A model and genomic evidence of imprinting DNA sequence on water structure

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A novel model is presented of DNA-water interactions within the cell nucleus, proposing a mechanism for continuous self-reorganization of water structures around DNA. The model suggests that DNA sequences may imprint information onto water through shifting layered structures, facilitating sequence-specific chromatin folding. A key feature of this model is the homologous sequence-specific adhesion of repetitive DNA elements, particularly transposons. In this process, two identical double-helical DNA sequences stick to each other in head to head orientation via transverse water layers, without unwinding or separating their strands. This adhesion is proposed to drive perpetual, dynamic chromatin refolding by pairing identical transposons to form large DNA loops and helices to form 30nm fibers and higher-order chromatin structures. The model postulates the existence of a chromatin code based on the positions of transposons in introns and intergenic sequences, offering a new perspective on the functional significance of these often overlooked genomic regions. Predictions based on this structural model were tested using genome sequence data, revealing specific patterns in purine sequence distribution and nucleotide homology that provide preliminary support for the model. This framework suggests novel functions for repetitive DNA sequences and proposes that sequence-specific chromatin refolding may serve as a mechanism for cellular sequence-guided information processing and self-regulation. While largely theoretical, the model generates testable predictions and suggests new directions for research. Several experimental approaches to validate the model are proposed, emphasizing the importance of in vivo studies or experiments closely mimicking nucleoplasm conditions. This work may have significant implications for understanding gene regulation, developmental biology and physiology, with potential applications in fields such as regenerative medicine and cancer research.

Introduction

Regenerative medicine has made remarkable progress in recent years, yet the complete regeneration of complex organs remains a challenge. This highlights the need for a deeper understanding of morphogenesis—the process that governs the development of an organism's shape. Current knowledge of mechanisms such as chemical, morphogenic protein, neuronal,

electrical, and mechanical signaling does not fully explain morphogenesis and morphostasis, the maintenance of an organism's shape.

In the late 18th century, Franz Mesmer introduced the concept of animal magnetism, using energy from his hands to treat patients. A committee headed by Benjamin Franklin investigated Mesmer's claims in 1784 and concluded that the results were due to the placebo effect, possibly providing the first description of the placebo effect. In the early 19th century, vitalism emerged as a prominent theory, with proponents like Marie François Xavier Bichat and Jöns Jacob Berzelius suggesting that life is driven by a vital force. Johannes Peter Müller, a prominent and respected experimental physiologist in the 19th century, made significant contributions to neurophysiology. In 1840, he argued that the presence of a soul makes each organism an indivisible whole. He suggested that light and sound waves indicate that living organisms possess a unique life energy unexplainable by physical laws.

Hans Driesch introduced the term "biofield" in 1892 through his experimental work on sea urchin eggs. In the 1920s, Alexander Gurwitsch, Hans Spemann, and Paul Alfred Weiss independently proposed the concept of morphogenetic fields defining tissue organization during development. Gurwitsch experimentally demonstrated that light radiation allowed the morphogenetic field to control embryonic development. In the 1930s and 1940s, Harold Saxton Burr, a recognized experimentalist, developed the electrodynamic theory of life, describing "life fields" that contribute to biological organization. Burr conducted numerous experiments measuring voltage gradients in living tissues and studying the bioelectrical properties of cancer cells, embryonic development, and the nervous system(Burr and Northrop, 1935). In the 1940s and 1950s, Albert Szent-Györgyi, a prominent experimentalist, explored biological semiconductors and water properties in biological systems. He used muscle tissues from rabbits and conducted metabolic studies on humans. His experiments focused on muscle contraction, studying proteins like actin and myosin, and cellular respiration. Szent-Györgyi proposed that quantum processes, such as proton tunneling, facilitate bioelectrical activities within cells, advancing the understanding of bioelectrical processes at the molecular level (Szent-Györgyi, 2004).

The discovery of the DNA double helix in 1953 by Watson, Crick, Franklin, and Wilkins pivoted biological research towards molecular biology and led to modern genetics and genomics. Per-Olov Löwdin proposed quantum biology in 1963. His work focused on the quantum mechanical properties of DNA, such as proton tunneling and delocalized π electrons, and their potential implications for various biological processes at the nanoscale. In 1969, Stanford Goldman introduced the concepts of biological quantum mechanics and DNA holograms, emphasizing the role of DNA in biological systems from an electrical engineering perspective and highlighting the deep connections between biological functions and quantum mechanics.

In 1972, Richard Alan Miller (a coathor in this study) and Burt Webb developed and presented a comprehensive model describing the DNA hologram as a biofield. They proposed that DNA functions as a quantum-holographic field capable of storing and transmitting information. This model integrated DNA's interaction with electromagnetic fields, resonance properties, nonlinear dynamics, and quantum coherence, connecting molecular biology with quantum physics and systems biology (Miller and Webb, 1972, 2002). Their work laid important groundwork for understanding DNA's role beyond its linear sequence, aligning with our current model's

emphasis on DNA's influence on surrounding water structures and chromatin organization.

In the early 1980s, Fritz-Albert Popp developed experiments on biophotons and demonstrated that living organisms emit weak electromagnetic radiation, which plays a role in biological processes (Popp and Gu, 1992). James Oschman's work in the 1980s and beyond explored energy medicine, focusing on how weak electromagnetic fields influence biological systems. He investigated how the body's connective tissues, particularly fascia, act as a network for bioelectrical signals. Oschman's research linked these fields to morphogenesis, health, and healing, providing a scientific framework for therapies like acupuncture and Reiki (Oschman, 2000).

In 1988, Jacques Benveniste experimentally demonstrated that water could retain the biological activity of substances after their serial dilution, suggesting that water possesses memory-like properties, can form various biologically active structures, and these water structures can be replicated (Davenas et al., 1988). Luc Montagnier proposed in 2009-2015 that DNA sequences can imprint their structure on water, highlighting a potential mechanism for the transmission of genetic information via the propagation of water structures (Montagnier et al., 2011).

The classical morphogenetic gradient model, while foundational, is insufficient for explaining the geometric perfection observed in biological structures. Gradients alone often fail to account for the precise and symmetrical patterns seen in nature. Studies have shown that bioelectric signals significantly influence cell behavior and tissue patterning, providing a more robust mechanism for achieving these perfect structures. For example, Michael Levin's work has demonstrated how bioelectric gradients can regulate apoptosis and proliferation in embryonic development (Pai et al., 2015) and alter muscle patterning (Lobikin et al., 2015).

Given these limitations, the biofield concept emerges as a more comprehensive explanation. This concept proposes that DNA not only produces the biofield but also communicates with it, creating a feedback loop. The biofield, an electromagnetic field generated by the body, regulates genes and guides their function and position. This dynamic interaction accounts for the body’s intricate patterns and precise symmetry. The holographic idea extends this concept, transforming linear DNA into a three-dimensional body structure. This transition from one dimension to three dimensions involves the morphogenetic field, which is responsible for creating the body’s shape, while other components of the biofield maintain that shape and regulate physiological processes (Miller et al., 2011, 1975; Miller and Webb, 1972, 2002).

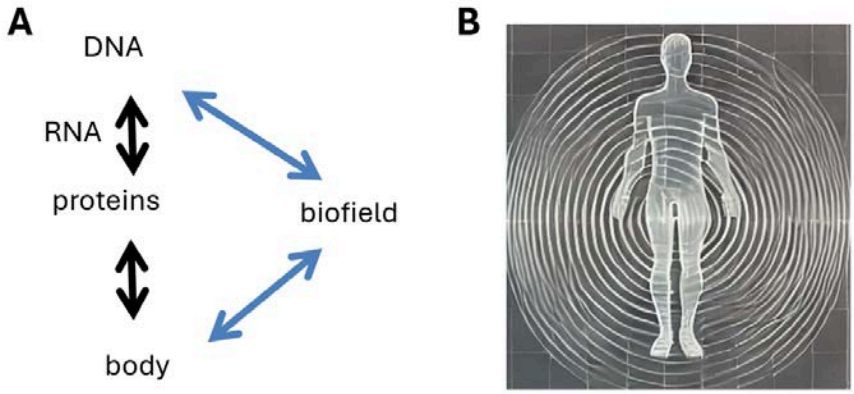


Fig. [Biofield]: Conceptual model of biofield interactions with biological systems. A. Diagram showing interconnections between DNA, RNA, proteins, body, and biofield. Black arrows represent the central dogma of molecular biology, while blue arrows indicate proposed biofield interactions. The bidirectional DNA-biofield arrow emphasizes genomic DNA's role in creating the biofield via the holographic principle. B. Artistic representation of a human body surrounded by concentric rings, symbolizing the morphogenetic field shaping the physical body, extending the concept of DNA-originated biofields to organismal level.

Moreover, in Miller's 1972 presentation, it was proposed that consciousness might be intricately tied to the biofield and DNA. This idea suggests a profound connection between our biological structures and consciousness, highlighting the biofield's potential role in mediating the grounding of consciousness in the physical body via DNA (Miller and Webb, 1972, 2002).

In multicellular organisms, DNA is not naked; it is wrapped around nucleosomes, forming almost two turns around a histone core. This arrangement resembles a snake coiled around a napkin ring, Fig. [Nuc]. The double helical DNA is structured in about two turns around the nucleosome, creating a perfect, intricate crystal structure. The tetranucleosome, depicted in Fig. [Nuc], represents the largest orderly DNA structure. Beyond this, nucleosomes and tetranucleosomes are arranged randomly, lacking a specific order.

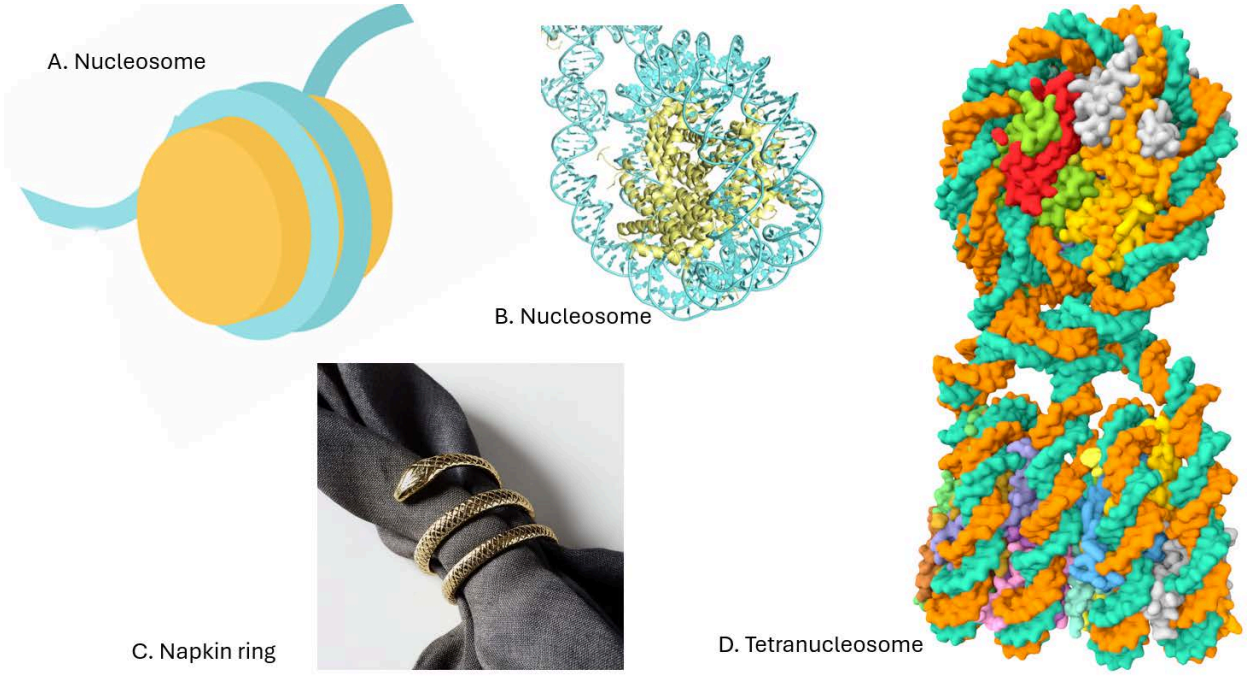


Fig. [Nuc]. Structural organization of DNA in chromatin. A. Simplified schematic of a nucleosome, showing DNA (blue) wrapped around histone proteins (yellow). B. Molecular model of a nucleosome, illustrating DNA (blue) coiled around the histone core (yellow). C. Napkin ring analogy for DNA wrapping around histones, demonstrating the coiling nature of DNA in nucleosomes as a left-handed helix. D. Tetranucleosome structure, displaying four nucleosomes connected by linker DNA.

