DNA tug of war

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A mathematical model created by Aalto University (Finland) researcher Timo Ikonen explains for the first time how the DNA chains in our genome are translocated through nanopores that are only a couple of nanometres thick.

A research paper soon to be published in *Physical Review E* explains the basic physics related to the phenomenon referred to as polymer translocation. Exploring this phenomenon could help to create third generation genome sequencing technologies.

With the help of these technologies, sequencing a patient's genome could become a routine health care procedure.

Full genome sequencing is one of the major accomplishments of humankind. The method for sequencing the millions of base pairs that make up the human DNA molecule chain was revealed in the 1970s, but the entire human genome was not sequenced until 2001.

Sequencing the first human genome cost almost 3 billion dollars. The analysis is still extremely laborious: sequencing the genome of one person costs over 10,000 dollars.

The translocation phenomenon examined by Ikonen enables researchers to use a much simpler method for determining the base sequence of genes. As early as in the 1990s, researchers discovered that when a DNA chain is forced through a small nanopore with the help of an electric current, different types of bases can be identified by monitoring the changes occurring in the current.

Experimental physicists hurried to find out whether the phenomenon could be applied to determining the base sequence of a genome. A small number of theorists began exploring what happened during the actual translocation process. The first translocation theory was presented by Professor Sung's group in 1996. Sung is now Ikonen's research partner.

The first DNA sequencer based on translocation will soon be on the market, but the theory itself has been controversial. Tests have revealed that when an electric current is used to drive a DNA chain through a pore that is only a couple of nanometres thick, the first monomers of the chain go through the pore very rapidly. Then the process slows down, but later on it speeds up again.

"The million dollar question has been why this happens," researcher Timo Ikonen says.

In his article, Ikonen presents a mathematical model that explains the events of the translocation process. The researcher compares the DNA chain to a garden hose curled up on the ground.

"As the curled up hose gradually straightens and the length of the part being pulled grows, pulling the hose becomes harder," Ikonen explains.

Finally the entire hose will be moving and this is when pulling it along will require the most effort. When more than half of the DNA strand has gone through the nanopore, the tail end of the base chain begins to shorten and the speed of the translocation process increases.

Ikonen realised how the translocation friction of a DNA strand was dependent of time during a research visit to South Korea in January 2011. Professor Sung's doctoral candidate presented a research paper by

Japanese professor Takahiro Sakaue in which the progression of translocation had been described in a similar manner.

Ikonen corrected some of Sakaue's hypotheses and soon the new model was producing results that were in almost perfect accordance with the molecular-level simulations. "It was unbelievable," Ikonen describes his feelings after receiving the first results.

His first presentation on the subject attracted the deserved attention at a conference held by the American Physical Society (APS).

In the article to be published, titled "Unifying model of driven polymer translocation", Ikonen also explains how the length of the molecule chain affects the translocation time. His model reveals why computer simulations and previous mathematical models have produced conflicting results.

- Previously, researchers have been comparing apples and oranges. The simulations have been performed using chains of no more than a thousand monomers, whereas the mathematical models have been designed for chains of infinite length.

Ikonen noticed that the total length of a DNA chain does not cease to affect the progress of the translocation process until it is approximately 100,000 bases long. The new theory and simulations produce similar results for chains of all lengths.

- This proves that our idea about the force progressing through the chain is in line with what actually takes place during translocation.

Ikonen's model represents basic research and it can be applied in various fields. Understanding the basic physics of translocation is valuable to the developers of new gene sequencers. With third generation equipment, the price of full genome sequencing may drop to less than 100 dollars.

Translocation also occurs in many other biological processes, such as when viruses inject their genome through cell walls. The new model provides researchers with the information needed to understand how long polymer chains travel through nanometre-scale holes. Observing these nanoscale phenomena in nature is extremely difficult. Now researchers will be able to use regular desktop computers instead of the supercomputers normally used for simulations.

The "Unifying model of driven polymer translocation" research paper has been pre-published in the arXiv service.

Provided by Aalto University

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