Atomistic simulation of DNA supercoiling

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Introduction

Supercoiling occurs when turns are added to or removed from the DNA double helix.

Prokaryotic & eukaryotic genomes are persistently supercoiled, and supercoiling plays an important role in gene regulation.

DNA minicircles (hundreds to thousands of bp) are of special interest: prokaryotic genomes & artificial vectors are circular, and fixed ends are useful to study topology.

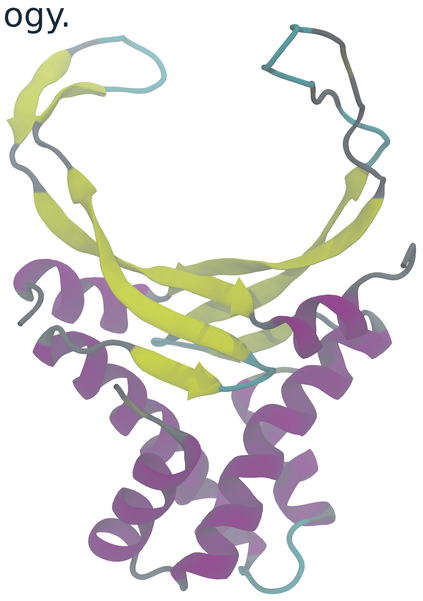

Figure 1.
IHF (*pictured*) and HU are both dimers with alpha-helix "bodies" and two "arms" that bind to DNA.

The end of each arm features a proline that intercalates between base pairs of bound DNA.

IHF & HU (fig. 1) are histone-like DNA-bending proteins that compact DNA and have been linked to negative supercoiling.

They are so important & ancient that a version exists in all known prokaryotes.

Background: DNA topology

Two DNA strands coil around one another to form the double helix; the number of coils is the linking number, Lk.

The twist, Tw, is the number of turns the strands make around the helix axis. This cannot deviate too far from its relaxed value.

So too much ΔLk causes the helix axis to coil around itself; the number of coils is the writhe, Wr, of the system. (figs. 2 & 3)

Topological constraints mean $Lk = Tw + Wr$ at all times.

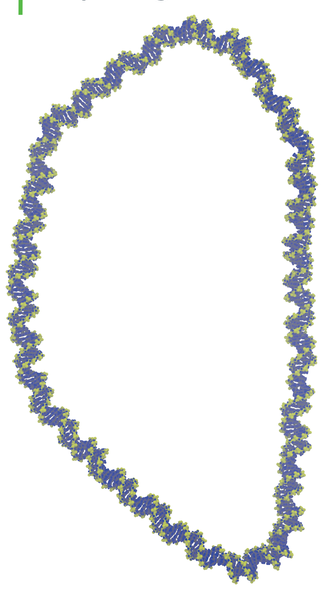

Figure 2.
A 336 bp DNA minicircle with $\Delta Lk = 0$ is relaxed and roughly circular...

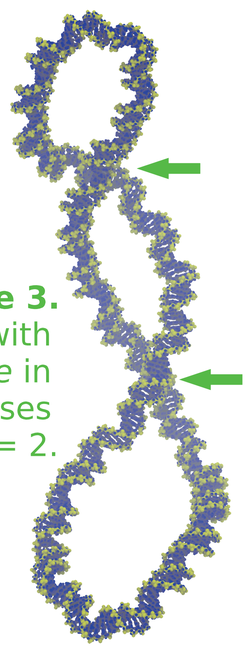

Figure 3.
... while a similar minicircle with $\Delta Lk = -3$ forms a *plectoneme* in which the helix axis crosses itself twice, so $|Wr| = 2$.

Method: Molecular dynamics

Molecular dynamics simulation gives atomistic insight into dynamic behaviour.

Atoms & their positions are defined, then a potential is integrated at every time step — a powerful but computationally expensive process.

This work used AMBER with the ff14SB + parmbsc1 potentials.

Implicit solvent (Generalised Born) speeds up simulations by treating water & ions as a dielectric continuum.

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Results: DNA compaction & bridging

When IHF and HU bind to a plectoneme, they are always positioned at the apex.

Both proteins significantly enhance compaction of negatively supercoiled minicircles, reducing the radius of gyration by up to 16% for $\Delta Lk = -3$ (fig. 4).

This brings distal sites closer together, sometimes allowing IHF to form stable additional contacts that bridge the minicircle (fig. 5).

