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Hydrogen Bonds and Stacking Interactions on the DNA Structure: A Topological View of Quantum Computing

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1. Introduction

Throughout these centuries, the origin of life is an intriguing question that still remains unanswerable (Nadeau & Subramaniam, 2011). Moreover, the growth and evolution of each living species in nature is governed by a life code, an acronym widely famous as DNA that means deoxyribonucleic acid (Rittscher, 2010). With a function of organic acid, the great DNA action consists into the organization and regulation of the genetic informations, which are simply so-called as genes (Gräslund *et al*, 2010). Thus, due to the immensity of genes to be taken into account, the DNA composition transformed it into a large olygomer formed by nucleotide subunits (Jung & Marx, 2005), and therefore DNA is considered one of the largest macromolecules ever known. Within the cellular environment, the DNA is organized into some very long structures so-named chromosomes, which are duplicated through the cell division process.

In the view of the recent history, however, in fact DNA is considered the cornerstone of the biological science, and therefore the appealing to investigate its structure was always an exciting task. Briefly, in 1868 the physicist Miescher (Dahm, 2008) has proposed the first DNA evidences. After that, precisely in 1878, the nucleic acid was isolated as primary nucleobases by Kossel (Jones, 1953). However, only in the beginning of the last century that these nucleobases were understood as being formed by phosphate groups linked by ester bonds of the 2-deoxyribose (see Fig. 1). Some time later, the discovering of the X-ray diffraction by Röntgen (Frankel, 1996) has aided Astbury (Astbury, 1947) to conclude that DNA had a regular structure. Furthermore, it was by the X-ray diffraction studies of Franklin and Gosling (Franklin & Gosling, 1953), in 1952, that Watson and Crick (Watson & Crick, 1953) informed the most modern structure of DNA as a double-helix form (Watson, 1980).

The DNA double-helix is stabilized by means of hydrogen bonds between nucleotides as well as stacking interactions among the aromatic nucleobases widely known as adenine (A),
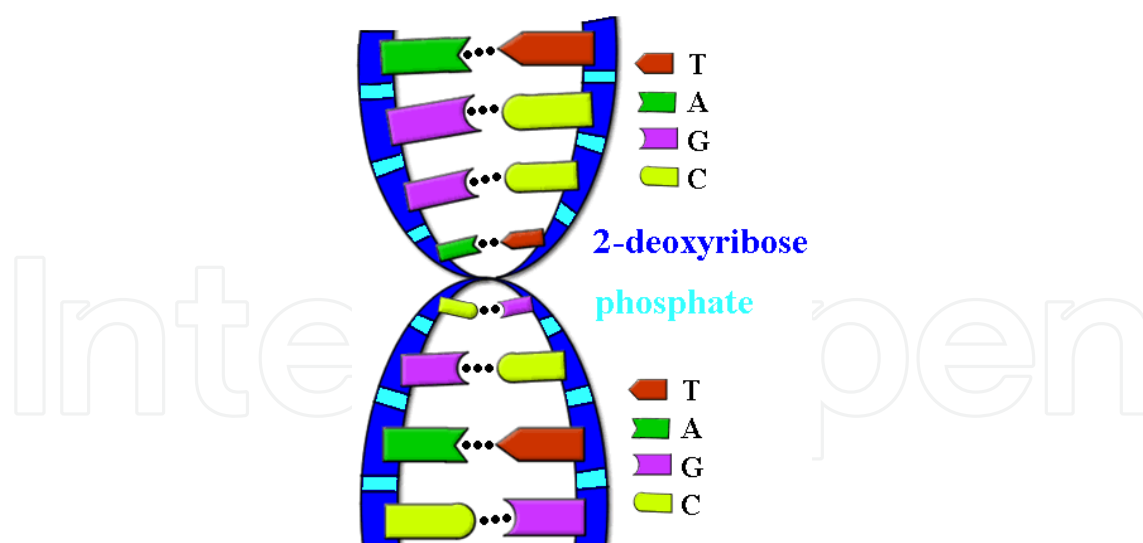
Fig. 1. Representation of the DNA structure.

