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.

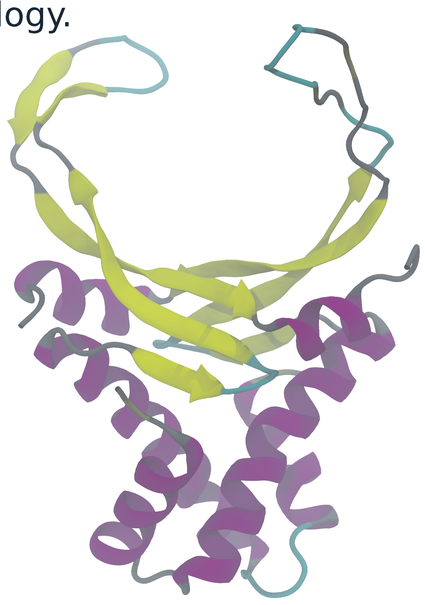

Figure 1.
IHF (*pictured*) and HU are both dimers with alpha-helix "bodies" and two "arms" that bind to DNA.

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.

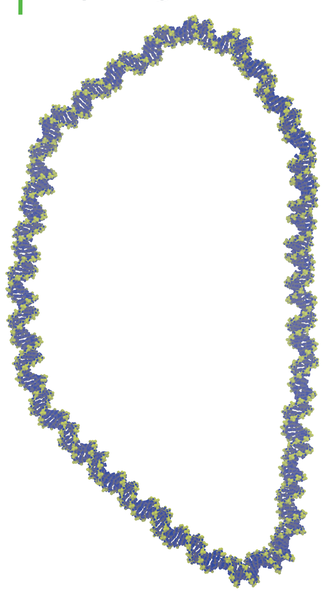

Figure 2.
A 336 bp DNA minicircle with $\Delta Lk = 0$ is relaxed and roughly circular...

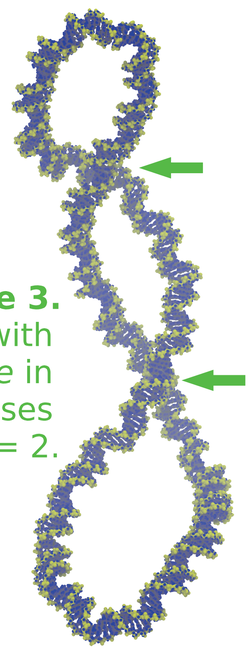

Figure 3.
... while a similar minicircle with $\Delta Lk = -3$ forms a *plectoneme* in which the helix axis crosses itself twice, so $|Wr| = 2$.

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 set of dielectric spheres.

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Results: IHF bridges DNA minicircles

IHF and HU are always positioned at the apex of a plectoneme.

IHF can bridge negatively supercoiled DNA by forming stable additional contacts, significantly compacting the minicircle (fig. 4).

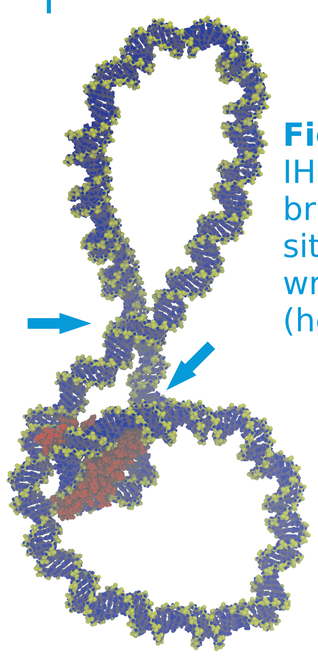

Figure 4.
IHF (red) can form a bridge between distal sites of a negatively writhed minicircle (here, $\Delta Lk = -3$).

