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Computational Study of Deoxyribonucleic Acid (DNA) Methylation and Orbital Interaction, Band Gap and Binding Energies Associated with the Process

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Abbreviations: DNA: Deoxyribonucleic Acid; cDMRs: DNA-Methylated Regions; 5-mC: 5-Methylcytosine; cDMRs: Cancer-Specific Differentially DNA-Methylated Regions; DNMT: *De Novo* Methyltransferase; PBE: Perdew Burke-Ernzerhof; GGA: Generalized Gradient Approximation; TS: Tkatchenko-Scheffler

Abstract

DNA encodes genetic instructions relevant to the development and functioning of living organisms and viruses. One of the primary regulators of gene transcription is DNA methylation. DNA methylation occurs at specific sites in DNA, referred to as genetic hot spots or CpG islands. However, aberrant DNA methylation patterns such as hypermethylation and hypomethylation have been recognized in variety of human malignancies. As a result, the process has become one of the most thoroughly investigated epigenetic modifications in mammals. Experimental evidence shows cancer-specific differential DNA-methylated regions correspond to the loss of sharply defined methylation boundaries at CpG islands. Developing effective cancer therapeutic requires a proper understanding of gene silencing and gene expression associated with methylation and demethylation. However, the relevance of methylation or demethylation to cancer is far from being well explained. As an approach, dispersion-corrected density-functional calculations were used to study the Interactions between nucleic acids and graphene. The constructed double-strand DNA sequences with different percentages of methylation show that the increasing methyl concentration decreases the binding energy and increases the average distance between the strands. Consequently, normal regulation of gene can be disrupted. Energy gap between filled and empty orbital in the methylated double strand DNA increases with increasing concentration of methyl group in the DNA. Results indicate that abnormal DNA methylation is affecting the electronic structure of the DNA and hence effecting the proper bio functioning of vertebrates.

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Introduction

DNA carries the genetic instructions relevant to the development and functioning of living organisms and viruses. According to the base pairing rule (Arginine (A) with Thiamine (T) and Cytosine (C) with Guanine (G)), hydrogen bonds bind nitrogenous bases of two polynucleotide strands into double-stranded DNA. Modified by covalent attachment of methyl groups to cytosine (Figure 1), DNA methylation is a primary regulator of gene transcription [1].

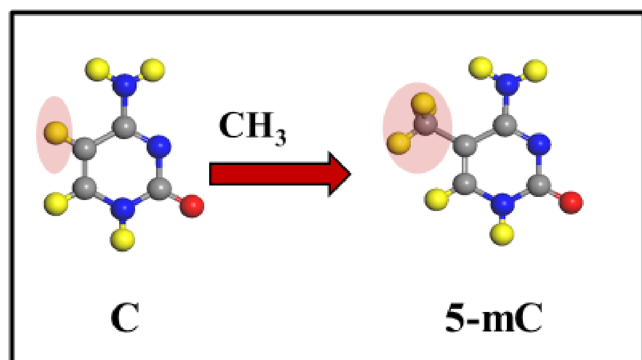

Figure 1: Ball and stick representation of methylation of Cytosine (C) to 5-Methylcytosine (5mC). Carbon, hydrogen, nitrogen and oxygen atoms are represented by gray, yellow, blue and red respectively.

As an important factor in human epigenetics, altered DNA methylation is common in a variety of tumors and has also been associated with aging. The fifth base 5-Methylcytosine (5-mC) has generated much interest and considerable controversy during attempts to understand its significance. A wealth of evidence has shown that genes with high levels of 5-mC in their promoter region are transcriptionally silent. DNA methylation continuously accumulates upon long-term gene silencing. Aberrant DNA methylation patterns, like hypermethylation and hypomethylation, compared to healthy tissue have been associated with a variety of human malignancies. Global hypomethylation has been recognized in the development and progression of cancer [1-8].

