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The Constrained Disorder Principle Defines Mitochondrial Variability and Provides A Platform for A Novel Mechanism for Improved Functionality of Complex Systems

Yaron Ilan

Abstract

Traditionally viewed as static structures, new advancements in molecular biology and imaging have revealed the dynamic nature of mitochondria. Exploring the functional implications of mitochondrial DNA variability provides insight into the mechanisms underlying physiological processes and potential associations with metabolic disorders. The Constrained Disorder Principle (CDP) is a fundamental law that applies to all living and non-living systems in nature. The principle describes every system in terms of its inherent variability, which is bounded by dynamic boundaries, allowing it to adapt to environmental changes. According to the CDP, inherent variability is necessary for complex systems to function correctly. This paper aims to explain how the CDP defines mitochondrial variability. The CDP explains how mitochondria adapt to the demands and pressures placed on them by the cellular environment. Evidence linking mitochondrial variability to various diseases demonstrates the importance of CDP-defined dynamic boundaries of variability in complex systems. An artificial intelligence platform based on CDP is presented as a potential tool for diagnosing and treating mitochondrial diseases, which could be used to improve system functionality and overcome disease states.

Keywords: Mitochondrial variability; constrained disorder principle; artificial intelligence; complex systems

Abbreviations

CDP: constrained disorder principle; mtDNA: mitochondrial DNA; ROS: reactive oxygen species; ncDNA: nuclear DNA

Introduction

The mitochondria are two-membraned organelles found in eukaryotic cells, including humans. Their functions include energy production, regulating apoptosis, and participating in various cellular processes [1]. Cell metabolism, calcium homeostasis, and reactive oxygen species (ROS) are all controlled by mitochondria [2]. The mitochondria contain mitochondrial DNA (mtDNA), passed down maternally [3]. While nuclear DNA undergoes recombination, mtDNA is predominantly inherited as a single unit, making it easier to study its variability across populations [4]. Most cells contain multiple mitochondrial genomes, ranging from hundreds in some cells to several hundred thousand in human oocytes. Human mitochondrial genome alterations are associated with numerous disorders affecting almost all tissues [5]. The Constrained Disorder

Affiliation:
Faculty of Medicine, Hebrew University, and Hadassah Medical Center, Jerusalem, Israel

***Corresponding author:**
Yaron Ilan, Faculty of Medicine, Hebrew University, and Hadassah Medical Center, Jerusalem, Israel.

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Principle (CDP) defines the inherent variability in complex systems as mandatory for their proper function [6]. Per the CDP, the system's variability is bounded by dynamic barriers crucial for adapting to changing environments.

This paper explores mitochondrial variability, delving into genetic diversity, evolutionary dynamics, and the functional implications of this intriguing aspect and potential links to health and disease. It describes how the CDP defines mitochondrial variability, providing insights into the role of mitochondrial dynamics in cellular function, adaptation, and potential therapeutic implications. A CDP-based second-generation artificial intelligence platform for improving diagnosis and therapies for mitochondrial diseases is presented, suggesting a method for using mitochondrial variability to improve systems functionality.

The constrained disorder principle accounts for the improved function of complex systems.

All natural systems are characterized by a certain level of variability and noise [7-20]. Several processes in cellular biology are affected by stochastic processes in some way [21-23]. Variability at the genome level, apoptosis-inducing factors, stem cell fate decisions, and bacterial phenotype bet-hedging are examples of cellular processes affected by noise [24, 25]. Genes under identical regulation exhibit different expression levels in the same cell due to intrinsic noise originating within the gene. The variation can also be caused by extrinsic sources, resulting in cell-to-cell gene variations under identical regulation [26]. Observations in transcription rates and protein expression levels suggest that both intrinsic and extrinsic noises play a role in influencing these levels [21, 27]. Cell-to-cell variability in transcription and translation rates affects the intrinsic dynamics of gene expression. Intrinsic noise can be influenced by external noise [28]. The CDP is a fundamental law that describes all systems in nature based on their degree of variability [6]. According to the CDP, inherent variability must exist for the system to function correctly under continuous intrinsic and extrinsic environmental pressures. There is a dynamic nature to the degree of variability in a system. It constantly changes due to perturbations that force the system to adapt to environmental changes. Within the dynamic boundaries of the variability, there can be an increase or decrease in the internal variability [29]. As a result of the dynamic nature of the boundaries, systems can improve their functionality under pressure. Living systems are characterized by wider borders and a potentially higher degree of variability than non-living systems with narrower border dynamicity. Dysfunctional borders are associated with diseased states because they lead to an inability of the borders to respond to pressures [30].

