Warsaw, 24 June, 2023

Unravelling the shapes of DNA minicircles

A collaboration of researchers from the Faculty of Physics of the University of Warsaw, Polish Academy of Sciences, Baylor College of Medicine, Rice University, University of Montana and University of Lethbridge show quantitatively that at very small scales the behaviour of DNA is determined by elastic forces. The results of the research, published in the journal "Nucleic Acids Research", show how to study elastic properties of DNA using hydrodynamic measurements.

The story of the geometry of DNA does not end at the double helix shape. Inside the cells, where the DNA performs its most important functions, it is subjected to replication and transcription machinery, which results in transient under- and over-twisting of that helical double-strand. You can observe such shapes also at the human scale, e.g. by grabbing an end of a string (or headphones; see diagram) and twisting it—after a few rotations you see how it coils up, a term called "supercoiling" for DNA.

"We continue to be amazed by how different supercoiled DNA is from the form we know a lot about—the so-called "B-form" DNA double helix that you see depicted in sculpture, architecture, and art," says Prof. Lynn Zechiedrich of Baylor College of Medicine, co-contributing author on the study. "Active DNA looks very different from that form and we are so excited to continue to discover the ways access to the primary genetic code is regulated."

Studying the under-twisting and over-twisting mechanics is particularly challenging – most research on the topic of DNA geometry is conducted with short linear fragments. Even were they twisted the ends would spontaneously relax the twist. "For illustration, twist a shoelace—if you let go of either end, the shoelace just becomes straight (untwisted) again", says Radost Waszkiewicz, who is the leading co-author of the paper and a PhD student at the Faculty of Physics of the University of Warsaw.

The twist relaxation does not occur if the ends of the DNA segment are attached together—this way the twist is 'locked in' within the loop and cannot escape through the ends. A group of researchers from Baylor College of Medicine and Rice University, Dr. Jonathan Fogg and Dr. Daniel Catanese, led by Zecheidrich, figured out how to do just that using small (336 base pair long) DNA minicircles.

When the DNA is under- or over-twisted more and more before closing it in a minicircle, its shape becomes more and more compact. These minicircles with precise defined degrees of twist were investigated in three distinct ways – their shapes were explored by the Zechiedrich group using biochemical and biophysical methods, including an electron microscopy technique capable of capturing 3D images of these DNA nanoparticles; the group of Prof. Borries Demeler at the University of Montana and University of Lethbridge used analytical ultracentrifugation (AUC), a very precise “first principles” (meaning the read out is direct; no need to compare to reference to infer) method of measuring how quickly the molecules sediment, which depends upon their diffusion and sedimentation coefficients. Maduni Ranasinghe, a PhD student at Lethbridge, performed AUC measurements for different supercoiling density of the minicircles. Increasing the compactness of the DNA molecules was shown to increase the diffusion coefficient.

The theoretical approach, developed by Radost Waszkiewicz, Prof. Maciej Lisicki, and Prof. Piotr Szymczak at the Faculty of Physics, University of Warsaw, in collaboration with Prof. Maria Ekiel-Jeżewska at the Institute of Fundamental Technology Research of the Polish Academy of Sciences, combined two main components. “We assumed that the DNA can be modelled as a uniform elastic beam, behaving like a miniature rubber band”, says Radost Waszkiewicz. “For a given amount of twist, we determined the shapes that minimise the total elastic energy, and these are the shapes that we see in experiments! We then used these shapes to calculate their hydrodynamic properties, that is to see how fast they diffuse and sediment in solution,” he adds.

To understand the dynamics of DNA, or generally small objects in aqueous solvents, we need to explore the mechanics of very viscous fluids. “Microscale flows are dominated by viscous effects and inertia is completely negligible. Our modelling approach relies on the mathematical properties of these so-called Stokes flows,” says Lisicki, who was a co-investigator specialising in modelling hydrodynamic interactions.

“The elucidation of the properties of DNA minicircles is an example of interdisciplinary cooperation between specialists from different fields: physics, chemistry and biology, combining theoretical and experimental approaches”, adds co-investigator Szymczak. “We hope that the results we obtained will open doors to further study of the dynamic hydroelastic effects in DNA”.

Faculty of Physics of the University of Warsaw
Physics and astronomy at the University of Warsaw appeared in 1816 as part of the then Faculty of Philosophy. In 1825, the Astronomical Observatory was established. Currently, the Faculty of Physics at the University of Warsaw consists of the following institutes: Experimental Physics, Theoretical Physics, Geophysics, the Department of Mathematical Methods and the Astronomical Observatory. The research covers almost all areas of modern physics, on scales from quantum to cosmological. The Faculty's research and teaching staff consists of over 200 academic teachers, 88 of whom are professors. About 1,100 students and over 170 doctoral students study at the Faculty of Physics at the University of Warsaw.

SCIENTIFIC PUBLICATION:

R. Waszkiewicz, M. Ranasinghe, J. M. Fogg, D. J. Catanese, Jr., M. L. Ekiel-Jeżewska, M. Lisicki, B. Demeler, L. Zechiedrich, P. Szymczak
DNA supercoiling-induced shapes alter minicircle hydrodynamic properties
Nucleic Acids Research, 51, 8, 4027–4042 (2023)
DOI: 10.1093/nar/gkad183

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http://softmatter.fuw.edu.pl
Website of Prof. Maciej Lisicki at the Faculty of Physics, University of Warsaw, Poland

https://www.cch.uleth.ca
Website of the Canadian Center for Hydrodynamics, directed by Prof. Borries Demeler

https://www.bcm.edu/research/faculty-labs/lynn-zechiedrich-lab
Website of Prof. Zechiedrich at Baylor College of Medicine, Houston, TX USA

https://www.fuw.edu.pl/press-releases.html
Press service of the Faculty of Physics of the University of Warsaw, Poland

GRAPHIC MATERIALS:

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https://www.fuw.edu.pl/tl_files/press/images/2023/FUW230623b_fot01.jpg.
You can observe the formation of twisted structures (at the human scale) by grabbing an end of a string (or for example headphones) and twisting it – after a few rotations, a characteristic perpendicular shape is formed. (photo: Radost Waszkiewicz, source: Faculty of Physics of the University of Warsaw)

FUW230623b_fot02
https://www.fuw.edu.pl/tl_files/press/images/2023/FUW230623b_fot02.png
Self-touching shapes of DNA loops as predicted by the model for increasing supercoiling density (top to bottom). When the DNA is twisted more and more, its shape becomes increasingly compact (source: Radost Waszkiewicz)