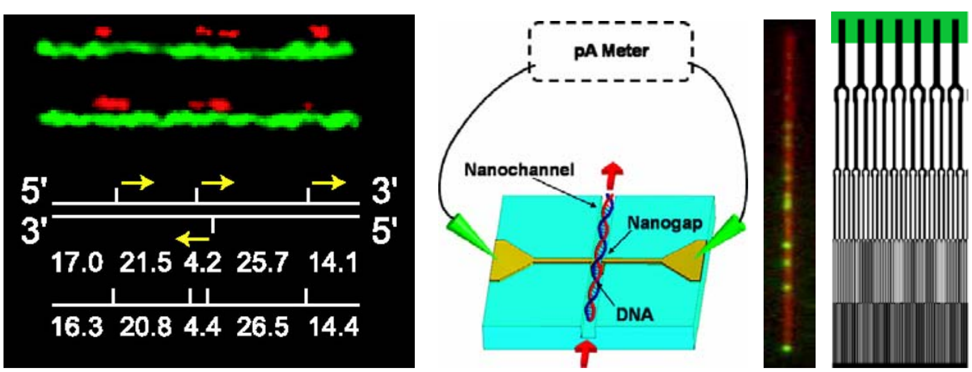
Nanoconfinement for DNA Analysis

The genetic instructions in our DNA specify much about our bodies, our health, and our risks for many diseases and disabilities. Recent years have witnessed an explosion of knowledge of on the DNA sequences that contain critical information. But DNA analysis remains complex and costly, and most methods only give local views of our large genomes. Each of our cells contains 6 billion DNA bases arranged in 46 chromosomes, each of which is in turn a few hundred million bases long. That’s a mismatch to most analysis methods that can only handle DNA fragments that are a few hundred bases long! The fragments must be stitched together by computer to make sense of the information. However, medical researchers are finding increasing evidence that long-range analysis provides essential information for understanding the relationship between changes in DNA and disease.

Inside cells, proteins wrap and pack DNA to keep it organized When we isolate DNA from cells to analyze it, the long DNA molecules collapse into coils In the past few years, nanotechnology has enabled a new approach to genome analysis. Physicists understand that long, randomly-coiled biopolymers such as DNA can be stretched out by virtue of a phenomenon called confinement. If a coiled DNA molecule is driven by an electrical force out of a chamber in which the DNA is coiled, into a channel that approximates the DNA polymer’s “persistence length,” the DNA stretches out. The persistence length of DNA is about 50 nm. Until recently it wasn’t possible to routinely fabricate devices with long, smooth channels of this dimension, to confine the DNA. Recently, several groups have solved this problem, each in a different way, and the solutions are being adapted for the analysis of information displayed along long DNA molecules. One device with very narrow and smooth channels can incorporate electrodes to measure signals as DNA passes by. Another has channels whose dimension can be changed in real time so DNA can be loaded into wide channels and then stretched as the channel narrows. A third is made so inexpensively that the chip can be replaced after each use, which is important for many diagnostic tests. Some of these devices can analyze very large numbers of molecules in every test to provide medically-meaningful data.



Left image is from ref 1. Second image is from ref 3. Two right-most images are from http://www.bionanomatrix.com/upload/files/081106%20ASHG%20FINAL.pdf

Figure: The left panel shows a map of made from single DNA molecules that are 115,000 bases long. The molecules (green) were stretched in nanochannels and labeled (red) at the locations of specific sequences along their length. The second panel is a schematic of a device with a very long nanochannel through which DNA flows past a nanogap for electrical measurements. The DNA image in the third panel was produced on a device such as that shown on the far right with capability to analyze many molecules in parallel; it shows a DNA fragment (red) about 100,000 bases long with labels (green) at sites where different peoples’ DNA differs from each other.

With these technologies and their descendents it will soon be possible to analyze pieces of DNA that are 10s of thousands or perhaps even millions of bases long. This information will initially be used to better understand the genes that contribute to diseases that affect millions of people, such as heart disease, diabetes and cancer. Eventually that knowledge will allow similar devices to be used for diagnosis and treatment of individual patients.

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