Two-Phase Dynamics of DNA Supercoiling based on Model of DNA Polymer Physics

Biao Wan[1], Xinliang Xu[1], Jin Yu[2]

wanbiao@csrc.ac.cn

[1]Complex System Research Division, Beijing Computational Science Research Center, Beijing, China

[2]Department of Physics and Astronomy, Department of Chemistry, Simons Center for Multiscale Cell Fate Research, University of California, Irvine, CA 92697, USA

Introduction

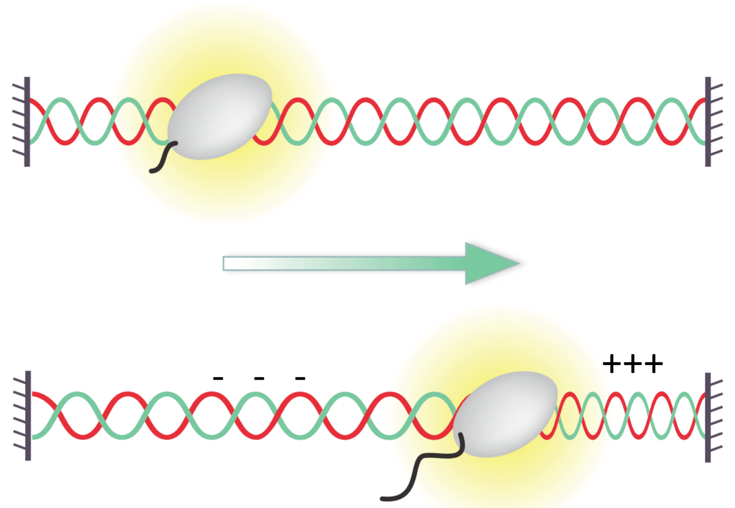
DNA supercoils are generated in genome regulation processes, such as transcription and replication and provide mechanical feedback to such processes. Under tension, DNA supercoil can present a coexistence state of stretched and plectonemic phases. Experiments have revealed the dynamic behaviors of plectoneme, e.g. diffusion, nucleation and hopping(*Loenhout.M.T et al (2012) Science,338, 94-97*). We demonstrate fast dynamics of DNA on torque transport and reaching equilibrium within the two phases. Correspondingly, we could average out the fast dynamics and drive the dynamics via slow degrees of freedom identified as phase-boundaries, thus provides a numerical description of supercoiling dynamics at trivial computational cost. Our two-phase model can be made consistent with generally used discrete worm-like chain method and it well reproduces the diffusion and hopping of plectoneme measured experimentally.

Supercoiling's role in genome regulation processes

DNA Supercoils generation and feedback to transcription

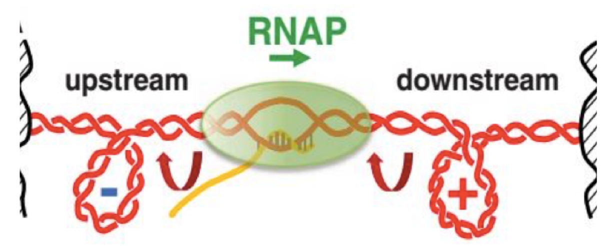
Formation of twin domain model of DNA supercoiling during transcription elongation

Liu,L.F. and Wang,J.C. (1987) Proc.Natl.Acad.Sci.USA 84,7024-7027



During transcription, RNAPs generate the positive supercoils (+) downstream and the negative supercoils (-) upstream. The build up supercoils slow down transcription elongation