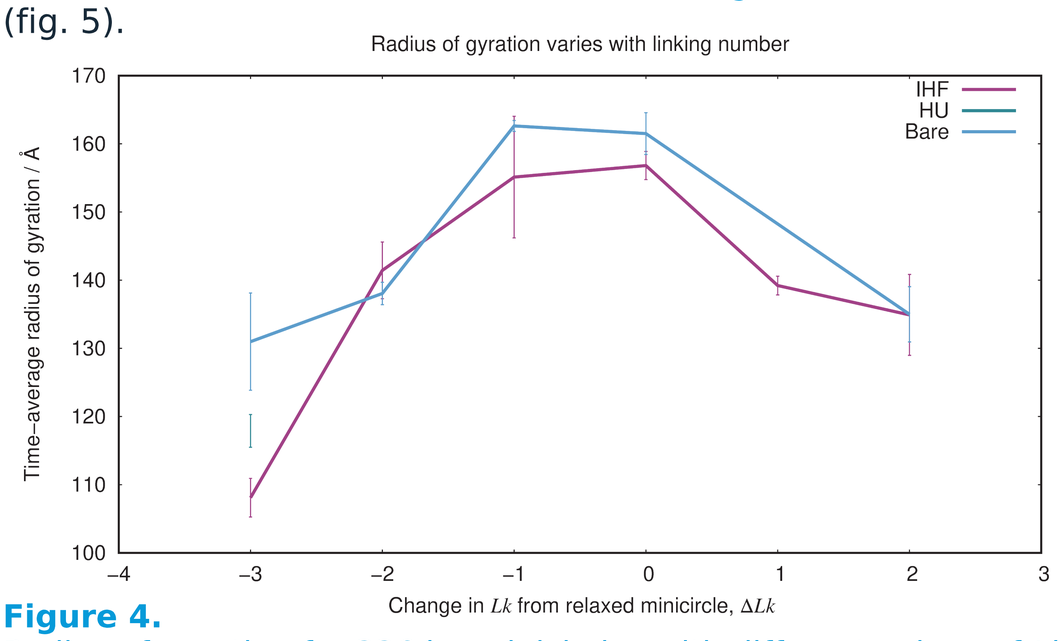

Figure 4.
Radius of gyration for 336 bp minicircles with different values of Lk. There is a significant difference between bare and protein-bound minicircles — especially for $\Delta Lk = -3$.

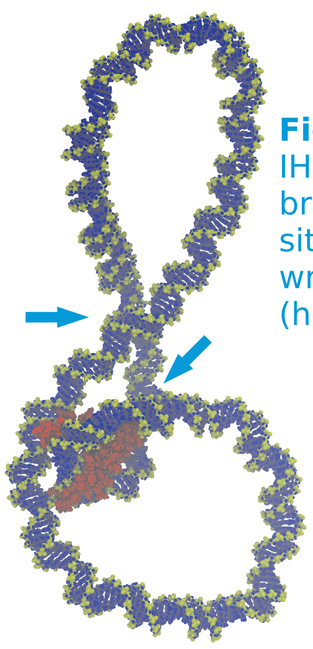

Figure 5.
IHF (red) can form a bridge between distal sites of a negatively writhed minicircle (here, $\Delta Lk = -3$).

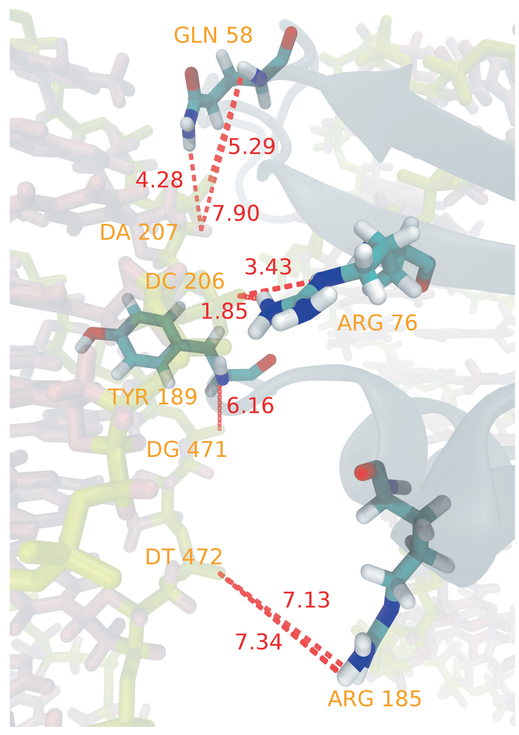

Figure 6.
The hydrogen bonds involved in this bridge can be investigated in great detail. (Lengths shown in Å)

The additional contact is dominated by ~4 amino acids, which are not conserved between IHF and HU. Determining whether HU forms similar bridges is a future aim of this work.

Studying the hydrogen bonds in the system (e.g. figs. 6 & 7) may shed more light on the nature and dynamics of these interesting interactions.

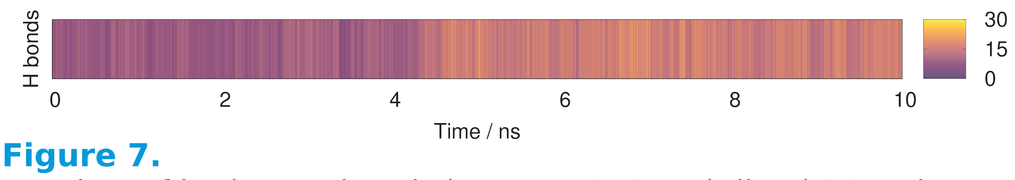

Figure 7.
Number of hydrogen bonds between IHF and distal DNA sites over 10 ns of a simulation featuring a protein bridge. A second additional contact forms at ~4.5 ns.

Discussion: Significance & outlook

The compaction of DNA and regulation of supercoiling by IHF & HU could be involved in gene regulation.

Additional protein bridges formed by IHF divide DNA into topological domains, and could regulate gene expression or even form the basis for the stability of biofilms.

Further work will involve studying interactions between multiple proteins bound to distal sites.

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