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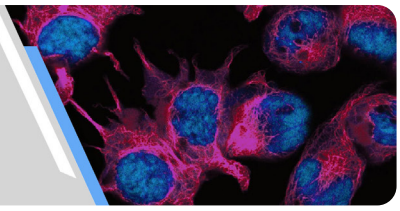

The Constrained Disorder Principle Accounts for The Structure and Function of Water as An Ultimate Biosensor and Bioreactor in Biological Systems

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Abstract

The constrained disorder principle (CDP) defines living organisms as systems that comprise an intrinsic disorder bounded by dynamic boundaries. Water plays a substantial role in multiple biological processes affecting nucleic acids' and proteins' structure and function. The paper describes the CDP-accounted water structure dynamicity and variability in water isomers ratio. Per the CDP, the variability in the ratios between water isomers is mandated for the inherent variability of biological systems. This variability underlies water's unique functions and enables the flexibility and adaptability required to cope with internal and external environmental changes. The CDP-dependent water structures also determine energy usage. The paper presents water molecules as ultimate biosensors for stimuli in the environment and as the ultimate bioreactors that respond to perturbations by changing the structure and function of the molecules in their vicinity. Finally, it describes the potential of using water-based signatures of variability to improve artificial intelligence-based algorithms developed for correcting disturbances of biological systems by increasing the degree of disorder in systems or tightening the disorder's boundaries.

Significance statement

The constrained disorder principle accounts for water structure dynamicity and variability. Water isomers are mandated for the inherent variability of biological systems. This variability underlies water's unique functions and enables the flexibility and adaptability required to cope with internal and external environmental changes.

Non-standard Abbreviations: CDP: constrained disorder principal

Introduction

Liquid water is central to life, but its roles in sustaining life are imperfectly understood [1, 2]. The oversimplifying view is that water is a passive solvent that functions as a vehicle for the diffusive motions of electrolytes, proteins, and nucleic acids. Nonetheless, water plays an active role in multiple biological processes [3]. Hydrophobic attraction forces determine macromolecular conformations and associations to form different structures and play a role in information-transfer processes in the cell and hydrodynamic processes [1, 4]. Water is a nucleophile and proton donor and acceptor, mediating electrostatic interactions, and undergoes fluctuations and phase-transition changes as part of its functions in the body [5].

The constrained disorder principle (CDP) defines systems based on their intrinsic disorder confined within dynamic boundaries [6]. The CDP accounts

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for the disorder that characterizes the inherent variability of the genome, cellular functions, and whole organs [7-11]. The paper summarizes the role of water in biological systems and describes CDP-based methods for using water to improve diagnosis and therapy.

The Constrained disorder principle determines the structure and function of living and non-living organisms

The CDP defines living and non-living systems based on their degree of variability bounded by arbitrary dynamic boundaries [12]. Per this principle, living and non-living systems differ by their degree of disorder. The non-living system, similar to artificial machines, has a relatively low degree of disorder bounded by narrow boundaries. In contrast, living systems are characterized by a high degree of inherent disorder, providing them the flexibility and adaptability required to function under numerous internal and external random perturbations [12].

The CDP provides a platform for correcting disturbances of biological systems by increasing the degree of disorder in systems that lost the disorder or by tightening the boundaries of the disorder when it is out of control [12, 13]. Using the CDP to correct the malfunction of biological systems and improve organ function necessitates the determination of signatures of variabilities that characterize biological systems from the genome level to whole organs, such as variabilities of heart rate, breathing, gait, and brain function [7-11, 14-26]. The use of signatures of variability in artificial intelligence (AI)-based algorithms that quantify and implement them into therapeutic regimens is being studied to improve the response to therapies for chronic diseases [27-46].

The CDP accounts for the fluctuating hydrogen bonds structure of water

The CDP accounts for the dynamic structure of water molecules. Water in the cell is a versatile, adaptive component that engages in a wide range of biomolecular interactions. Part of the versatility of water depends on the water's hydrogen-bonding capacity [3]. The interactions between water, hydrogen bonds, and the molecules in their vicinity impact the structures and functions of these molecules [3, 47]. Molecules do not merely exist in the water, as do the particles of a simple liquid. They are held apart by hydrogen bonding, which imposes geometric constraints on the molecular positions [3, 48].

