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Constrained Disorder Principle-Based Second-Generation Algorithms Implement Quantified Variability Signatures to Improve the Function of Complex Systems

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Abstract

Improving the efficacy and overcoming the malfunctions of systems are significant challenges. Variability characterizes all levels of complex biological systems. We reviewed the relevant publications and described a method for improving the systems' function. The constrained disorder principle (CDP) defines the function of living systems based on their degree of variability. Per the CDP, the boundaries of a system define its function and efficiency. The present paper aims to describe the role of variability in biological systems and the generation of CDP-based second-generation artificial intelligence (AI) algorithms designed to improve effectiveness and correct malfunctions of biological organisms by focusing on implementing personalized variability signatures. The paper describes some of the challenges of first-generation AI systems, focusing on the three steps process of establishing the second-generation platforms comprising: the use of a pseudorandom number generator in an open-loop system, implementing variability based on feedback in a closed-loop system, and quantifying variability signatures in a personalized way for improving algorithm' output. Examples of its use in humans are provided. The CDP provides a platform for improving disturbed systems' functions using second-generation AI systems.

Keywords: artificial intelligence; variability; defective engineering; complex systems;

Introduction

Improving the efficacy of complex biological systems and overcoming malfunctions are significant challenges. The constrained disorder principle (CDP) defines the function of living systems based on their degree of variability [1]. The CDP serves as a basis for newly developed algorithms for overcoming malfunctions.

Alan Turing formulated a model that explained how random fluctuations drive the emergence of patterns and structures from initial uniformity [2]. The notion evolved is that the appearance of pattern and form in a system is far from its equilibrium state characterizes many natural processes. Turing's model explains this course, identifying a general mechanism for generating order from macroscopic uniformity and microscopic disorder [3].

The present paper describes a CDP-based artificial intelligence (AI)-system for improving effectiveness and correcting malfunctions of complex biological systems based on implementing variability signatures.

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Methods

We reviewed the relevant studies on variability in complex biological systems and the concept of using CDP-based platforms in biology. We describe the data on the use of CDP-based second-generation AI systems for improving the function of systems, describing several clinical trials where using these platforms improved biological functionality.

Results

Variability is inherent to complex biological systems

Variability and randomness are inherent properties of complex biological systems4. Variability is the constantly oscillating output of a system having random or quasi-random behavior, and randomness refers to a system's irregular, complex, and unpredictable behavior [4,5]. These properties characterize all levels of the biological organization hierarchy, from the molecular, subcellular, and cellular levels to complex organs and systems, as well as in biological development and evolution processes. [1 4, 6-10]

At the genome level, the three-dimensional organization of genomes in the cell nucleus arises from DNA loops, chromatin domains, and higher-order compartments characterized by stochasticity in transcription and variability of chromatin architecture in individual cells [11]. The stochasticity in genome organization works parallel to the deterministic processes and has functional implications. Gene expression in individual cells is stochastic, reflected by cell-to-cell variability or noise in proteins [12]. It is reflected by the number of mRNA copies of a particular gene which varies among cells of the same tissue and across time within a single cell under constant environmental conditions [4,13]. Variability in gene expression is one of the reasons for the phenotypic diversity of genetically identical cells and incomplete penetrance of genetic diseases at the organism level [4,11,14]. The highly variable genes are responsible for the specific cell-type specialized functions and do not overlap between different cell types [13]. It implies that variability is a non-incidental property of a biological system crucial for its fundamental functions.

Randomness in morphogenesis instability, biological rhythms (e.g., cell-cycle period), and asymmetric cell divisions generate intercellular variability in proteins [4,5,10,13-17]. Numerous mRNA/proteins are expressed at low-copy numbers, and significant errors are incurred in partitioning molecules between two daughter cells [18].

There are several formulas for assessing the noise in protein levels when the cell-cycle duration follows a general class of probability distributions [19, 20]. The total noise is decomposed into components from stochastic expression, partitioning errors at the time of cell division, and random cell-division events. Random cell-division times generate additional extrinsic noise and critically affect the mean protein copy numbers and intrinsic noise components [21].

