. The CDP implies that systems are part of larger disordered organizations. The Markov blankets, boundaries, and attractors have a degree of randomness, indicating that systems are dynamic and random within their arbitrary boundaries. Per this principle, biological self-organization is continuously dynamic under random internal and external stimuli. It balances maximizing with minimizing free energy and uncertainties with information. Systems are ensembles of Markov blankets that are random and self-organize into global random systems. Systems are affected and influence their milieu. Randomly states of systems impact the functional and structural states of other systems [20,100–102]. Per the CDP, existence means having certain degrees of disorder, errors, and free energy.

The free energy theory suggests that self-organization means minimizing free energy or maximizing the evidence for their models of the world [103]. Systems remain in non-equilibrium steady states by restricting themselves to a limited number of states [104]. Existence means resistance to a dispersion of structure and molecules by random fluctuations [21, 67, 72 105]. If systems are in non-equilibrium steady-state existence, the gradient flow balances the dispersion caused by the random fluctuations [18,72,106–113]. It suggests that systems with random dynamical attractors minimize their free energy and engage in active inference, acting upon their external milieu to maintain an internal homoeostasis [38,85,96,98,114–120].

The CDP implies that disorder is a mechanism for keeping systems' existence and operation under highly random, continuously changing internal and external milieu. It defines a dynamic balance between random fluctuations with the gradient flow and between uncertainties with accuracy. It implies balancing between random dispersive fluctuations and opposing random construction forces. Per this principle, a certain degree of random fluctuation is not associated with molecule dispersion and is part of the processes that underlie their structure under fluctuating conditions. Cyclic processes in the cell cycle exemplified this principle [6–9,24,73]. The CDP implies that the disorder and its arbitrary boundaries are individualized. What is surprising for a system may not be surprising for another system under identical settings.

C. The constrained disorder principle defines biological systems as purposeless machines that operate under random internal and external stimuli

i. The constrained disorder principle is independent of systems' trajectories.

The CDP specifies that the disorder is mandatory for the systems' existence, evolution, and operation. Systems are machines that do not strive to reach a target. A process of balancing disorder and order is intrinsic to systems' operation in highly dynamic random environments. Randomness is intrinsic to biological systems and is part of the evolutionary process, manifesting in variabilities at the genome level, microtubules, protein sequences and structure, cell organelles, and whole organs [12,73,74,121–125].

The CDP specifies that systems do not strive to reduce uncertainty. Existence and proper operation reflect an ongoing balance between uncertainty and surprise with information and precision [20,126]. The principle implies that systems' functions under dynamic random settings require degrees of uncertainty and free energy. A constrained degree of the disorder is mandatory for systems' flexibility and adaptability. When the degree of the disorder is too low or too high, the system is disturbed.
The free-energy theory is about optimizing systems; it suggests gaining information to create an accurate world model and keeping an open mind on the future [127–130]. It suggests that minimizing free energy optimizes empirical priors informed by sensory data to enhance prior expectations [84,131–135]. Systems aim to reduce surprise, resolve uncertainty, and minimize prediction errors. This theory suggests that systems behave, select information, and ignore information that contradicts their beliefs [2, 19, 127,136, 137, 138]. The theory suggests that minimizing free energy maximizes efficiency and that systems aim to fulfill the requirements created for themselves and their environments [138].

The CDP defines systems as purposeless operating machines that function within boundaries of disorder and errors, and that value is not inversely proportional to surprise. Operations are independent of actions’ potential values and costs. It means that existing in a continuously random dynamic world necessitates a degree of errors and uncertainty and implies an ongoing dynamic balance between opposing random trajectories. The principle entails keeping a degree of entropy as part of the requirement for system existence.

The CDP implies that organisms possess numerous states that randomly change and are associated with higher entropy mandatory for operation. It specifies that operating in random milieus requires a degree of surprise, and actions do not follow trajectories of consequences and rewards. Systems are machines that do not look into the future and significance of their actions when selecting their activities. The future is entirely random, and internal and external settings continuously change and are unpredictable; hence organisms do not make extrapolations about the outcomes of their activities.