Water is a dynamic entity that forms fluctuating hydrogen bonds with an average lifetime of around a picosecond [49]. 10–25% of water molecules in cells have slower reorientation dynamics [50]. The "slow water" hydrates macromolecules and other cytoplasmic solutes. The H_2O molecule forms a tetrahedral shape that serves as a building block of ephemeral five- and six-membered rings containing a space providing ice a lower density than the liquid [51]. A balance between water-solute and water-water interactions, including hydrogen bonds, electrostatic and van der Waals forces, and the entropic significances of the hydrogen bonding, is conditioned by variables of the interfaces of the microenvironment [1, 52]. Water molecules show a relatively large range in bond angle and lengths [53]. In addition, there is much variability in the water contact angle, which may reflect an inherent structure variability and parameters related to the external environment and the measurement methods [54, 55].

The CDP determines the dynamicity of water-based systems

The interactions between proteins and water involve fluctuations over a wide range of timescales from milliseconds to picoseconds, influencing several aspects of protein function [56]. Per the CDP, this dynamicity is necessary for the correct function of proteins under continuously changing internal and external stimuli [6]. The dynamical behavior of both the solvent and the macromolecules, including proteins, underlie all reactions [1]. Per the CDP, dynamical degrees of freedom in the hydration shell enable mandatory fluctuations for proteins to undergo the conformational changes required for their chemical function [57]. Enzymes' actions involve conformational freedom requiring both structure and dynamics [58]. A decline in enzymatic activity is associated with weakening "soft" phonon modes [59]. Short-wavelength fluctuations evolve from hydration layers, whereas large-scale protein motions result from solvent fluctuations [1, 60].

This continuous dynamicity evolves from the fluctuations in the interactions between the water and the molecules it interacts with [61]. The interactions are subject to changes in the microenvironment. The degree of disorder, which characterizes the water-molecule shell, provides them with the level of freedom, flexibility, and adaptability mandatory for appropriate function [47, 62, 63]. This dynamicity follows the CDP and is mandatory for the function of biological systems.

CDP-based dynamicity determines the function of water in biological systems

The CDP-accounted water structure dynamicity underlies its unique functions. The distinctiveness of the H2O molecule accounts for much of its properties. Water serves more than simple solvents and plays a role in multiple biological processes [3]. Water keeps macromolecular structure and is associated with molecular recognition [64]. It is associated with protein dynamics and provides a switchable communication channel across membranes and inside and outside proteins [65]. Water molecules can engage in directional, weak bonding enabling reorientation and reconfiguration of three-dimensional structures [3, 66].

The biological function of molecules depends on

Ilan Y., Int J Appl Biol Pharm 2023
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the interaction between the water and molecules in its environment1, 3. Water molecules mediate the folding of proteins [3]. Numerous proteins possess dehydron units concentrated at sites associated with other proteins and assist in protein-protein interactions [3, 67]. Protein-protein contacts mediated by water are linked to recognition and docking and play a mechanistic role in protein function [3, 68]. Proteins can use bound water as functional units to interact with other proteins and substrate molecules [3, 69]. The hydration environment's sensitivity and the water molecules' motions contribute to small changes in protein conformation, impacting their behavior [70]. The structure and dynamics of the hydration shell provide feedback to the proteins. Nucleic acid structure necessitates water. The hydration structure of DNA has a functional role in determining its conformation [71]. The conformational state of double-stranded DNA in solution is susceptible to hydration [3, 72]. The DNA undergoes conformational transitions in polar solvents and can lose its double helix [73]. The structure of water molecules transmits sequence information to remote locations from the DNA bases [74].