Ma,J et al (2013)Science 340,1580-1583

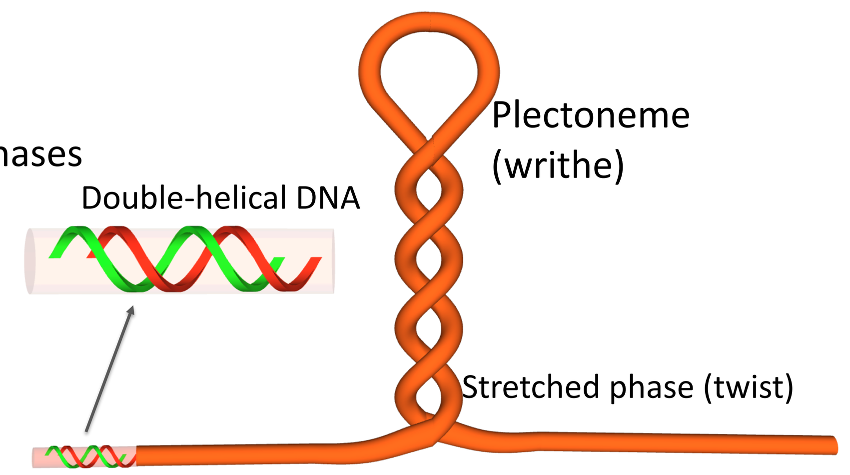


Gilbert N and Allan,J. (2014) Current Opinion in Genetics & Development 25,15-21

Supercoiling Dynamics

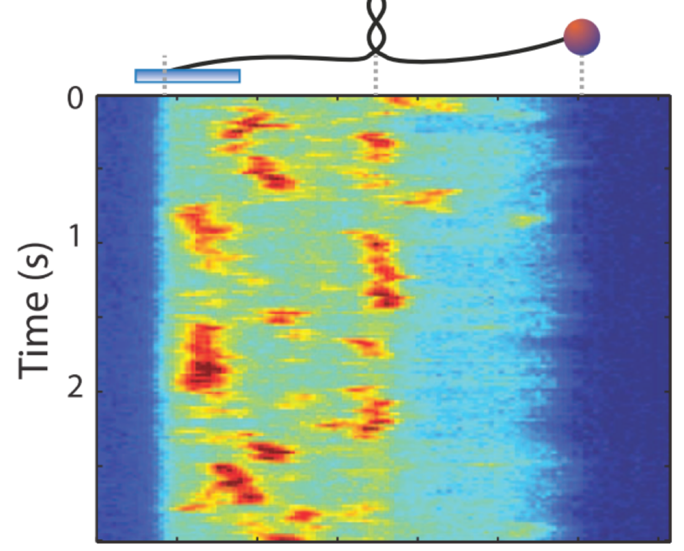
Coexistence state of plectonemic and stretched phases

The thermodynamics of the coexistence state of DNA supercoiling can be seen in *Marko,J.F(2007) Physical Review E 76,021926,* where DNA is regarded as a polymer, specifically, a worm-like chain.



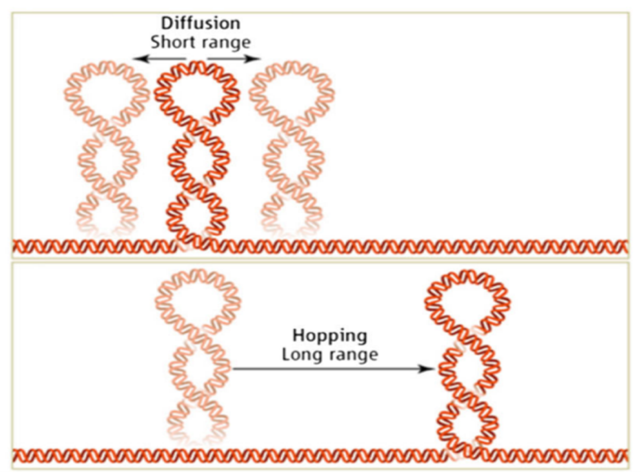
A twisted DNA molecule buckles to form plectoneme

Kymograph of plectonemes



Loenhout.M,T et al (2012) Science,338(6103), 94-97

Schematic view of supercoiling migration by diffusion or hopping



Sheinin.M.Y and Wang.M.D (2012) Science,338(6103),56-57

Diffusion of plectoneme allows a conformational rearrangement of DNA at about hundreds bps per second.