Biological systems do not strive to reach perfection, and a degree of imperfection is intrinsic to their reality. Improving efficiency does not underlie systems’ function. They are machines that function under continuous perturbations and alarms and are not mandated to move toward specific targets. This machinery provides a solution for systems to cope with continuously randomly evolving internal and external milieus. How disorder contributes to flexibility varies for diverse systems, differs under different settings, and is yet to be determined.

ii. The constrained disorder principle defines the cross relations between biological systems and their internal and external environments.

The CDP defines homeostasis as an ongoing process without perfection and a total balance. Biological systems function under unpredictable internal and external stimuli but do not monitor or react to them [20]. Systems do not strive to eliminate surprise and do not violate the second law when interacting with their environments. If the internal and external milieus are random, and the organisms are models of their surroundings, it implies a degree of disorder and a limit to free energy minimization. Systems’ operation in real life reflects the randomness in their internal and external milieus. There are cross-reactions between systems’ randomness and their milieus’ randomness.

The free-energy theory suggests that organisms are close to becoming models of their environments and that organisms have beliefs about the world, making these beliefs happen, minimizing expected surprise, and resolving uncertainty by actively sampling their milieus [20,139–141]. Adaptive active inference implies that organisms actively change their environmental relations by occupying states with minimum free energies [20,142].

Per the CDP, systems’ and environments’ operations reflect the numerous dynamic random stimuli that affect them. This machinery underlies the proper function of systems and enables them to operate under continuously changing random stimuli. At the cellular level, each cell’s environment has embedded irregularities at the tissue level, and the cell manifests irregularities as part of its phenotype [4–7,143]. Under the CDP, systems exist within random domains, and their relations with their milieus are random processes that reflect the multiple unpredicted opposing dynamic forces, necessitating a degree of free energy.

iii. The constrained disorder principle defines the personalized random boundaries required for systems’ functionality.

The CDP specifies that the disorder and its boundaries are random, personalized, and mandatory for existence and function. Boundaries continuously fluctuate in a subject’s-tailored way. Systems are disturbed when there is no disorder or the disorder is out of control. Moving outside the boundaries increases the energetic thermodynamic burden on systems and reduces their functionality. Different organisms exhibit diverse responses to random internal and external stimuli. A controlled degree of variability keeps a balanced degree of free energy. If the variability gets out of the arbitrary boundaries, systems lose control.

Heart rate variability (HRV) is an intrinsic irregularity in the heart rate determined by a balance between the sympathetic and parasympathetic nervous systems. It is an easily measurable parameter for modeling variability in biological systems. HRV exemplifies how a degree of variability intrinsic to the heart’s proper function varies under random stimuli, such as exercise and sleep, while keeping a healthy cardiac function [144–147].

HRV is an example of a disorder within boundaries that change. If HRV is uncontrolled, it manifests in severe cardiac disease and increased mortality and alters the response to chronic medications [148–152]. Loss of HRV is associated with increased cardiac death, implying that the system lost part of its normal function. However, short-term HRV measurements are not always markers of healthy cardiopulmonary interaction. The concept of heart rate fragmentation (HRF) was introduced to overcome this challenge. It is based on the observation that sustained physiologic changes in heart rate cannot persist at frequencies higher than those at which the entire parasympathetic nervous system operates. The primary variable of HRF is an overall increase in the frequency of changes in heart rate acceleration sign [153,154]. Both coronary artery disease and older age are associated with higher levels of HRF [153]. Both HRV and HRF measurable variables, similar to additional quantifiable variability parameters, can assist in determining trends of systems but may be insufficient for formulating the CDP with complete accuracy.

D. The constrained disorder principle provides a method for correcting disturbed biological systems

i. The constrained disorder principle defines health and disease.

