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Normal and impaired charge transport in biological systems

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ABSTRACT

We examine the physics behind some of the causes (e.g., hole migration and localization that cause incorrect base pairing in DNA) and effects (due to amino acid replacements affecting mitochondrial charge transport) of disease-implicated point mutations, with emphasis on mutations affecting mitochondrial DNA (mtDNA). First we discuss hole transport and localization in DNA, including some of our quantum mechanical modeling results, as they relate to certain mutations in cancer. Next, we give an overview of electron and proton transport in the mitochondrial electron transport chain, and how such transport can become impaired by mutations implicated in neurodegenerative diseases, cancer, and other major illnesses. In particular, we report on our molecular dynamics (MD) studies of a leucine→arginine amino acid replacement in ATP synthase, encoded by the T→G point mutation at locus 8993 of mtDNA. This mutation causes Leigh syndrome, a devastating maternally inherited neuromuscular disorder, and has been found to trigger rapid tumor growth in prostate cancer cell lines. Our MD results suggest, for the first time, that this mutation adversely affects water channels that transport protons to and from the *c*-ring of the rotary motor ATP synthase, thus impairing the ability of the motor to produce ATP. Finally, we discuss possible future research topics for biological physics, such as mitochondrial complex I, a large proton-pumping machine whose physics remains poorly understood.

1. Introduction

Transport of charged particles – electrons, holes, protons, and heavier ions – plays a vital role in living organisms. Studies by our group and others suggest that (1) charge transport and localization, and lower hole energies on guanine, likely cause the observed higher mutation rates at guanine sites in DNA [1]; and (2) biological charge transport can be altered, often adversely in a manner that causes cancer, neurodegenerative disease, or other diseases, by amino acid replacements encoded by certain DNA point mutations, as discussed in the next sections.

2. Charge transport and localization in DNA

DNA is a double helix containing two chains of repeated sugar and phosphate groups, held together by base pairs connected via hydrogen bonds. Under normal circumstances, guanine (G) pairs with cytosine (C) while adenine (A) pairs with thymine (T). However, through a mechanism known as tautomerization [2], a hole localized on guanine (G*) can alter the hydrogen bonds and cause "incorrect" pairing G*:T in the next replication. After additional replications, this will lead to the point mutation G:C→A:T in some of the DNA offspring molecules. Guanine has a lower energy of oxidation (electron removal or hole formation) than other bases. Thus, a hole forming at a nearby site may migrate and become localized at the lower-energy guanine site.

Mitochondria (discussed in the next section) have their own DNA molecules, each of which encodes key proteins within the mitochondrial electron transport chain. Mitochondrial DNA (mtDNA) has fewer repair mechanisms than nuclear DNA and is exposed to potentially damaging reactive oxygen species [3]. Thus mtDNA has a much higher mutation rate than nuclear DNA. Numerous mtDNA mutations have been implicated in cancer [4,5], various neurodegenerative diseases [6], and diseases such as type 2 diabetes and heart disease [7].

For both mitochondrial and nuclear DNA, each amino acid in a protein is encoded by a 3-letter base sequence read from one of the two DNA chains. For example (after transcription to messenger RNA and translation by the ribosome), the DNA sequence TGT encodes the amino acid cysteine, whereas TAT encodes tyrosine. Thus, a G→A mutation in the TGT sequence (T**G**T→T**A**T) in a

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region of coding DNA causes a cysteine→tyrosine amino acid replacement in a protein, possibly affecting the biological machinery. However, some mutations (e.g., CT**C**→CT**T**, where both encode leucine) are silent mutations due to redundancy in the genetic code, and have no effect on the amino acid sequences in the proteins.

We have begun a study, initially focusing on mtDNA, to examine the physics behind some of the causes (e.g., hole migration and localization) and effects (due to amino acid replacements) of disease-implicated point mutations. The first part of this study, discussed here, employs quantum mechanical computations to model hole transport and localization in DNA. We use a simplified two-strand ladder model to represent DNA (Fig. 1), including coupling matrix elements between adjacent bases and incorporating different hole-formation energies of the DNA bases. The Hamiltonian is written as follows:

$$\hat{H} = -\sum_{\langle l,m\rangle\sigma}^{N} \left(t_{lm} c_{l\sigma}^{\dagger} c_{m\sigma} + t_{ml} c_{m\sigma}^{\dagger} c_{l\sigma}\right) + \sum_{l\sigma} \in_l n_{l\sigma} \tag{1}$$

where $c_{m\sigma}$ represents a hole destruction operator on strand m of the double helix with spin projection σ; $\langle l,m\rangle$ represents a nearest-neighbor interaction on the ladder, and t_{lm} is the hopping amplitude between the bases m and l. In our model we use two types of hopping terms, along and perpendicular to the chain, respectively, $t_x = 1.0$ eV and $t_y = 0.5$ eV, as shown in Fig. 1. The last term of the Hamiltonian represents the on-site energies for guanine, *EG*, thymine, *ET*, adenine, *EA*, and cytosine, *EC*. These hole energies are selected using ionization potentials of the respective nucleobases reported in references: $EG = 7.75$ eV, $EC = 8.87$ eV, $ET = 9.14$ eV and $EA = 8.24$ eV. Fig. 1 shows the simple two-dimensional ladder model of DNA.

