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Physical Genomics: Why Gene regulation is Tug of War between Polymer Physics and Biochemistry

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Abstract

DNA–protein interactions underlie genome activity, governing gene expression as well as the physical organization of DNA. Until recently, DNA-protein complexes were predominantly described at atomic resolution using short DNA fragments, concealing how proteins recognize and manipulate the long, supercoiled DNA present in cells. Now single-molecule imaging and cryo-electron microscopy (cryo-EM) are showing how longer DNA sequences are recognised by proteins and computations are predicting how these elements influence larger-scale genomic structure. Here we discuss how the polymeric nature of DNA influences its atomic level structure and dynamics, as well as the implications for DNA recognition and ultimately biological function. We emphasize how theory and simulation help interpret these effects, which are difficult to replicate using conventional experimental settings.

The importance of DNA as a long polymer has been overlooked

Understanding how DNA sequence yields biological function requires both a multidisciplinary and a multiscale approach. Studies of 3D nuclear architecture have shown chromosomal DNA is organized hierarchically into topologically associated domains (TADs) (1), while omics methods have revealed the many proteins interacting with DNA (2) (3). Yet most atomic structures in the Protein Data Bank (PDB) and the Electron Microscopy Data Bank (EMDB) contain short, linear DNA fragments whose free ends eliminate the torsional constraints present in vivo. In cells, the DNA ends are typically fixed, with bending and twisting stresses distributed throughout the entire constrained region. This implies that DNA interactions are inherently non-local within this region (4) and communicated throughout the domain, which can influence processes such as DNA looping (5). Here we explore the importance of the long polymeric nature of DNA and provide examples of where DNA topology and non-locality change the biochemistry of the duplex and influence the mechanics of gene regulation.

DNA is bent and twisted (supercoiled) in cells

Within crowded cellular environments, proteins continuously bend, twist, loop, and locally melt DNA. Even in the absence of enzymatic activity, architectural proteins impose constraints that distort local structure to accommodate looping or packaging (6) (7) (8) (5). The close coupling of structural elements underlies the so-called supercoiling of DNA, i.e., the coiling of the helix itself, and the resultant compaction and accompanying long-range interactions of the polymer chain (as reviewed by (9) and (10)). The twin supercoiling domain model describes how transcription (and replication) introduce positive supercoils ahead and negative behind RNA (and DNA) polymerase (11, 12) (see Figure 1). The amount of DNA supercoiling injected is still not understood and is likely to be context dependent. For example, ribosomes coupled to transcription increase the frictional drag, thereby preventing rotation and increasing the

amount of supercoiling introduced into the DNA (13). Processes such as transertion (where transcription, translation and insertion of nascent proteins into the bacterial membrane are coupled) further modulate supercoiling and contribute to organising the nucleoid (14, 15) (16).