cytosine (C), guanine (G) and thymine (T), which are tied to ester/phospate. In this context, it is widely established that these two types of base pairs form different hydrogen bonds. In other words, A and T form two hydrogen bonds N–H···O and N···H–N, whereas G and C form three hydrogen bonds O···H–N, N–H···N, and N–H···O, as can be seen in the Fig. 2. On the other hand, the stability of the DNA is also ruled by the interactions formed by G and C, which are recognized as intra-strand base type of stacking.
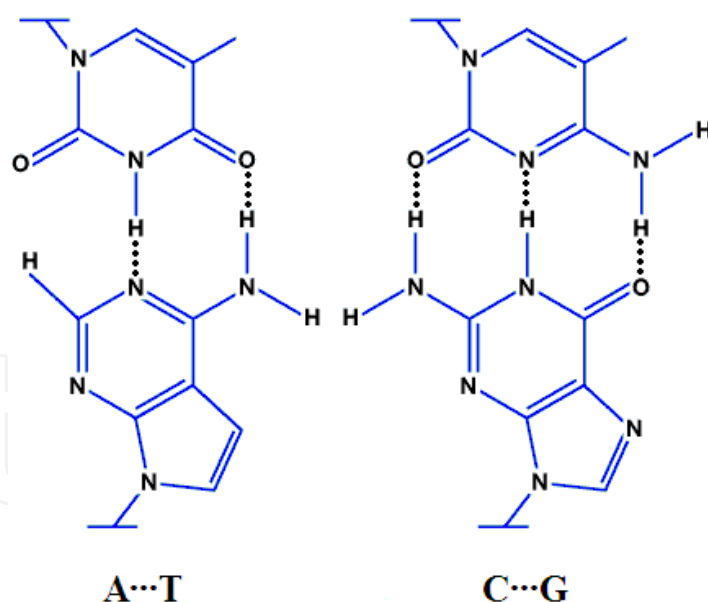

Fig. 2. Illustration of the hydrogen bonds between nucleotides.

The biological science is well-known as one of the most interdisciplinary areas due to the large number of molecular processes occurring simultaneously within the living organisms (Cech & Rubin, 2004), in particular those related to the DNA functionality. Until nowadays, however, the discovery of the DNA structure is seen as one of the most important scientific conquests of all time. It was by this bioscientific scenery that an immense variety of contexts were grouped to congregate one unique idea: molecular recognition and its biochemical

functionality (Iqbal *et al*, 2000; Laskowski, 1996). According to Hitaro (Hitaro, 2002), the biological understanding is closely related to the examination of structure and dynamics of the cellular functions in a cooperative way, not in isolated parts of the own organism. In corroborating to this, as a guide Stahl et al (Stahl et al, 2010) affirm that the molecular recognition is stated whether an attractive interaction provoked by the approaching of two molecules, which possess at least a slight difference of electronegativity between them. So, we would like to emphasize that a careful attention to the knowledge about the profile of the interaction types seems to be necessary.

Some time ago, a historical review signed by Martin and Derewenda put in proof a ransom of the concepts related to the hydrogen bonding (Martin & Derewenda, 1999). It was quoted some important researchers in this regard, such as Linski, Orgel, Nernst, Werner, and finally Lewis, that is considered one of the pioneers of the contemporary chemistry at work with systems formed via hydrogen bonds. However, Latimer and Rodebush have published the first report about hydrogen bond investigations in aqueous medium. Well, Astbury suggested a structure to the alfa-queratine caused by interactions of the NH and CO groups on the peptide bonds. Pauling and Mirsky revisited the protein structure and emphasized that peptide bonds were formed through the hydrogen bonds between the oxygen and peptide nitrogen. In meanwhile, Huggins has carefully analyzed the results reported by Astbury (Astbury, 1947), and noted that the amide hydrogen to behave out of the plane unless molecular resonance effects were enhanced, so that the single pair of electrons of nitrogen was also in the peptide chain.

Nevertheless, the theory cyclol of proteins in the peptide chain advocated by Wrinch have the form $-C(OH)\cdots N$ instead of $-(CO)\cdots(NH)-$, as it was known. In theory, no classical hydrogen bond could be formed. Thus, Pauling was quick to recognize the flaws in your publishing model in July 1939, in which he emphasized the planarity of the peptide bond. Pauling published his article weeks before the Nazis invaded Poland on September 1. However, the same year Pauling also released his classic book '*The Nature of the Chemical Bond*', who was one of the leading spokesmen for the dissemination and development of the history of chemical bond and hydrogen bond, so far. After several years of insights and discussions, Pauling affirmed in its theories that hydrogen bonds $(Y\cdots H)$ are formed by electronegative differences between proton donors (H) and their acceptor ones (Y), as already mentioned (Pauling, 1939). However, Pimentel and McClellan did not agree with this electronegative criterion, and they stated that hydrogen bonds can exist if the hydrogen is bound to any other atom (Pimentel & McClellan, 1960). Some years later, theoreticians established some physical conditions in order to unveil the nature of the hydrogen bond. For instance, when the electrostatic attractive is the dominant phenomenon undoubtedly the intermolecular system is stabilized by means of hydrogen bonds (Umeyama & Morokuma, 1977). In opposition to this, van der Waals systems are widely known as weakly bound because the London dispersion forces are the main contributions (Cukras & Sadlej, 2008).