At the cellular level, microtubules (MTs) have unique dynamic properties, and at any point in time, a subset of MTs is rapidly growing while others are shrinking [22]. Individual microtubules switch randomly between growing and shrinking states, sometimes changing repeatedly in their lifetime. The combination of growth, shrinkage, and rapid transitions is called dynamic instability [23]. Dynamic instability has functional implications, allowing the cell to reorganize the cytoskeleton rapidly when necessary. MTs growth and shrinkage are active processes, consuming energy so that MTs adapt quickly to environmental changes and cellular needs [24-28].

Numerous biochemical processes involve variability, essential for their function under continuously changing perturbations [29]. An inherent disorder characterizes immune responses and the effect of immunomodulatory interventions, a mechanism for the flexibility necessary for generating a proper response to antigens [29-33].

Heart rate variability (HRV) is an example of the importance of variability for proper organ functions, evolving from the balance between the autonomic sympathetic and para-sympathetic nervous systems [34,35]. Variability characterizes bone's geometrical microarchitecture during the organism's development [10], blood pressure [36], breathing [37], and gait [38]. Variability in complex systems, such as the central nervous system, arises from the independent contribution of the individual cells' variabilities and the variability in intercellular connections originating from spatiotemporal configurations, grouped firing, and heterogeneous cross-correlations [4,39-42]. From an evolutionary perspective, randomness and variability underlie the diversity of life and provide the platform for selection to occur [43].

Defective engineering in non-living systems is an example of the advantages of having a degree of variability that can improve product functions [44,45]. The inherent variability of all biological systems levels is an example of the need for noise for proper functions [4,6-9 24-29,32 ,33 ,46].

Randomness in biology does eliminate order

Randomness in biological systems does not eliminate the existence of order, regularity, and organization. Process unpredictable outcomes are constrained and generated from a restricted repertoire of possibilities or under limitations, which show variability over time [10,16] The stochastic nature of biology does not imply that the outcome of a process is entirely random. An underlying disorder may be essential for higher degree order via a selection process. A healthy immune system function is based on an uncountable assortment of randomly generated antibodies originating

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from a limited set of genes. The selected epitope-directed immune element operates at a specific time according to the environmental circumstances [43,47].

The constrained disorder principle defines complex systems by their degree of inherent disorder

The constrained disorder principle (CDP) defines biological systems based on their degree of variability constrained within dynamic borders [48]. The degree of disorder differentiates living from non-living systems. Non-living systems are characterized by a relatively low degree of disorder and narrow borders, while living organisms have a high degree of disorder within broad dynamic boundaries, enabling adaptability to the continuous changes in the internal and external environments [48].

Per the CDP, the boundaries of a system express its function and efficiency. Systems malfunctions are defined as narrow boundaries limiting the degree of disorder to an insufficient level for dealing with dynamic perturbations in the environment or in cases where the degree of disorder is too high getting out of the boundaries, reducing system functionality [1].

Healthy biological systems operate at the "edge of chaos," not necessarily aiming to maintain steadiness under every condition, as indicated by their oscillating output even under resting conditions [4,5,8]. These fluctuations represent the interactions of multiple regulatory mechanisms. This dynamicity enables flexibility, which is essential for the proper function of a nonlinear transformable system in an unstable environment.

The steps of generating CDP-based second-generation artificial intelligence systems

First-generation artificial intelligence (AI) systems are designed to look into big data sets and analyze them for developing diagnostic and prognostic schemes. These algorithms are affected by biases related to the data, end-users, and the dynamic nature of biological systems 49. Numerous first-generation apps remind patients to take their medications to improve adherence. However, the low engagement of patients and physicians in using these systems remains a significant challenge [50-52].

Second-generation AI systems are generated based on the CDP for controlling complex systems' degree of variability to overcome malfunctions and improve efficacy [5]. These systems personalize the output based on continuously dynamic inputs from the subject and the environment. These systems are focused on meaningful endpoints, ensuring improved engagement by end users [5,53,54].

Second-generation AI systems are created in three steps [5,55,56]. In the first step, implementing variability into a system is conducted. It is an open-loop system, and no feedback is received. Implementing randomness improves function in cases where the degree of disorder is too low due to narrow non-flexible borders. In the second stage, a closed-loop system is implemented where the degree of the disorder is adapted based on pre-defined endpoints. Feedback is received from the end-user and the environment. In the third step, the algorithm receives quantifications of variability signatures from a targeted system and implements them into machine learning to improve the pre-defined endpoint. These signatures are personalized cell or organ variabilities, where variability is quantified and implemented into the algorithm. Second-generation AI systems' dynamicity enables them to adapt continuously to internal and external changes.

