Detection of base-pair mismatch in DNA via graphene nanopores

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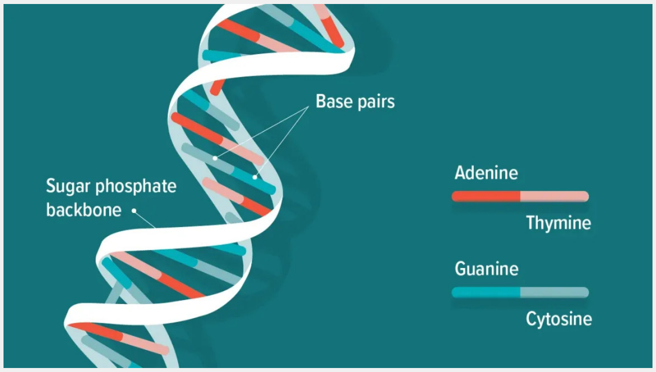
The advent of artificial intelligence (AI) is altering paradigms faster than ever. In hindsight, the 2024 Nobel Prizes in Physics and Chemistry were a recognition of this remarkable phase of human endeavour. This essay attempts to acquaint the general reader to underpinning developments that has led to such a surge. Creative harnesses that facilitated the Nobel recognitions are invoked, along with emergent opportunities and subtle caveats.



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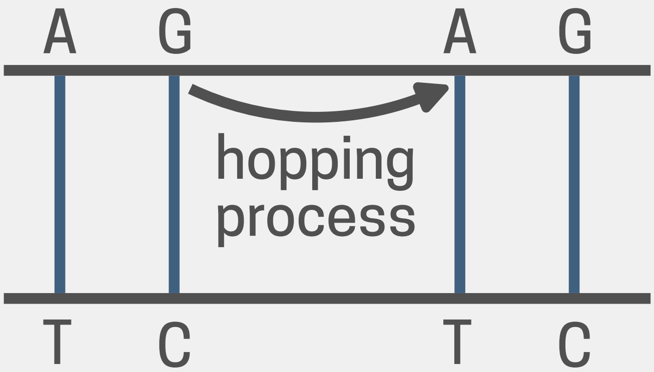

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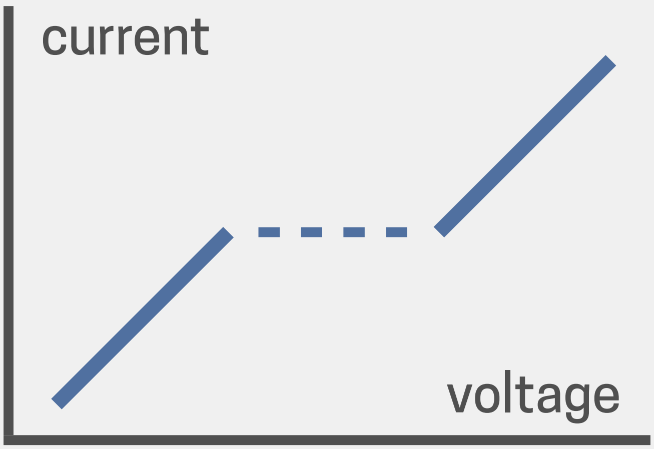
The field of quantum transport in DNA begins with a fundamental question: "Is DNA a metal, insulator, or semiconductor ?" For the first time in 1961, D.D. Eley, in his paper [4] , studied the current-conducting ability of Penicillium DNA under a certain voltage and he observed a very small departure from Ohm's law. Eley took the first initiative, paving the way for an entirely new and intriguing area of research, which is now referred to as DNA Nanotechnology.

DNA, the basic building block of life, is composed of four nitrogenous bases (A, T, G and C), forming a double helix with complementary base pairing (A-T, G-C). The two nitrogen bases of a given pair are connected via a hydrogen bond, whereas different bases are connected via covalent bonds that form the two rungs of the double-helix. The sequence of the different bases along the rungs is vital, as it controls different biological processes, e.g., DNA replication, transcription, and protein synthesis in living organisms. When a base pair mismatch occurs during DNA replication, it can lead to faulty protein production, which may result in genetic diseases and cancer. [6]

In 1998, at Delft University of Technology, Cees Dekker and his team conducted a groundbreaking experimental [3] measurement of DNA conductivity. They used double-stranded poly(G)-poly(C) DNA, which is 10.4 nm long and consists of 30 base pairs, placed between platinum-coated electrodes at room temperature. The uniqueness of the experiment lies in the simplicity of both the method used and the idea implemented, as well as the high precision of the results obtained . It was observed that below a certain threshold voltage, the DNA behaved as an insulator, conducting very little current .The I-V response curve revealed non linear behavior, indicating the presence of a bandgap. Interest in this field surged around 2000, marking a significant milestone in bioelectronics.