Twenty-one years ago, in 2003, the concept of DNA resonance was presented by MMR, the leading author of this chapter, at Michael Levin's seminar. It was observed that nucleosomes resemble electric magnets, and it was established that DNA functions as an electric conductor. When alternating current passes through the DNA around the nucleosomes, these nucleosomes act as antennas emitting electromagnetic waves. Nucleosomes with identical oscillation patterns

and natural frequencies would resonate. A DNA resonator was defined as a sequence with a specific oscillation pattern or frequency. When two resonators communicate through waves, they develop resonance and exchange information, enhancing each other's oscillation. Biochemical energy is necessary to transmit electromagnetic waves; one cell spends energy to send a signal, and another cell with similar resonators receives and transforms it into a biochemical signal, such as RNA transcription Figure [Res] (Polesskaya et al., 2017).

Figure [Res] visually represents the DNA resonance concept. Panel A, presented in 2003, illustrates how nucleosomes, resembling electric magnets, can emit electromagnetic waves when alternating current passes through the surrounding DNA. Panel B demonstrates how this principle might apply to gene regulation. Here, specific DNA sequences acting as resonators can be activated by transcription factors and fueled by ATP. The resulting electromagnetic waves can propagate to other resonators with matching oscillation patterns, leading to gene activation. This model provides a potential explanation for the coordinated expression of distant genes and offers insight into how resonance signaling in chromatin can contribute to gene regulation.

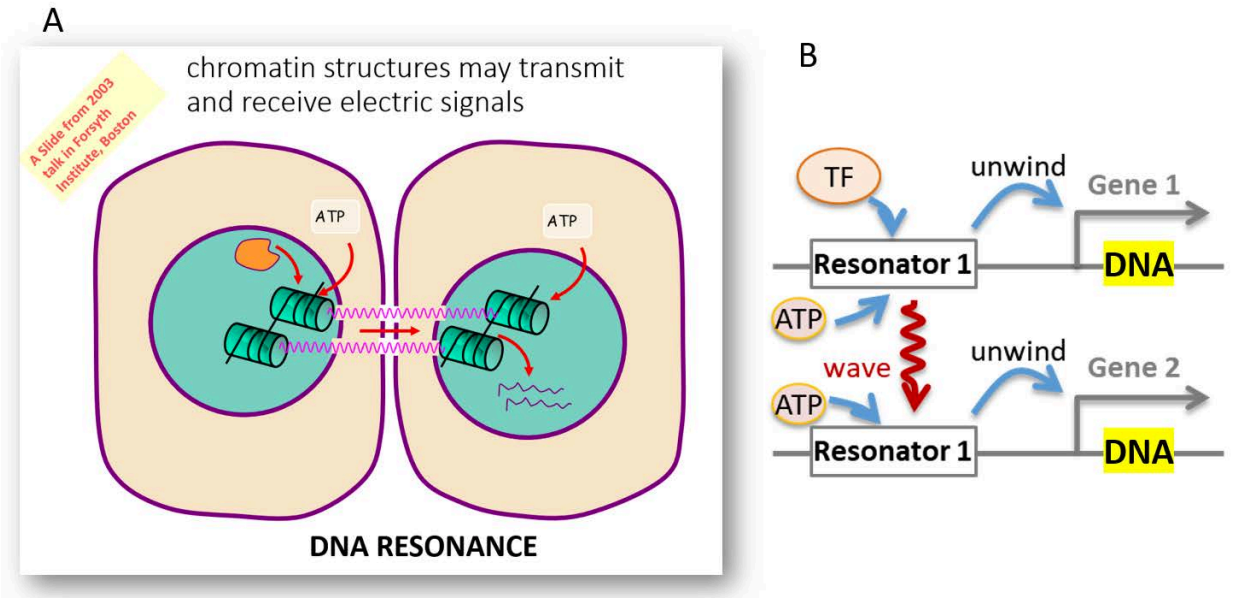


Figure [Res]: Conceptual model of DNA resonance and its potential role in gene regulation. A. Chromatin structures transmitting electric signals via ATP-driven oscillations as presented by MVM in 2003. B. Schematic of DNA resonance-mediated gene activation, showing how resonators may facilitate coordinated gene expression.

In parallel, we explored the concept of crystal propagation in water. While DNA signaling through electromagnetic waves represents patterns in time, crystal propagation in water structured by DNA represents patterns in space. We hypothesized that DNA might initiate the microcrystallization of water and imprint its sequence onto the water structure, a process we termed crystal pattern propagation or snowflake signaling. In snowflakes, patterns propagate in multiple directions and change with distance from the center. Similarly, in biology, microtubules self-crystallize from monomers, growing when monomers are abundant and shrinking when sparse, demonstrating a dynamic, self-regulating process. We proposed that in the nucleus, DNA propagates its pattern by imprinting it onto the surrounding water, creating liquid

microcrystalline structures. These water-based patterns then extend beyond the DNA, forming larger, coherent crystal structures. This concept illustrates how DNA's influence can permeate its immediate environment, suggesting a mechanism for transmitting genetic information through structured water.

Fig.[Snowflake] Snowflake

Within the cell, the nucleus houses the chromosomes in a liquid called nucleoplasm, surrounded by the nuclear wall. The nucleoplasm, a thick and heavy fluid, is rich in DNA. Our body contains about 200 to 300 grams of DNA, and within the nucleoplasm, DNA makes up about 1%. This is significant because DNA is a very long polymer, making the nucleoplasm quite thick. In total, DNA and proteins constitute about 19% of the nucleoplasm. The remaining components are lower molecular weight substances, and water comprises only about 78% of the nucleoplasm, creating a thick, moving gel.

It has been proposed that within the cells, there are small clusters of structured water, forming soft liquid crystals. Experimental studies support this concept, revealing that water near biopolymers can exist in ordered states. For instance, NMR and X-ray diffraction studies have shown evidence for two structural states of water in hydrated biomolecules (Denisov et al., 1997). Infrared spectroscopy has demonstrated unique vibrational properties of water near biological interfaces, suggesting the formation of structured water clusters (Cherkasova et al., 2020). Additionally, cryo-electron microscopy and neutron scattering have provided direct observations of ordered water clusters around DNA and proteins, essential for their stability and function (Ebbinghaus et al., 2007). Gilbert Ling was among the early proponents of this idea, suggesting that cellular water is organized in multilayers around proteins and other components (Ling, 1962). More recently, Gerald Pollack has advanced the notion of a "fourth phase of water" or "exclusion zone water" near hydrophilic surfaces, which he argues may play a crucial role in cellular functions (Pollack, 2001). Martin Chaplin has extensively reviewed the potential structures and behaviors of water in biological systems (Chaplin, 2006). The structuring of water in cells is likely dynamic around biopolymers in the cells (Ball, 2008).

Within the cell, the nucleus contains chromosomes suspended in nucleoplasm, a dense and viscous fluid due to its DNA content. Approximately 20% of the nucleoplasm consists of DNA and proteins, while water makes up about 77%, together forming a thick, moving gel. We propose that there are small clusters of structured water within the nucleoplasm. This structured water contributes to the gel-like properties of the nucleoplasm. Chromatin within the nucleus

exhibits significant dynamic movement, particularly during interphase, when chromosomes are unwound and actively moving. This movement resembles a self-organizing gel, similar to the flexible movements of an octopus. This dynamic environment is critical for the interaction between the physical gel-like nucleoplasm and the biofield, an electromagnetic or subtle field. The optimal interaction occurs when the gel is actively moving and self-organizing, influenced by crystallization and dissolution processes, allowing the biofield to exert its influence on cellular processes.

Component	w/w %	mM
Water	77 %	43,000 mM
Proteins:		
Histones	11 %	1-2 mM
Nuclear matrix proteins (Lamins, Nuclear pore complex proteins, Actin, Spectrin-repeat proteins)	3 %	0.1-0.5 mM
Other proteins: (hnRNPs, RNA polymerase II, Topoisomerase II)	5 %	0.5-2 mM
DNA	1 %	0.01 mM
RNA	3.5 %	0.5-1 mM
Small molecules and ions (K+, Na+, Glutamate, NAD+, Cl-, ATP, Glycine, Inorganic Phosphate, etc.)	0.5 %	150-200 mM

Table: Estimated concentrations of nucleoplasm components. The relative concentrations of all components are variable depending on the cell type and activity. Only the absolute amount of DNA is constant.

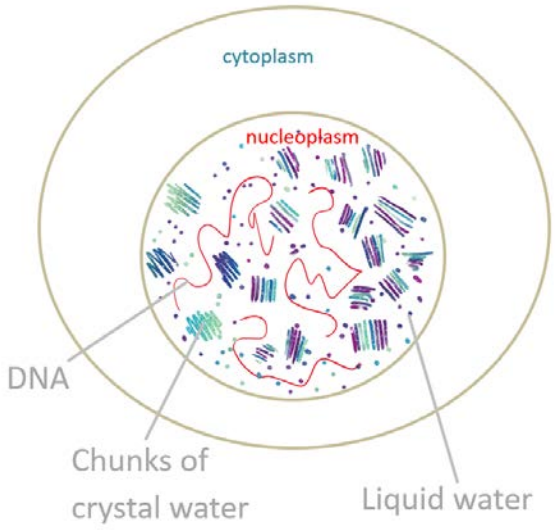


Fig. [Chunks] Chunks of structured water in the nucleoplasm

Building upon our understanding of the nucleoplasm's composition and structure, the concept of biofields and their interaction with physical cellular components forms a complex, dynamic

system. This system extends beyond the gel-like nucleoplasm to encompass subtle fields, electromagnetic fields, and acoustic waves generated by the movement of charged macromolecules and organelle surfaces within the cell. The biofield acts as a living, self-organizing interference pattern interacting with the cell's physical components, particularly the nucleoplasm. Within this dense, viscous fluid, the movement of DNA, proteins, and structured water clusters creates a dynamic environment rich in electromagnetic activity and acoustic patterns. The bidirectional interaction between the biofields and the material gel of the nucleoplasm is most effective during active movement and self-organization, especially during processes of crystallization and dissolution of the structured water clusters.

Within the nucleoplasm, electromagnetic vortexes form through the interplay of moving charged particles, electromagnetic induction, and fluid dynamics (V. Savelyev et al., 2019). The circular motion of charged molecules generates magnetic fields, inducing currents that reinforce the original motion. This self-amplifying process creates stable EM vortexes at various scales. The principles of magnetohydrodynamics govern these interactions, where the conductive nucleoplasm behaves as both a fluid and an electromagnetic medium. Lorentz forces act on moving charges, while induced currents generate additional magnetic fields, creating a complex feedback system of fluid flow and electromagnetic phenomena (V. Savelyev et al., 2019).

We introduce a molecular model inspired by the hexagonal structure of polywater, as described in Lippincott's 1969 work (Lippincott et al., 1969), Fig. [Polywater], and its potential interaction with DNA basepairs. The hexagonal patterns in DNA basepairs (G-C and A-T) are very pronounced not only inside the bases but also in the space between the bases that houses hydrogen bonds. We propose DNA basepairs might fit and align into the Lippincott's honeycomb water structure.

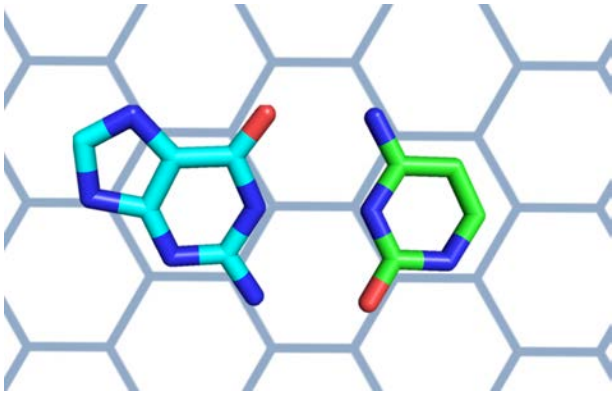


Fig.[Embedding] Proportions of the basepair GC embedded in the Lippincott's honeycomb water layer. The hexagonal symmetry of the basepair is proposed to serve as a guide for the construction of the honeycomb water layer around the DNA.

We believe that Lippincott's polywater has the same water structure as Pollack's EZ water, which forms near negatively charged biopolymers such as DNA. Unlike Pollack's EZ water, Lippincott's polywater structure is electrically neutral overall, featuring a honeycomb pattern with gaps (which we term "canyons") that facilitate continuous dynamic self-reorganization. It

contains incomplete hexagons and spaces for single water molecules, allowing for dynamic growth and dissolution.