Figure 1 presents the three steps for using variability to overcome malfunctions in complex biological systems by providing a method for regulating the degree of variability in a targeted system in a personalized way.

CDP-based second-generation artificial intelligence systems for overcoming drug resistance in subjects with chronic conditions

Prescribing medication stationary and regularly does not capture inter and intra-individual variability in drug response and disease course; thus, it may not be suitable for all patients [55,56]. In contrast, constant alterations in timing and dosing of drug administration within a physician-approved range may overcome and correspond to the system's integral variability, thus improving the drug effect [4]. In patients with chronic diseases, including heart failure, hypertension, epilepsy, depression, cancer, chronic pain, and inflammatory diseases, loss of response to chronic medications is a significant challenge [57].

The CDP provides a platform for refining and optimizing interventions. Drug holidays and arbitrary alterations (dose escalation or reduction) in drug administration are variability-based methods for improving medical therapies. Alternate-day statin prescription showed no difference in LDL-C reduction and equal tolerability compared to daily-dosing statins [58]. Implementing variability into anti-cancer therapies by alternating periods of drug cessation and re-administration delays the emergence of drug resistance [59-62]. Variable dosing intervals of basal insulin in diabetic patients showed similar efficacy compared to fixed-time insulin administration [63,64].

The second-generation AI system serves as a basis for the digital pill, which comprises any drug the algorithm regulates its administration [55]. The digital platform is used for improving response to chronic medications. The digital pill is designed to regain the drug's effect and improve the response to drugs by implementing variability into therapeutic regimens in a personalized way [29,54,65-83].

The second-generation AI-based digital pill involves

three steps based on the above-described scheme. In the first stage, physicians provide subjects with an app with a range for drug administration within the therapeutic window of that medication. The app reminds the patient to take the drug at different times and dosages within the pre-defined range. The algorithm comprises a pseudorandom number generator that randomly selects a dose and time of administration from a physician's range.

The following three clinical trials exemplified the benefits of using the first step of a second-generation AI system in patients with chronic diseases.

In patients with congestive heart failure, in whom diuretics are the primary therapy, the development of resistance is widespread [84]. Using the digital pill in patients with heart failure and severe diuretic resistance improved the clinical and laboratory parameters, reducing admissions and hospitalizations due to heart failure exacerbations [85]. A high engagement rate of patients and providers to the app was documented, as users experienced a significant clinical improvement when taking their diuretics as their cell phone app instructed.

In patients with multiple sclerosis treated with Tacfidera, drug tolerance, a lack of maximal response, and prohibiting side effects limit its use [86,87]. The digital pill in these patients stabilizes disease progression and improves clinical parameters. A high engagement rate of patients with the app was recorded during the study. (unpublished). The administration of medical cannabis suffers from a lack of adherence, inability to titrate the dosage, and loss of effectiveness [80]. In a real-world follow-up of patients who received prescribed medical cannabis for chronic pain due to multiple indications, digital medical cannabis increased patients' adherence to the treatment regimens and improved the clinical response assessed by the pain score (unpublished).

A closed loop is implemented in the second level of the algorithm, which collects data on the pre-defined clinically meaningful endpoint. The algorithm adapts the variability in dosages and administration times, a chronobiology-dependent effect, to the endpoint in a personalized way. As an example, it can identify that males should receive a drug within 5-9 PM to achieve a better clinical response. As the algorithm is personalized and dynamic, it changes the regimen provided to patients over time.

For the third level, personalized biological variability signatures are quantified and implemented into the algorithm. These include HRV in patients with cardiac disorders, variability in cytokine secretion in patients with arthritis or inflammatory bowel disease, blood pressure variability in patients with hypertension, and breathing variability in patients with chronic lung disorders5 [55,56].

Using variability signatures to generate a relevant time-specific personalized patient-disease-drug-environment-based output presents a clinical challenge. The algorithm aims to bring the system to a desired physiological endpoint by up or down-regulating the external variability source based on alterations in internal variability signatures. These signatures are inferred from the patient's and physician's reports. By applying them to the deep learning algorithm, the system determines the optimal strengths and intervals of drug administration. The second-generation AI system can operate using only single patient continuous data [56]. However, the system can refine its performance and precision based on other users' data and the patient's response [56].