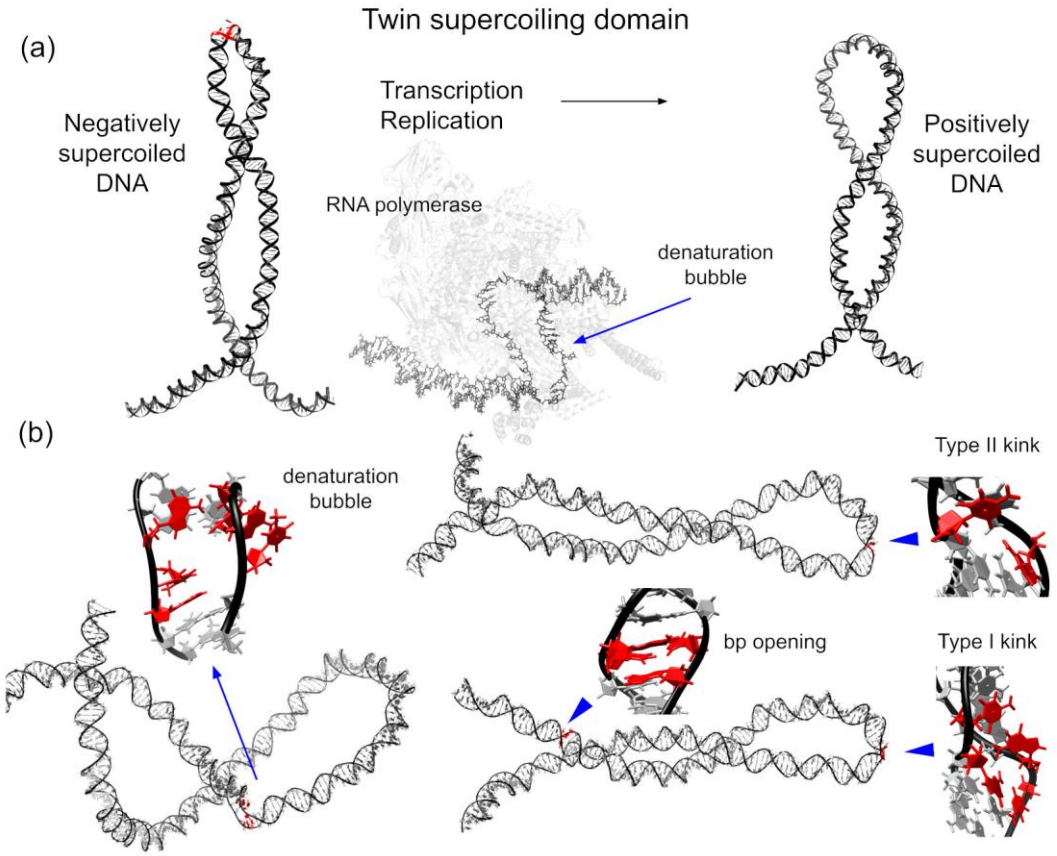

Figure 1. a) Representation of the twin supercoiling domain constructed at atomic level using the structure of the initiation transcription complex (PDB 6EDT), together with representative structures of supercoiled DNA loops or plectonemes obtained from simulations (17). (b) All-atom simulations of supercoiled linear DNA in explicit solvent show that undertwisting alone can induce denaturation, generating various types of defects at the tips and along the arms of plectonemes (17).

The biological importance of controlling supercoiling is evident from the ubiquitous presence of topoisomerase enzymes in all kingdoms of life. In bacteria, the DNA is maintained at a superhelical density of around –0.06 by DNA gyrase, with up to 6% fewer complete helical turns than relaxed, linear DNA (18). This level of supercoiling is directly linked to the cell's energy state, i.e., the ATP/ADP ratio, given that gyrase requires ATP to introduce negative supercoils. There is increasing evidence that DNA processing machines act co-operatively to enable processes such as transcription, and that control of DNA topology is an essential component. For example, the transcription factor and proto-oncogene MYC nucleates the "topoisome", which increases topoisomerase engagement in cells (19).

The sequence context of DNA, in addition to its chemical sequence, also matters, as relocating a DNA sequence can alter its biological behaviour. Analysis of gene expression data in *E. coli* shows that transcription-coupled DNA supercoiling provides a consistent explanation for the strong positive coupling observed between the gene expression patterns of neighbouring

genes (20). Supercoiling-sensitive genes preferring highly negatively supercoiled DNA are enriched in divergently orientated neighbours (whose transcription proceeds away from each other), whereas genes preferring relaxed DNA are enriched in convergently orientated neighbours (with transcription proceeds toward one another) (20). This is consistent with the pattern of positive and negative supercoiling predicted by the twin-supercoiling domain model. In divergent genes, negative supercoils generated behind the transcription complex will enhance transcription. In convergent genes, positive supercoils generated ahead of RNA polymerase will offset the basal levels of negative supercoiling present in bacteria, thereby making the DNA in these genes more relaxed, again enhancing transcription. This dependence on both location and orientation of genes has implications for mobile genetic elements such as bacterial plasmids and eukaryotic extrachromosomal circular DNA (eccDNA), which may behave differently compared to when they are located within a chromosome. EccDNAs are often associated with genomic instability leading to cancer. They can carry both oncogenes and enhancers that can drive elevated transcription and lead to tumour heterogeneity and resistance to chemotherapy. These DNAs provide an interesting case because they present a large range of sizes from megabases down to just hundreds of base pairs (21) (22). Understanding the behaviour of circular DNA as a function of size, sequence, and level of supercoiling can reveal much about how context influences gene regulation.

