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A common topology for bacterial and eukaryotic transcription initiation?

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DNA supercoiling is a major regulator of transcription in bacteria. Negative supercoiling acts both by promoting the formation of nucleoprotein structures containing wrapped DNA and by altering the twist of DNA. The latter affects the initiation of transcription by RNA polymerase as well as recombination processes. Here, we argue that although bacteria and eukaryotes differ in their mode of packaging DNA supercoils, increases in DNA twist are associated with chromatin folding and transcriptional silencing in both. Conversely, decreases in DNA twist are associated with chromatin unfolding and the acquisition of transcriptional competence. In other words, at the most fundamental level, the principles of genetic regulation are common to all organisms. The apparent differences in the details of regulation probably represent alternative methods of fine-tuning similar underlying processes.

Keywords: DNA supercoiling; HMGB proteins; plectonemic DNA; RNA polymerase; TFIID

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Introduction

Although there are many similarities in the protein components of the transcription–initiation machinery of prokaryotes and eukaryotes, the DNA geometry of the transcription–initiation complex—in relation to its context in the chromosome—has not been formally addressed. This geometry—or, more strictly, topology—determines the energy required for untwisting the DNA prior to initiation. Here, we propose that this geometry is highly conserved among prokaryotes and eukaryotes.

In all organisms, the genomic DNA encodes a periodic signal that reflects regularity in the spacing of particular short DNA sequences that are correlated with DNA bending (Satchwell *et al*, 1986). In eukaryotic DNA, this signal has a periodicity of approximately 10.2 base pairs (bp), whereas in bacteria the periodicity is approximately 11.1 bp (Widom, 1996; Worning *et al*, 2000). These periodicities represent the helical repeat of a DNA molecule relative to the real or virtual surface about which it is formally wrapped (White *et al*, 1988); therefore, they are indicative of the geometry of the packaging of the polymer. For eukaryotes, the 10.2-bp periodicity is simply the average separation of, for example, two inward-facing minor grooves of DNA wrapped on the surface of the histone octamer (Satchwell *et al*, 1986). Similarly, in bacteria, the 11.1-bp periodicity generalizes the helical repeat of DNA found in tight repression loops formed by, for example, the AraC and LacR proteins, and in the tight loops required for DNA inversion (Lee & Schleif, 1989; Law *et al*, 1993; Haykinson & Johnson, 1993).

However, these differences in the helical repeat between bacteria and eukaryotes represent a more profound functional difference in DNA topology. Although both bacterial and eukaryotic DNA are—with few exceptions—negatively supercoiled, a supercoiled DNA duplex can, in principle, assume either a toroidal form or a lower energy plectonemic (interwound) form (Fig 1; Bauer & Vinograd, 1968). In a nucleosome core particle, DNA is wrapped as a toroid, whereas the dominant form of supercoiled DNA in bacteria is a plectoneme (Crisona *et al*, 1999). This difference is important not only because it reflects different modes of packaging DNA, but also because the extent and direction of the alteration of DNA by supercoiling depend on whether it is toroidal or plectonemic. Importantly the twist of DNA—or, more correctly, the intrinsic twist—is not the same quantity as the inverse of the helical repeat, which is a measure of the axial path of DNA. Instead, it can be regarded as a torsional quantity that determines, in part, the energy required for DNA melting or complete untwisting. In the nucleosome, the DNA is marginally overtwisted (Zivanovic *et al*, 1988; White *et al*, 1988), whereas in its plectonemic form, when free in solution, negatively supercoiled DNA is significantly undertwisted (Boles *et al*, 1990). Undertwisting, but not overtwisting, should facilitate the strand separation required for transcription initiation or DNA recombination.

