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Review Article

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DNA Undergoing Phase Transitions as a Quasicrystalline Molecule

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Abstract

DNA has a capacity to switch among alternative conformations and can be viewed as a quasicrystalline, soft-matter polymer whose order can be modified by phase transitions. Flipons—sequence elements that switch conformation under physiological stresses can be viewed within the broader chromatin context where liquid–liquid phase separation (LLPS) and mesoscale condensates organize the genome and modulate non-B structures. It is noted how transposable elements (TEs) and retroelements, activated by environmental challenges, can generate new sequences and regulatory architectures that may underlie punctuated evolutionary patterns, such as the Cambrian explosion.

Keywords: DNA, Quasi Crystalline, Phase Transitions, Cambrian, Chromatin, Hypothesis, Review

1. Introduction

DNA is often depicted as a linear code on a flexible polymer. However, it also exhibits ordered packing and self-organization reminiscent of soft-matter crystalline and quasicrystalline phases. *In vitro* and *in silico*, DNA-programmed interactions can generate highly ordered aperiodic lattices and dodecagonal quasicrystalline motifs in colloidal and tile-based systems [1-3]. This suggests that nucleic-acid–encoded bonding rules can realise quasiperiodic order (and stability via phason disorder) in soft matter. *In vivo*, chromatin displays hierarchical organisation from nucleosomes to compartments underpinned by physicochemical interactions and phase separation, imparting mesoscale order that is dynamically remodelled by cellular processes [4,5].

These alternative nucleic acid structures - flipons – are short sequence-encoded elements that switch conformation in response to energy inputs, thereby altering local topology, nucleosome phasing, and recruitment of structure-specific proteins and RNAs [6,7]. Flipon switching can proceed along multiple paths with sequence- and context-dependent barriers, a hallmark of phase transition phenomena in soft matter [6,8]. It is hypothesised that DNA behaves as a quasicrystalline material: its mesoscale ordering and sequence-encoded folds together enable tunable phase transitions that reconfigure chromatin condensates and regulatory outputs. In addition, transposable elements (TEs) and repeats propagate flipons across genomes, enabling stress-responsive, heritable regulatory variation that may scale to macroevolutionary events such as the Cambrian explosion [7].

2. Phase Transitions

Phase transitions among DNA conformations encode responsive information. For example, B↔Z transitions can be tuned by mechanics, sequence, and chemistry. Studies show that torsional strain, supercoiling, and bending forces lower the barrier for the B→Z transition, with cytosine methylation and ionic milieu further modulating the equilibrium [9]. Single-molecule and computational work quantify sequence-specific energetic penalties and the interplay of bubbles, plectonemes, and Z segments under torque, highlighting how different repeats act as torsion absorbers or buffers [10]. In permeabilized, metabolically active nuclei, the level of Z-DNA tracks torsional strain generated by transcription and topoisomerase activity, supports mechanics-driven switching in cells [9].

G-quadruplexes (G4s) and i-motifs (iM) assemble under sequence- and environment-dependent rules with live-cell imaging, chemical mapping, and in-cell biophysics providing evidence for G4 formation and context-dependent iM folding [5]. In nuclei, phase

separation and protein condensates oppositely modulate G4 and iM folding and kinetics: charge-driven condensates destabilize G4 while stabilizing iM and tune-folding relevant for gene regulation [5]. These trends could arise from specific interactions with intrinsically disordered regions (IDRs), linker histones, and RNA, and from excluded-volume and ion effects that bias secondary-structure ensembles [5]. Collectively, these observations position G4/iM switches as local microenvironment sensors within transcriptional condensates and chromatin sub compartments.

Triplex-forming sequences (T-flipons) support sequence-specific RNA:DNA:DNA architectures that can anchor condensates and phase nucleosome positioning, thereby orchestrating promoter response states and long-range regulation [11]. T-flipons often incorporate RNA third strands and interface with helicases and polymerase release factors within noncoding-RNA–seeded condensates, highlighting how conformational codes intersect with RNA scaffolds to shape transcriptional outcomes [11].