Bending and supercoiling change DNA structure and dynamics

Most dramatically, negative supercoiling promotes the formation of noncanonical DNA structures such as the G-quadruplex (G4), Z-DNA, hairpins, cruciforms and R-loops (reviewed by (9) (23) and (24)). These structures not only alter local geometry but also absorb supercoiling, thereby influencing the topology and regulation of entire domains. Non-B DNA structures are enriched in regulatory regions, appearing mainly in operon regulatory sites in *E. coli* (25), and in developmental genes in mammals which require careful regulation (26). Their formation and associated mutagenesis have also been linked to various diseases (27).

DNA minicircles up to a few hundred base pairs are particularly useful tools for studying the effect of bending and supercoiling because their size and superhelical density can be controlled, and they are small enough for fully atomistic computer simulations. Biochemical experiments using enzymatic probes (28) and atomistic simulations (29) of circular DNAs containing between 60 and 100 base pairs show that circles containing ~65 base pairs develop kinks in their double helical structure in response to the extreme bending stress. Kinks are defined as deformations where base stacking is disrupted while complementary base pairing remains intact (Figure 1). Simulations of larger ~200 base pair circles reveal a complex phase diagram where writhing competes with denaturation as a mechanism to relieve superhelical stress (30) (31). Circles of ~330 base pairs visualised with cryo-electron microscopy (32), atomic force microscopy (33) and atomistic simulations exhibit a myriad of exotic conformations including plectonemes, trefoils and needle-like structures. These shapes are promoted by the local melting of DNA, which provides flexible hinges for tight bends to form.

Enzymatic probes have also detected bubbles in even longer (~700 base pair) circles, showing that denaturation is not limited to only very tiny circles (34). The location of denatured sites around the DNA circle is a complex competition between DNA sequence and circle geometry (4, 34, 35), providing an additional mechanism whereby topology enables “action at a

distance". Recent atomic-level simulations on linear supercoiled DNA provide a similar picture: bubbles can be induced purely by DNA undertwisting, without requiring high bending strain (17) (see Figure 1). These simulations also show that bubbles preferentially form in AT-rich regions, independently of the underlying DNA topology, thereby helping to determine the positions of supercoiled loops in longer DNA molecules (36).

Regardless of sequence, DNA subjected to twisting and bending stress is more dynamic than relaxed DNA. Atomistic molecular dynamics simulations of linear relaxed DNA find a marked absence of helical dynamics over micro to millisecond timescales (37). In contrast, in negatively supercoiled circles, corresponding simulations detect increased levels of base breathing, even when no denaturation occurs (4). Box 1 summarises some of the mechanical principles found from atomic-level studies of DNA minicircles.

Bending stress alone is enough to cause kinks in DNA for very small (~60 base pair) circles. Sufficiently high levels of supercoiling produce denatured regions or "bubbles" where complementary base pairs are broken. Lower levels of negative compared to positive supercoiling are required for bubbles to form, implying that the double helix is more susceptible to under-twisting than over-twisting. Bending reduces the amount of negative supercoiling required for denaturation to occur, meaning that tightly bent DNA denatures at less negative superhelical densities. AT sequences are generally softer and more prone to melting, although base stacking interactions also play a role. Denatured sites prefer to distribute evenly around small circles; when this is not possible the circle becomes frustrated and dynamically switches between states. Complex and diverse DNA circular shapes are possible when denaturation allows sharp bends to form.
Box 1: Summary of mechanical principles in short circular DNA

This complexity may be highly relevant to gene regulation, because the native level of superhelical stress maintained in bacterial cells is on the threshold of being sufficient to produce denaturation bubbles. Small changes in superhelical stress on either side of this threshold may lead to dramatic switching in structure (34). Interestingly, stressed lipid vesicles form ellipsoidal shapes with pores at the tips when under electrical stress much like the melted base pairs in DNA plectonemes (38), and the composition of membranes is thought to be maintained on the threshold of a miscibility phase transition (39), showing how equivalent physical principles apply across diverse areas of biology (see (40) for a discussion of this idea as a general principle). DNA has the competing biological functions of both protecting the DNA sequence but also being available for accessing the genetic code by transcription and replication. DNA binding proteins are capable of both imposing and storing superhelical stress, as we now discuss.