Although toroidal and plectonemic wrapping might be regarded as the dominant modes of packaging in eukaryotes and bacteria, respectively, both contain proteins that can stabilize the other mode. In the bacterial nucleoid, negatively supercoiled DNA is constrained by the abundant HU heterodimer, and also by the equally abundant heat-stable nucleoid-structuring protein (H-NS; also known as H1) and its paralogues (Azam *et al*, 1999; van Noort *et al*, 2004; Rimsky, 2004). HU stabilizes plectonemic DNA and,

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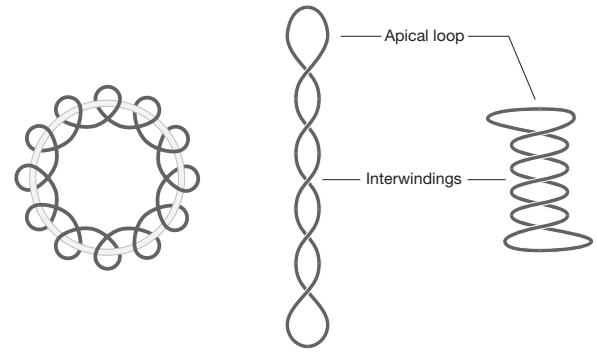

	High pitch angle	Low pitch angle
High negative writhe High twist	High negative writhe High twist	Low negative writhe Low twist
High bend angles	Low bend angles	High bend angles

Fig 1 | Geometry of toroidal and plectonemic supercoiled DNA. The illustration shows a single form of toroidal DNA and two geometries of plectonemes with the same superhelical density. Interconversion of a long narrow plectoneme into a short broad one involves a change in DNA bending and an untwisting of the DNA duplex. We propose that heat-stable nucleoid-structuring protein (H-NS) and HU could respectively stabilize these two plectonemic forms.

although the trajectory of supercoiled DNA bound by H-NS has not been directly established, the available evidence indicates that H-NS also wraps DNA as a plectoneme (Schneider *et al*, 2001). However, the factor for inversion stimulation (FIS), which is another abundant nucleoid-associated protein, can, in appropriate situations, locally stabilize a DNA toroid (Maurer *et al*, 2006), in addition to binding at crossovers in plectonemes (Schneider *et al*, 2001). Similarly, in eukaryotic nuclei, the high-mobility group box (HMGB) proteins are abundant, and have DNA-binding characteristics that are consistent with binding to plectonemes and not to toroids. Most notably, HMGB proteins can functionally replace the bacterial HU protein both in the establishment of global negative superhelicity and in maintaining the geometry—and, hence, the helical repeat—of both repression and DNA-inversion loops (Becker *et al*, 2005; Haykinson & Johnson, 1993). These findings indicate that in bacteria, the HMGB proteins can stabilize plectonemic DNA in a similar manner to HU. Similarly, *in vitro*, HMGB1 constrains plectonemic DNA (Stros *et al*, 1994). In addition, HMG-D, which is a comparable *Drosophila* protein, untwists DNA at its binding site to an extent that would facilitate binding to an underwound plectoneme (Murphy *et al*, 1999). We conclude that in the eukaryotic nucleus, negatively supercoiled DNA is normally constrained in a toroidal form but can form a plectoneme in places, whereas in bacteria the converse pattern is observed.

These patterns of higher-order folding are consistent with determinations of supercoil availability in the bacterial nucleoid and the eukaryotic nucleus. In the cell, two classes of DNA supercoil can be distinguished: those that are unavailable or constrained by packaging proteins, and those that are free or unconstrained. Measurements using the cross-linking agent 4,5′,8-trimethylpsoralen, which forms interstrand adducts on untwisted DNA, showed that a significant proportion of bacterial DNA exists as unconstrained plectonemic supercoils *in vivo*, whereas little if any of the DNA in the eukaryotic nucleus is in this form (Sinden *et al*, 1980).

