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Methylation effect on the ohmic resistance of a poly-GC DNA-like chain

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ABSTRACT

We determine, by using a tight-binding model Hamiltonian, the characteristic current–voltage (IxV) curves of a 5-methylated cytosine single strand poly-GC DNA-like finite segment, considering the methyl groups attached laterally to a random fraction of the cytosine basis. Striking, we found that the methylation significantly impacts the ohmic resistance (R) of the DNA-like segments, indicating that measurements of R can be used as a biosensor tool to probe the presence of anomalous methylation.

1. Introduction

Theoretical and experimental investigations of the electronic and optical properties of biological self-assembled systems have attracted a great interest in recent years (for reviews see Refs. [1–3]). In general, within the context of molecular electronics, they present a wide range of different effects induced by the electric fields due to the unusual quality and quantity of their electric parameters, as well as a consequence of their chemical modifications. [4,5].

As a bold example, the nucleic acids (DNA and RNA) and the proteins are not only biologically important polymers but also basic functional materials, surpassing the conventional one in many aspects due to its unique transport properties [6,7]. However, the possible manipulation of these biopolymers via their charge transport between two conducting electrodes is still a challenge open problem, with several possible applications in the field of nanoelectronic devices (for a review see Ref. [8]).

From the experimental point of view, some previous works have addressed the charge flow in DNA segments, unveiling important issues regarding their electrical conductivity [9–13]. On the other hand, theoretical investigations of the charge transport in DNA are being made by using a quantum formalism based on a single electron tight-binding Hamiltonian exploring its distinct aspects [14–18]. Focusing on the DNA case, the model consider Watson–Crick pairs attached to the sugar-phosphate backbone condensed into a single nucleotide site. Although it was successful employed to describe numerous experimental data [8], it has some critical assessment [19]. A relevant consideration is the topology of the double-helix, which is not a rigid object, with the different constituents of DNA moving relative to each other presenting linear deformations of its structure in response to the charge arrival at this particular site (polaronic effects) [20].

In general lines, the DNA Hamiltonian is constructed by assuming that the transmission channels are along their longitudinal axis, consisting of a π-stacked array of DNA nucleobases formed by a symbolic sequence of a four letters alphabet, namely guanine (G), adenine (A), cytosine (C) and thymine (T) [21,22]. It is important to emphasize that under this formalism, the effective model of real DNA segments corresponds to a low-dimensional disordered structure. Therefore, the electronic eigenstates become localized due to the scattering by the intrinsic disorder (Anderson localization), resulting in an insulator-like behavior [23].

Several mechanisms have been considered to provide a good understanding of the electronic transport properties of the DNA molecule, some of them related to the internal DNA correlations [24,25]. For instance, the presence of long-range correlations within the disorder distribution can promote electronic delocalization [26]. However, an instructive debate within the literature

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suggests that the type of correlations present in real DNA segments is not strong enough to play a major role in their electronic transport. Besides, disorder effects in synthetic DNA-segments can be minimized, opening up the way to tailor the electronic properties required to operate distinct device functions [27,28].

The focus of this work is on the investigation of the electronic charge transport properties in a poly-GC DNA segment. Specifically, we are interested to identify an electrical signature due to the presence of methyl groups randomly connected to the cytosine nucleobases in this structure, the so-called 5-methylcytosine, a well-studied epigenetic pathway implicated in gene expression control and disease pathogenesis. Usually, the 5-methylcytosine-based DNA methylation occurs through the covalent addition of a methyl group at the 5-carbon of the cytosine heterocyclic aromatic ring by an enzyme called DNA methyltransferase, a very important repressor of transcription in the human genome which contains over 60% repetitive DNA, much of which being transposable sequences of viral origin that are kept inactive in part by DNA methylation [29,30]. Unfortunately, a growing number of human diseases have been found to be associated with aberrant DNA methylation, leading to new and fundamental insights about the roles played by DNA methylation and other epigenetic modifications on the human genome in the form of epigenetic marks that are heritable during cell division but do not alter the DNA sequence [31].

One of the most complex and challenging question is how to detect small methylation fractions along DNA segments. Considering that, we set up here a quantum Hamiltonian approach to describe electronically a finite poly-GC segment with a variable methylation fraction p and nearest-neighbor hopping terms, to numerically compute its density of states, electronic transmittance profiles, and the current–voltage (IxV) characteristic curves, looking for a kind of signature that can be useful for the development of nanodevices as diagnostics tools for methylation-related diseases.