The CDP defines mitochondrial inherent variability as a mechanism for adaptability to cellular pressures, which enables proper function.

According to the CDP, mitochondria possess various structural elements that allow them to adapt to the needs of cells due to the diversity of their structural elements [31]. Advances in DNA sequencing technologies have revolutionized the study of mitochondrial variability. With high-throughput sequencing, mtDNA genomes can be analyzed rapidly and cost-effectively, making large-scale population studies possible [32-35]. The size, shape, and organization of mitochondria are structurally variable [33]. There are functional differences between mitochondria, with elongated mitochondria favoring oxidative phosphorylation, while fragmented mitochondria are associated with apoptosis and cellular stress [34, 35]. Per the CDP, optimal variability is mandatory for proper mitochondrial function. Environmental noise plays a vital role in mitochondrial biology. The noisy environmental pressures are reflected in mitochondrial genome variations, copy number variations, and mutations occur [29]. As outlined in the CDP, these changes reflect the dynamicity of the boundaries of the variability within systems. The degree of variability is dynamic in response to pressures from the intracellular and external environments and enables adaptation and maximizes the function of the mitochondria under dynamic conditions. For mitochondria to function correctly and cells to maintain homeostasis, the boundaries must function correctly. Based on the CDP, mitochondrial dynamics are adaptable across different organisms, demonstrating that mitochondria can adapt to different environments [6, 29].

The inherent variability of the mitochondria is mandatory for its proper functionality and illustrates how the CDP is necessary for the system's efficiency. Variability is a characteristic of mitochondrial function [36]. Mitochondrial function is variable due to distinct subpopulations with specialized roles. Functional diversity is essential to maintain cellular homeostasis and respond to environmental cues. By maintaining a balance between the events, mitochondria can maintain a functional network. As defined by the CDP, mtDNA sequence variability influences oxidative phosphorylation efficiency, contributing to individual differences in energy metabolism [37]. As a result of the mitochondrial fission and fusion processes, these organelles are dynamic and adaptive [38-40]. The mitochondria perform various functions beyond energy production, such as calcium regulation, ROS generation, and apoptosis. Through oxidative phosphorylation, mitochondria produce cellular energy [41]. Variability in mitochondrial dynamics enables cells to adapt to changing energy demands, cellular stress, and environmental stimuli, illustrating mitochondria's adaptability [35].

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As defined by the CDP, mitochondrial masses can be distributed widely within a cell population, demonstrating that extrinsic variables can influence organelle variables [42]. Cells differ in their mitochondrial functionality [43]. Mitochondrial mass and membrane potential are linked to cellular ATP levels, and transcription rate is determined by ATP concentration [44]. Modifying mitochondrial functionality through anti- and pro-oxidant treatments alters cell-to-cell variability in transcription rates, with antioxidants significantly reducing variability and pro-oxidants increasing it [45]. As mitochondrial mass and functionality differ from cell to cell, extrinsic noise in the transcription rate propagates downstream [21].