3. Flipons and Z-Binding Proteins

Flipons trade energy for information by coupling environmental inputs to nucleic-acid structure [6]. Z-flipons are enriched in promoters and telomeres and overlap editing, splicing, and expression QTLs. Deep learning maps validated by chemical footprinting tie Z-flipons to transcriptional reinitiation and promoter architecture, while Alu elements supply widespread flipon motifs and contribute to dsRNA formation, editing, and condensate seeding, with Z- and G-flipons acting as regulatory binary switches [7,10]. Z-binding proteins translate structural states into cellular decisions: the ADAR1 p150 isoform's Zα domain recognizes Z-DNA/Z-RNA (ZNA) at Alu inverted repeats to gate innate immune self-recognition, while ZBP1 engagement by ZNA triggers inflammatory cell death pathways when left unchecked [7].

ADAR1, ZBP1, and ZNA are linked to disease and to evolutionary constraints on retroelement spread, underscoring how conformational recognition integrates immunity with gene regulation [7]. Together, these data support a model in which flipons microcode promoter conformations and RNA processing, dynamically interfacing with structure-specific proteins to modulate transcripts compiled from the same linear sequence [7,10].

4. Chromatin LLPS

Chromatin LLPS and mesoscale ordering tune non-B DNA and gene control with chromatin folding emerging from physicochemical interactions among nucleosomes, DNA, RNAs, and multivalent proteins, producing mesoscale domains and compartments that can be described through LLPS and polymer physics [4,5]. "Nucleosome clutches" can be bridged by HP1 or Polycomb proteins to yield microphase-separated heterochromatin-like complexes [12]. There is evidence that phase-separated subcompartments (nucleolus, RNAPII clusters, pericentric heterochromatin) concentrate factors and regulate access, while the folding of the chromatin polymer drives partition into TADs and compartments [5].

Non-B structures are sensitive to the local microenvironment. LLPS and IDR-mediated interactions can stabilize i-motifs while destabilizing G4s while linker histones co-condense with G4-bearing ssDNA to condense chromatin, and crowding and ionic composition further tune equilibria [5,13]. Together, this implies formation of noncanonical DNA within condensates and help explain chromatin-state–dependent activity of flipons.

5. Transposable Elements: Stress-Responsive Engines of Change

Transposons migrate through the genome via specific biochemical mechanisms, broadly divided into two classes based on their transposition strategy. These processes are well-understood and involve enzymes that recognize, excise, and reintegrate DNA segments.

- Class I: Retrotransposons (Copy-and-Paste) These elements transpose via an RNA intermediate starting with the transcription of the transposon into RNA by the host cell's machinery. This is then reverse-transcribed into complementary DNA (cDNA) using a reverse transcriptase enzyme (often encoded by the transposon itself). The cDNA is then integrated into a new genomic location by an integrase enzyme which results in a net increase in transposon copies, as the original remains intact [14].
- Class II: DNA Transposons (Cut-and-Paste) These move directly as DNA without an RNA step. A transposase enzyme (encoded by the transposon) binds to terminal inverted repeats (TIRs) at the element's ends, forming a complex. The transposase then cleaves the transposon from its donor site, creating a double-strand break (which the host repairs). The excised transposon is inserted into a target site elsewhere, often with a preference for specific sequences (e.g., TA dinucleotides in some cases) [15].

The genomic repertoire of repeats and transposable elements (TEs) responds to environmental and physiological stress, with mobilization and epigenetic modulation generating regulatory diversity and novel sequences [16]. Mobile DNA and regulated DNA restructuring are activated by infection, hybridisation, and other stresses, enabling rapid, multi-trait changes at key evolutionary junctures [16]. Recent studies situate TEs as regulators and substrates for exaptation, producing enhancers, promoters, and noncoding RNAs that rewire developmental networks; under certain conditions, TE bursts and regulatory recombination can drive rapid morphological divergence [17].

