GA

DETECTING NEUROTRANSMITTERS WITH DNA-WRAPPED NANOTUBE SENSORS

Allocation: Innovation and Exploration/200 Knh
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EXECUTIVE SUMMARY

The rapid and efficient detection of modulatory neurotransmitter molecules stands to be transformative for studies of neurological diseases. Polymer-wrapped carbon nanotube (CNT) sensing platforms are well suited to address this critical need. Using the Blue Waters supercomputer, the research team performed extensive equilibrium and enhanced-sampling all-atom molecular dynamics simulations and obtained free energy landscapes that demonstrate that short DNA polymers can wrap CNTs in highly ordered ring conformations that can suppress the optical signal of the CNTs. In microseconds-long trajectories, dopamine neurotransmitters were shown to bind to DNA rings and disorder them on the CNT surface, which the research team associated with increased optical emission. The project's experimental collaborator, Markita Landry at the University of California, Berkeley, demonstrated that these ring DNA-wrapped CNTs constitute an ultrasensitive "turn on" nanosensor for the neurotransmitters dopamine and norepinephrine with a strong relative change in optical signal of up to 3,500%, appropriate for *in vivo* neuroimaging.

RESEARCH CHALLENGE

There is a critical need to develop neurotransmitter sensors that will eventually be able to probe the emergence, diagnosis, and treatment of multiple neurological diseases related to altered patterns of neurotransmission. However, a broadly utilized optical imaging technology to address the quantitative sensing of neurotransmitters does not exist. This project's computational group has teamed up with an experimental lab to design and understand the functional mechanisms of novel sensors of neurotransmitters, based on carbon nanotubes wrapped by nucleic acid polymers.

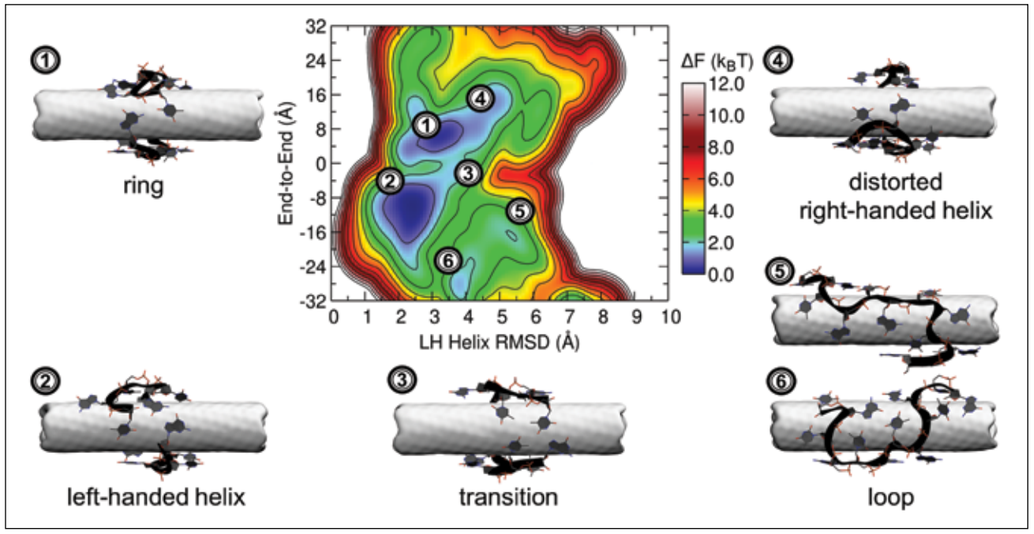

Figure 1: Free energy landscape of a short $(GT)_6$ DNA wrapping a (9,4) carbon nanotube. DNA favors ring (1) and left-handed helix conformations (2), shown in blue regions in the contour plot.

METHODS & CODES

The research team performed microseconds-long equilibrium and enhanced-sampling replica exchange all-atom molecular dynamics simulations with the latest version of the NAMD software, a GPU-accelerated, highly parallelized code for high-performance simulations of biomolecules.

RESULTS & IMPACT

In this study, the research team performed multiscale simulations of short and long DNA polymers (12 to 30 nucleotides) with different sequences, wrapping (9,4) and (6,5) carbon nanotubes to disclose mechanisms responsible for a strongly quenched baseline fluorescence and a large nanosensor response to neurotransmitters observed in experiments. While longer 30-nucleotide DNA polymers remained in helical conformations in molecular dynamics (MD) simulations, shorter 12-nucleotide $(GT)_6$ DNA polymers rearranged from initial helical conformations into ringlike conformations in each of the five independent trajectories performed. To confirm that the ringlike conformation is a favorable adsorbed state of a $(GT)_6$ DNA on the (9,4) CNT, the team calculated the free energy landscape of the DNA (Fig. 1) on the (9,4) CNT surface at room temperature (T = 300K), using replica exchange MD. The landscape revealed two distinct stable conformations for $(GT)_6$: a left-handed helix and a nonhelical ringlike conformation. The team next performed quantum calculations of the systems and developed a quantum model of an exciton at the CNT surface in the electrostatic environment generated by the DNA polymers, solvent, and neurotransmitter analytes. With the help of the simulations performed, the research team proposed the mechanisms behind the low optical signal of the ring-DNA-wrapped CNTs, and how the adsorbed dopamine neurotransmitter molecules distort ring-conformations of short DNAs and increase the optical signal of CNTs. Furthermore, the team has been screening short DNA polymers of different sequences that can form ring conformations on CNTs in order to identify novel polymer CNT wrappings for selective and sensitive detection of other neurotransmitter molecules.

WHY BLUE WATERS

To overcome the computational timescale limitations, the project required the use of replica exchange MD simulations, which can usually be performed only with access to the large resources of a petascale machine such as the Blue Waters supercomputer.

PUBLICATIONS & DATA SETS

A. G. Beyene *et al.*, "Ultralarge modulation of fluorescence by neuromodulators in carbon nanotubes with self-assembled oligonucleotide rings," *Nano Lett.*, vol. 18, p. 6995, 2018, doi: 10.1021/acs.nanolett.8b02937.

R. Nissler *et al.*, "Quantification of the number of adsorbed DNA molecules on single-walled carbon nanotubes," *J. Phys. Chem. C*, vol. 123, p. 4837, 2019, doi: 10.1021/acs.jpcc.8b11058.