2. Theoretical model

Our theoretical model consists of a quantum one-dimensional tight-binding Hamiltonian describing a methylated single-strand poly-GC DNA sandwiched between two metallic electrodes, namely:

$$H = \sum_n \epsilon_n |n><n| + \sum_{(n,m)} t_{n,m}(|n><m| + c.c) + H_L + H_R. \quad (1)$$

Here, ϵ_n represents the on-site energy related to the poly-GC segment, (n,m) represents a sum over nearest-neighbor sites, and $t_{n,m}$ is the hopping term between the poly-GC DNA basis. Also H_L and H_R mean the quantum Hamiltonian describing the left and right metallic electrodes, respectively. Following [32], we will consider these electrodes as metallic systems whose Hamiltonians have diagonal ionization energy term $\epsilon_E = 5.36$ eV and non-diagonal internal hopping $t_E = 12$ eV. The coupling between the methylated single-strand poly-GC DNA and the semi-infinite metallic electrodes is measured by a hopping amplitude $t_{EP} = 0.63$ eV. The on-site distribution of the poly-GC segment is, from the theoretical point of view, an alternate sequence of cytosine (C) and guanine (G) basis, whose ionization energies (hopping amplitudes) are $\epsilon_C = 8.87$ eV and $\epsilon_G = 7.75$ eV ($t_{CG} = 0.282$ eV and $t_{GC} = 0.144$ eV). The 5-methylcytosine-based DNA methylation, taking into account the attachment of methyl groups in the 5-carbon of a random fraction p of the cytosine basis, is characterized by an ionization energy (hopping term) $\epsilon_M = 7.02$ eV ($t_{MG} = 0.145$ eV and $t_{GM} = 0.210$ eV).

Having defined the Hamiltonian model, we now briefly describe the methodology employed to investigate the electronic transport in a finite methylated synthetic poly-GC DNA segment with N basis, starting from the calculation of the electronic density of states of long segments (DOS) by using the Dean's method [33]. To do that, we solve the secular equation $\det(H_{GC} - EI) = 0$, where E is the eigenvalue, I is the identity operator, and H_{GC} is the Hamiltonian of the methylated poly-GC DNA segment, i.e., the Hamiltonian of eq. (1) without the electrodes terms.

Defining a polynomial $g_m(E)$ (with $m = 1, ..., N$, N being the number of nucleobases), such that $g_N(E) = \det(H_{GC} - EI)$, the use of the co-factors method yields $h_m(E) = E - \epsilon_M - t_{MG}^2/h_{m-1}$, where $h_m = g_m(E)/g_{m-1}(E)$. The integrated density of states ($IDOS$) then follows by taking into account the signal changes in the set of the h_m functions. Furthermore, the density of states (DOS) is thus obtained by using a simple direct numerical derivative $DOS = d(IDOS)/dE$.

Due to the random nature of methylation of cytosine sites, the electronic eigenstates become exponentially localized (Anderson localization) on very long single strand DNA's geometry, strongly suppressing its electronic transmission spectrum. However, finite transmission can still be achieved in shorter DNA's segments associated to the presence of resonant states. In what follows, we will explore the electronic transmission spectra by considering a shorter DNA's finite segment with $N = 30$ bases, closer to the realistic size of a DNA primer, which is a short single strand structure that serves as a starting point for the DNA synthesis. For such realistic DNA's segments, the DOS is composed of a sequence of delta-like peaks signaling the eigenstates of the finite Hamiltonian matrix.

The transmission coefficient is computed by considering a plane wave being injected at one of the ends of the methylated poly-GC single strand segment. The transmission coefficient $T_N(E)$, that gives the transmittance spectra through the chain and is related to the Landauer resistance, is then defined by [21]:

$$T_N(E) = (4 - X^2(E))\Big[-X^2(E)(\mathcal{P}_{12}\mathcal{P}_{21} + 1) + X(E)(\mathcal{P}_{11} - \mathcal{P}_{22})(\mathcal{P}_{12} - \mathcal{P}_{21}) + \sum_{i,j=1,2} \mathcal{P}_{ij}^2 + 2\Big]^{-1}, \quad (2)$$

where $X(E) = (E - \epsilon_j)/t_j$, and $\mathcal{P}_{ij}$ are elements of the transfer matrix $\mathcal{P} = M(N+1)M(N-1)\cdots M(2)M(1)M(0)$, with [34]

$$M(j) = \begin{pmatrix} X(E) & -t_{j-1}/t_j \\ 1 & 0 \end{pmatrix}. \quad (3)$$

Here the matrix $M(j)$ is computed using the methylated poly-GC segment. Also, $M(0)$ and $M(N+1)$ represent the local transfer matrix related to the contacts at the ends of the poly-GC DNA model. For a given energy E, $T_N(E)$ measures the level of backscattering events for electrons (or holes) transport through the chain.

The transmission coefficient $T_N(E)$ is a useful quantity to describe the transport efficiency in quantum systems. However, from the experimental point of view, the electronic transport properties are more easily investigated by measuring their current–voltage (IxV) characteristics curves. The theoretical calculation of the IxV curves can be done by applying the Landauer–Büttiker formulation [35,36], i.e.:

$$I(V) = \frac{2e}{h} \int_{-\infty}^{+\infty} T_N(E)[f_L(E) - f_R(E)]dE, \quad (4)$$

where $f_{L(R)}(E)$ is the Fermi–Dirac distribution at the left (right) side of the electrodes, i.e.:

$$f_{L(R)} = \Big[\exp[(E - E_F \mp eV/2)/k_BT] + 1\Big]^{-1}. \quad (5)$$