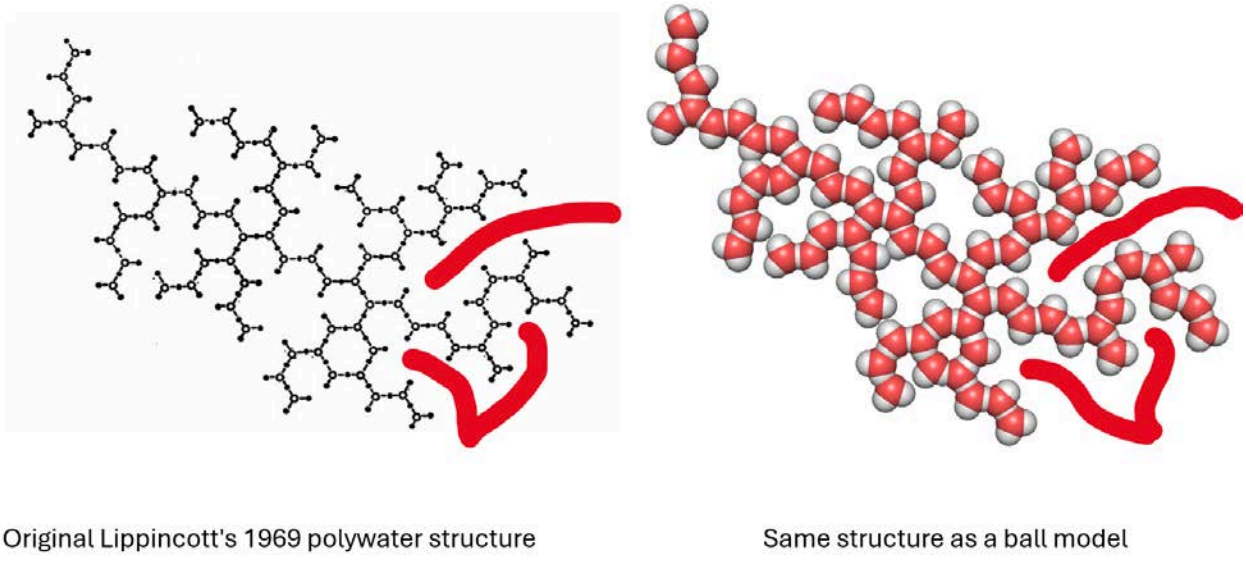


Fig.[Polywater] Lippincott's honeycomb structure of polywater (Lippincott et al., 1969). An example of a canyon gap is shown in blue.

The interplay of order and chaos in polywater layers

The polywater structure (Fig. [Polywater] above) contains spaces for single water molecules, allowing for a dynamic interplay between structured and liquid water. As the structure grows, it accumulates a negative charge. This accumulation of charge creates an inherent instability: if the structure grows too far in one direction, it becomes energetically favorable for it to begin dissolving, thereby reducing the negative charge. This results in a continuous process of growth and dissolution, potentially at opposite ends of the structure or even at the same end. This dynamic, imperfect nature of polywater, with its capacity for continuous reorganization and information encoding, provides a compelling model for the "living water" of the nucleoplasm.

As previously mentioned (Montagnier et al., 2011, 2009), DNA solutions were proposed to embed sequence information in water structures. This aligns with our model of DNA and its surrounding water structure where every other layer of water is coplanar with DNA basepairs. On the other hand classical ice models, are unsuitable for imprinting DNA sequences. In classical ice, the layers are not flat and are strongly bound to each other via hydrogen bonds, prohibiting shifts between layers. This rigidity doesn't allow for the flexibility needed to imprint DNA sequences.

For this reason, we turned to Lippincott's polywater model, published in 1969. Unlike classical Ice IV, the polywater structure has flat layers with weak hydrogen bonds between them, allowing for shifts in multiple directions, Fig. [Shift]. This flexibility is crucial for our hypothesis of DNA imprinting its sequence onto water structures. The ability of polywater to shift and reorganize makes it a suitable structure for encoding and transmitting biological information.

We propose that when DNA moves through the nucleoplasm, its high negative charge dissolves existing water structures and initiates the crystallization of new polywater layers. These layers form perpendicular to the main axis of the DNA double helix, with the hexagonal shapes observed in DNA base pairs serving as nucleation points for the honeycomb polywater structure. Our size estimates suggest that for every basepair of DNA, there are two polywater layers.

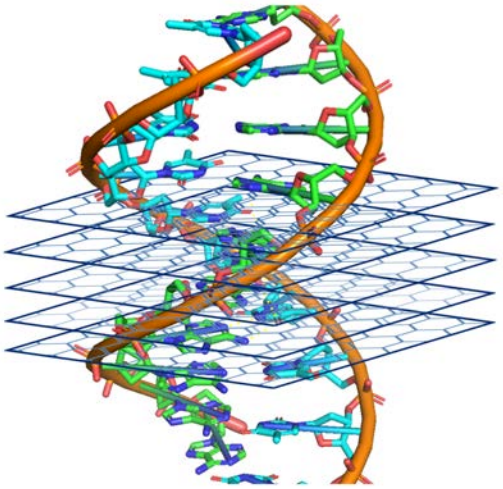


Fig. [Layers] Layers of polywater initiated by DNA and crystallized around the DNA perpendicular to the main axis of the double helix

A crucial property of this polywater model is the shifting of layers, Fig. [Shift]. Each layer can shift in one of six directions relative to the adjacent layer, potentially encoding DNA sequence information. Considering three consecutive layers, the third layer can occupy 19 different positions relative to the first layer: 12 points on the outside, 6 points on the inside, and 1 central point, distributed across 12 possible angles of movement.

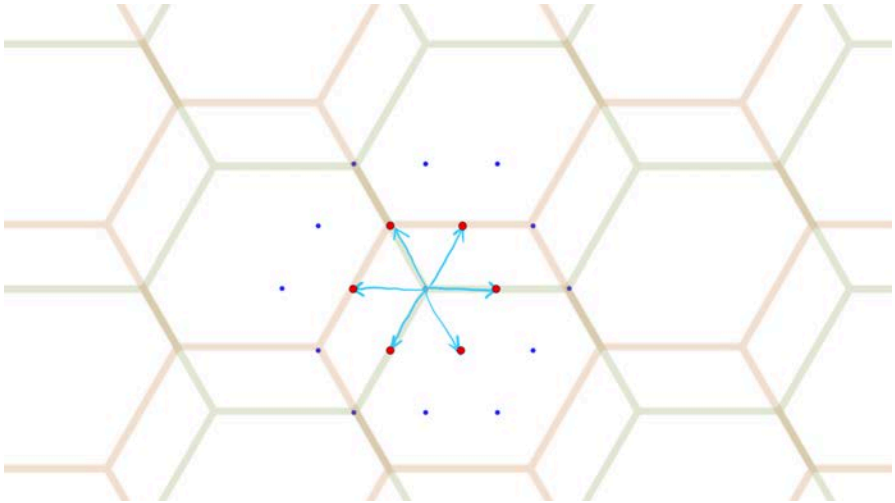


Fig. [Shift]. Multi-layer shifting patterns in polywater structures. The hexagonal lattice represents the honeycomb structure of polywater layers. Blue arrows indicate the six possible directions of shift between adjacent layers. Red dots mark the six potential positions for oxygen atoms in the next (second) layer relative to the central position. Blue

dots represent the additional 12 possible positions for oxygen atoms in the third layer. Together, the 18 red and blue dots illustrate all possible positions of the third layer relative to the first. This two-step shifting mechanism allows for complex three-dimensional arrangements, potentially encoding information such as DNA sequences in the polywater layer structure. The figure demonstrates how each layer can shift to one of six positions, and then the subsequent layer can shift again in any of the six directions, including a shift that returns it to alignment with the first layer.

In developing our model, we made several unconventional choices that warrant explanation. First, we posit that water forms planar layers. Second, we propose that these water layers are oriented perpendicular to the DNA axis, a seemingly arbitrary arrangement. Third, we suggest that these water layers consist of polywater honeycombs rather than ice-IV honeycombs.

We acknowledge that alternative water structures may exist that do not rely on layers, have layers oriented differently relative to DNA, or consist of structures other than Lippincott's honeycomb. However, the appeal of our model lies in its being the simplest and most elegant structure that allows for both the imprinting of DNA sequences onto water and the lossless propagation of this imprinted information through the water medium away from DNA.

Henceforth, we will refer to our model as the "pintumbler" model, reflecting its key feature of imprinting DNA sequences onto water through the shifting of honeycomb water layers as in pin tumbler lock. We propose that the composition of nucleoplasm may have evolved to create conditions favorable for pintumbler water structures, as this would enable DNA sequences to imprint information onto water, potentially serving important biological functions. In the following sections, we will elaborate on the structural details and potential functions of this model.

When considering three consecutive layers of polywater, our model predicts that the third layer can occupy 19 different positions relative to the first layer: 12 points on the outside, 6 points on the inside, and 1 central point. These positions are distributed across 12 possible angles of movement.

This arrangement allows for a sophisticated encoding system. We propose that the specific shifts between layers could correspond to the sequence of base pairs in the DNA. For instance, the presence of a purine (A or G) or a pyrimidine (C or T) in the DNA sequence might dictate the direction and magnitude of the shift between adjacent water layers.

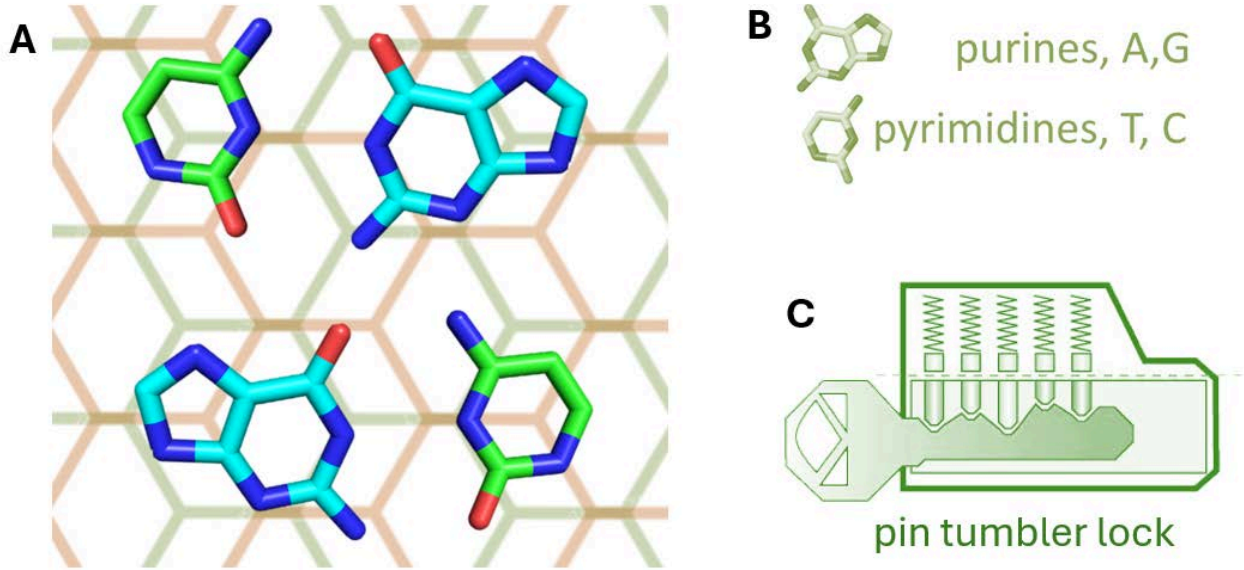


Fig. [Purines] A. The principle of imprinting purine sequences on water by shifting honeycomb layers. Basepairs CG (top) and GC (bottom) are aligned vertically to maintain their position relative to the sugar-phosphate backbone, demonstrating the horizontal shift that occurs when the basepair is flipped. B. The general structures of Purines (A, G), with their two fused rings, and pyrimidines (T, C), with one ring. C. The pins are shifted by the bumps on the key in the pin tumbler lock.

The pintumbler model proposes a mechanism for DNA to imprint its sequence information onto surrounding water structures. Figure [Purines] illustrates how this might occur at the molecular level. The key to this process lies in the structural differences between purines (A and G) and pyrimidines (T and C) and their alignment with the honeycomb water structure. Crucially, the base pairs in the figure are aligned in Fig. [Purines] to maintain their alignment with to the sugar-phosphate backbone. This alignment reveals an important feature: when the basepair is flipped, there is a horizontal shift of the hexagonal part of the basepair relative to the backbone. This way, not all the information of the DNA sequence is imprinted on water, but only its purine-pyrimidine sequence. This partial information transfer can be referred to as degeneration.

Therefore, only the purine-pyrimidine sequence of DNA influences the shifting pattern of the surrounding water layers, creating a unique "watermark" that reflects the underlying DNA sequence. This shifting pattern could propagate as the layers grow, potentially allowing for medium- or long-range transmission of purine sequence information of DNA. Such water-mediated information transfer could be involved in various biological processes, including long-range DNA-DNA interactions, dynamic chromatin organization, and signaling.