Control of chromatin transitions by DNA twist

In both eukaryotes and bacteria, the switch from transcriptionally silent to transcriptionally competent chromatin correlates with a structural change in DNA packaging. The question is whether such changes are associated with, or perhaps driven by, a change in DNA topology. In bacteria, at least some transcriptional silencing is mediated by H-NS. When complexed with DNA, this protein forms long thin fibres that contain two DNA duplexes (Dame *et al*, 2000; Schneider *et al*, 2001). Both the degree of compaction and the constraint of negative superhelicity by H-NS suggest that these duplexes are interwoven (Dame *et al*, 2000). The structure of this silenced DNA might therefore be regarded as a long narrow plectoneme, in which the DNA is bent only gently. Such a structure is analogous to that proposed for the binding of histone H1 to DNA (Clark & Thomas, 1988). By contrast, HU—similar to its eukaryotic counterparts, the HMGB proteins—bends DNA substantially (Swinger *et al*, 2003). A change in the bending of the interwindings of a plectoneme would have important consequences. If the superhelical density remained constant, increased bending would convert a long narrow plectoneme into a short broad one, with an increase in compaction and a concomitant decrease in the intrinsic twist of DNA. This is because, in a plectoneme, the writhe is proportional to $\sin\gamma$, where γ is the pitch angle; hence, as γ decreases, some negative writhe is repartitioned to twist (Fig 1). Although the pitch of free plectonemic DNA is relatively constant *in vitro* (Boles *et al*, 1990), in this model substitution of HU for H-NS would change the form of a plectoneme and untwist the DNA. Consistent with this interpretation, a gain-of-function mutant of *Escherichia coli* HU results in a more compact and transcriptionally active nucleoid (Kar *et al*, 2005). Importantly, this mutation also overrides the silencing of the *proV* locus by H-NS. In practice, it is likely that HU constrains a higher negative superhelical density than H-NS (E. Bouffartigues, M. Buckle, C. Baudet, A.T. & S. Rimsky, unpublished data) and, consequently, the reduction in twist on binding HU will be greater.

A similar process has been proposed for the folding and unfolding of the eukaryotic chromatin fibre (C. Wu, A. Bassett & A.T., unpublished data). In this case, twisting of the linker DNA between nucleosome core particles by linker histones is posited to drive the folding of the chromatin fibre into a compact structure, whereas untwisting of the linker by proteins—including the HMGB proteins—drives its unfolding to a transcriptionally competent state. Therefore, for both bacteria and eukaryotes, changes in DNA topology correlate with functional changes in DNA packaging.

Does RNA polymerase prefer apical loops?

Despite extensive studies, little is known about the topography of RNA polymerase–DNA complexes. However, it has been reported that at the *E. coli tyrT* promoter, the RNA polymerase holoenzyme and the activator FIS together wrap approximately 150 bp of DNA as a left-handed toroidal loop (Maurer *et al*, 2006). This structure is equivalent in form not to the interwindings of a plectoneme but rather to its apical loop, which is geometrically distinct (Fig 1). Although this single polymerase–promoter structure is not necessarily

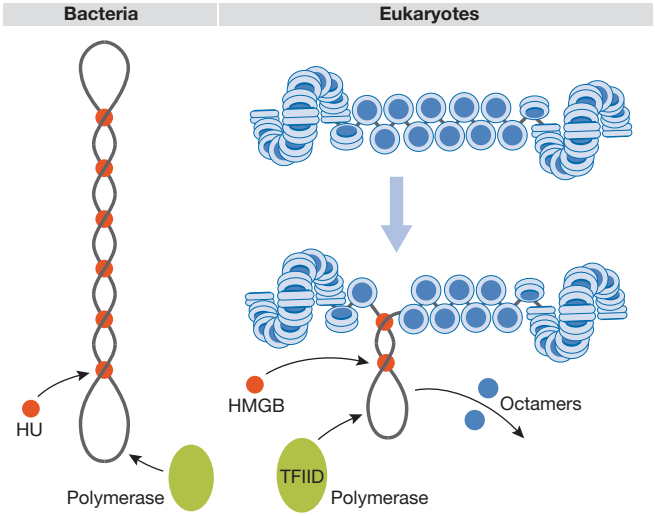

Fig 2 | A conserved geometry for transcription initiation in eukaryotes and bacteria. The illustration compares the binding of RNA polymerase to an apical loop in a bacterial plectoneme with a similar binding of a polymerase-initiation complex to a short plectoneme generated by the removal of two nucleosomes. These plectonemic structures would be stabilized by HU in bacteria and high-mobility group box (HMGB) proteins in eukaryotes. The proteins are shown binding to crossovers but would also probably bend the interwindings. TFIID, basal transcription factor.