Recent experimental studies show that cancer-specific differentially DNA-Methylated Regions (cDMRs) are correlated to loss of sharply defined methylation boundaries at CpG islands (C and G repetitive sequence areas) [9]. The hot spots in DNA contain (CGCG) repeated sequence of cytosine and guanine dinucleotide. In vertebrates, a methyl group is attached to the fifth carbon atom of the cyclic ring in cytosine, resulting in 5-methyl cytosine. Processes of methylation and demethylation are driven by *De Novo* Methyltransferase (DNMT) enzyme (Figure 2). The enzyme methylates both strands of the CpG island in the double-strand DNA, resulting in a homomethylated DNA. Replication of the homomethylated DNA produces hemimethylated DNA in which one strand of the DNA remains methylated while the other strand is unmethylated.

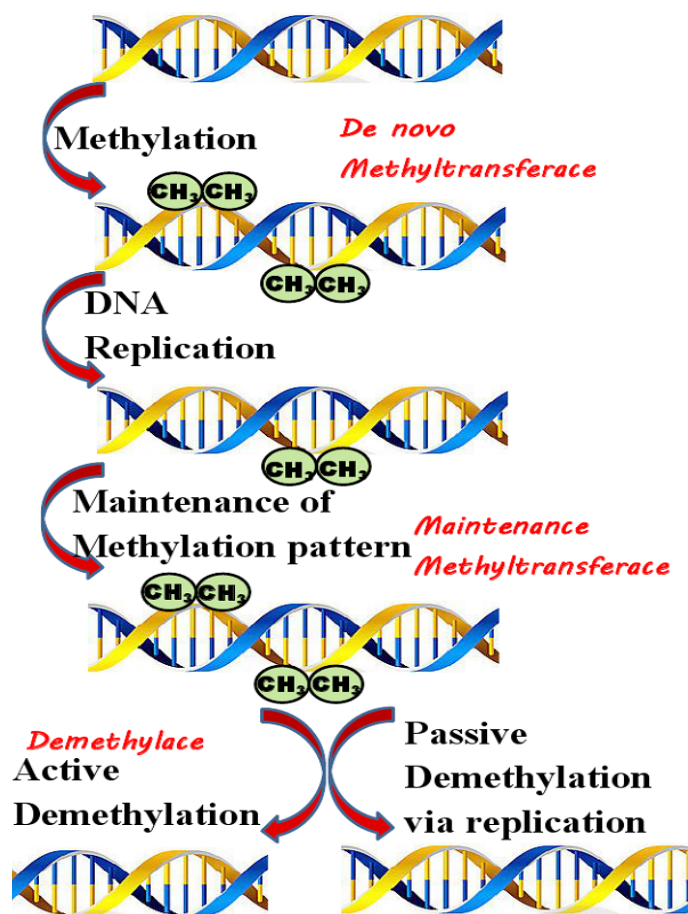

Figure 2: Enzymes and reactions involved in the establishment of DNA methylation patterns.

Hemimethylated DNA transforms to homomethylated one by maintenance-methyltransferases-enzyme. Maintenance-methyltransferase activity handles the methylation of synthesized DNA strands based on the template of a single parent strand. Maintenance methyltransferase activity recognizes the hemimethylated pattern of the parent strand and then faithfully reproduces the pattern on the daughter strand, allowing for the process to be heritable after DNA replication and cell division. One of the DNA methyltransferases, DNMT1, was shown to have both *de novo* methylation and maintenance. Other potent de-novo methyltransferases are *De Novo* Methyltransferase 3A (DNMT3A) and 3B (DNMT3B). On the other hand, DNA demethylation can occur passively by several rounds of replication in the absence of maintenance-methyltransferase. As epigenetic changes are relevant to aging and cancer, identifying and interpreting epigenetic changes associated with such phenotypes (aging and cancer) may benefit from integration with protein interactome models [10]. The model considers a whole set of protein-protein and molecular interaction network in a specific cell [10]. In essence, two genetic models correlate DNA methylation and cancer. One describes the amplification of the proto-oncogenes that handle cell growth and proliferation. The other characterizes silencing of tumor suppressor genes. Both models take the disruption of normally controlled cell proliferation balance into account. Interruption of proliferation control directs the tissue into malignant status.