Some of the variability in mitochondrial function can be attributed to genetic diversity in mtDNA [36]. Several nuclear genes encode proteins essential to mitochondrial function, and variations in these genes can affect mitochondrial phenotypes. A mitochondrial cell possesses its genetic material (mtDNA), and the multiple copies add to its variability [3]. Maternal inheritance contributes to the unique patterns of variation in mtDNA. Unlike nuclear DNA (ncDNA), mtDNA is typically inherited without recombination [46]. The non-recombinant nature of mtDNA results in clonal transmission from generation to generation, enabling the precise tracing of maternal lineages [47]. Per the CDP, mutations that are part of the cellular responsiveness to pressures can be beneficial, while those leading to pathological conditions reflect the malfunction of the boundaries, enabling increased noise, which can be deleterious [29]. Mutations in mtDNA occur more frequently than in ncDNA, affecting cellular bioenergetics. Mutations in mtDNA can be neutral or pathological depending on whether somatic or inherited [48]. These mutations can be linked to various pathological conditions [49]. Based on mtDNA sequences and per the CDP, the molecular clock hypothesis estimates divergence times between populations and species by assuming a constant mutation rate over time [50]. A mitochondrial genome consists of numerous copies per cell and is polyploid. As a result, a mitochondrial mutation can be homoplasmic if it appears in every copy of DNA and heteroplasmic if it appears in only some copies of DNA [4, 48, 50]. Different tissues have different mutational loads, and some mutations are tissue-specific. Pathological changes are observed above a threshold ratio of wild-type to mutant mtDNA copies at the heteroplasmy level [48, 51]. These thresholds vary depending on oxidative phosphorylation and mutation type [48].

The role of the CDP in evolutional changes is reflected in the analysis of ancient mtDNA [29]. mtDNA analysis has revealed distinct haplogroups, or clusters of closely related haplotypes, providing insights into human evolution [52]. Studies on diverse populations are required to capture the full spectrum of human genetic diversity due to mitochondrial variability, which exhibits population-specific patterns [53]. Based on mtDNA sequences, phylogenetic trees reveal migration patterns, demographic events, and population expansions of these haplogroups [54]. Ancient DNA extracted from archaeological remains provided information about the genetic diversity of past populations. As a result of mtDNA analysis, distinct haplogroups, clusters of closely related haplotypes, have been identified, offering insights into the evolutionary history of human populations [55]. Recent data supports the CDP-based mechanism, which accounts for the mtDNA variation. The number of genes that can be inherited from mtDNA is one-fourth that of ncDNA. Due to the higher effect of genetic drift on mtDNA, mtDNA haplotype diversity (h) is predicted to be lower than ncDNA heterozygosity (HE). In mammalian populations, mtDNA diversity is higher than in nuclear microsatellites [56]. The results of a study involving 739 populations of 108 mammalian species (66 terrestrial and 42 marine) showed that 54.9% of the populations had higher HE. In terrestrial species, h has a significantly higher variance than HE, while in marine species, h has a different frequency distribution [56]. The Genome Aggregation Database (gnomAD) demonstrated mtDNA variation across 56,434 individuals [57]. According to the study, heteroplasmic variants are occurring at a rate of 10% or greater. Nearly all haplogroup markers and thousands of additional rare homoplasmic variants were called homoplasmic.

As defined by the CDP, the epigenetic modifications in mtDNA, such as DNA methylation and histone modifications, regulate mitochondrial function [58]. Mitochondrial epigenetics and their variability influence cellular processes [60]. Environmental factors such as diet, exercise, and environmental stressors can affect mitochondrial function and variability [59, 60].

The CDP B=F Formula in the mitochondrial context

The CDP is schematically formulated by the B=F formula, where *B* stands for the variability borders and *F* for the system's functionality and efficiency. As a result of its dynamic nature, the boundaries can adapt to environmental pressures as they arise. A system can have a range of variability boundaries that can be either broader or narrower, depending on how much variability is required [6, 20, 29, 30]. The B=F formula applies to the mitochondria, where B represents the dynamic boundaries (e.g., fusion/fission), and F signifies the functionality (e.g., bioenergetics and ATP production). The mitochondrial dynamics, including fusion and fission processes, act as dynamic boundaries, allowing mitochondria to adapt to cellular needs and environmental changes. Per the CDP, when the degree of variability within the mitochondria changes inappropriately, it can result in malfunctions and diseased states in the organism. It can occur if the boundaries do not allow for sufficient variability when needed or have too high variability, leading to diseased states [30].

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The CDP accounts for the effect of mitochondrial variability on other systems and disease conditions.