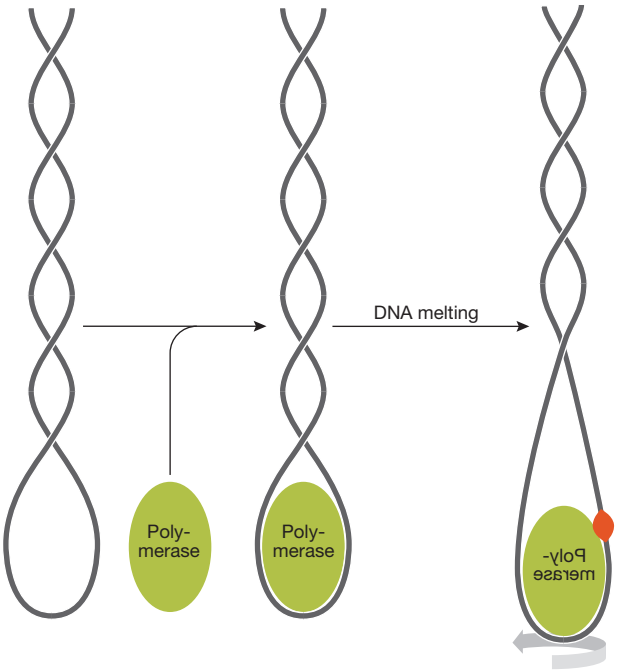

Fig 3 | Mechanism of initiation by bacterial RNA polymerase on supercoiled DNA. The initial binding of the enzyme to an apical loop is followed by strand separation at the transcription start point, which concomitantly removes a single node from the adjacent interwindings. The red marker indicates the melting of the DNA double helix at the transcription start point.

representative of all polymerase–promoter complexes, intrinsically bent DNA, which is preferentially located at the apex of a plectoneme (Laundon & Griffith, 1988), frequently occurs upstream of strong bacterial promoters (Pedersen *et al*, 2000). This suggests that the promoters are similarly located and that the configuration of the promoter DNA is conferred by the DNA sequence organization. These observations indicate that the polymerase can reside in an apical loop and melt the DNA close to the proximal DNA crossover of the interwindings. The DNA structure bound by the polymerase is therefore a normal feature of supercoiled plectonemic DNA.

Does supercoiling have a similar role in eukaryotic transcription? The induction of transcription at some promoters (for example, the yeast acid phosphatase promoter for PHO5) is associated with the remodelling (Almer *et al*, 1986; Verdone *et al*, 1996) and, in some cases, the ejection of histone octamers (Reinke & Hörz, 2003; Boeger *et al*, 2004). Each octamer would normally constrain a single toroidal DNA supercoil; however, when released, this supercoil would convert to a plectonemic form, assuming that there is no immediate change in linking number (Fig 2). We propose that, in addition to untwisting linker DNA, one role of HMGB proteins is to transiently stabilize the plectoneme, or at least to convert it to a configuration that can interact effectively with components of the transcription–initiation machinery. Indeed, the binding of the TATA-binding protein (TBP) transcription factor to the TATA box of the fibroin and adenovirus major late promoters—although not to the heat-shock protein 70 (hsp70) promoter—is facilitated by negative supercoiling (Mizutani *et al*, 1991; Tabuchi *et al*, 1993). Furthermore, HMGB1 interacts directly with the TBP component of the basal transcription factor TFIID and inhibits subsequent transcription (Stelzer *et al*, 1994; Ge & Roeder, 1994). A short plectoneme bounded by nucleosome arrays would contain, at most, a single apical loop. Although no eukaryotic ternary transcriptional complexes have been visualized in detail, a low-resolution electron-microscopy study of an RNA polymerase II complex at the vitellogenin promoter revealed that it is often associated with a DNA loop with a total bend of approximately 180° (ten Heggeler & Wahli, 1985), which is again consistent with a location at an apical loop. The RNA polymerase II initiation complex, like the analogous prokaryotic complex, contains an essential unwinding protein: a TFIIH DNA helicase in eukaryotes and a σ factor in prokaryotes. The occurrence of TBP in both eukaryotes and archaea (Rowlands *et al*, 1994) indicates that the architecture of the transcription–initiation complexes in these groups of organisms is also conserved.