Traditionally, besides oxygen, but fluorine and nitrogen are the most known proton acceptors in systems stabilized at light of the $H\cdots F$ and $H\cdots N$ hydrogen bonds. However, the proton character is a quite accepted parameter, and thereby, the hydrogen bond model leads to $X-H^{+\delta}\cdots Y^{-\delta}$. It can be perceived a charge separation interpreted as charge transference between HOMO and LUMO orbitals of the proton donor and acceptor,

respectively. With this in mind, it was established that other proton acceptor types can be useful, such as the unsaturated hydrocarbon centers, by which the X–H$^{+\delta}\cdots\pi^{-\delta}$ hydrogen bonds emerged with great evidence. In this scenery, it become stated that a single element is not answerable for the formation of the hydrogen bond, but ideally the cornerstone of this interaction is site with high electronic density, which at this time is assumed as formed by electronegative elements or unsaturated bonds. The magnificence of the π centers becomes reliable upon the formation of the $\pi^{-\delta}\cdots\pi^{-\delta}$ sandwich stacking, whose profile is known as one of the weakest interaction with strength in range of 1-3 kcal/mol, being considered then as London's dispersion forces beyond the van der Waals contacts often devoted to weak hydrogen bonds.

The interpretation and forward comprehension of all kind of events and phenomena inherent to the DNA environment is not an easy task (Šponer *et al*, 2001-2002), but in recent years the applicability of the chemical methods, physical theories and spectroscopy analyses have been decisive in accurate investigations of the biological systems (Shogren-Knaak *et al*, 2001). On the other hand, this has yielded intense debates among the expert theoreticians, and a lot of computational approaches have been implemented with the purpose to decompose the total energy into the following terms: electrostatic, dispersion, charge transfer, polarizability, and exchange potential (Umeyama & Morokuma, 1977). Surely, other interaction types also occur, such as dihydrogen bonds, halogen bonds or stacking, but in practice the most important is the availability of appropriated methodologies to the examination of all properties of these interactions. In general, this requirement is displayed on the basis of theoretical calculations, such as those from *ab initio*, semi-empirical or DFT nature, where all of them are always implemented to seek and find the deeper potential energy surface.

On the other hand, a long time the scientific community would felt a necessity of a theoretical method by which the chemical bond content could be elucidated in its essence. Indeed, this theoretical method has emerged 40 years ago due to an insight of Bader based in catching information computed directly from the electronic density. Baptized as Quantum Theory of Atoms in Molecules (QTAIM) (Bader, 1990), this method models all points of molecular surface through the integration of the electronic density by taking into account the formalism of quantum mechanics for subspace. Thus, the principle adopted by Bader was purely based in quantum mechanics, but with the purpose to describe the atomic behaviour within the molecular environment. By revisiting the trajectory of the QTAIM development, Bader simply took into account the atomistic cooperative activity, by which atoms were defined in a molecule as open systems able to exchange charge and momentum with their neighbours.

The QTAIM benchmark is treat confined systems by means of boundary conditions, in which the molecular or atomic surfaces and their shapes are enable to transfer momentum.

$$\nabla\rho(r).n(r) = 0 \text{ for all points on surface } S(\Omega) \tag{1}$$

In a recent chapter, Bader (Bader, 2009) has discussed that proper open system are defined by equation of motion for an observable Ĝ as follows:

$$\left(\frac{N}{2}\right)\left\{(i/\hbar)\int \psi^*[\hat{H},\hat{G}]\psi d\tau + cc\right\} = \left(\frac{1}{2}\right)\left\{\oint dS(\Omega,r)J_G(r).n(r) + cc\right\} \tag{2}$$

Where the expressions for $J_G(r)$ and its property density $\rho_G(r)$ are given by:

$$J_G(r) = \left(\frac{\hbar}{2mi}\right) N \int d\tau \left\{\psi^* \nabla_r\left(\hat{G}(r)\psi\right) - \nabla_r\psi^*\left(\hat{G}(r)\psi\right)\right\} \tag{3}$$

$$\rho_G(r) = \left(\frac{N}{2}\right)\left\{\int d\tau\, \psi^*\left(\hat{G}(r)\psi\right) - \psi^*\left(\hat{G}(r)\psi\right)\right\} \tag{4}$$