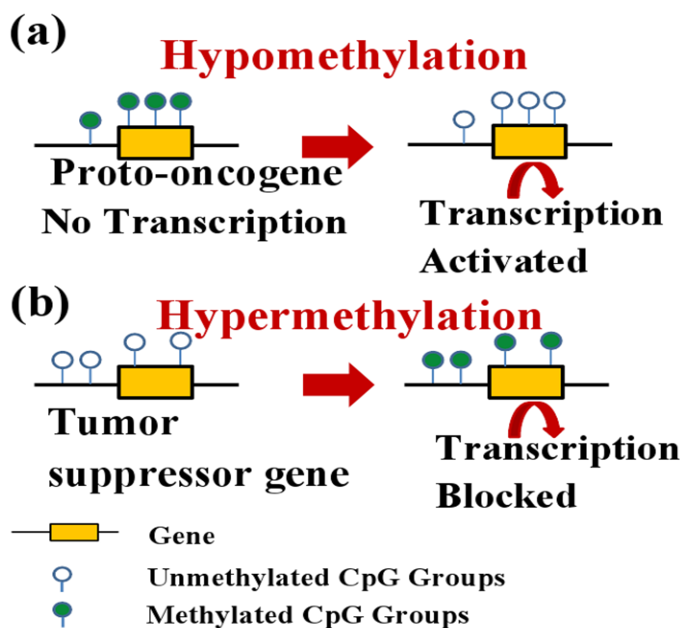

Figure 3: Mechanism of carcinogenesis induced by methylation events. (a) Activation of silent proto-oncogenes after hypomethylation. (b) Silencing of tumor suppressor genes after methylation of gene promoter region.

Demethylation is connected to the relief of transcriptional silencing, which may reactivate the expression of quiescent proto-oncogenes and induce the cell proliferation events (Figure 3). Alternatively, methylation in the promoter regions of a tumor suppressor gene can lead to the silence of the transcription and the gene fail to suppress proliferation of the cell that drives the cell into malignant status [11].

Biologically, 5-methylcytosine in CpG islands of the genome is involved in cellular phenomena, most notably in cancer. Most of those cellular aspects are attributed to the interaction of specific proteins with the methylated DNA. This specific protein-DNA binding makes the DNA inaccessible. The proteins can bind to DNA sequences and disturb the gene regulation [12-16].

A wide range of genes silenced by DNA methylation is found in various types of cancer cells. Global hypomethylation of genes, which induces genomic instability and contributes to cell transformation, has been found to be abundant in cancer cells.

There is no doubt that understanding fundamental properties of DNA methylation is of critical importance. As a result, this project is focus on a computational study on the electronic properties and their variation in DNA methylation.

The structure and electronic properties of the double strand DNA and each nucleotide were investigated using dispersion-corrected first-principles density-functional calculations we used the Perdew Burke-Ernzerhof (PBE) parameterization of the Generalized Gradient Approximation (GGA) [17,18]. The General-Gradient-Approximation (GGA) results were subsequently rectified through the inclusion of dispersion correction. Tkatchenko-Scheffler (TS) dispersion correction accounts for the relative variation in dispersion coefficients of differently bonded atoms by weighting values taken from the high-quality ab-initio database with atomic volumes derived from partitioning the self-consistent electronic density. The inclusion of dispersion-corrections is essential to correctly describe the non-covalent interactions between molecules.

Results and discussion

As an approach to studying the interaction between proteins and the methylated DNA, we have analyzed the interaction between nucleic acids and graphene [19]. Since graphene and protein both have π orbital which can interact with molecules, graphene is used as an effective model for the protein. Nucleic acids have been shown to assume a planar orientation on graphene due to the influence π–π interactions (33). The phosphate-sugar backbone attached to the nucleotide bases is highly polar. The high polarity of the backbone can perturb the structural attachment of single strand DNA and double strand DNA to graphene. Base-oriented conformations tightly bind to graphene, in comparison to the phosphate-oriented end.