A short supercoiled plectoneme formed at a eukaryotic promoter in this way would be structurally equivalent to the environment of a bacterial promoter. In both cases, the initial formation of a transcription complex would depend on the geometry of the loop, and undertwisting of the interwindings would facilitate the melting of DNA in the proximity of the crossover adjacent to the loop. Furthermore, the formation of the transcription bubble could be topologically compensated by the concerted loss of a single interwinding of the plectoneme (Fig 3). Prevention of the required rotation by, for example, HMGB proteins would inhibit transcription. We note that plectoneme formation in eukaryotes might also be associated with other phenomena. HMGB proteins have a high affinity for lesions in DNA (Thomas & Travers, 2001) and, by inducing

plectoneme formation, could enhance accessibility for enzymes involved in DNA repair and/or recombination.

The structural singularity of an apical loop has a further implication. By recognizing such a structure, an RNA polymerase could, in principle, initiate transcription with moderate accuracy without the direct participation of specific sequence elements. Accuracy could be refined by the incorporation of both torsionally and axially flexible DNA sequences—such as TATA—into such a 'promoter,' and by sequence-specific recognition by a σ factor or a conventional transcription factor. A situation in which sequence-specific recognition evolves as a refinement of structure-specific recognition provides a simple scenario for the generation of transcriptional complexity.

A structural hierarchy for transcriptional control

The model we propose also provides a structural basis for the regulatory hierarchy of transcription factors (Babu & Teichmann, 2003; Blot *et al*, 2006). In *E. coli*, the transcription factors at the apex of the hierarchy—for example, FIS, cyclic AMP receptor protein (Crp) and H-NS, which have been shown to directly regulate the greatest number of other transcription factors and genes—are those that stabilize a particular organization on supercoiled DNA and, in many cases, confer sensitivity of expression to variations in superhelicity (Blot *et al*, 2006). FIS and Crp can promote the toroidal wrapping of DNA around RNA polymerase at the tip of an apical loop (Buckle *et al*, 1992; Eichenberger *et al*, 1997; Maurer *et al*, 2006), whereas H-NS has the potential to block the flexibility of an apical loop by tightly constraining the adjacent interwindings (Dame *et al*, 2002). The abundant leucine-responsive regulatory protein (LRP) and integration host factor (IHF) proteins might also act as structural regulators. *E. coli* LRP binds to a negatively-supercoiled loop (Pul *et al*, 2006) and is therefore likely to constrain the apical loop of a plectoneme, whereas the role of IHF is currently less well defined. In eukaryotes, TBP, which bends DNA to a similar extent to Crp, could perform an analogous role by also stabilizing the tip of an apical loop.

Conclusions

Despite remarkable differences in the complexity of transcription regulation between eukaryotes and bacteria, both encounter the same mechanistic problem: the need to locally untwist DNA at the transcription–initiation site. We propose that the main difference between eukaryotes and bacteria in their compacting of DNA is in the relative proportions of toroidal and plectonemic supercoils, which reflect the different complexities of the genomes. However, the fundamental mechanism of transcription initiation is similar and involves a topological transition in the chromatin facilitated by DNA architectural proteins. In both eukaryotes and bacteria, the topological change associated with transcriptional activation leads to the formation of underwound plectonemes, whereby undertwisting of DNA at the interwindings facilitates the melting of the initiation site by RNA polymerase, which recognizes the apical loop of the plectoneme. This mechanism provides a molecular framework for the regulation of transcription by DNA supercoiling (Travers & Muskhelishvili, 2005) and underscores the fundamental role of DNA. The apparent complexity of transcriptional regulatory processes (Struhl, 1999) probably reflects a fine-tuning of this simple manipulation of DNA.

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