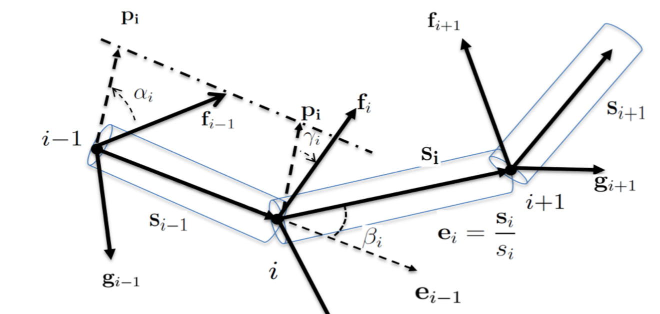
Comparing with diffusion of plectoneme, hopping is fast and long range, e.g. tens of milliseconds for a displacement of thousands of bps.

Measuring torque transport within two phases

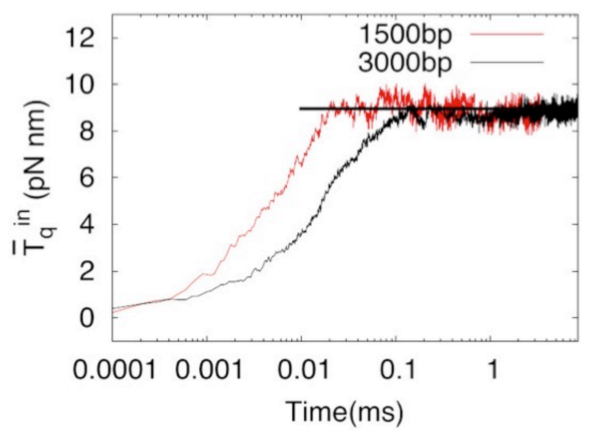
The discrete worm-like chain method(dWLC)

K.Klenin and J.Langowski (1998) Biophysical Journal Volume 74, 780-788

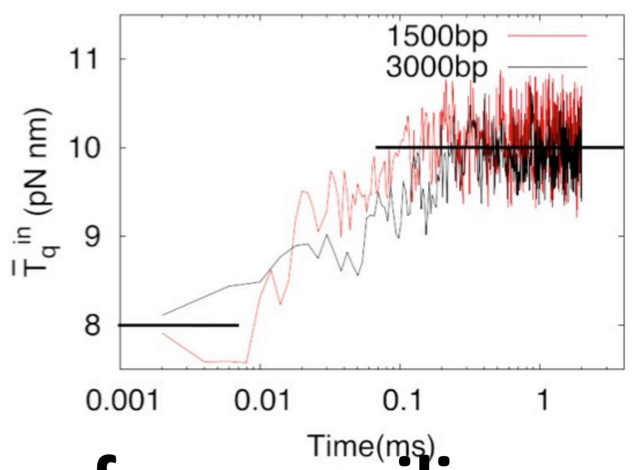
Double-helical DNA is coarse-grained as the descrete segments represented by cylinders. The cylinders are described by vertices (i-1,i,i+1) and vectors (e,f,g) to mimic the conformation of DNA and its torsional properities.



Torque transport on the stretched phase



Torque transport on the plectonemic phase

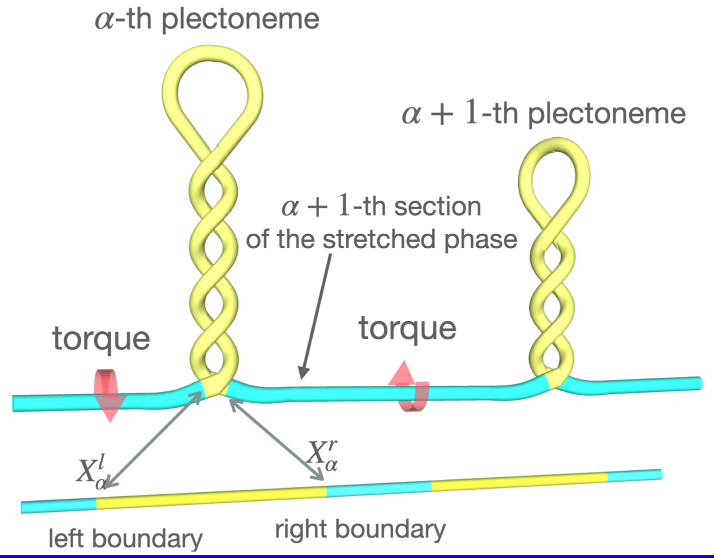


Torque transport can be analytically described, also can be directly measured with simulation based on discrete worm-like chain method.