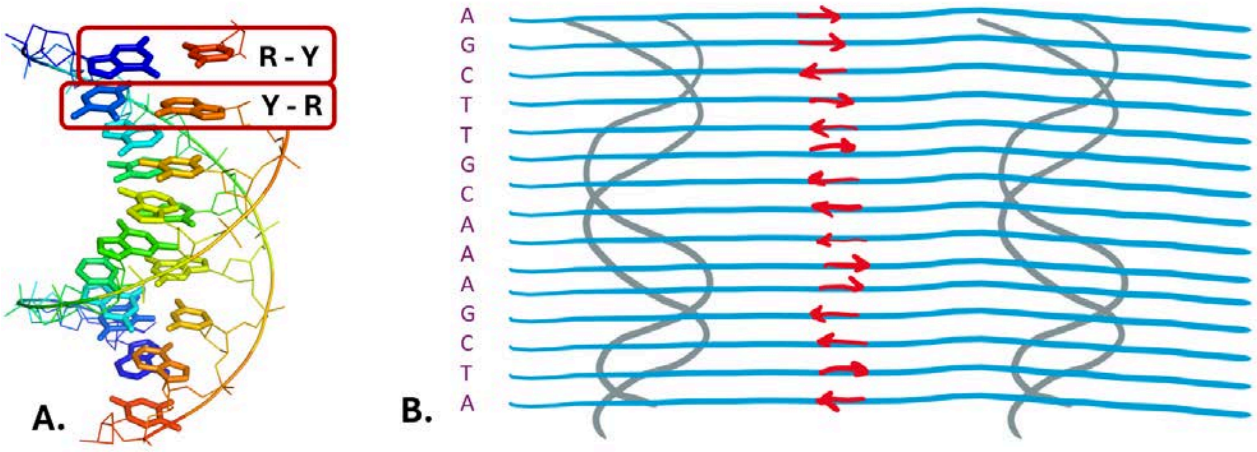


Fig. [Imprint] Imprinting of DNA sequence on water structure

Figure [Imprint] demonstrates the pintumbler model's concept of DNA sequence imprinting on surrounding water structures. The image juxtaposes a DNA double helix (A) with a simplified representation of adjacent water layers (B).

In part A, two basepairs are highlighted with red boxes labeled "R-Y" and "Y-R". These labels emphasize that each base pair contains one purine (R) and one pyrimidine (Y), with their orientation flipping as dictated by the DNA sequence. This flipping of the R-Y pattern is key to understanding how DNA sequence information is imprinted onto the water structure.

Part B shows how this R-Y pattern influences water layer shifts, indicated by red arrows. The imprinting depends on the orientation of purines and pyrimidines within each pair, reflecting the alternating pattern seen in part A. Purines A and G shift layers to the right, and pyrimidines C and T shift the layers to the left.

While this 2D representation illustrates the principle, it is a simplified representation of a more complex 3D structure where each basepair rotates 1/10.5 turns per step. The proposed honeycomb water structure accommodates these three-dimensional shifts, though our flattened illustration doesn't reflect this complexity.

It's worth noting that while not explicitly shown, our model posits that each basepair corresponds to two water layers. This relationship between DNA sequence and water structure forms the foundation of the pintumbler model, suggesting a mechanism by which genetic information might be imprinted on its aqueous environment beyond the immediate molecular boundaries of DNA.

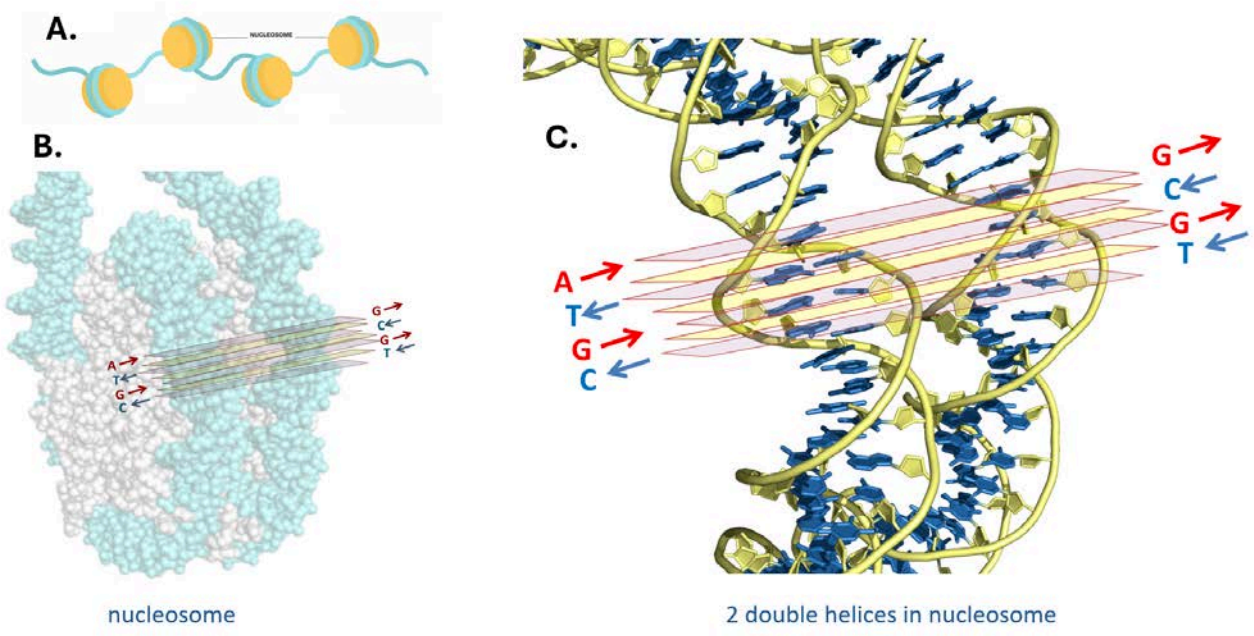


Figure [Nuc]. Nucleosome structure and DNA organization in chromatin. A. Schematic representation of the "beads on a string" chromatin structure. B. Molecular model of a nucleosome with DNA wrapped around the histone core. C. Detailed view of two DNA duplexes on a nucleosome surface, linked by a bridge made by honeycomb polywater sheets. The arrows indicate the shifts of the sheets guided by the purine-pyrimidine sequence of DNA. The bridge would make a more perfect structure when the purine-pyrimidine sequences of the 2 duplexes are identical.

The organization of DNA within the nucleus plays a crucial role in gene regulation and cellular function. Figure [Nuc] illustrates the hierarchical structure of DNA packaging and its potential relevance to our pintumbler model.

Panel A provides a simplified overview of chromatin's "beads on a string" structure, where nucleosomes (depicted as yellow spheres) are connected by linker DNA (blue line). This basic unit of chromatin packaging is fundamental to understanding how genetic information is stored and accessed within the cell.

Panel B offers a detailed molecular view of a single nucleosome. The histone core, shown in light blue, serves as a scaffold around which approximately 147 base pairs of DNA (gray) are wrapped. A short section of DNA is highlighted with red and blue arrows, indicating the purine-pyrimidine (R-Y) orientation of base pairs. This orientation is key to our pintumbler model, as it may influence the structure of surrounding water layers.

Panel C provides a zoomed-in perspective of two DNA double helices as they wrap around a nucleosome. The DNA backbones are represented in yellow, with base pairs shown as blue (pyrimidines) and yellow (purines) structures. Red lines between the DNA strands suggest potential water layers, relative shifting of which, according to our model, could be influenced by the R-Y pattern of both DNA strands. The arrows and letters (A, T, G, C) explicitly show the orientation and identity of specific bases in the DNA sequence.

This figure underscores several important aspects of our pintumbler model within the context of chromatin structure. It demonstrates that the alternating R-Y pattern of base pairs is maintained

as DNA wraps around the nucleosome and highlights how two sections of the DNA double helix come into proximity on the nucleosome surface. This proximity creates a space where water layers could form and be influenced by the R-Y patterns of both DNA strands, potentially facilitating water-mediated interactions in chromatin.

Purine Jump patterns

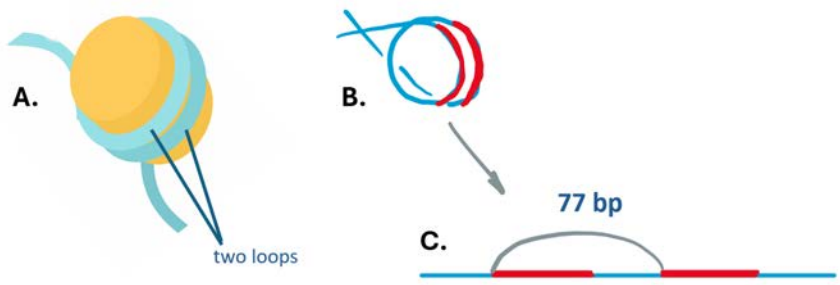


Figure [Loops]: DNA looping and nucleosome structure. A. Schematic representation of a nucleosome with two DNA loops. B. Top view of DNA wrapping around a nucleosome. C. Linear representation of DNA loops on a nucleosome, highlighting the 77 base pair distance (which we call JUMP).

Figure [Loops] illustrates the structure of DNA as it wraps around nucleosomes, providing insight into spatial relationships that inform our predictions about genomic sequence patterns. The figure demonstrates how segments of DNA that are somewhat distant in linear sequence are brought into close proximity when wrapped around a nucleosome. Panel A shows a 3D representation of two DNA duplex loops, which are highlighted in red in the top view (B). These loops are then depicted unwrapped into a linear sequence in panel C, emphasizing the approximately 77 base pair distance (which we call JUMP) between the corresponding start points of the red segments. We called this 77 Based on the potential for these loops to be connected by water layers, as illustrated in Figure [Nuc], we hypothesized that evolution might have favored similarity between purine-pyrimidine sequences in such proximal loop regions. In the results section we will show the enrichment of such similar sequence patterns in the genome.

METHODS

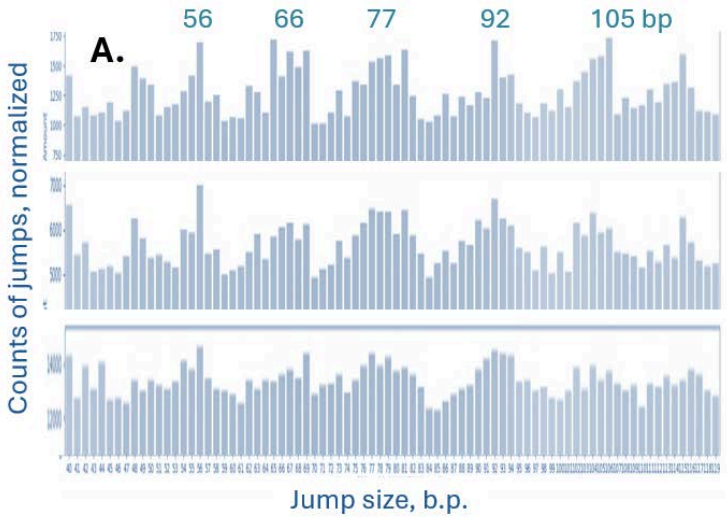
Even-purine data analysis

This is the methodology for verifying the hypothesis that there is more homology between purine-pyrimidine sequence pairs separated by even-numbered jump sizes.

Data Description Chromosome sequences for analysis were downloaded from the Ensembl repository (https://ftp.ensembl.org/pub/release-109/fasta/homo_sapiens/dna/). Both unmasked chromosome sequences (e.g., Homo_sapiens.GRCh38.dna.chromosome.1.fa.gz) and masked

sequences (e.g., Homo_sapiens.GRCh38.dna_rm.chromosome.1.fa.gz) were downloaded. In masked sequences, all repeats and low-complexity regions were replaced with N. Coordinates of intergenic regions were also downloaded from Ensembl (https://ftp.ensembl.org/pub/release-109/gtf/homo_sapiens/). The file with nucleosome coordinates was downloaded from https://generegulation.org/NGS/stable_nucs/hg38/ (GSE114511_70yo_Teo_stable_100bp_hg38.bed.gz). To assess conservation, chr{c}.phyloP100way.wigFix files (one file per chromosome) were downloaded from UCSC (http://hgdownload.soe.ucsc.edu/goldenPath/hg19/phyloP100way/). These files contain conservation scores for each position in the chromosome (these values were obtained based on multiple sequence alignments of hundreds of species). For each chromosome, the 20th and 80th percentiles of the conservation score were calculated. Then, all intergenic regions were divided into short fragments of 50 base pairs. Within these 50-bp fragments, the average conservation score was calculated. If this conservation score was above the 90th percentile, such a region was considered conservative. If the conservation score was below the 10th percentile, such a region was considered non-conservative. Then, conservative and non-conservative regions were merged if there were at least eight consecutive 50-bp blocks (thus, the minimum length was 400 bp). Then, purine jump analysis was performed in the resulting intergenic conservative and non-conservative regions.

During the analysis, the following designations were used to denote conditions. Repeats: RepUn = repeat masker unique, RepRe = repeat masker repeats only included, RepEv = repeat masker everything included. Nucleosomes: NuOn = Nucleosomes only, NuEv = Nucleosomes, everything included, NuEx = everything excluding nucleosomes. Conservation: ConTop90 = Conservation top 90th percentile, ConEvery = everything = any conservation, nothing excluded by conservation, ConBot10 = bottom 10th percentile.



B.

jump, bp	number of DNA turns (approx. 10.5 bp per turn)
56	5
66	6
77	7
92	8
105	9

Figure [Jumps]: Analysis of purine sequence jumps in genomic data. A. Histogram showing the counts of purine sequence jumps at different basepair jump sizes. B. Table relating jump sizes to the number of double-helix twists that fit one circle of DNA duplex around the nucleosome.