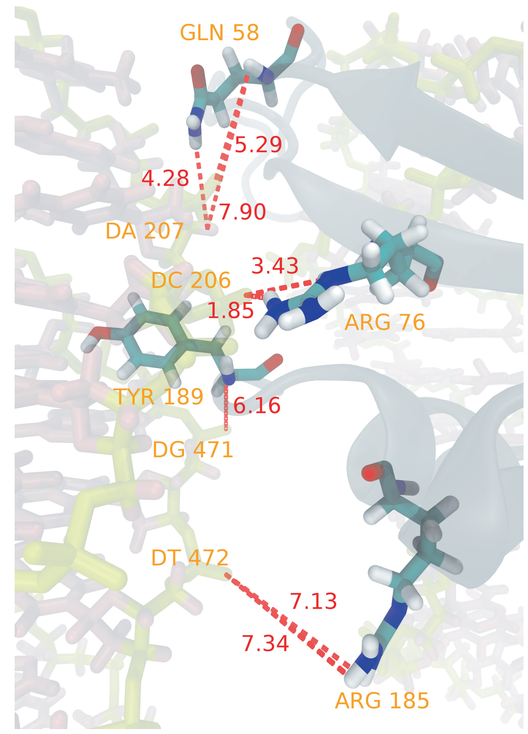

Figure 5.
The hydrogen bonds involved in this bridge can be investigated in great detail. (Lengths shown in Å)

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. fig. 5) may shed more light on the nature and dynamics of these interesting interactions.

IHF binding depends on DNA topology

IHF is observed to exhibit two binding modes, which depend on the topology of the bound DNA (fig. 6).

An AT-rich sequence has little trouble binding even when torsionally relaxed, but other DNA regions are more likely to bind IHF when strongly supercoiled.

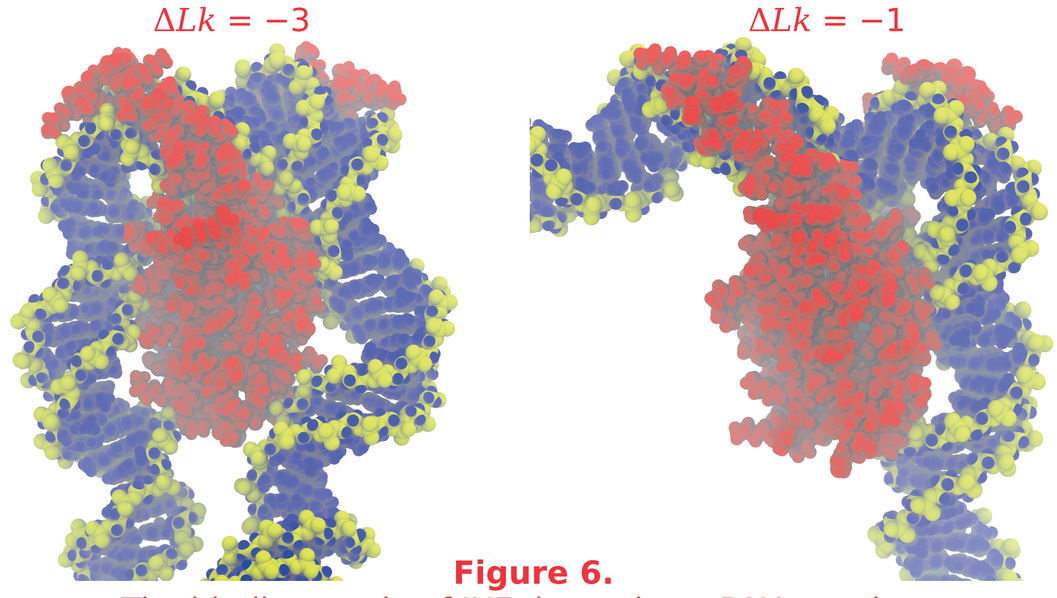

Figure 6.
The binding mode of IHF depends on DNA topology. When highly supercoiled (left), DNA wraps around the protein symmetrically, but when the DNA is superhelically relaxed (right), IHF only binds the AT-rich region.

Discussion: Significance & outlook

The compaction of DNA and regulation of supercoiling by bound proreins are 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.

The dependence of IHF binding on DNA topology adds to this complex regulatory network.

Further work will involve studying interactions between multiple proteins bound to distal sites & scaling up to converge with single-molecule experiments.

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