The theoretical exploration of suitable charge conduction mechanisms through DNA began following these experimental works. Researchers have attempted to understand the underlying physics using methods such as Density Functional Theory or the computationally modest tight-binding model Hamiltonian approach.The most commonly used model is the Dangling Backbone Ladder Model, which represents DNA as a traditional ladder with backbones attached to the outer sides . The Hamiltonian for DNA includes hopping terms along the rungs of the double-helix, following the covalent bonds. "Hopping" refers to the movement of electrons to their nearest neighbors, representing the kinetic energy terms. Experiments revealed that current flows through the **π**-stacked bases along the rungs of the double-helix.



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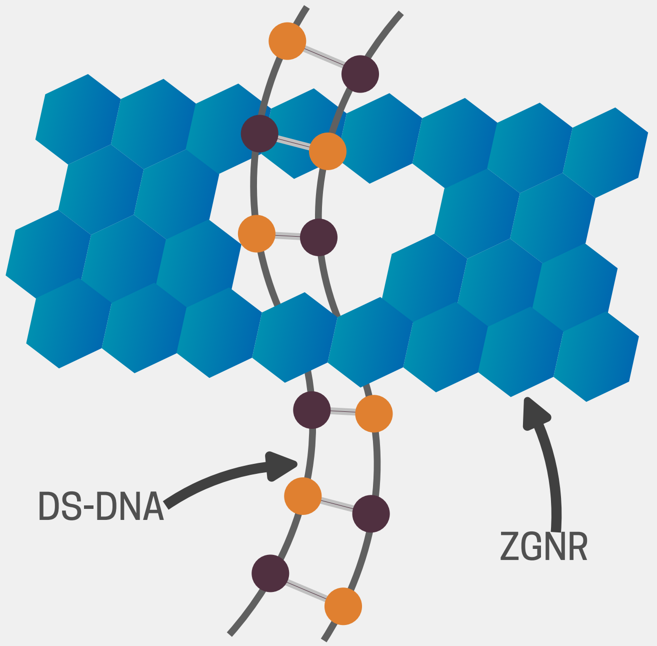

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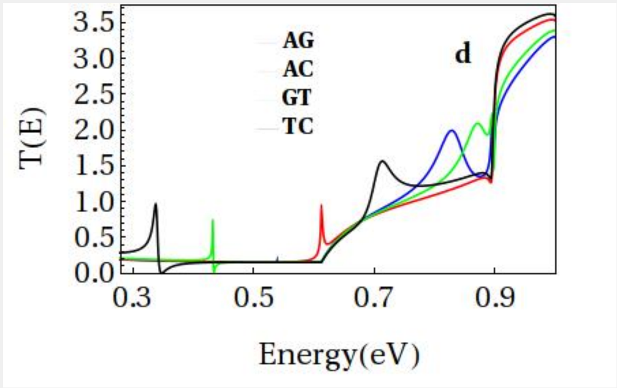
Sourav and coworkers [1] expanded on the ladder model to mimic double-stranded DNA, aiming to detect base-pair mismatches by incorporating both nearest-neighbor and inter-layer hopping between the nitrogen bases of the two helices in their analysis.

They examined changes in local density of states, conductivity and I-V characteristics by inserting a ds-DNA chain into a graphene nanopore. The traditional technique for the DNA sequencing is the Sanger [5] method, which uses chain-terminating dideoxynucleotides to determine the sequence of a DNA strand. However, its main drawback is that it is a time-consuming process, and sequencing an entire human genome using this method costs around 1,000 USD.The advantage of using graphene nanopores is that it is a unique and more cost-effective technique for DNA sequencing.Their study explores techniques for detecting DNA base-pair mismatches through conductance and I-V response analysis, which revealed distinct patterns.

They successfully identified unique signatures related to base-pair mismatches that can lead to different genetic diseases, offering significant potential to early detection genetic disorder and medical diagnostics. This work could lead to the development of a fast and cost-effective DNA sequencing device.



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Prof. Sengupta is a strong proponent of interdisciplinary and collaborative research. Her group at IISER Kolkata (mCED) probes molecular machinations of diverse biological systems with physics and data based methods.