Figure [Jumps] presents the results of our genomic analysis, verifying the predictions of our pintumbler model. Panel A displays a histogram of purine sequence jump frequencies across different base pair distances derived from an analysis of the human genome.

Our analysis began with the entire human genome sequence of approximately 3 billion base pairs. We then applied several filters to focus on the most relevant genomic regions:

1. We selected only intergenic regions, which comprise about 45% of the genome.
2. From these, we extracted fragments bound by nucleosomes.
3. Finally, we further narrowed our focus to fragments conserved in evolution.

For brevity, we will call the purine-pyrimidine sequence (e.g., RYYYRRY) the "purine sequence." Within these highly conserved sequences, we searched for purine sequence jumps ranging from 40 to 140 base pairs in length. The x-axis of the histogram represents the jump size in base pairs, while the y-axis shows the count of these jumps in the genome. Several distinct peaks are visible, occurring at approximately 56, 66, 77, 92, and 105 base pairs. The peak patterns of purine jumps repeat in three subsets of the genome, confirming their non-random nature and indicating specific intervals of sequence similarities.

Panel B contextualizes these peaks by relating them to the structure of DNA wrapped around nucleosomes. The table shows how each observed jump size corresponds to a specific number of double-helix twists that complete one circle around a nucleosome, based on the 10.5 base pairs per twist of the DNA double helix.

The approximately 77 bp jump, corresponding to 7 twists, is particularly significant as it aligns with the typical length of DNA associated with a single nucleosome. This correspondence between our genomic findings and the well-known nucleosome structure provides support for our pintumbler model.

Even purine results

The analysis of DNA ladder step angles in our model of DNA-water interactions predicted a prevalence of even-sized jumps in purine sequences. To test this prediction, we conducted an analysis of purine-pyrimidine patterns in the human genome. We refer to these patterns as the "purine code," where R represents purines (A and G) and Y represents pyrimidines (T and C), for example, RYRRRYYY.

In this analysis, we examined "jumps" within the purine code. A jump occurs when two similar purine sequences appear in tandem, potentially separated by an insert, for example:

```
Sequence1-Sequence2-Sequence1
RRYRYryyyyyrryrRRYRY
     |    |    |    |
----5----10---15---20
```

Fig.[Jump] Sequence 1 RRYRY labeled blue is repeated as a tandem repeat with the black insertion between the repeated parts. The JumpSize is the coordinate difference between the starts of the repeats; in this example,

JumpSize=15.

We defined the jump size as the distance between the starts of these two sequences. We then compared the frequencies of even-sized and odd-sized jumps in the genome.

Our analysis focused on untranscribed regions and considered several variables: repetitive versus unique sequences as defined by the Repeat Masker, conservation status, and known nucleosome binding (based on UCSC experimental nucleosome binding data).

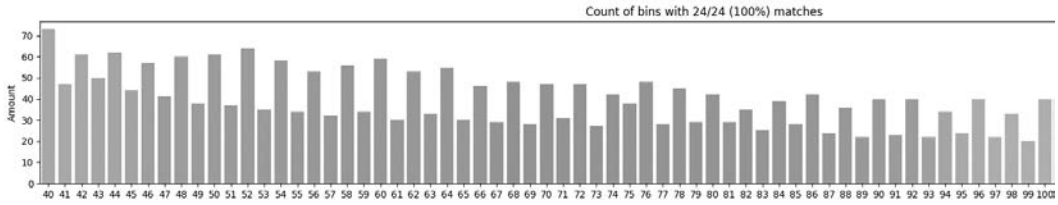


Fig. [Even0]: Frequency distribution of purine sequence jumps in genomic data. The x-axis represents jump sizes from 40 to 100 base pairs, while the y-axis shows the count of jumps. Light gray bars indicate even-numbered jumps, and dark gray bars represent odd-numbered jumps. The graph demonstrates a clear alternating pattern, with even-sized jumps consistently showing higher frequencies than odd-sized jumps across the range of jump sizes analyzed.

The results showed a higher frequency of even-sized jumps compared to odd-sized jumps, but only in repetitive sequences. This pattern was consistent across both simple repeats and more complex repetitive elements like transposons. We checked and did not observe clear effects of nucleosome binding or conservation on the enrichment of even-sized jumps over odd-sized jumps.

These findings provide initial support for our model's predictions about the prevalence of even purine jumps in the genome. They suggest that the genome evolved by retaining simple repeats and transposons that contained even jumps, which were capable of forming nucleosomal and non-nucleosomal DNA double duplex loops bound by polywater honeycomb sheets.

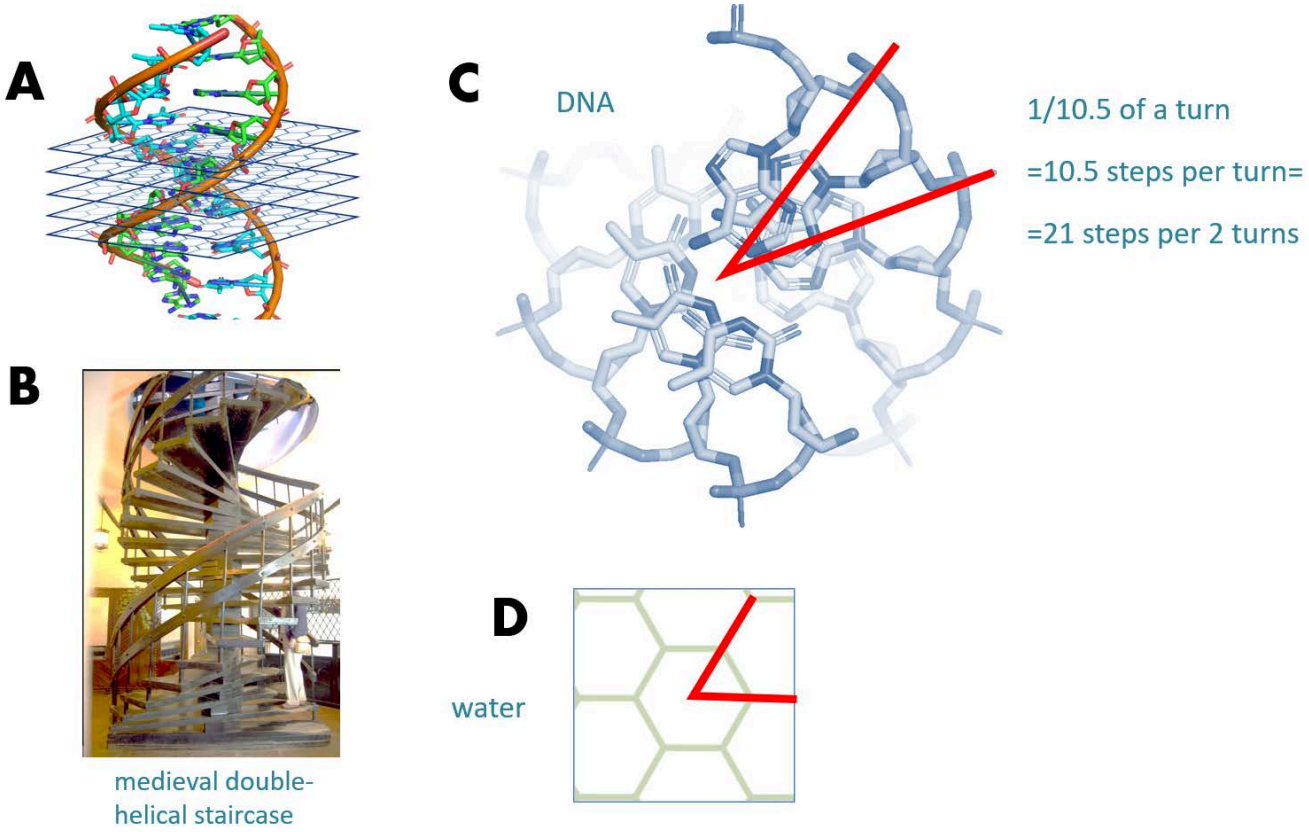


Fig. [Even1] Comparison of symmetry in DNA and water structures. Top left: DNA double helix surrounded by water layers. Top right: Hexagonal symmetry of water, repeating every 1/6 of a turn. Bottom left: Medieval double-helical staircase illustrating the helical nature of DNA. Bottom right: DNA structure, showing 1/10.5 of a turn per step, resulting in 10.5 steps per turn or 21 steps per two full turns.

Figure [Even1] illustrates the structural characteristics of DNA and water relevant to their potential interactions. Panel A presents a model of DNA surrounded by layers of structured water. Panel B shows a medieval double-helical staircase, which serves as a visual analogy for DNA's helical structure, with each step representing a base pair and contributing to the overall twist. Panel C depicts the hexagonal symmetry of structured water, repeating every 1/6 of a turn. Panel D shows a molecular model of B-form DNA, highlighting its helical nature. In this form, DNA completes one full turn every 10.5 base pairs, or 21 base pairs per two full turns. This means each base pair contributes a rotation of approximately 34.3 degrees (360°/10.5) to the overall helix. The difference in rotational symmetry between DNA (1/10.5 turn per step) and water (1/6 turn repeat) creates a structural mismatch that may influence their molecular interactions in biological systems.

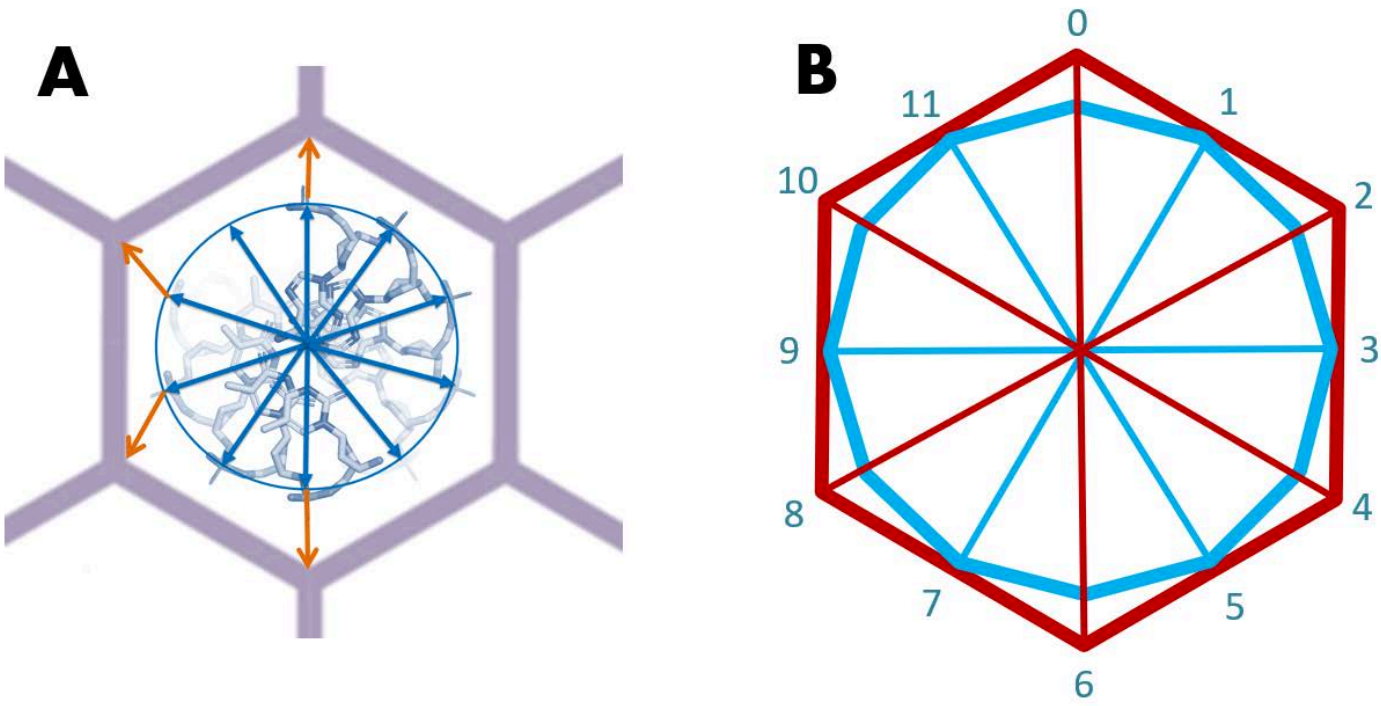


Figure [Even2]: Alignment of DNA core and hexagonal water structures. (A) Top view of DNA double helical core (blue circle, representing 4 base pair steps) embedded in a hexagonal water structure (purple). Orange arrows indicate potential alignment points, illustrating the mismatch between DNA's natural 10.5 base pairs per turn and water's hexagonal symmetry. (B) Schematic representation of a hypothetical DNA structure with 12 base pairs per turn (blue dodecagon) relative to water's hexagonal symmetry (red hexagon). Numbers 0-11 represent DNA base pair positions. This model demonstrates how every other base pair could align with the water structure's vertices in a more tightly wound DNA configuration.