The Hamiltonian Eq. (1) is represented as a matrix, where the hopping terms and on-site energies are off- and on-diagonal elements, respectively, and we employ periodic boundary conditions. By diagonalizing the Hamiltonian for a segment of mtDNA containing 50 sites along the horizontal axis, we have found the hole probabilities near various cancer-implicated mutation sites [5]. Fig. 2 shows hole probabilities around the locus of a T→C mutation implicated at site 3329 of the coding mtDNA sequence.

Fig. 2 shows computed hole probabilities on and near the 3329 site before the mutation, where the diamonds (green curve) represent a portion of the mtDNA sequence (read in the 5′→3′ direction) that encodes amino acids in the ND1 subunit of complex I. (complex I will be discussed in Section 4.) The circles (red curve) depict hole probabilities for the guanine rich complementary sequence of the H-strand. The cancer-implicated 3329 T→G mutation encodes a leucine-to-proline replacement in subunit ND1 of complex I [5]. The computed amplitudes reveal that hole probabilities are highest at the guanine sites, especially on the H-strand (circles, red curve) whereas the thymine sites have the lowest hole probabilities (and high electron probabilities). Note that, guanine rich regions also increase hole probabilities on nearby bases. Moreover, the rate of charge transfer vs. distance depends

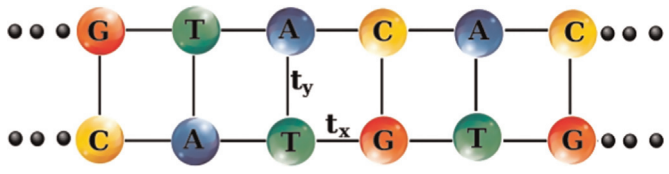

Fig. 1. Model of DNA chain. The DNA chain is represented a two-dimensional, ladder-type lattice. A hole (or electron) can move via hopping amplitudes between two adjacent bases. On-sites energies for thymine, guanine, adenine and cytosine are chosen using reported ionization potentials [8,9].

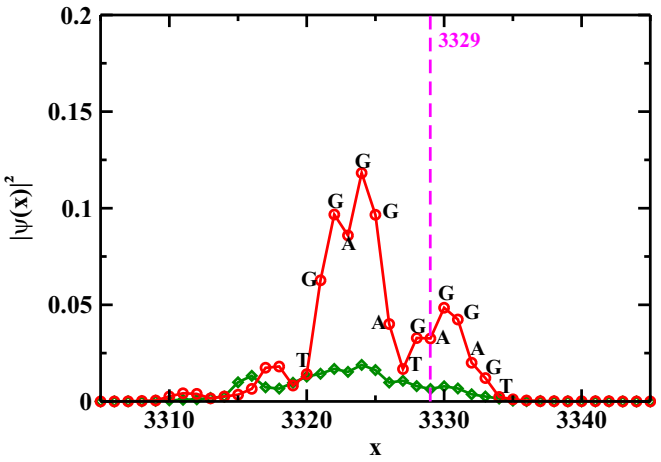

Fig. 2. mtDNA hole probabilities vs. nucleotide position around the cancer-implicated 3329 T→C mutation [5]. The diamonds (bottom curve, green) and circles (top curve, red) represent hole probabilities for the mtDNA L-strand and H-strand, respectively. The L-strand is the coding sequence obtained from MITOMAP. Regions with more guanines have higher hole probabilities, especially prevalent on the guanine-rich H-strand (circles, upper curve, red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

strongly on base-pair sequence, as observed in several experiments [10–12].

One can clearly see how holes tend to localize in regions with more guanine, either on the coding or the complementary DNA strand, potentially leading to tautomerization and a subsequent mutation. At locus 3329 in the (5′→3′) L-strand, the sequence change CT**C**→C**C**C encodes the amino acid replacement leucine-to-proline within a core subunit of complex 1, ND1. This subunit plays a crucial role in extracting energy from donated electrons to pump protons across the mitochondrial inner membrane. The 3329 T→C mutation is found to correlate with ovarian serous cystadenocarcinoma, a cancer that kills many women each year [5].

After a given mutation occurs, the hole probability distributions change. Fig. 3 shows that, in the complementary mtDNA H-strand (circles, red curve), the hole probability at and near locus 3329 increases dramatically after the T→C mutation (causing an A→G base replacement on the complementary strand). Note the greatly increased hole probability (circles, red curve) at the mutated complementary guanine site, where the probability is seen to increase from 0.03 to 0.175. Also note how guanine presence positively influences hole probabilities at adjacent base sites. Finally, it has been found experimentally that charge transfer rates increase significantly when **A:T** base pairs are replaced with **G:C** pairs [10–12].

By far the most common (about 60% of the total) cancer-implicated mtDNA mutations are G→A base replacements, as pointed out by Larman et al. [5]. An example of such a mutation is at the guanine site 3778. Before the mutation, the energy corresponds to the lower ionization energy for guanine. A hole thus has a higher probability of being found on or near this site, as shown in Fig. 4. Again, the diamonds (green curve) represent the coding (primary, L-strand) 5′ to 3′ mtDNA strand, while the circles (red curve) depict hole probabilities for the complementary (3′→5′) H-strand.

The change of base sequence due to the 3778 mtDNA mutation, **G**GC→**A**GC, encodes the replacement of glycine with serine, an amino acid with a polar side chain, at position 158 of subunit ND1 in complex I. This mutation has been found to correlate with colon adenocarcinoma [5]. Colon cancer is the second leading cause of cancer fatalities, after lung cancer.