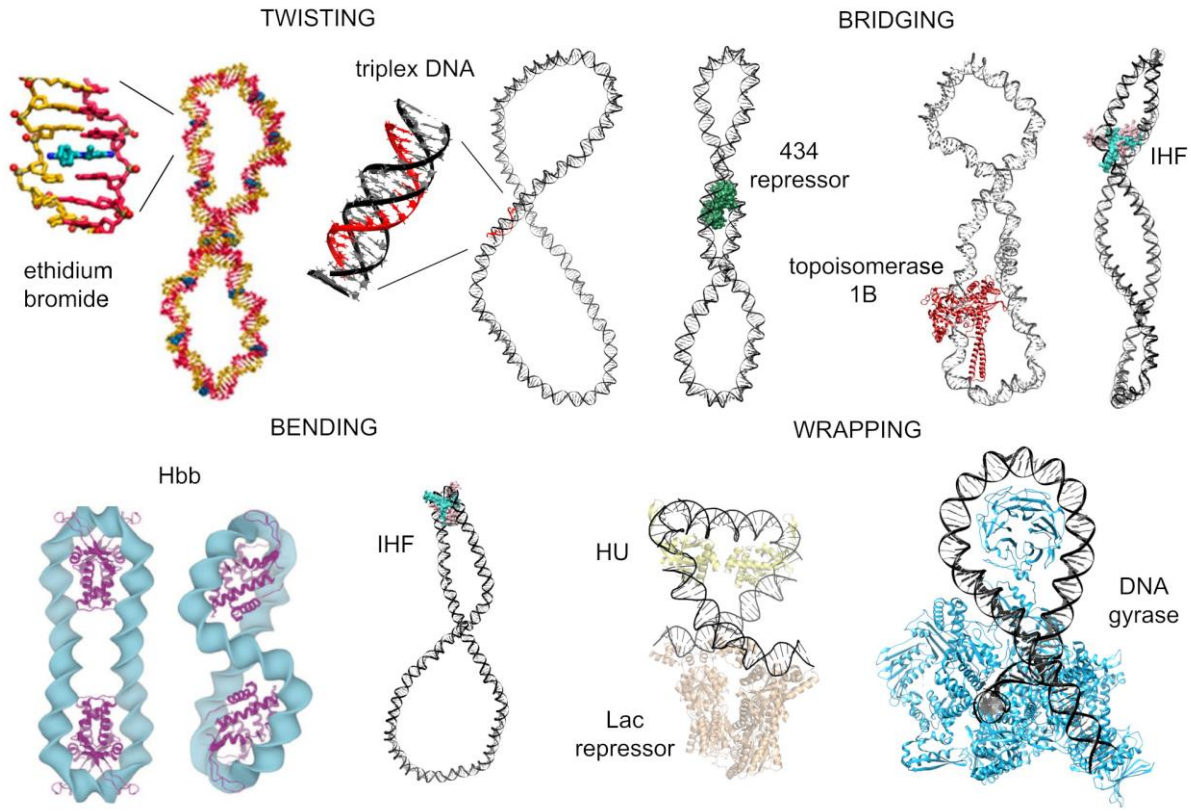

Figure 2. Representative structures of proteins and ligands showing supercoiling-dependent DNA recognition that has been characterized by all-atom or base-pair–level simulations. These complexes modulate distinct modes of DNA deformation, including DNA twisting (ethidium bromide (41), triplex DNA (33)), DNA bending (Hbb (42) IHF (43)), DNA wrapping (HU (6) (7)), and unexpected DNA bridging (434 repressor (6), topoisomerase 1B (44), IHF (43)) The DNA–gyrase complex is the only known example of an experimental high-resolution structure determined with supercoiled DNA (PDB_ID 8QDX) (45).

Bending and twisting affect DNA recognition, and vice versa

The intimate connection between supercoiling and DNA recognition is so significant that it enables quantitative measurement of supercoiling in single molecule experiments (8) and in cellular DNA (46) (47). Intercalators bind easy to undertwisted DNA and can be used to map the positions of negative supercoiling, for example through fluorescence detection (8). Proteins that recognise positive supercoiling can map transcription throughout the bacterial genome (48). As well as being of fundamental biological interest, the supercoiling dependence of DNA-protein interactions has important technological consequences, as it can generate off-target effects in CRISPR-Cas9 procedures and enhance DNA mismatch repair by MutS (49).