Figure [Even2] illustrates the potential alignment between the DNA double helix core and the hexagonal symmetry of water. Panel A depicts a top view of the DNA double helical core (blue circle, representing approximately 4 base pair steps) within a hexagonal water structure (purple). The orange arrows indicate potential alignment points between DNA and water structures. With the natural 10.5 base pairs per turn of B-form DNA, achieving consistent alignment is challenging. The DNA core would need to constantly twist, alternately aligning different base pairs, while some would always remain misaligned with the water structure.

Panel B presents a hypothetical scenario where DNA is more tightly wound, with 12 base pairs per turn instead of 10.5. The red hexagon represents the hexagonal symmetry of the water structure, with its six-fold rotational symmetry. The blue dodecagon represents DNA base pair positions, numbered 0 to 11. This configuration, while only occurring in a small percentage of genomic DNA, presents an intriguing possibility for optimal energy interactions between DNA and water.

In this model, the water structure remains stationary, while the DNA core may undergo slight

twisting motions. The alignment of every other base pair (positions 0, 2, 4, 6, 8, 10) with the water structure vertices suggests the potential for favorable crystallization and energetic interactions between the DNA core and the surrounding water molecules.

This observation leads us to propose the "even purine" hypothesis. We suggest that in regions where DNA adopts this more tightly wound configuration, even-numbered base pairs might play a more significant role in DNA-water interactions due to their favorable alignment with the water structure. While most DNA in the genome maintains 10-11 base pairs per turn (averaging 10.5), the existence of these tightly wound regions could have important implications for DNA-water interactions and potentially for genomic function.

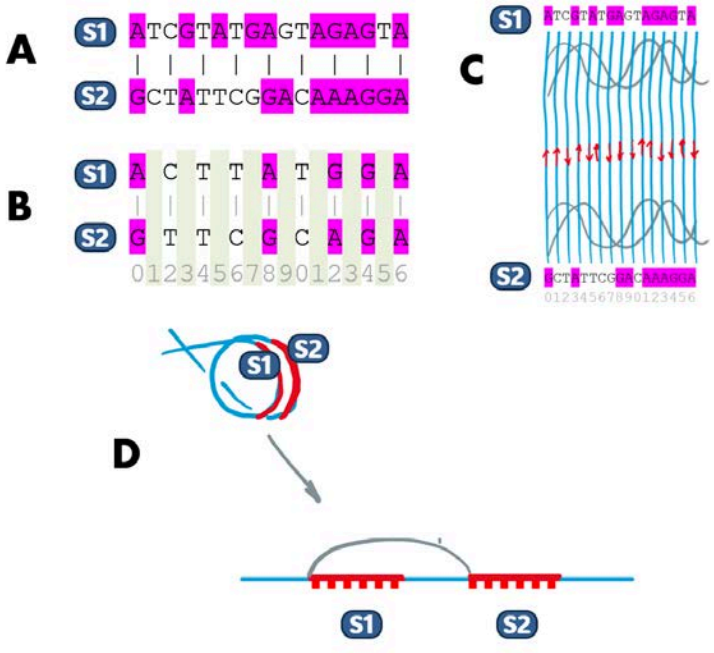


Figure [Even3]: Translation of 3D molecular model to 1D genomic predictions. (A) Full DNA sequences S1 and S2 with purines highlighted in pink. (B) Even-purine code extracted from sequences S1 and S2. (C) Schematic representation of DNA double helix with water layers (blue lines) and potential shifts (red arrows). (D) Hypothetical model of DNA loops on a nucleosome, showing potential water-mediated interactions between segments S1 and S2.

To translate our 3D molecular model of DNA-water interactions into testable genomic predictions, we developed a method to represent these interactions in terms of linear DNA sequences. Figure [Even3] illustrates this transition from 3D structural considerations to 1D genomic patterns.

Panel A shows two quite different DNA sequences, S1 and S2, with purines (A and G) highlighted in pink. These sequences represent potential interacting segments of DNA. In panel B, we extract what we term the "even-purine code" from these sequences. This code considers

only the purine (R) or pyrimidine (Y) nature of bases at even-numbered positions, reflecting our hypothesis that these positions align more favorably with the hexagonal water structure.

We introduce the concept of "even-purine homology," defined as the similarity between two sequences when only one phase (odd or even nucleotides) is considered in terms of their purine-pyrimidine pattern. As illustrated in panel B, when examining only the even positions, the two seemingly different sequences appear identical in their purine code, demonstrating even-purine homology.

Panel C provides a schematic representation of how these sequences might interact through water layers in a 3D context. The blue lines represent water layers, while the red arrows indicate potential shifts in these layers induced by the DNA sequence. This model suggests that even-purine homology between two DNA segments could promote their interaction through structured water.

Finally, panel D presents a hypothetical model of how these interactions might occur in the context of chromatin structure. It shows two segments of DNA (S1 and S2) potentially brought into proximity by looping around a nucleosome. The red marks underneath represent the even-purine positions that might mediate water-structured interactions.

This conceptual framework allows us to formulate testable predictions about genomic sequences. Specifically, we hypothesize that genomic regions involved in long-range interactions or specific chromatin structures might show increased even-purine homology. This similarity would not be apparent from standard sequence comparison methods but could be detected through specialized analysis of purine-pyrimidine patterns at even-numbered positions.

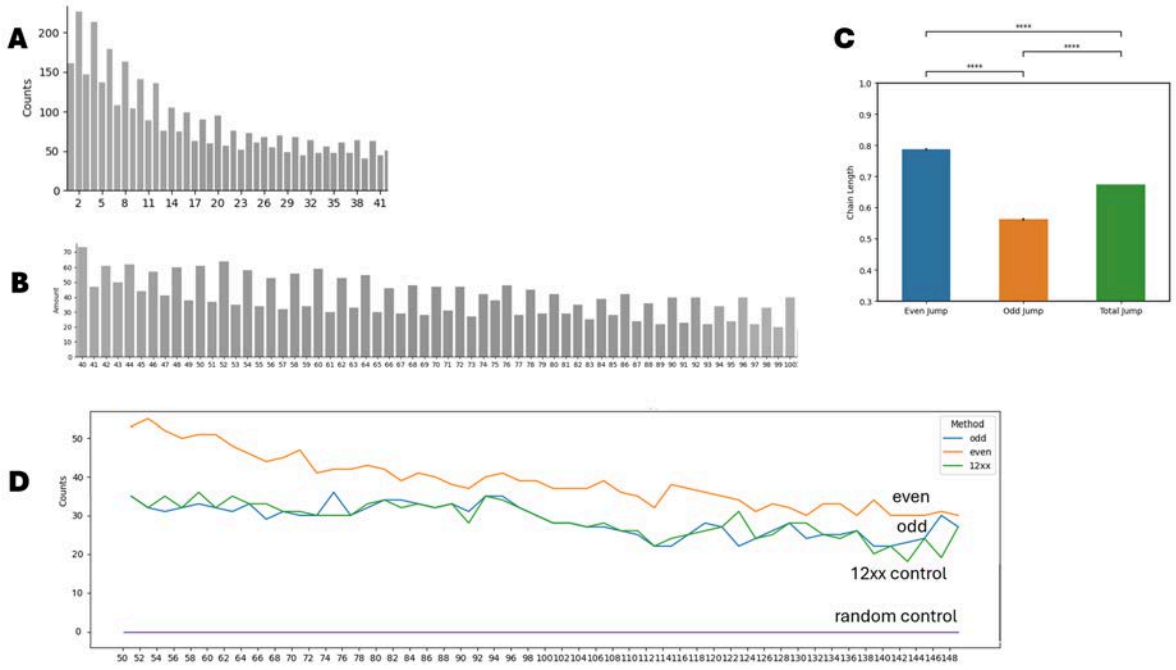


Figure [Even4] Even sized jumps are more frequent in repetitive regions. Panels A and B demonstrate the frequency of purine jumps across various sizes, with a clear predominance of even-sized jumps. Panel A, covering jump sizes from 2 to 41 base pairs, shows consistently higher bars for even-numbered jumps compared to their odd-numbered counterparts. This pattern continues in Panel B, which extends the analysis to jump sizes of 40-100 base pairs. (This panel was shown previously as Fig.0). While both panels reveal a general trend of decreasing frequency as jump size increases, the alternating pattern of higher even-numbered jumps persists throughout. This striking alternation between even and odd jumps is maintained despite local fluctuations, strongly suggesting a non-random distribution favoring even-numbered purine jumps in the genomic sequences analyzed. Panel C presents a statistical comparison of homology in even jumps, odd jumps, and total jumps. The bar graph shows significantly higher homology in even jumps compared to odd jumps and total jumps. The asterisks (****) indicate that these differences are statistically significant ($p < 0.0001$).

In our analysis depicted in Panel A, we observed a higher frequency of even jumps compared to odd ones, a pattern consistent with the observations in Panel B. For Panel **D**, we hypothesized the existence of DNA fragment pairs predominantly exhibiting purine jumps only in one of the odd-even phases (odd or even). Specifically, in such areas, alternate nucleotides - either odd or even - would conform to a pattern of even-purine jumps, while the alternate phase exhibited significantly less homology. We conducted our analysis by searching for pairs of 24 bp fragments within 400 bp bins. Our focus was solely on even-purine homology separately in each (odd or even) phase, selecting jump pairs that demonstrated 100% homology within the 24bp fragment pairs. The bins were arbitrarily selected from repetitive genome regions, without specific selection for odd or even phases; phases were chosen randomly. The counts of found 24bp fragment pairs with a 100% homology in one the the two phases are plotted in **Panel D** vs jump sizes. To assess the randomness of these patterns, we randomized the entire genome by dividing it into 2bp bins and randomly flipping the order of the nucleotides within these bins, which altered the even and odd nucleotide positions, plotted as "random control" on panel **D**. This control found zero 24bp fragment pairs with 100% purine homology. Furthermore, we plotted the 12xx curve, where we divided each bin into 4bp subbins and looked for 100% purine homology solely at positions 1 and 2, disregarding positions 3 and 4. The comparison of all 4 curves in panel D indicated a non-random, higher occurrence of even jumps compared to odd, 12xx, and random curves.

In summary, we observed two key phenomena in repetitive genomic regions:

1. Even-purine jumps occurred more frequently than odd jumps, with strong statistical significance.
2. A divergence in homology where 100% purine homology was observed in only one phase (even or odd), while the other phase showed much less homology.

Both these observations align with the even purine hypothesis, which originated from the observation that only one sequence phase (even or odd) aligns with the hypothetical transverse honeycomb water structure outlined in Figure [Even2]. This hypothesis suggests that the alignment between DNA base pairs and the proposed water structure occurs predominantly at even-numbered positions, leading to the observed patterns in purine jumps and homology divergence.

Homadhesion

Let's now explain the idea of homadhesion. Homadhesion is our new term and stands for homologous adhesion. The idea is that two DNA duplexes would adhere to each other in the nucleoplasm if they have somewhat similar sequences. DNA duplex or duplex is a term used as a short form of the term DNA double helix.

List of new terms in this chapter:

1. **Sequa**: DNA-sequence imprinting water state (from SEquence and aQUA)
2. **Kaoqua**: Water that is restructured and has chaotic arrangements (from KAOs and aQUA)
3. **Inaqua**: Water that is restructured by imprinting non-DNA order, such as primitive unidirectional shift (from INorganic AQUA)
4. **Seprinting**: DNA Sequence Imprinting on Water (from SEquence imPRINTING)
5. **Homadhesion**: Sequence-specific HOMologous adHESION between DNA duplexes
6. **Indepaction**: INtron-mediated compaction and DEcomPACTION of chromatin

The concept of homadhesion emerges from the need to explain two genomic mysteries: the persistence of large amounts of repetitive DNA despite evolutionary pressure, and the seemingly random distribution of transposons throughout the genome. Evolutionary processes typically remove or mutate unnecessary or detrimental sequences quickly, yet 55% of the genome remains repetitive. This includes tandem repeats in telomeres and centromeres, as well as interspersed repeats or transposons scattered throughout the genome.

The traditional view of transposons as mere selfish, parasitic elements is challenged by this hypothesis. While partly true, it's proposed that a control system exists to select which transposons to retain and where, serving an as-yet unclear positive function. Barbara McClintock, who discovered transposons, believed they acted as control elements for gene expression. Building on this, we propose that transposons define patterns and logic of chromatin folding, making them key to cellular logic and "thinking." Specifically, we propose that transposons and all repetitive sequences adhere to each other in a sequence-specific manner via homological adhesion that is homadhesion.

The relationship between DNA structure and water layer shifts is more intricate than initially proposed. While our model initially focused on purine and then even-purine homology, the mechanism of homadhesion can include these and also exact homology alignment in the original AGCT sequence. This more precise alignment is made possible by the geometric relationship between DNA and water structure. Due to the relative distances between water layers and DNA basepair steps, approximately two water layers correspond to one DNA step. This arrangement allows for 18 possible positions in the three-dimensional shift of water layers, as illustrated in Figure [Shift] above. These 18 positions provide sufficient variability to allow imprinting of the four possible base pairs (A-T, T-A, G-C, C-G) and potentially even DNA methylation (5mC) onto water structure. . The specific shape and chemical properties of each base pair can influence the exact shifting pattern of the surrounding water layer, effectively

imprinting the precise DNA sequence information onto the water structure. This refined model explains how homadhesion can respect exact sequence alignments rather than just purine patterns.