Two-phase dynamics of supercoiling

Compared to the fast dynamics of DNA: from 0.01~0.1millisecond for 10^3bp.
Phase boundaries can be identified as slow variables to describe the dynamics.

A dynamics can be derived using the formula of the free energy based the worm-like chain model (*Marko,J.F(2007)Physical Review E 76,021926*)



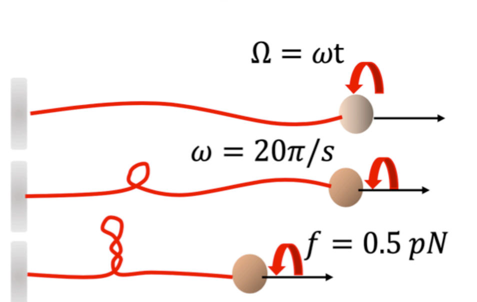
The left boundary or the right boundary of the α-th plectoneme follows

$$\dot{X}_{\alpha}^{l/r} = -\frac{1}{\gamma_{\alpha}}\nabla_{X_{\alpha}^{l/r}}\Phi_0(\mathbf{X}) + \sqrt{\frac{2k_BT}{\gamma_{\alpha}}}\dot{W}$$

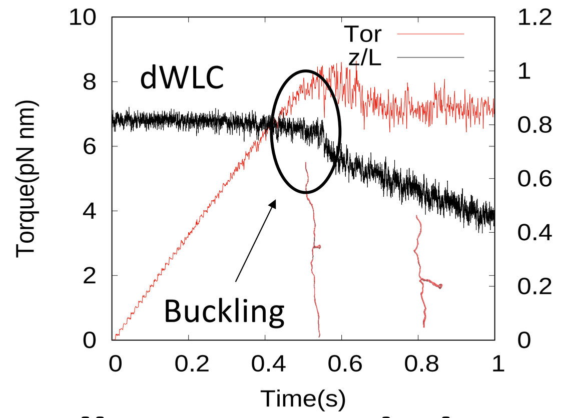
where γ_{α} is the fricition felt by the plectoneme,Φ_0 is the free energy associated with $X_{\alpha}^{l/r}$ accompanied with 0 nucleating events, and $\dot{W}$ is the Gaussian noise.

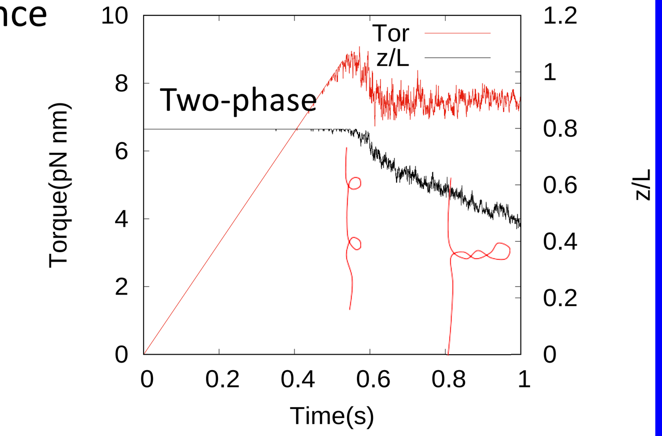
Comparing with the discrete worm-like chain method(dWLC)

Supercoiling accumulation



The discontinuities on torque and extension curves indicate the buckling transition followed by phase-coexistence