Water molecules create hydrogen bonding with surface groups for hydrophilic interfaces, such as acidic residues in proteins. For hydrophobic surfaces, observed in protein-ligand binding, water forms structures that preserve the hydrogen bonds and are dominant in molecular biology [1, 75]. Water can fine-tune protein functionality, as in the case of alkaline phosphatase enzymes and the chloride-pumping of the retinal protein halorhodopsin of halophiles [76, 77]. Much of the water in the cell is constrained. The average distance between macromolecules in the cytoplasm is 1 nm, corresponding to four molecular layers of water [78, 79]. A solute can alter the hydrogen bonding. Small polar solutes like urea require minor solvent rearrangement. The hydrophobic solutes are enclosed in a cavity surrounded by water molecules that preserve their hydrogen bonding [80]. Large proteins necessitate truncation of the hydrogen bonds81. Water plays a distinctive role in electron transfer between proteins and other biomolecules, which is critical for biological processes such as photosynthesis and respiration [3, 82]. Water is a channel for fast passive and active proton transport supporting proton translocation through and into proteins [83]. Hydration networks play a role in interacting water molecules within the active site and allosteric conformational shifts [84]. A specific order of bound water exists in antifreeze proteins, which bind to the ice to control crystallite nucleation [85].

The CDP-accounted water isomers determine their properties and are a regulatory mechanism of the inherent variability of biological systems

Per the CDP, molecules and organs mandate a degree of disorder for their proper function [6]. The principle is supported by the findings that the molecular degrees of freedom impact chemical reactivity [86]. Hydrogen atoms in water molecules have a magnetic orientation and spin. When the two hydrogens from water attach to either side of an oxygen atom, they are in two configurations. Water exists in para(p)-water and ortho(o)-water, distinguished by the quantum number values of the total nuclear spin [86]. In the case the two spins opposite ways up, the structure is termed para-water, and when the structure of the spins is symmetrical, it is termed ortho-water [86]. The ground state of para-water is the final rotational ground state, and ortho-water is the first excited rotational state [87]. The water in nature is a mixture of both. Water molecules in isolation stay in their ortho or para form. In water's liquid, room-temperature state, constant molecular collisions between molecules quickly mix the two forms. Nuclear-spin symmetry is usually conserved in collisions, electromagnetic radiation, and chemical reactions [86, 88]. Per the CDP, this continuously dynamic process of changing the ratios between the two isomers under dynamic conditions determines their properties and functions.

The para- and ortho-isomers of water differ in their behavior. Reaction-rate constants strongly depend on molecular conformation—the two ground states of para- and ortho-water show different responses to an electric field [89, 90]. Para-species reacts faster than the ortho-isomer under specific conditions, attributed to the shorter rotational averaging of the long-range ion-dipole interaction than the ortho-species [87, 86]. A difference in reactivities is a rotational effect induced by the nuclear-spin symmetry via the generalized Pauli principle. It suggests an interplay between nuclear spin and rotational symmetry and its ramifications on chemical reactivity, implying exchange symmetry in chemical processes [86, 91]. Various models, including the confined rotor model, determine the isotope effects on water dynamics, enabling the assessment of the mechanisms and rates for ortho-to para-nuclear spin isomer interconversion in water [92, 93].

The CDP implies that variabilities are essential for proper function. The variability in the ratios between water isomers is mandated for the inherent variability of biological systems. Variability is inherent to the structure and function of the genome at the DNA, RNA, and translation levels [7]. It characterizes multiple cellular processes such as the microtubules and enzymatic chemical reactions [14-17, 38, 94-98]. Stochasticity is also inherent to the function of organs, such as heart rate variability, respiration, and gait [99-101]. Accordingly, the ratio between the two water isomers determines the function of the solvent, its interactions with other molecules, and information transfer capabilities. Per the CDP, this ratio is dynamic and enables the flexibility and adaptability required to cope with internal and external environmental changes. The ortho-to para-nuclear spin isomer interconversion is a constrained disorder variability-based regulatory method for biological processes.

Ilan Y., Int J Appl Biol Pharm 2023
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Most biological systems function under numerous unpredictable stimuli. The random alterations in the ratios between the two states of water, ortho, and para, under continuously dynamic states, provide the required freedom for the proper function of systems. The degree of freedom manifested by the disorder's structure and function within the dynamic boundaries of subcellular, cellular, and whole organs enables them to adapt and function under continuously changing settings. The variability in water structures, and the different isomers, provides a unique platform for the intrinsic variability in the structure and function of molecules impacting the numerous chemical reactions and organs' functions.

