第77回応用物理学会秋季学術講演会 講演予稿集 (2016 朱鷺メッセ (新潟県新潟市))

Development of Tunnel-Current Identification by Nano-gap Integrated Device Toward Single-Molecule Electrical Sequencing

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Single-molecule electrical genome sequencer is one of the important technologies for a realization of personal medicine. We have been proposed a tunneling-current based identification as candidates for a single-molecule DNA/RNA sequencing. This methodology is based on sequentially reading the tunneling-current across individual single-nucleotides in the sequence, resulting in a high-speed electrical discrimination of the individual nucleotides without chemical probes and PCR amplifications.

The tunneling-current intensity between nano-gap electrodes is closely related to the individual electronic conductance, which is due to the individual molecular energy level. Calculations based on density functional theory indicated that the order based on the highest occupied molecular orbital (HOMO) energy are similar to experimental conductance results.

We have developed the nano-gap electrode device, in which electrophoretic electrodes, nano-fluids, and pillar are integrated (Figure 1). The nano-gap electrode was prepared by mechanical-breakdown of gold-wire on insulated polymer, resulting in forming a pair of gold nanoelectrodes. After the formation of nanogap, by using piezo-controller, the gap distance was tuned to be the size of mono-nucleotide molecules. We applied dc-voltage between the nano-gap electrodes and measured the current at high-speed data-acquisition rate. A dc-voltage are also applied between the trans-chambers of electrodes for induction of electrophoretic flow across the gap-electrodes.

Based on the electrical conductivity-time profiles, we identified the sequences in the fragmented sample biopolymer. On the basis of a reconstruction of the read fragment sequences, we determined some partial sequences in sample biopolymer. Until now, we have applied this single-molecule electrical identification method to chemical species-typing of oligonucleotides and oligopeptide ([1]-[4]).

Based on the determined polymer sequence, we also obtained the molecular behaviors of sample biopolymers around the electrodes. They suggested that these molecular-behaviors would be due to the straight translocations of nucleotide molecules induced by an electrophoretic flow, which could serve to obtain longer right-read signals.

These results suggested that this conductance profiling analysis successfully achieved discrimination for the sample nucleotides, and could be useful for single-molecule electrical biopolymer profiling.

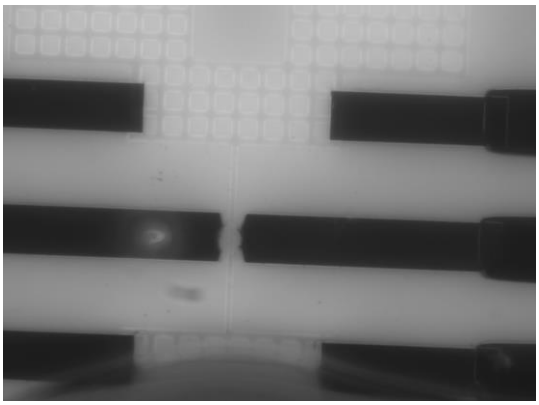

Figure 1 Single-molecule tunnel-current based electrical detection by using a metal-Gap Electrode device. The device of the optical microscope image are shown. The fluid and electrophoretic electrode are integrated on the nano-gap electrodes device.

Reference [1] *Nat.Nanotech.*, 9, 835-840,(2014). [2] *Sci.Rep.,* 2012;2, 501. [3] *J Am Chem Soc.* 2011 Jun 15;133(23):9124-8. [4] Nano Lett 2008, 8 (1), 345-349.