Many fundamental cellular processes are affected by noise, including transcription, translation, stem cell differentiation, and medication response [7-20, 27]. Following the CDP, inherent variability can improve functionality when kept within proper limits. According to the CDP, mitochondrial variability profoundly influences several physiological and pathological processes. According to the CDP, a malfunction of a system may be attributed to a disturbance at the dynamic borders of its variability. There are a variety of diseases that are associated with mitochondrial dysfunction. Various clinical signs are associated with mitochondrial diseases, partly because the respiratory chain malfunction leads to aberrant cell signaling [48]. When the mitochondrial electron transport chain malfunctions, the cell suffers dramatic consequences, including decreased ATP and calcium uptake and increased ROS. Cells can become dysfunctional or die as a result of these effects [48]. Per the CDP, these reflect borders malfunction, enabling an inappropriate degree of variability in a system.

A wide range of cellular processes and properties are affected by mitochondrial and transcriptional variability [21]. Mitochondrial volume, function, and cell cycle dynamics are linked to transcription rate variability and profoundly affect downstream cellular processes [61]. During eukaryotic cell division, noise is generated by mitochondrial variability in eukaryotic cells. According to the CDP, induced transcription rate variability significantly affects bipotent cells' stability due to cell-to-cell variability in mitochondrial mass and function. The transcription rate can be affected by noise in mitochondrial segregation and variability in mitochondrial mass and functionality [42]. The effects of mitochondrial variability dominate the variability in protein expression [62, 63]. Cell cycle asynchronicity and gene expression levels can be affected by mitochondrial noise, which can dominate other extrinsic noise sources. Extrinsic noise in transcription rate causes significant variability in the behavior of regulatory network-based models for stem cell differentiation [21].

According to CDP, an abnormal alteration in the degree of mitochondrial variability can result in various diseases [6, 29]. There are mutations and polymorphisms in mtDNA that are associated directly with muscle and nervous disorders; others seem to increase the risk of diabetes, Alzheimer's disease, Parkinson's disease, bipolar disorder, and cancer [64-66]. In addition, mitochondrial polymorphisms are associated with individual differences in cognition, personality, athletic performance, and longevity [67]. By altering mitochondrial matrix pH and intracellular calcium dynamics, mtDNA polymorphisms also play a role in the pathophysiology of complex diseases [67]. By targeting ratiometric pericam (RP), a fluorescent calcium indicator, to mitochondria and nucleus, mtDNA polymorphisms were demonstrated to have functional significance within the cell. Two closely related nonsynonymous polymorphisms increased the basal fluorescence ratio of mitochondria-targeted RP. In the cybrids with 8701A/10398A, mitochondrial matrix pH was lower than in those with 8701G/10398G, indicating that mitochondrial calcium levels were likely to be responsible for the difference observed by RP. Parkinson's disease, Alzheimer's disease, bipolar disorder, and cancer are associated with 10398A, whereas longevity is associated with 10398G [68, 69].

Cancer development is associated with CDP-based mechanisms that account for inappropriate mitochondrial variability [70]. Certain tumors have variations in the mtDNA sequence. Carcinogenesis and cancer progression are affected by subtle changes in mtDNA [71]. Mutations that occur de novo act as 'inducers' of carcinogenesis, while functional variants act as 'adaptors,' allowing cancer cells to thrive in different environments. Among these, mtDNA variants are inherited and passed down from generation to generation, somatic mutations originating within each cell, and variants associated with ancient mtDNA lineages. These haplogroups allow for adaptation to changing tissue or geographical environments. Cancers can also be caused by differences in mtDNA sequence, copy number, and nucleoplasmic transfer of mtDNA. Nuclear DNA-encoded mitochondrial genes play a critical role in mitochondrial metabolism in cancer, affecting mitochondrial reactive oxygen species production, redox state, and chromatin-modifying enzyme substrates [72, 73].

Throughout cancer, mtDNA is altered by mutations, deletions, and changes in copy number [74]. MtDNA levels tend to be depleted in bladder, breast, and kidney cancers compared to normal tissue. A correlation between mtDNA content and several somatic alterations, including gliomas, was described. mtDNA content correlates with respiratory gene expression in some cancer types but not with immune response and cell-cycle genes. Tumors may compensate for mtDNA depletion by retaining respiratory proteins [75]. A cell's mitochondrial content determines its apoptotic fate and modulates its dying time. Cells with higher mitochondrial content are more likely to fail. The leading cause of tumor resistance to chemotherapy is fractional killing. The phenomenon occurs even in genetically identical cancer cells in homogeneous microenvironments. It was reported that mitochondria play a different role in apoptosis as the global regulator of apoptotic protein expression [76]. As per the CDP, these changes can be attributed to the inappropriate function of the borders of the variability, which allows for an unavoidable increase in the variability within the cells.