This sequence-specific homadhesion is exemplified by the Alu transposon. The Alu transposon, with 1.1 million copies per haploid genome (2.2 million in diploid cells), exemplifies this concept. Alu has over 30 subtypes with minor sequence variations. We predict that each subtype adheres to itself, forming codirectional duplex pairs and accordingly are responsible for sequence specific folding and reversible sticky fastening of chromatin loops. For instance, two dsDNA fragments of the AluSx subtype might stick together, closing a chromatin loop. We propose that transverse polywater layers connecting these adhered duplexes are responsible for the sequence specificity of this adhesion.

Importantly, homadhesion differs from traditional DNA base pairing. The duplexes remain intact, adhering via transverse water layers rather than opening and forming complementary base pairs. This adhesion is likely weaker than that between complementary DNA strands, allowing for dynamic formation and dissolution at physiological temperatures.

This mechanism is hypothesized to be active in eukaryotes, particularly in multicellular species, which are as we know functioning at temperatures from 0 to 43°C. In a typical cell during interphase, a significant portion of chromatin is condensed as heterochromatin near the nuclear envelope, occupying about 50% of the nuclear volume. The inner part contains active, unpacked euchromatin. Our model proposes that euchromatin consists of dissociated duplexes, while heterochromatin comprises adhered double duplexes. This creates a dynamic balance between chromatin compaction and decompaction, correlating with gene expression. Compaction occurs through sequence-specific pairing and homadhesion of repetitive sequences, primarily transposons. Given the numerous copies of specific transposon subfamilies, many combinations of duplex pairs are possible, leading to constant competition in partner formation. This process resembles a molecular dance with continually switching partners, albeit undifferentiated by gender. Possibly, identical transposon copies create not only paired homadhesive structures but create larger multiloop structures such as helices or other multiloop fibers.

One more interesting consequence arises from the realization that some repetitive elements are present in the genome in large numbers. Given that Alu and LINE elements make up over 30% of our genome, the structured water formations are likely dominated by imprints from these two types of transposable sequences.

Linkers vs. nucleosomes

One of the questions to address is on possible molecular mechanisms of adhesion. Homadhesion is a combination of two components: homology and adhesion. While we already proposed the principle which ensures the **homology** of homadhesion via the transverse layers of polywater, the mechanism of **adhesive** component of the homadhesion should be further discussed.

For the adhesion mechanism, several forces could be considered: electrostatic, including ionic, hydrophilic-hydrophobic, hydrogen bonding, van der Waals, and other weak forces. Since we observe quick dynamic chromatin condensation and decondensation, this might hint at the mechanisms of adhesion and dissociation of duplex pairs, and for that reason, we don't think DNA duplexes are opened – we think they stay nearly intact. Although we suggest that the primary chemical responsible for adhesion is polywater, we don't exclude the possibility of other nucleoplasmic components taking an active part in homadhesion. These could include histones, other proteins, and low molecular weight chemicals abundant in the nucleoplasm.

It is also important to explain how the highly negatively charged DNA duplexes overcome electrostatic repulsion to adhere to each other. For that, they must be neutralized by positive ions. The choice of positive ions in the nucleoplasm includes proton (H+), hydronium ion (H_3O^+), histones which are positively charged, other positively charged proteins and peptides and other positively charged low molecular weight ions, such as Na^+, K^+, Mg^{2+}, and polyamines like spermine and spermidine.

Yoo et al. (2016) provided experimental evidence for sequence-dependent attractive interactions between double-stranded DNA molecules, which is highly relevant to the concept of homadhesion. Using a combination of molecular dynamics simulations and single-molecule FRET experiments, they demonstrate that DNA duplexes can attract each other over distances up to 2-3 nm in the presence of polyamines like spermine. Importantly, AT-rich sequences show stronger attraction than GC-rich sequences, and this attraction does not require sequence homology. DNA methylation enhances these interactions, making methylated GC-rich sequences interact as strongly as AT-rich ones. The mechanism involves polyamines mediating the interactions, with methyl groups on thymine or methylated cytosine affecting polyamine positioning. The Yoo study demonstrates that sequence-specific long-range attractions between DNA molecules exist and could play a role in chromosome organization and gene regulation. This work provides experimental support for the homologous attraction and adhesion.

As we well know most of the genomic DNA is wrapped on nucleosomes. Only a small fraction is unwrapped and is actively transcribed. In the nucleosome wrapped part, about 2/3 of the sequence is wrapped onto a nucleosome and is therefore rounded, and the remaining linker sequence is free and forms a straight line. In our model, we are not sure whether it is nucleosome-wrapped sequence or internucleosomal linear linkers that undergo homadhesion. Primarily due to charge, we think that linkers would repel a lot while nucleosomes from transposon sequence pairs would easily stick to each other. Therefore we currently prefer the idea that it is nucleosomes that undergo homadhesion. The nucleosomal core charged positively will, therefore, overcome the electrostatic repulsion of the two DNA duplexes from each other.

The structure of transverse water layers would be a bit different for nucleosomal homadhesion as opposed to linker homadhesion. In the nucleosome, the transverse water layers would be radial. This radiality requires including additional flexibility in our model. One addition is that radial sheets of water must be separated by wedge-shaped gaps (or canyons) filled with unstructured water or wedge-shaped water structures. Another addition is that radial water layers must bend similarly to blades in a turbine rotor to maintain the approximate distance and

parallelism of the radial polywater layers Fig.[Turbine]. Moreover, the necessary presence of canyon gaps in the polywater makes it quite stretchable, allowing for more complex structures such as turbine blades. These additions introduce additional imperfection mechanisms to our model: gaps and bending.

Fig.[Turbine]. Bending of polywater layers to resemble blades in a turbine rotor would allow maintenance of the approximate distance and parallelism between radial polywater layers.

Lee et al. (Lee et al., 2014) provided theoretical support for sequence-dependent interactions between intact DNA duplexes. Their model incorporated electrostatic forces and sequence-dependent DNA shape variations, predicting lower interaction energies for pairs of DNA fragments with parallel homologous sequences compared to those with uncorrelated sequences. This interaction was modeled without strand separation, considering the aqueous environment through parameters that account for electrostatic screening in solution. Their work suggests a potential mechanism for homology recognition between intact DNA duplexes prior to strand invasion.

The concept of homadhesion between intact DNA duplexes relates to questions about how similar DNA sequences interact in the genome. Barzel and Kupiec (Barzel and Kupiec, 2008) reviewed models and evidence for the pairing of similar DNA sequences across different organisms. They noted an important observation in yeast: matching DNA sequences can locate each other and recombine efficiently, even when these sequences are in different genomic locations. This occurs despite the large amount of genomic DNA present. The authors presented two main hypotheses to explain this: one where the search for matching sequences is initiated by DNA damage, and another where similar sequences are paired as part of the genome's basic organization. The efficiency of this homology recognition process highlights the potential importance of mechanisms like homadhesion in facilitating DNA-DNA interactions.

Lechelon et al. (Lechelon et al., 2022) provide experimental evidence for long-range attractive forces between proteins, supporting concepts of homologous attraction from a distance. The study shows that proteins excited out of thermal equilibrium can interact over distances up to 100 nm (about 300 base pairs of DNA length). These interactions are based on a phenomenon called Fröhlich interactions, named after physicist Herbert Fröhlich who proposed the idea in his seminal 1968 paper (Fröhlich, 1968). The key idea is that when proteins are driven out of equilibrium (in this case by light), they can enter a state of collective oscillation. These

oscillations create fluctuating electromagnetic fields that can couple with similar oscillations in other proteins. When the oscillations match in frequency, it leads to an attractive force. This force is selective (only works for matching frequencies) and long-range (works over distances much larger than typical molecular interactions). While the basic principle has been around for decades, this chapter provides some of the first clear experimental evidence for these interactions in a biological context. The authors suggest that such forces could play a role in how biomolecules find and recognize each other in the crowded environment of a cell, potentially complementing random diffusion. Accordingly, we suggest that Fröhlich interactions based on electromagnetic and electroacoustic collective vibrations are the mechanism for sequence-specific attraction and homadhesion of identical DNA fragments in chromosomal territories in the cell nucleus.

On Possible Intron Function

The concept of homadhesion introduced in this chapter may shed light on the long-standing mystery of intron function. Introns occupy a surprisingly large portion of the genome, with classical protein-coding genes transcribing into long unprocessed mRNA. This genomic sequence contains three types of sequences: exons that code for protein aminoacid chains, and introns that are spliced out and not translated and untranslated terminal regions. Exons comprise 4.5% of the genome, introns 50%, and the remaining 45% is intergenic sequence.

Over 50% of both intergenic and intronic sequences are repetitive, consisting mostly of transposons. Despite this information being available since 2000, the function of introns remains largely unknown. The commonly accepted role of introns in producing splice variants is unsatisfactory, as it fails to explain their large genomic fraction. Observations of sequence evolution suggests that such a large amount of DNA would not be retained if it served only this limited function.

Building on the concept of homadhesion and the idea that perpetual chromatin refolding serves as a mechanism for cellular computation and decision-making, we propose that introns play a role in determining when and under what circumstances their associated genes should be expressed. Specifically, we suggest that introns control gene decompaction, a key mechanism of gene expression regulation alongside transcriptional complex assembly.

We introduce the concept of intron-mediated compaction and decompaction, termed "indepaction" (INtron mediated compaction and DEcomPACTION). In normal cells, the chromatin of most genes and intergenic sequences is compacted and located in the inner periphery of the nucleus, while actively transcribed genes are decompacted and centrally located. This arrangement adheres to chromosome territory rules, with each chromosome occupying a distinct 3D segment in the nucleus.

For silent genes, we propose that the repetitive parts of intronic dsDNA pair with identical repetitive DNA sequences, ensuring compaction through homadhesion. In the decompacted state, we suggest that spliced-out intronic RNA stabilizes decompaction by homologically pairing with both repetitive and non-repetitive parts of the intronic DNA. This is possible since intronic RNA is a copy of intronic DNA. This process prevents compaction via homadhesion with homologous repetitive sequences from elsewhere in the genome.

We hypothesize that the cellular machinery switches between these two states - compacted via homadhesion and decompacted via intronic RNA-DNA pairing - by sending additional RNA sequences to regulate the process. Decompaction may be mediated by repetitive RNA sequences produced elsewhere in the genome that come to the intron, align homologically to its identical repetitive part, and this way initiate decompaction. Conversely, compaction might be induced by antisense RNA that pairs with the stabilizing intronic RNA, potentially leading to its degradation and subsequent gene compaction.

The structural basis for homological adhesion in the proposed Indepaction mechanism could potentially involve two distinct molecular configurations. One possibility is the formation of DNA-RNA heteroduplexes, where the RNA displaces one strand of the DNA, creating a localized R-loop structure (Costantino and Koshland, 2015). Alternatively, the mechanism might involve the formation of triple-helical nucleic acid structures, where the RNA binds to the major groove of the DNA double helix through Hoogsteen or reverse Hoogsteen base pairing (Felsenfeld et al., 1957). Both of these molecular arrangements could provide sequence-specific recognition and stable binding, consistent with the proposed function in regulating chromatin compaction states.

The chromatin-opening and stabilizing RNA sequences could be medium and long (100-10000 nt), while the decompacting antisense RNAs could be short (15-30 nt). This proposed indepaction mechanism generates testable predictions using existing public genomic data. We hypothesize that co-expressed genes may stabilize each other's expression by sharing common patterns in their introns, with their intronic RNAs cross-stabilizing the introns of co-expressed genes. Similarly we predict that gene activation parthays may include RNA copies of repetitive DNA as mediators via proposed Indepaction mechanism.

To summarize the results, our model of DNA-water interactions proposes a "pintumbler" mechanism where DNA imprints its sequence information onto surrounding water structures, creating layered structures that shift based on the DNA sequence. Genomic analyses revealed patterns of purine jumps and even-odd nucleotide homology aligning with this model's predictions. We introduce the concept of "homadhesion" - homologous adhesion between DNA duplexes mediated by these water structures - and propose an "indepaction" mechanism for intron-mediated gene regulation. These concepts suggest a novel form of cellular information processing through dynamic chromatin reorganization. This concept of chromatin as a genome sequence-programmed 'biocomputer' extends earlier ideas proposed by Miller and Webb (Miller and Webb, 1972, 2002), who suggested that DNA functions as a quantum-holographic field. Their work, like our current model, emphasized DNA's capacity to process and transmit information beyond its linear sequence, through its physical organization and interaction with electromagnetic fields.

Discussion

This study presents a novel model of DNA-water interactions and their potential role in chromatin organization. At its core, our model proposes a perpetual dynamic interplay between the tendency towards order (perfection) and the continuous disassembly of that order (imperfection) as a fundamental principle of life.

