Unexpected new dynamics for large DNA molecules in liquid suspension

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Polymer physicists at the University of Massachusetts Amherst are today reporting the unexpected and previously unknown behavior of a charged macromolecule such as DNA embedded in a charged hydrogel, where it displays what they call a "topologically frustrated" inability to move or diffuse in the gel, a phenomenon they describe in the current *Nature Communications*.

Polymer physicist professor Murugappan "Muthu" Muthukumar, with postdoctoral researcher Di Jia, used light-scattering techniques to study large DNA molecules' behavior in a geomesh of 96 percent water, where they expected it to move very slowly, but to eventually diffuse as all previously known systems would behave.

Muthukumar explains, "Scientists have known for more than a century that all molecules have Brownian motion, that is they move around and diffuse, including DNA and other very large molecules. How fast they diffuse depends on the molecule, and large ones can be very slow. This is normal and is what we have observed for more than 100 years."

But what Jia discovered and Muthukumar confirmed with theoretical calculations is that she could design a hydrogel of 96 percent water using a many-compartmented gel to capture a large DNA molecule that is unable to diffuse at all. Hence their term, "topologically frustrated dynamics," where topological refers to the idea that a single molecule is held in many different chambers constituting the gel. Jia notes, "The DNA molecule cannot move at all, it is stuck."

Muthukumar adds, "The technique of capturing polymers and molecules in a liquid suspension is important to gene therapy, for example, and in tissue therapy where we want to deliver macromolecules and large drugs to a specific location and keep them there."

To understand Jia's design, it helps to imagine a molecule trapped in a cubic mesh of 30 roughly equal compartments, Muthukumar says. In order to diffuse, one of the compartments has to initiate movement, "but to do that, it has to drag all the other 29 compartments along with it. It will try to move, but it will become frustrated, fluttering its wings so to speak, and the whole thing will be stuck. Locally it has some dynamics, but mobility overall is frustrated."

He adds that the discovery was a surprise, "but when you think about it, it makes sense that the body and its tissues would want a system that can hold onto macromolecules like DNA, to keep them in place. Now that we have made a theoretical understanding of this discovery, we think it's a universal phenomenon in the body, where DNA needs to be trapped in place."

Further, "This physical model can explain an observed biological phenomenon," he says. "I think biologists will discover that our observation is happening in crowded environments like the cell, and researchers working on drug delivery will discover how to use it."

Andrew Lovinger, the National Science Foundation (NSF) program officer who supported the research, says, "This new dynamical state truly is a surprising discovery. It revises scientists' long-established understanding of polymer diffusion, and will help drive fundamental research in polymer science for both biological and synthetic systems."

To study such systems, Jia sets up experiments where she manipulates variables such as gel structure, polymer concentration and the probe molecules' molecular weights. She then captures several different molecules inside different gels and uses light-scattering to observe their behavior. Dynamic light-scattering analysis works by tracking light scatter that emerges after a light beam is sent into a liquid with polymer suspended in it. A trained researcher can determine the polymer's molecular structure, how fast and other characteristics of its movement. Jia is an accomplished expert in the technique, Muthukumar notes.

For this work, Jia says she experimented with both synthetic and natural molecules and both exhibited the same phenomenon. Also, she was able to show that if each chamber of the gel structure is not large enough and the macromolecule gets partitioned into very tiny pieces, it will then be able to diffuse.

Muthukumar says he has been thinking for 20 years about how to harness a polymer's conformations, making them useful for a variety of applications. "To explore this you have to create barriers," he points out. "I asked myself, what if multiple barriers have to be simultaneously overcome, what will happen? What I think we see is simultaneous negotiations going on. The matrix has its own slight movement in gel dynamics, and the molecule has its own dynamics. In the end, we found the result is so simple for such a large complicated system."

More information: Di Jia et al, Topologically frustrated dynamics of crowded charged macromolecules in charged hydrogels, *Nature Communications* (2018). DOI: 10.1038/s41467-018-04661-3

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