The CDP-dependent water structures determine the energy usage

The association between structure, energy, and function characterizes multiple biological systems [102, 103]. The CDP determines the energy associated with biological processes 104. Per the CDP, the water structure and fluctuations are inherent for their proper function and energy usage while kept within the dynamic boundaries and are a mechanism that enables energy regulation. The changes in the energy of binding and the contributions from enthalpy, the sum of the system's internal energy and the product of its pressure and volume, and entropy, the measure of a system's thermal energy per unit temperature that is unavailable for doing valuable work, are determined by the rearrangements or displacements of water [105-107]. Entropy is essential for hydrophobic interaction and is affected by the chemical nature, size, and geometry of the interacting particles and the water dynamics and fluctuations [108, 109]. Water molecules have specific positions around a macromolecule beyond the van der Waals forces [110, 111]. The hydration shell is an active biomolecule and contributes to the intra-molecular rearrangements and inter-molecular recognition processes [1]. Water mediates the interactions between a protein and a substrate to increase the selectivity and recognition of substrates [112, 113].

Analysis of the energetic and electronic structure of various water dimer isomers showed that the linear dimer has the highest interaction energy, followed by the ring dimer and the bifurcated dimer [114]. The electron density distribution among the interacting water molecules is associated with the different water isomers [114]. The hexamer is the smallest water cluster with a three-dimensional hydrogen-bonding network as its minimum energy structure [115]. Several possible low-energy isomers determine the molecules' stability and interaction with other molecules. Comparative subsets of isomers at different expansion conditions determine structures with minimum energy [115]. The sp3 hybridized oxygen atom creates a tetrahedral coordination geometry, with each H2O molecule coordinated with four others [116]. Since the molecules are mobile in the liquid, the four hydrogen-bonding sites are not fully occupied [3, 117]. The tetrahedral hydrogen-bonded geometry underlies the water's density anomaly on freezing. The solid-state density is lower than that of the liquid since, in crystalline ice, hydrogen bonding constraints are inflexible [118]. When the lattice melts, the three-dimensional hydrogen-bonded network is distorted, enabling molecules to approach one another more closely [3, 119].

The hydronium ion (H3O+) is relevant to multiple processes in the body. Analysis of the energy linked with the isomers of H3O+(H2O)n showed the relevance of dividing individual fragments into subsets by the number of H3O+ and water molecules and the hydrogen-bonding associations. Structures of different isomers correlate with diverse body interactions by leading to various types of hydrogen bonding [120]. It emphasizes the importance of a numerous-body representation of inductive electrostatics and charge transfer in modeling the hydration of an excess proton in water [120]. The data support CDP-dependent dynamicity in water structure as a biological regulatory mechanism of energy usage.

The CDP-dependent water isomers are the ultimate biosensors and bioreactors of biological systems

The CDP-dependent inherent variability in water structure makes the isomers fundamental biosensors and bioreactors. Water molecules can sense their environment as the ultimate biosensor for the dynamicity of the stimuli encountered by molecules, cells, and organs [121, 122]. Similarly, water molecules can serve as the ultimate bioreactors, which by changing their structures or ratio of isomers, impact the structure and function of nucleic acids, proteins, biological processes, and organ function [64, 123, 124]. The structure and behavior of hydrogen ions in an aqueous solution are determined by the ability of water to incorporate ions in a dynamic network of hydrogen bonds [125]. Structural variability characterizes the structure of water and complicates the development of a reliable molecular-level description of water under different settings [110]. Water's orientation-dependent hydrogen bonding leads to open tetrahedral cage-like structuring that underlies its volumetric and thermal properties, enabling it to exert structure-dependent effects on its environment. Tautomerism is a phenomenon where a chemical compound exists in two or more interconvertible structures that differ in one atomic nucleus's relative position, usually hydrogen1 [26]. It is a mechanism for determining the function of molecules. Water plays a role in this process, providing a means for determining the ratios between different structures [127]. Alterations in the structure of water molecules, or the ratios of their isomers, is a method for changing water-dependent tautomerism [128]. Per the CDP, this water variability is one of the mechanisms underlying systems' variability from the genome to the whole organ [12].