In the chromatin context, KRAB-ZFP recognition of TEs seeds heterochromatin-like complexes, and DNA methylation changes reshape compartmentalization—pathways through which TEs influence 3D genome organization [12]. These insights align with flipon biology, as Alu repeats and SVA elements disseminate non-B motifs genome-wide, program alternative conformations, and interact with ZNA sensors in innate immunity [7].

6. Quasi Crystalline Perspectives

Programmable DNA self-assembly and theoretical models show quasiperiodic tilings and aperiodic order can be realized with DNA tiles or arise in mesoscale assemblies - DNA may form hybrid order at multiple scales [2]. Nanotechnology and theoretical studies demonstrate routes to quasiperiodic assemblies (Penrose-like tilings) and aperiodic biological order providing bridges between nanoscale sequence programmability and mesoscale aperiodic/ quasi crystalline architectures.

Subtle cellular shifts, such as variations in ion concentrations, pH, temperature, oxidative stress, or metabolic status, can modulate DNA supercoiling through topoisomerases. These enzymes actively introduce or relax supercoils, but their activity is sensitive to the cell's internal conditions:

- Ion Levels and pH: Magnesium ions (Mg^{2+}) and potassium ions (K^{+}) stabilize DNA structure and influence topoisomerase function. For example, low Mg^{2+} can inhibit gyrase, leading to reduced negative supercoiling (a shift to a lower-energy state) [18]. Similarly, pH fluctuations affect the binding affinity of these enzymes, altering the torsional energy stored in DNA.
- Metabolic and osmotic stress: Changes in nutrient availability (e.g., switching carbon sources like glucose) correlate with adjustments in supercoiling levels. In E. coli, preferred growth conditions relax supercoiling slightly, while stress tightens it, transducing environmental signals into topological changes [19].
- Temperature and oxidative stress: Heat or reactive oxygen species can denature DNA locally or activate stress-response pathways that modify supercoiling. Negative supercoiling, for instance, lowers the energy barrier for strand separation, making DNA more prone to melting under stress. This is a homeostatic mechanism where the cell maintains a balance, but disruptions propagate mechanical stress along the DNA backbone, potentially disrupting base pairing at distant sites [20].

Although much of the *in vivo* evidence centres on liquid-like condensates and conformational phase transitions, DNA also forms ordered lyotropic mesophases ex vivo, and DNA nanostructures can be programmed into aperiodic or quasiperiodic tilings—offering conceptual bridges between sequence programmability and quasiperiodic order [8]. The combined presence of mesoscale order (liquid-crystalline packing) and sequence-encoded fold polymorphism (flipons) implies the "quasicrystalline" framing at the level of functional organization - DNA is an aperiodic informational polymer capable of locally ordered, switchable domains whose collective behaviour exhibits phase transitions relevant to gene control [7,8].

As a result, DNA interactions can realize dodecagonal quasicrystals and quasi-periodic square–triangle tilings in colloidal systems, as shown using DNA-coated decahedra, sticky-end–mediated facet alignment, and seed-assisted growth [2]. Coarse-grained oxDNA and patchy-particle simulations demonstrate stable quasicrystals from DNA star tiles and free-energy favourability over approximants, clarifying design rules for soft quasicrystalline order with DNA-mimetic building blocks [1]. These precedents, coupled with the polymer physics of chromatin condensates and mesoscale ordering, allow chromatin to be viewed as a quasicrystalline soft-matter system whose local aperiodic motifs (e.g., repeated non-B structures, structured RNA hubs) tessellate into dynamically maintained, functionally specialized domains [4,5].