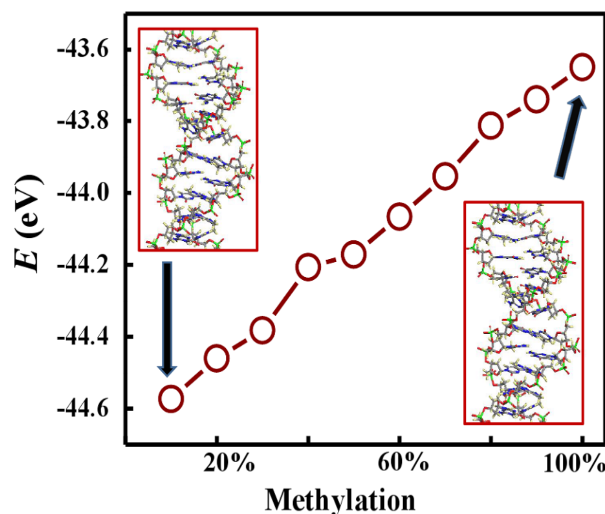

Figure 4: Binding energy E per atom for double strand DNA with different methyl concentrations. Inserts: the optimized structures of 10% methylated and hypermethylated double-strand DNA.

Several structures of double strand DNA were constructed with different methylation concentrations from 0% to 100% methylations on them. The structures were geometrically optimized by using PBE parameterization and GGA approximation. The geometrically optimized structures showed in Figure 4 inserts. The constructed double-strand DNA sequences contain only C and G in the double strands for simplicity. CpG islands are the localities where methyl groups are attached to cytosines. The constructed structures vary from an unmethylated DNA (0% or hypomethylated), to 10% methylated DNA, and to 20-100% (hypermethylated) DNAs. Figure 4 shows the binding Energy (E) per atom, along with the optimized unmethylated and methylated DNA conformations. Increasing methyl concentration decreases the binding energy. The average distance between the strands were increase between the strands. Both of these observations are evidence for the weaker interaction between the strands. Consequently, normal regulation of gene can be disrupted by weaker inter molecular interaction (hydrogen bonding) and lower binding energies between the strands. This will effect on proper bio functioning and epigenetic mechanism in vertebrates.

Figure 5 shows that the gap between Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) increases with increasing concentration of methyl group in the DNA. In addition, there is a significant temperature effect on the energy gap between HOMO and LUMO. HOMO and LUMO interactions are important for excitations relevant to biological functions.

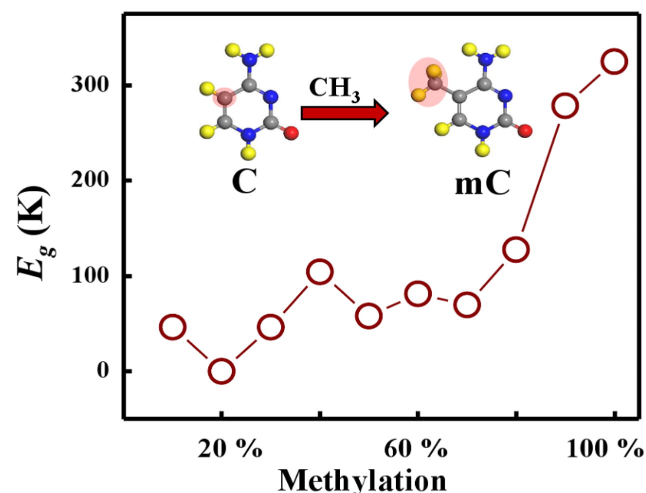

Figure 5: Binding energy E per atom for double strand DNA with different methyl concentrations. Inserts: The optimized structures of 10% methylated and hypermethylated double-strand DNA.

In addition to increasing energy gap between HOMO and LUMO, there is a significant temperature effect on the energy gap. Energy gap between HOMO and LUMO will effect on the electronic properties of the molecules. Unusual electronic properties and orbital interactions are important for excitations relevant to biological functions. When the gap between empty and filled orbitals is increased, the excitation responsible for gene expression is interrupted. Methylation patterns affect the alignment of the overall gap structure. The interrupted excitations may prevent the expression of the gene and result in gene silencing.

Conclusion

By the close analysis of the results, it is evident that the methylation patterns affect the alignment of the overall energy gap between the heist occupied molecular orbital and the lowest unoccupied molecular orbital of the structure. The interrupted excitations may prevent the expression of the gene and result in gene silencing. Weaker binding between the strands and increasing distance between DNA strands can affect the normal functioning of genes. In contrast, demethylated and methylated patterns with sharp boundaries will help proper gene regulation. . As a result, the proper bio-functioning and epigenetic mechanism in vertebrates will be interrupted.

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