Figure 2 illustrates some of the variability-inspired disease-specific indices that can be used for the third stage of the algorithm.

Figure 2: A schematic presentation of several variability-inspired disease-specific indices that can be used for the third stage of the algorithm

A scheme for improving the effectiveness of biological systems by implementing quantified variability signatures

The malfunction of systems remains a significant challenge

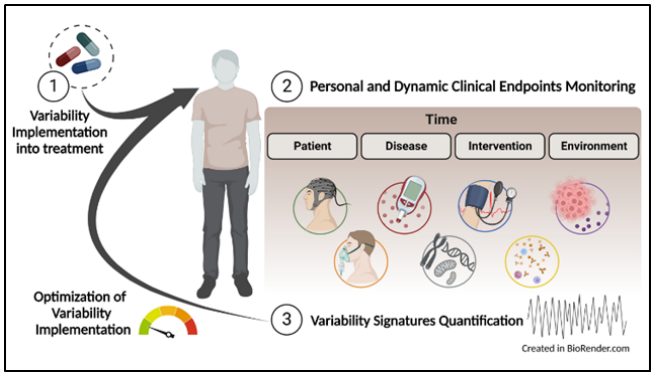

Figure 1: A schematic presentation of the three steps for using variability to overcome malfunctions in complex biological systems using a method for regulating the degree of variability in a personalized way.

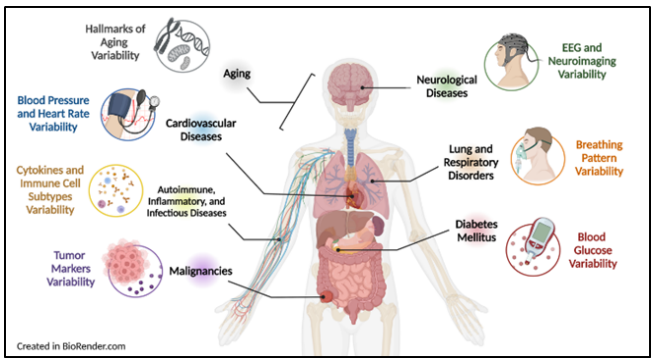

Figure 2: A schematic presentation of several variability-inspired disease-specific indices that can be used for the third stage of the algorithm

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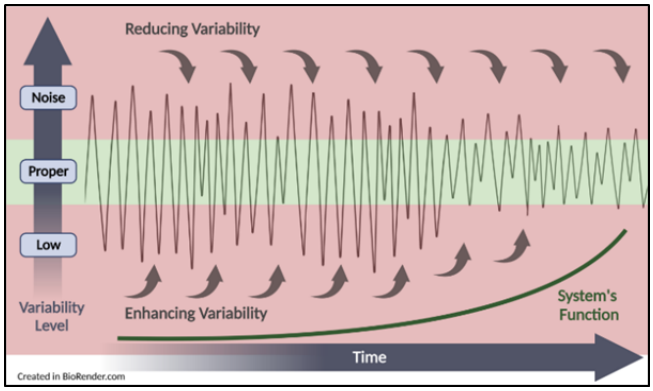

Figure 3: A pictorial presentation for overcoming malfunctions and improving the effectiveness of biological systems by differentiating between inherent variability and unwanted noise. The system implements machinery to regulate the disorder, increasing it when it is low and reducing disturbing unwanted noise.

in all areas. Differentiating the inherent variability required and the noise resulting from malfunctions is mandatory. This differentiation is one of the most significant challenges when looking into malfunctions of biological systems. Per the CDP, "unwanted noise" represents a high degree of variability outside the borders that must be regulated.

Figure 3 presents a scheme for overcoming malfunctions and improving the effectiveness of biological systems by differentiating between inherent variability and unwanted noise. The system implements machinery to regulate the disorder, increasing it when it is low and reducing disturbing unwanted noise.

In summary, the CDP provides a platform for defining biological systems and improving disturbed systems' functions. The use of CDP-based second-generation AI systems is a promising method for making use of noise in a biological system. Ongoing studies are expected to improve the ability to differentiate the inherent variability from unwanted noise in complex systems, which can further improve the algorithm.

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Abbreviations: CDP: constrained disorder principle; AI: artificial intelligence; MT: microtubules; EDSS: The Kurtzke Expanded Disability Status Scale

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