7. Hypothesis

It is hypothesised that flipon-mediated phase transitions encode adaptive chromatin microstates and that the genome uses a conformation-based instruction code, implemented by flipons embedded within TE-rich regulatory landscapes, to rapidly and reversibly explore transcriptional microstates. Mechanical work from transcription and replication, epigenetic base modifications, and local ionic/protein environments drive phase transitions among B-, Z-, G4, iM, and triplex states. Structure-specific proteins (ADAR1 Zα, ZBP1, helicases) interpret these states to direct editing, splicing, and innate immune gating; condensate scaffolds and mesoscale chromatin ordering constrain and tune these transitions [5,7,10]. TE activity and exaptation distribute and update the flipon repertoire, enabling rapid, context-aware regulatory rewiring in response to environmental change [7,16,17].

This suggestion predicts: (i) conserved flipons in core promoters with measurable effects on reinitiation; (ii) condensate-dependent biases in non-B folding kinetics; (iii) stress-specific TE expression and chromatin rephasing that alter flipon accessibility; and (iv) genetic interactions between ZNA sensors and flipon-rich repeats in immunity and development [5,7,10]. This synthesis—transposons as vectors for flipon motifs that enhance DNA's quasicrystalline properties (e.g., aperiodic order with dynamic, adaptive switches)— extends biophysical/evolutionary views with mathematical quasicrystal theory, and potentially explains how genomes achieve evolvability through structured yet flexible soft-wiring.

8. Cambrian Explosion and Punctuated Patterns

Multiple frameworks propose that rapid morphological innovation can stem from bursts of regulatory rewiring rather than gradual coding changes. Developmental gene hypotheses argue that conserved, mutation-intolerant developmental regulators enforce stasis, while punctuations arise when TE-derived regulatory elements and recombination remodel these networks [17].

Within this framework, TE-driven dissemination of flipons and the advent of structure-specific readers (e.g., ZNA-binding modules) would provide a scalable mechanism for rapid changes in promoter microcoding, splicing patterns, and innate immunity–development crosstalk. Although direct fossil-era evidence for flipon/TE bursts is inferred, the convergence of TE exaptation, regulatory condensation, and conformational coding offers a principled mechanistic substrate for punctuated equilibria during episodes such as the Cambrian explosion [16,17].

Rapid radiations require mechanisms that generate heritable phenotypic diversity at regulatory levels. TE bursts, coupled with flipon propagation, provide a potential route for widespread rewiring of gene expression programs in response to environmental and ecological upheavals, possibly contributing to pulses of morphological innovation analogous to punctuated equilibria. While multiple factors underlie the Cambrian diversification, TE-driven regulatory novelty—especially in developmental regulatory networks—offers a mechanistically grounded substrate consistent with fast phenotypic exploration without extensive coding innovation [7].

9. Implications and future directions

Evidence across molecular biophysics, chromatin organization, and genome evolution supports a unifying hypothesis of DNA as a quasicrystalline, soft-matter polymer whose function emerges from phase transitions among alternative conformations embedded within a mesoscale condensate architecture. Flipons and TEs encode a responsive conformation-based program, read by structure-specific proteins and tuned by LLPS, that underlies context-dependent gene regulation and may help explain punctuated patterns in evolution.

This quasicrystalline, phase-transition view frames DNA as an active material: (i) Promoter architecture is defined by conserved flipons that set reinitiation kinetics and splicing windows, with condensate microenvironments modulating non-B kinetics [5,10]. (ii) ZNA sensors link conformational states to immunity and editing, constraining retroelement spread and shaping disease risk [7]. (iii) TE mobilization under stress updates the genome's conformational lexicon, driving adaptive rewiring [16,17]. Key experimental tests include: perturbing LLPS components to quantify bidirectional effects on G4/iM kinetics in living cells; editing flipon sequences in conserved promoters to measure transcription reinitiation and splicing impacts; and mapping condition-dependent ZNA occupancy and editing at TE-rich loci alongside single-cell condensate state readouts [5,10].

Conflict of Interest

The author declares there is no conflict of interest. No funding has been received for this paper.

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