The CDP provides a platform for defining longevity [77]. Longevity is linked to mtDNA variability and is affected by

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mitochondrial genetic variability [78]. Numerous studies have demonstrated that mtDNA is crucial in age-related pathology, although many correlate rather than causal [78].

A CDP-based system that implements variability can improve the response to therapies [79]. A significant association between mtDNA variants and drug efficacy, toxicity, and resistance was suggested [80]. It supports the requirement for a regulated degree of variability for proper response to therapeutic interventions [81]. A key area of active research is the interaction between genetic variability in mtDNA and susceptibility to mitochondrial-linked diseases [82]. Identifying specific mtDNA variants with functional implications can illuminate the molecular mechanisms behind these diseases and pave the way for targeted therapeutic interventions [83]. Per the CDP, the linkage of mitochondrial variability to disease state reflects the dysfunction of the degree of mitochondrial variability. While a certain degree of variability is mandatory for adapting to changing environments, the inability to respond to pressures can decrease or increase the degree of variability associated with disease states [20, 29].

Future directions and implications of CDP-based platforms which comprise mitochondrial variability.

The CDP provides a method for using noise and variability to improve the performance of ש system [6, 84]. To make malfunctioning systems more efficient, a second-generation artificial intelligence (AI) platform based on the CDP has been designed to improve their functionality [85]. It is a system that is based on three steps. As a first step, introducing variability into existing systems enables them to overcome malfunctions caused by habituations. It is an open-loop system based on randomly increasing system variability [79]. In the second step of the process, a closed-loop algorithm can be used to regulate the degree of variability according to system functionality and predetermined outcomes that are determined in advance [86]. During the third step of the algorithm, the algorithm quantifies the variation signatures of the system and integrates them into it while monitoring the outcomes of the process [79, 81, 85-87]. As a result of using CDP-based second-generation artificial intelligence systems, biological systems can be improved in functionality and efficiency [16, 30, 70, 77, 88-107].

Using mitochondrial variability as a source of variables can enable their implementation into the CDP-based platform. The algorithm is intended to treat mitochondrial-linked diseases where regulating mitochondrial variability is expected to be an effective means of improving the overall functioning of the system. It can be done using the CDP-based digital pill, an algorithm that regulates the degree of mitochondrial-targeted therapies based on the CDP [79].

Table 1 illustrates several methods to use CDP-based platforms and mitochondrial variability to improve the diagnosis and treatment of mitochondria-associated diseases. Mitochondrial variability-based measures can improve the accuracy of digital twins designed for improving diagnosis, monitoring, and therapies of chronic diseases associated with mitochondrial dysfunction [84]. The CDP provides a mechanism for improving personalized precision medicine, which can be implemented in treating mitochondrial-related diseases [86]. Studies are ongoing to investigate the therapeutic potential of interventions based on understanding mitochondrial variability, such as targeted treatments for mitochondrial disorders and diseases associated with mitochondrial dysfunction. Studies on diverse populations must be conducted to capture the characteristics of mitochondrial variability specific to each population to capture the full spectrum of human genetic diversity. By integrating data from ethnicities and regions, we can better understand mitochondrial variability and the potential implications for global health. In the context of personalized medicine and targeted treatments for mitochondrial diseases, ongoing studies will better dissect the implications of mitochondrial variability.

Conclusion

Genetic diversity, evolutionary dynamics, and functional implications are all part of mitochondrial variability. Interdisciplinary research approaches and advances in sequencing technologies continue to unravel some of the questions of mtDNA variability. Epigenetic studies of mitochondrial variability add a new dimension to understanding mitochondrial variability, paving the way for future discoveries in mitochondrial biology. The CDP provides a fundamental law to define mitochondrial variability. Integrating nuclear and mitochondrial genomics and population-specific studies using CDP-based second-generation AI systems can further refine the understanding of this crucial aspect of cellular biology as research advances. By using the variability, it is possible to improve the response to therapeutic intervention in mitochondria-related diseases by improving the effectiveness of the interventions.

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