The CDP defines undisturbed healthy states and disturbed diseased states. It implies that a system’s operation necessitates an intrinsic disorder restricted within its continuously changing random boundaries. Loss of disorder, or getting out of its boundaries, a too-high degree of disorder, manifests in systems’ disturbances and disease states.

Getting out of the boundaries indicates a loss of the ability to adapt to the continuously fluctuating internal or external stimuli leading to diseases. It implies a loss of systems’ flexibility and adaptability, which are mandatory for existence and proper function. Disturbances at the organelles, biochemical pathways, or whole organs exhibit diverse phenotypes in different organisms [155,156].

Loss of or augmented HRV leads to increased cardiac-related morbidity and mortality [157–159]. Similarly, alterations in nor-
mal fluctuation in glucose level dynamics define metabolic diseases such as diabetes [160]. These examples, showing how variability is inherent to organ function and its loss is associated with diseased conditions, support the fundamental role of constrained disorder in biological systems.

ii. Using the constrained disorder principle for correcting disturbances in systems.

The CDP specifies that the proper structure and function of molecules, cells, and organs necessitate a randomly-bounded degree of disorder. The principle provides a method for improving function by introducing subject-tailored variability to improve the system’s functionality. Disturbed systems that lost their disorder can benefit from implementing personalized constrained-tailored variability into their operation scheme to correct malfunction and improve functionality.

| Theme | Existing theories | The constrained disorder principle |
|-------|-------------------|-----------------------------------|
| Order or disorder | The free-energy theory suggests that biological systems resist the tendency to disorder [33,130,186]. | - Randomness is intrinsic to biological systems. - Systems do not resist disorder but comprise a balance of disorder and order within arbitrary boundaries. - The disorder is required for systems’ existence, evolution, and behavior. |
| Living organisms | Evolution is about order and optimization [19,38,187,188]. | - Living organisms are purposeless machines. - They operate with a degree of disorder and errors. - The intrinsic disorder differentiates living organisms from non-living organisms. It provides living systems with adaptability to continuously changing internal and external milieus. - Evolution is about improving the balance of disorder and order in dynamic environments. |
| Formulas | Using formulas to describe biological functions enables a better understanding of complex systems. It is helpful for modeling processes that are far from equilibrium [19]. | - The disorder and its boundaries are random and have no rules. - Formulas based on descriptive analysis oversimplify biological processes and do not reflect biological reality. - One cannot formulate the constrained disorder principle. |
| The second law of thermodynamics | Systems violate the second law of thermodynamics and the fluctuation theory [19]. | - Systems function in alignment with the second law of thermodynamics. |
| Entropy | Systems maintain low-entropy distributions over their internal states and their Markov blanket [20]. The free-energy theory suggests that systems fit their observations, requiring complex models with lower entropy [19,189,190]. | - Systems always arrive at a state of thermodynamic equilibrium and highest entropy. |
| Efficiency | Proper function necessitate order [191]. | - Entropy is mandatory for existence. - Systems are not mandated to reach a complete elimination of entropy. - It is a continuous process of balancing opposing random forces within a range of arbitrary boundaries. - Systems are not mandated to improve their efficiency. They are machines that function with a range of errors. - A constrained disorder enables higher flexibility and adaptability in continuously changing internal and external milieus. - Systems are aimless machines that do not strive to reach a state of lack of uncertainty and surprise. - Existence and proper function require degrees of surprise, uncertainty, complexity, and errors. - Operations mandate moving between numerous states. |
| Surprise | Systems act and have intentions to reduce surprise, uncertainty, and prediction errors [20,38,126,190,192]. Systems remain in non-equilibrium steady-states by restricting themselves to a limited number of states [1–3,33,130]. | - Variabilities in Markov blankets fit the requirement for a degree of disorder in systems. - Systems comprise blankets over blankets that possess randomness, continuously change, incorporate variabilities, and have inconstant boundaries. |
| Markov blankets | Markov blankets are dynamically random [38,62]. | - Systems are not mandated to reach a complete elimination of entropy. - They operate with a degree of disorder and errors. - The disorder is required for systems’ existence, evolution, and behavior within arbitrary boundaries. - Randomness is intrinsic to biological systems. - Systems do not resist disorder but comprise a balance of disorder and order within arbitrary boundaries. - The disorder is required for systems’ existence, evolution, and behavior. |
| Self-organization in biology | Self-organization means resistance to the dispersive effects of fluctuations and minimizing free energy [18,38,94–98,103]. | - Systems exist in an ongoing balance between dispersive effects of fluctuations and boundaries on these fluctuations and between maximizing and minimizing the free energy. |
| Random fluctuations | At every level of self-organization, there are fluctuations [105]. If a system is in a non-equilibrium steady-state and exists, its flow counters random fluctuations [18,72,106–109,109–112]. | - Proper structures and functions mandate a degree of fluctuations. - A degree of random fluctuation is not associated with the dispersion of molecules’ structure and function. |
| Future | Systems look into the future, select their targets and act accordingly [12]. | - Systems do not look into the future for selecting their actions. - The future is random, and the internal and external milieus continuously change. - Systems do not act towards a target. Targets keep changing and are randomly selected. |
| Disturbed systems | Disturbances are associated with insufficient minimization of free energy and disorder [12]. | - The constrained disorder is obligatory for existence and proper operation. - An excessively low or high degree of disorder and getting out of its arbitrary boundaries leads to disturbances and disease. |
| Correcting disturbed systems | | - The constrained disorder principle provides a method for correcting disturbed systems. - Disturbed systems with a low level of the disorder can benefit from implementing constrained subject-tailored variabilities to correct their malfunction and improve functionality. - Systems that function outside of arbitrary boundaries benefit from tightening them. |
The principle applies to three types of biological systems: machines that function with a relatively minimal degree of errors, such as biochemical reactions; entirely random machines, manifesting unpredictable responses toward random stimuli; and biological systems, such as HRV, that operate along imprecise trajectories comprising a degree of random behaviors within arbitrary boundaries. For all three types of machines, applying the CDP to the disturbed systems implies implementing disorder into systems’ operation schemes with a lower degree of disorder or tightening the disorder boundaries for systems where their disorder is out of control.