Key aspects of the model:

1. DNA imprinting on water: We proposed that DNA may initiate microcrystallization of water, imprinting its sequence onto the water structure through a process we term "crystal pattern propagation" or "snowflake signaling."
2. Pintumbler mechanism: Our model suggests that the DNA imprints its sequence into water of nucleoplasm by defining shifting pattern of surrounding transverse water layers, creating a unique water structure that reflects the underlying DNA sequence.
3. Dynamic competition between perfection and imperfection: The model emphasizes a constant interplay between the formation of ordered, crystal-like water structures (perfection) and their continuous dissolution and reformation (imperfection) as basis for life.

The focus of this model is in highlighting of the perpetual, self-organizing nature of living systems. It suggests that the nucleoplasm exists in a state of continuous, dynamic reorganization, with three main components:

1. Recrystallization of polywater: Constant growth and dissolution of water structures around DNA.
2. Screwing oscillations: DNA's back-and-forth screwing-twisting movement within water layers due to imperfect alignment.
3. Chromatin dynamics: Sequence-specific homologous adhesion (homadhesion) of different parts of chromosomes through water-mediated structures.

This continuous state of flux, teetering between order and chaos, may provide the flexibility necessary for cellular processes while maintaining overall structure. A key insight of our model is the proposal that the refolding of chromatin in a sequence-specific manner is the primary mechanism by which cells process information - essentially, how cells "think." This dynamic reorganization of chromatin, guided by DNA-water interactions, may serve as a physical basis for cellular logic, decision making and fine tuning. As chromatin continuously refolds in response to various inputs, it creates a dynamic, three-dimensional DNA-sequence programmed information processing system within the nucleus. This concept of chromatin as a genome sequence-programmed "biocomputer" adds a new dimension to our understanding of cellular information processing. It suggests that the genome not only stores information in its linear sequence but also actively computes and responds to cellular needs through its physical reorganization. This dynamic, sequence-specific refolding could explain how cells integrate multiple inputs and make complex decisions.

Homadhesion is guided by biofields

Consider that dynamic continuous perpetual partly random self-organization processes are necessary for biofields to exert their influence. There are several self-organization levels:

1. Polywater continuously self-reorganizes.
2. Chromatin also continuously self-reorganizes.

There are waves of self-reorganization in chromatin. For example, in mammalian cells, there is a periodicity of reorganization cycles with a period of 2 minutes. This pulsation or breathing of chromatin was observed using a fluorescent LacO/LacI-GFP tandem array of repeated

sequences (Nagaich et al., 2004).

The influence of biofields on biological systems may be most effective in dynamic, self-organizing processes that are in a state of partial equilibrium. While this idea hasn't been directly stated in scientific literature, we can draw parallels from other fields where similar phenomena are observed. A key aspect of systems in dynamic equilibrium is their fluidity and sensitivity to even subtle forces. In such states, small inputs can potentially shift the entire equilibrium, leading to significant changes in the system's organization. This sensitivity makes these systems particularly suitable for observing the effects of subtle fields.

Consider experiments that visualize magnetic and acoustic fields:

1. Magnetic field visualization: Magnetic particles are suspended in a fluid or placed on a low-friction surface, allowing them to move freely with minimal resistance. When a magnetic field is applied, these particles self-organize into patterns that reveal the structure of the field. The near-frictionless environment enables even weak magnetic forces to noticeably influence the particles' arrangement.
2. Cymatics: In these experiments, sand or small particles are placed on a plate that is then vibrated with sound waves. The vibration essentially creates a low-friction environment where the particles can easily move. The particles reorganize themselves into complex patterns that represent the acoustic field's interference patterns.

In both cases, the key to visualizing these invisible fields is the dynamic, self-organizing nature of the particles in a state of low friction. They're free to move and reorganize in response to even subtle influences from the field, thereby making the field's influence visible.

We suggest that biofields might operate in a similar manner within biological systems. Living organisms are in a constant state of flux, with cellular components and molecules continuously moving and reorganizing. This dynamic state, akin to a fluid system with low internal resistance, might make biological systems particularly responsive to the subtle influences of biofields.

For instance, chromatin in the cell nucleus undergoes constant reorganization. This dynamic environment could potentially allow biofields to influence gene expression or other cellular processes by guiding the self-organization of chromatin and other cellular components. This way, even small influences from subtle biofields could, lead to significant shifts in cellular organization due to the system's inherent sensitivity when in a dynamic equilibrium state. This perspective suggests that to fully understand and potentially harness biofields, we should focus on studying biofields using biological systems in their dynamic, self-organizing states rather than in static or overly simplified in-vitro conditions.

The biofield concept aligns with earlier work by Miller and Webb (1972, 2002), who proposed that DNA functions as a quantum-holographic field capable of storing and transmitting information beyond its linear sequence. Our model provides a mechanism for such information transfer through interaction of electromagnetic, electroacoustic and subtle fields with DNA-mediated water structuring and chromatin organization.

While our model presents intriguing possibilities for DNA-water interactions and chromatin organization, it is largely theoretical at this stage. Although we observed genomic patterns that confirm our predictions, we also need to rule out alternative explanations. To build upon this initial work and rigorously test our hypotheses, we propose the following directions for future

research:

1. Chromatin Conformation: Utilize chromatin conformation Micro-C and Hi-C data to search for evidence of homadhesion in chromatin structure. In these experiments a combination of experimental crosslinking with sequencing is used to map with high resolution which fragments are positioned near each other in the cells. These data can demonstrate that repeats stick to each other in live cells.
2. Co-regulation: Conduct exploratory analyses of the gene regulation networks to check whether coregulated genes or whether pairs of genes that regulate each other have similar patterns of transposons in introns more frequently than by chance. Analyze genomic sequences for patterns of homology in primary sequence, purine and even-purine codes, focusing on co-regulated genes and gene pairs where one regulates another.
3. Structural Modeling: Develop and refine computational 3-dimensional chemical structure and dynamics models of DNA-water structures to better understand the structure and dynamics of the proposed pintumbler and homadhesion mechanisms.
4. Sequence manipulation: Use DNA sequence manipulations in cell culture to demonstrate homadhesion. That is introduce, modify or delete patterns of transposons in introns and measure how this affects gene expression. Similarly, modify patterns of transposons in intergenic regions and see how this affects DNA loop formation. These experiments should account for the need for natural nucleoplasm components, including proper 1% DNA and 20% protein concentrations. We could also measure loop formation rates when loops are closed by transposons, using FRET-based methods to measure DNA looping J-factors as we have done previously (Myakishev et al., 2001; Shoura et al., 2020, 2012).
5. Water-DNA Structure Studies: Employ a variety of techniques (NMR, optical spectroscopy, bioimpedance, acoustic spectroscopy, isotope studies, FISH with microscopic readout) to investigate water-DNA structures both *in vitro* and *in vivo*. Compare findings across different cell types (e.g., cancer vs. normal) and species. Additionally, we could employ atomic force microscopy techniques as we have done before (Vetcher et al., 2006) to directly visualize DNA conformational changes induced by water structuring and transposon-mediated looping.
6. Comparative Water-DNA Structure Analysis: Test the hypothesis that water-DNA structures differ significantly between species, cell types, and disease states, reflecting variations in genomic organization and cellular function. Investigate these structures using both in vitro and *in vivo* models, with emphasis on live nucleoplasm or reconstituted nucleoplasm in vitro. Employ a range of methods including NMR, optical spectroscopy, bioimpedance, acoustic spectroscopy, isotope studies, and FISH with microscopic readout. Utilize fluorescent LacO/LacI-GFP tandem array of repeated sequences (Nagaich et al., 2004) inserted in live cells to visualize dynamic changes in chromatin structure. Conduct comparative analyses between cancer and normal genomes, and across various classes of life species. We expect to find distinct water-DNA structural signatures correlating with genomic complexity, cellular differentiation states, and pathological conditions, potentially revealing the role of

water-mediated DNA organization in biological information processing.

7. DNA Sequence Imprinting on Water (seprinting). This could involve imprinting various DNA sequences on reconstituted nucleoplasm, removing the DNA, and then measuring the sequence-specificity of the remaining water structure as it affects the folding of newly introduced dsDNA. To separate sequence-imprinted water from DNA we could use DNA bound to beads, or semi-permeable membranes. Structured water isolated from human cells should have an imprint of the most abundant repetitive sequences such as Alu and LINE, comprising collectively over 30% of the human genome. This structured water should affect the conformation of newly added tagged DNA constructs containing Alu and LINE sequences in a sequence-specific manner compared to other control constructs that are not homologous to human DNA. Such conformational changes can be measured by FRET or intercalation fluorescent dyes, or by circular dichroic spectrometry, or by impedance spectrometry of DNA attached to a semiconductor chip. Also LINE1 structural and vibrational signatures should be common between human and mouse chromatin, while Alu is specific to primates, so its structural and vibrational signatures should be common to human and monkey but absent in the mouse. Our DNA sequence imprinting model provides molecular structural mechanism for the ideas of water memory proposed by Benveniste (Davenas et al., 1988) and Montagnier (Montagnier et al., 2011). We hypothesize that certain DNA structures may imprint on water more readily than others. Additionally, temperature and nucleoplasm content might be crucial factors in achieving proper imprinting of DNA sequence structure on water. These aspects of our model provide a framework for understanding how specific molecular information might be retained in water structures in the nucleoplasm. Therefore, *in vivo* experimentation or close reproduction of *in vivo* nucleoplasm conditions most likely will be required for proper verification of the water memory phenomenon. We suggest that for effective DNA sequence imprinting on water, any pre-existing structures would need to be randomized first. This randomisation might be hard to achieve in nucleoplasm, but *in vitro* in low-molecular weight solutions, this can be achieved using boiling and ultrasound.
8. DNA Twist Oscillations: Use polarization spectroscopy of fluorescence-labeled DNA chains to measure twist oscillations and measure the effects of homadhesion on DNA oscillations in live cells or reconstituted nucleoplasm. Check whether addition of homologous RNA disrupt homadhesion.
9. Polywater Structure Characterization: Adapt methods from Gerald Pollack's work on the "fourth phase of water" to investigate structured water formations around DNA in reconstituted nucleoplasm (Pollack, 2013). Employ techniques such as exclusion zone measurements, infrared imaging, and electrical potential recordings to characterize the properties of water layers adjacent to DNA molecules. Use DNA bound to beads or flat surfaces. Utilize microspheres, pH-sensitive dyes, and microelectrodes to map the extent and properties of these structured water regions.
10. Biofield Influence Studies: Microscopy, gene expression and chromatin conformation experiments to investigate how biofields might influence the dynamic self-organization of chromatin and water structures in the nucleus.

The use of nucleoplasm from multicellular organisms could be crucial for these experiments, as the proposed mechanisms may be more pronounced in multicellular organisms. However, when cell culture experiments are not possible (as in spectroscopic studies), reconstructing or isolating fully functional nucleoplasm is a challenging task. It is unclear whether the high protein concentration (about 20%) in the nucleus is critical for the formation of sequence-imprinted water (Sequa). If pure water, buffered solutions, or simplified imitations of nucleoplasm prove sufficient, this would greatly simplify the experiments. One might consider exploring alternatives such as typical buffers and media used in enzymatic reactions and cell culture, including PCR and restriction buffers, serum, and BSA dilutions. Additionally, commercially available kits for nucleosome reconstitution, which contain histones and other components for reconstituting chromatin, may provide a suitable approximation of the nucleoplasm. These approaches could offer practical alternatives to full nucleoplasm reconstruction while still allowing for the study of proposed DNA-water interactions.

Conclusions

In this study, we presented a novel model of DNA-water interactions within the cell nucleus. Our model suggests that DNA sequences can imprint information onto surrounding water structures, creating a unique "watermark" that reflects the underlying genetic sequence. We proposed that these water structures may mediate sequence-specific dynamic sequence-specific chromatin folding, providing the program and the mechanism for chromatin reorganization and and gene regulation.

In our model, we integrated concepts from biofield theory, polywater structure, and genomics of transposons to explain sequence-specific chromatin folding. We proposed testable mechanisms for DNA-mediated water structuring and homologous adhesion of genomic repetitive elements.

While our model was largely theoretical, our genomic analyses revealed patterns that aligned with its predictions. We proposed future research directions, including studies of chromatin structure, water-DNA interactions, and the influence of electromagnetic fields on cellular processes. These research should lead to significant advancements in our understanding of chromatin function, with potential implications for regenerative medicine, oncology and aging research.

This work offered potential explanations for several long-standing mysteries in biology. It provided a possible mechanism for how biofields influence genome function, suggested a structural mechanism for cellular thinking and decision-making, and proposed new functions for introns and intergenic sequences. We also proposed a new positive function of transposons in dynamic chromatin folding. This work not only suggests a structural basis for cellular information processing but also provides a framework for decoding the chromatin code embedded in introns and intergenic "junk" DNA. By understanding this hidden chromatin code, we may be able to interpret how chromosomal rearrangements in cancer disrupt normal cellular logic. As we validate our model experimentally, we anticipate developing the ability to read and potentially manipulate this code, which could lead to breakthrough therapies in regenerative medicine and cancer treatment.

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