Ilan Y., Int J Appl Biol Pharm 2023
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The CDP-based properties of water contribute to drug design

The structural participation of hydration water in biomolecular recognition assists in developing functional molecules. Water networks are affected and impact ligand binding [75, 106]. Solvent rearrangements can impact the binding cavity. The design of ligands and drugs that considers water-related relations may improve the ability to develop better products. The M2 proton channel of the influenza A virus targets drugs against the virus and is an example of a water network gate proton conduction [83, 129]. Hydrating the final protein-ligand complex is an example of water serving as a target [130]. Optimizing water layers covering hydrophobic thermolysin inhibitors augment the enthalpic contribution to binding free energy [131]. It implies that the CDP-associated flexibility provided to molecules by their interactions with water is fundamental for drug design.

Using the variabilities in water isomers ratios for correcting malfunction of biological systems

The CDP sets the basis for correcting malfunctioning systems by implementing variability into systems where the degree of variability is low or restricting disorder in systems where the disorder boundaries are too broad [12]. The CDP enables the design of water-based diagnosis and therapeutic methods based on analysis of the alterations of variability in molecule structures. The current limitations measuring the ratios of water isomers under different conditions in the human body preclude using water molecules as biosensors for diagnosis and as bioreactors that respond to perturbations and shape the response of their environments [132]. The inability to quickly determine the effect of different stimuli on water isomers makes it challenging to design controlled water-targeted therapies [133]. Simple maneuvers affecting disease states by changing the solutes in water are often unsuccessful due to the oversimplification of pre-defined fluids and the lack of understanding of their potential impact on water structure [134].

However, it does not prevent water use as a therapeutic target. Maneuvers that alter water structures, followed by testing the clinical results of drugs and clinical outcomes, may overcome technical constraints. Several methods are used for altering the ratio of H_2O *ortho-/para*-spin-isomers for different treatment procedures. The intensity of the *ortho*-isomer line increased after distilled water treatment, increasing proton density. The enrichment of the distilled water by *ortho*-H_2O molecules using cavitation bubbles collapse was achieved when the water passed through their supercritical state [135]. Magnetic water treatment violates the synchronism of para-isomers vibrations, with the subsequent destruction of ice-like structures due to the receiving of energy from collisions with the ortho-isomers [136]. Magnetic water treatment increases the number of more physically and chemically active *ortho*-isomers altering the nature and speed of the processes in aqueous solutions [136]. Maneuvers of peptides that share an identical primary structure but differ in their aqueous solubility, which is related to the alteration of protein-water interplay, affect the inhibitors of aggregation associated with amyloid diseases [137]. Using the CDP-based concepts of implementing variability to improve performance and response to molecular interventions [27-45] set the basis for dynamic alterations of water molecules to improve response to therapies. Second-generation AI systems regulate the degree of variability in the design of variability-based therapeutic interventions [13, 18-20]. These systems allow using water fluctuations and dynamicity and water isomers ratio as a quantifiable measure to be implemented into diagnostic and therapeutic schemes. Improving methods for measuring water isomers can make them powerful diagnostic and therapeutic targets. Using water as the ultimate biosensor and bioreactor provides a platform to improve our ability to intervene in diseased states. Implementing water-based quantitative variability measurements into therapeutic regimens can enable upscaling variability-based AI algorithms to improve the diagnosis and treatment of chronic diseases and aging.

Conclusion

In summary, water is a unique molecule that can be affected by and affect its environment. The ability of the water molecule to harbor different structures, along with its multiple potential functions, makes water the ideal biosensor and bioreactor. Improving the current techniques is expected to enable the use of water as a robust diagnostic and therapeutic platform.

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Ilan Y., Int J Appl Biol Pharm 2023
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