Figure 2 illustrates a selection of studies that reveal the intimate interplay between DNA architectural proteins and supercoiled DNA. In bacteria, supercoiling-generated bends facilitate the binding of architectural proteins such as HU, HBB and IHF (43) (42). Plectonemes bring distant strands of DNA together, promoting the formation not only of bridged DNA structures driven by specific interactions, such as those formed by the Lac repressor (5), but also of bridges arising from additional non-specific binding sites (see Figure 2 and (50) (6) (7) for a review of the unexpected behaviour observed in complex DNA topologies). DNA-processing machines, such as topoisomerases, are also supercoiling-sensitive. The structure of gyrase bound to supercoiled DNA reveals how protein-DNA contacts promote unwinding

and melting (45) (51) (Figure 2). The transcription machinery interacts functionally with topoisomerases to regulate both transcription and DNA topology (19, 52).

In eukaryotes, intercalating dyes which bind preferentially to negatively supercoiled DNA have been used to map the supercoils generated by transcription and how they affect chromatin structure. Dynamic supercoils have been detected 1.5 kilobases upstream of transcription start sites of active genes in human cells (46), which corresponds to around 6-8 consecutive nucleosomes. By mapping the over and underwound regions of the genome, and using three-dimensional (3D) DNA fluorescence *in situ* hybridization (FISH) experiments to probe distances within chromatin, it has been shown that gene rich underwound regions can be decompacted relative to overwound regions (47). Supercoiling has been shown to accumulate at the boundaries of topologically associated domains (TADs) in human cells, aligning with compartments of active chromatin (with negative supercoils) and inactive chromatin (with positive supercoils) (53). These findings suggest that changes in chromatin state during cellular or developmental processes may be regulated by supercoiling. At the molecular level, all-atom simulations have shown that torsional stress has an asymmetric effect on the free energy of nucleosome binding (54) and single-molecule experiments show that nucleosomes act as supercoiling storage devices (55). Therefore, the response of chromatin to supercoiling forces can be understood from the supercoiling-dependent mechanics of protein-DNA recognition.

The polymeric nature of DNA, combined with the supercoiling-dependent binding affinities of proteins, introduces a whole new level of complexity beyond individual protein-DNA recognition events. As a result, the position and affinity of bound proteins depend not only on the local DNA structure, as in linear fragments, but also on the presence of every other protein in the system and the overall DNA topology (see examples noted in Figure 2). Dynamic supercoiling introduced by transcription or replication further complicates this landscape, as its propagation can be blocked by DNA-binding proteins, or the same proteins can be removed by passing supercoils. Models have also shown collective behaviour among multiple transcription RNA polymerases during transcription (56). This form of long-range communication, termed “telestability” (57) (referring to the transfer of stability), describe the capacity of proteins to influence each other’s binding by transmitting structural information through the DNA. The resulting non-local and delicate interplay arising from polymer physics and biochemistry produces a highly complex and switchable system that is capable of storing information and adapting to environmental change.

How can we understand the additional information content of long polymeric DNA?

In spite of our knowledge of the DNA sequences of many organisms, we are still far from understanding how these sequences are regulated to give rise to a functioning organism. The organisation of the genome through folding and compartmentalisation into topological domains, coupled with the torsional and bending stresses generated as DNA undergoes its function, play an active role in gene regulation (58). We use the term “Physical Genomics” to describe the extra information content that the mechanical status of DNA contains, relative to just the chemistry of DNA. An alternative term “Topological Epigenetics (59)”, has also been used. As our ability to map DNA supercoiling has improved, we increasingly see that supercoiling is the hidden factor in the relationship between chromatin structure and function, in both bacteria (60) and humans (53).

There is a wealth of structural models of DNA across multiple scales, spanning from a quantum mechanical description of a few base pairs, to the polymer models used to infer the folded structures of chromosomes (61).