This method based on the CDP is similar to defective engineering of materials, suggesting that introducing a degree of error improves the structures and functions of various constituents [161–163].

Table 1 summarizes some of the differences between the CDP and several theories on biological systems.

Second-generation artificial intelligence platforms comprise algorithms based on the CDP for improving the therapeutic regimens for chronic diseases [164,165]. These platforms integrate the CDP into machine learning algorithms, getting them closer to the fundamentals of biology. They implement variability within pre-defined personalized boundaries into therapeutic regimens designed to improve clinical outcomes using personalized signatures of variability intrinsic to health and disease states [164–166].

The algorithms quantify variability signatures relevant to the disease, such as HRV in patients with cardiac diseases, variability in cytokines secretion in patients with inflammatory disorders, or variability in electro-encephalographic tests in patients with epilepsy, and implement them into the treatment regimens [10,143,167–184].

This CDP-based method overcomes the loss of response to drugs and the harmful compensatory mechanisms that reduce the effectiveness of chronic therapies [166]. Implementing variability-based algorithms enhances the response to interventions in multiple chronic diseases, including cancer, chronic pain, heart failure, epilepsy, hypertension, inflammatory diseases, diabetes, and liver diseases [2,5,6,8–10,143,164–180,185]. Using the CDP-based algorithms, which implement variability in a personalized way, the platform can overcome the challenge of drug resistance in patients with chronic disorders [164–166].

In summary, the CDP defines biological systems and the associations related to their existence and function. It describes health and disease by specifying the ongoing random process of balancing disorder and order and the personalized random boundaries of the disorder in systems. This principle provides a method for correcting disturbances of systems and, hence, improves therapies and outcomes for diseased states.

Disclosure

YI is the founder of Oberon Sciences.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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