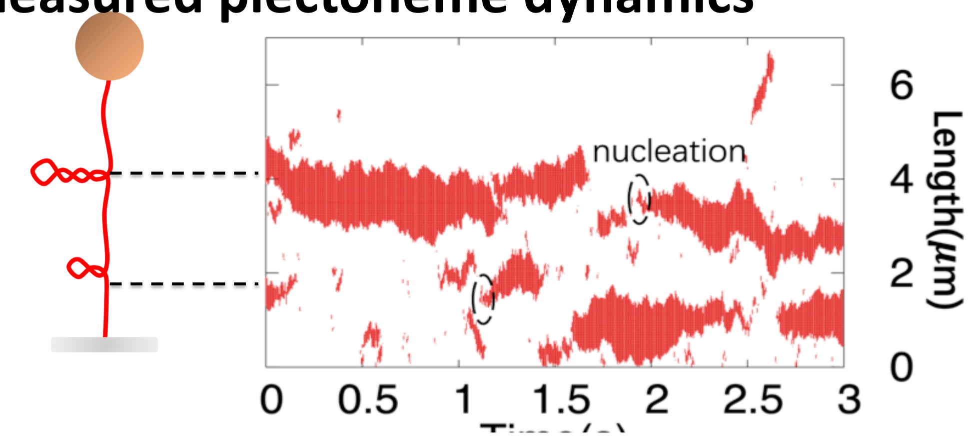




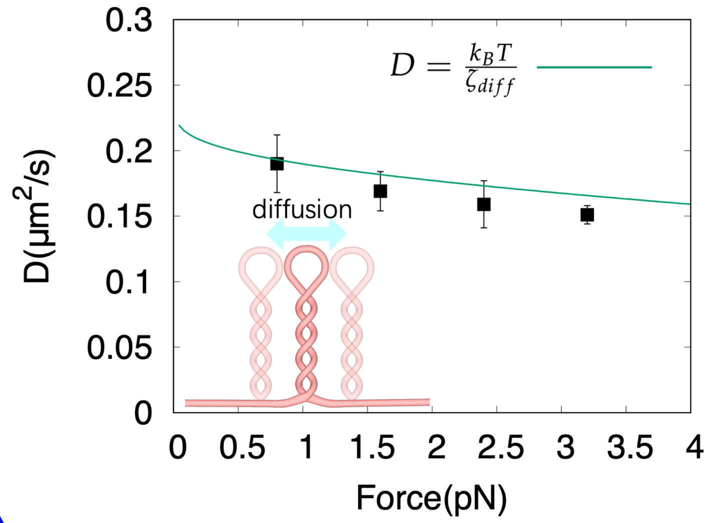
Reproducing experimentally measured plectoneme dynamics

Kymograph of plectonemes

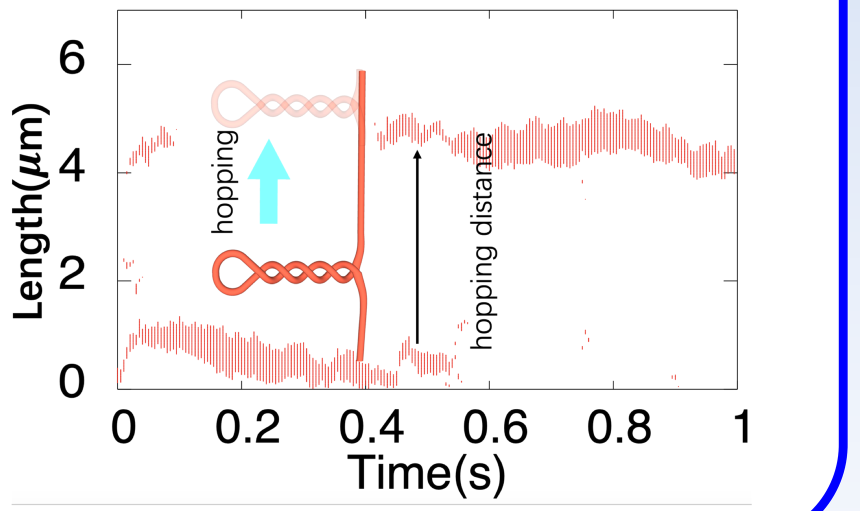
The coexistence of multiple plectonemes, the plectoneme nucleating and vanishing are all captured (21kbp).



Reproducing plectoneme diffusion



A plectoneme hopping (over 10 kbp)



Summary

Based on the polymer physics of DNA, we have constructed a two-phase dynamics of DNA supercoiling, and then have successfully reproduced the supercoiling dynamics, including plectoneme nucleation, diffusion and hopping at trivial computational cost. The studies can be further implemented to construct multi-scale physics model of supercoiling in gene regulations.

Acknowledgement

This work has been supported by National Natural Science Foundation of China [#11775016 and #11275022]. We also acknowledge the computational support from the Beijing Computational Science Research Center (CSRC).