Extremely precise DNA simulations introduce new possibilities for medical research

By Monisha Ravisetti
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Novel real-time computer simulations with an atomic level of precision captured exactly how DNA structures move within the body, providing insight that could one day be instrumental in drug development and organ regeneration strategies.

As gene expression and cell transformation are largely dependent on how DNA is packed and unraveled within cells, understanding what impacts the molecule's motion is vital for those who seek to regulate its outcomes. Addressing this, a paper published June 3 in *PLOS Computational Biology* enumerated two previously unknown features of DNA movement — with great detail.

"You can think of these as real-time movies," lead author Vlad Cojocaru, Hubrecht fellow at Hubrecht Institute in the Netherlands told *Fastinform.* "You basically follow this protein on the computer, and we know the methods are accurate enough to reflect a real motion of the molecules."

Within each cell lies about two meters of DNA. To fit inside, the strands wind around proteins called histones. Several of these histones together create nucleosomes, and the entire package constitutes what is referred to as chromatin.

"These types of DNA — really tightly wrapped around these histones — you need it to move," Cojocaru said. "We asked the question, 'How [do] these nucleosomes move, and what is the mechanism [that] drives their motion?"

Cojocaru's team is the first to show that specific DNA sequences directly affect the molecule's loosening around histones and that sites on the foundational proteins, namely their tails, have implications for unwrapping as well.

"People have done simulations with reduced representation where you don't have all atoms present," Cojocaru said. "But, we have shown with atomistic simulations that we can simulate the opening of these genomic nucleosomes."

The knowledge could be important for medical research because organ regeneration, among other important processes, is reliant on the way cells transition within the body. The loosening of DNA around histones and the consequent opening of chromatin occur during cellular conversion, particularly when stem cells are used as a seedling for other cell-types in the body.

"If you know that there are .. regions of the protein that are involved in specific interactions with certain types of DNA," Cojocaru said, "then you can target, specifically, that region — without knowing these kinds of details, you cannot."

Detailed visuals of the motion's mechanism could also inform therapeutic strategies that aim to create enzymes that can control the entire process, which is known as nucleosome breathing.

"You can manipulate the degree of which the chromatin is open or closed by targeting the sites on the histones," Cojocaru said. "You can target enzymes that modify the DNA."

In order to arrive at this new knowledge that could greatly aid in several aspects of health care, Cojocaru and the team simulated three types of DNA structures: two natural, based on genomic sequences from actual cells, and one engineered. All three were chosen based on where their transcription factors, which are proteins that control the activation of a gene, would bind.

"Each of these has binding sites for one of these very important transcription factors that can induce stem cell properties into adult cells," Cojocaru said.

The synthetic structure the team used, which has been engineered to have an overly stable genomic sequence and has been widely used by other researchers in the field, didn't open in the team's simulations — though Cojocaru

noted he anticipates that it would eventually move, albeit "not so fast, and not so much." Therefore, the researchers concluded that any attempted simulation of nucleosomes ought to consider the fact that specific sequences directly play a part in the system's motion.

"DNA that is wrapped around genomic sequences are more dynamic — so they move more," Cojocaru said, when "comparing [them] to the ones that are generally used in experiments."

The researcher noted that a limitation of having such pristine, atomic detail in each of their simulations was the significant amount of computing power required, another reason for why the team wasn't yet able to observe movement in the stable, engineered system.

"What we can now do," he said, is "routinely generate about one to five microseconds of these kinds of movies."

However, even through the short time frame, the team still is responsible for more than one novel discovery — the second being that histone tails impact the nucleosome's mechanism of motion, too.

Cojocaru remarked, "We actually found that — depending on the position and configuration of these tails — you can have either closed nucleosomes, or you can open the nucleosomes quite a bit."

While it's already known that these tails drive gene expression when modified, such as with acetylation and

methylation, the researcher noted that, until now, it was unclear whether they impact the motion of the nucleosome, so the study provides even more new information for future exploration.

The paper, "Histone tails cooperate to control the breathing of genomic nucleosomes," was published June 3 in PLOS Computational Biology. It was authored by Jan Huertas and Vlad Cojocaru, Hubrecht Institute, Max Planck Institute for Molecular Biomedicine and Westfälische Wilhelms University; and Hans Robert Schöler, Max Planck Institute for Molecular Biomedicine and University of Münster.