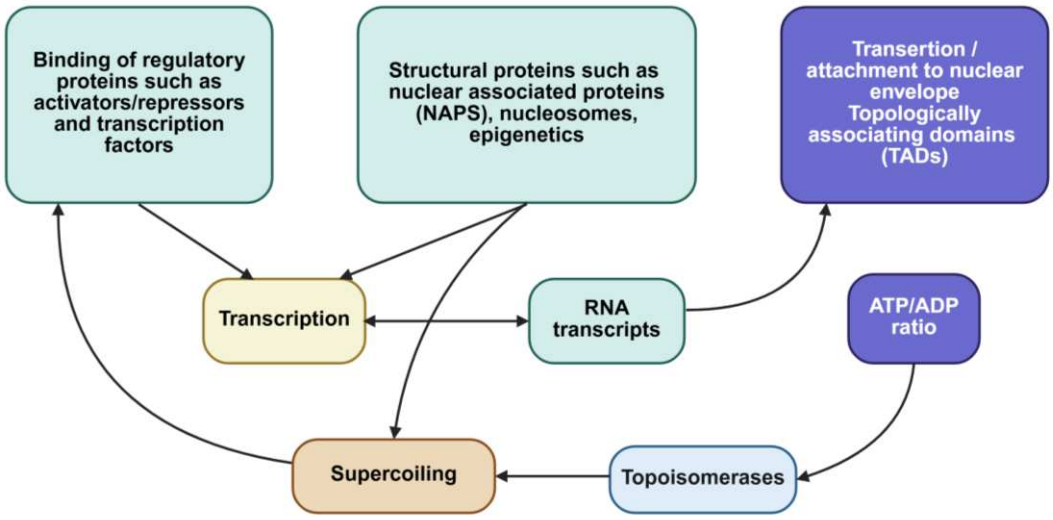

Figure 3: The complex interplay between factors controlling supercoiling, DNA topology and therefore gene expression. Note that the distinction between architectural proteins and transcription factors is not always well defined (62).

A holistic picture of gene regulation requires hybrid models that combine informatics and omics data with physical modelling because these factors act symbiotically to control transcription (see Figure 3). Such hybrid models reflect the interplay between the physics of DNA, and its biochemical context and composition. Models of DNA regulation that include the physics of superhelical and bending stress are emerging, but without representing DNA as a physical object (63). Other studies show the importance of spacer length and sequence context on promotor activity (64) and how supercoiling and sequence context combined can control gene expression (65) and place an evolutionary pressure on the position and orientation of bacterial genes (66). From the bioinformatics perspective, combining the local distribution of chemically modified nucleosomes with polymer models has revealed how epigenetics influences chromatin structure (67). As is common in biology, the interplay of multiple controlling factors leads to a highly complex system, and it is only by combining polymer physics with biochemistry that we will be able to bridge the gap between DNA sequence and the phenotype it encodes.

Highlighted papers:

*Burman et al PRL 2024: An atomistic simulation study of the DNA extension–rotation curves obtained by magnetic tweezers, showing that DNA denaturation is both topology- and sequence-dependent. (17)

*Perez AA, Nature Genetics. 2024: This paper highlights an exciting new method to determine the myriad of proteins that are bound to DNA, rather than just considering one protein at a time. This is important because the effect of protein binding is non-local in complex DNA topologies. (2)

*Junier I, Front Microbiol. 2023: Provides a review of how physics based methods have enabled us to understand the importance of supercoiling in bacteria. (10)

*Benham NAR 2023: Provdes a review of the mathematics of DNA topology and its biological implications. (9)

*Boulas NAR 2023: A combined experimental and simulation study highlighting the role of supercoiling in controlling transcription in bacteria. This paper is of particular interest because it shows how non-local effects generate signifcant complexity even when considering a single gene. (65)

**Gilbert & Marenduzzo Current Opinon in Cell Biology 2025: A highly insightful discussion of the importance of topology in gene regulation, where the term “Topological Epigenetics” is introduced and explained. (59)

**Hustmyer Mol Microbiol. 2024: Reviews the complex interplay between supercoiling, nuclear associated proteins and gene control in bacteria. (13)

*Matos-Rodrigues G Molecular Cell. 2023: Indicates the role of non-canonical DNA structures and how these arise from repeatitive sequences. (23)

**Yao Q, Nature Structural & Molecular Biology. 2025: Demonstrates that the importance of supercoiling is not just limited to prokaryotes but is also vital in human biology. (53)

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