The great goal here is transform each property into a particle density in a real space in according to the operation of $\int d\tau$, which sums the spins over all coordinates denoted by r in a surface space indicated by Ω. If we take into account that Schrödinger and Heisenberg's equations define the changes on state function and how these changes affect an average value of an observable. In this context, one of the most appropriated procedures to obtain a great relationship concerned to the observable, energy (E) for instance, is dedicated to the Ehrenfest's theorem, by which the time rate of change of the average values of an electronic position $\hat{r}$ and momentum $\hat{p} = i\hbar\nabla$ yields the following relation:

$$d\frac{<\hat{p}>}{dt} = <-\nabla\hat{U}(r) = <\hat{F}(r)> \tag{5}$$

$\hat{F}$ means a force exerted on an electron at position $\hat{r}$ by an average distribution of the remains electrons as well as by a nuclear framing yielding the force exerted on the electron density. In a real surface space, this kind of force is computed as:

$$\hat{F} = \int_\Omega \int d\tau \left\{\psi^*(-\nabla_r\hat{U})\psi\right\} = \int_\Omega dr\hat{F}(r) = -\oint dS(\Omega, r)\vec{\sigma}(r).n(r) \tag{6}$$

In this equation, the momentum of flux density of the QTAIM is distinguished by the stress tensor $\vec{\sigma}(r)$, whose physical nature indicates a dimension of energy density.

$$\vec{\sigma}(r) = \left(\frac{\hbar^2}{4m}\right)\left\{\psi^*\nabla(\nabla\psi) + \nabla(\nabla\psi^*)\psi - \nabla\psi^*\nabla\psi - \nabla\psi\nabla\psi^*\right\} \tag{7}$$

The stress tensor $\vec{\sigma}(r)$ is defined through the derivation of the Newton's equation of motion (Bader, 1991):

$$m\frac{d^2<\hat{F}>}{dt^2} = <\hat{F}(r) \tag{8}$$

The Lagrangian formalism should be used to account the kinetic (K) and potential (U) energies, what results in the next equation:

$$L = \frac{m\dot{q}^2}{2} - U(q) \tag{9}$$

To set out the QTAIM formalism, it was used the principle of least action for particle motion in subspace conditions. Well, the principle of least action states that a quantity (q) derived from wave function is minimized in space and time (t_1 and t_2) and the atomic surface of a open system is modelled as a zero-flux surface, by which the time variations in end points is zero (see Fig. 3), as well as the surface also is zero in the extreme of functions, what can be summarized as:

$$\delta W_{12}(q) = \int_{t1}^{t2} \left\{ \left(\frac{\partial L}{\partial q} - \frac{d}{dt} \left(\frac{\partial L}{\partial \dot{q}} \right) \right) \right\} \delta q dt = 0 \tag{10}$$
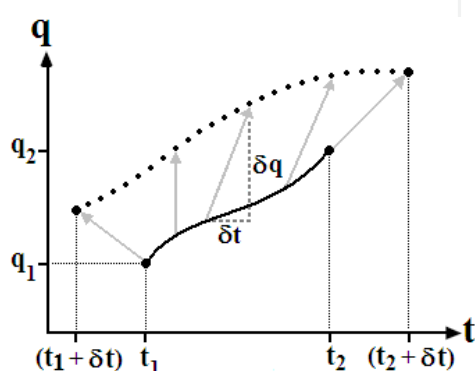

Fig. 3. Description of the principle of least action.

In this equation, L symbolizes the Lagrangian defined by the kinetic (K) and potential (U) energies. In surface, δW_{12} vanishes according to the Euler-Lagrange equation, and therefore, the Schrödinger's equation for normalized wave function can be determined as:

$$\hat{H}\Psi - E\Psi = 0 \quad \hat{H}\Psi^* - E\Psi^* = 0 \tag{11}$$

with $\hat{H} = -\frac{\hbar^2}{2m}\nabla^2 + \hat{U}$. In terms of quantum mechanics, the Lagrangian of the state functions is defined as: $L(\Psi, \nabla\Psi, \dot{\Psi}, t)$. In regards to the first-order variation in Ψ, it can be obtained the Schrödinger's equation $i\hbar\left(\frac{\partial\Psi}{\partial t}\right) = \hat{H}\Psi$ as the Euler-Lagrange equation $\Psi(q,t)$ dependent of time. In this context, by solving the Schrödinger's equation $\hat{H}\Psi = E\Psi$ on the basis of the classical Hamilton-Jacobi equation for a stationary state reduces the quantum Lagrangian to $J(\psi, \nabla\psi)$ in order to minimize the total energy. If the wavefunction is normalized, an undetermined multiplier in $J(\psi, \nabla\psi)$ is executed, thereby a new functional $G(\psi, \nabla\psi)$ is obtained. Moreover, it should be pointed out that $G(\psi, \nabla\psi)$ and $L(\Psi, \nabla\Psi, \dot{\Psi}, t)$ are functional of $\nabla\psi$ and $\nabla\Psi$ whose kinetic energy are respectively given as follows: $+\left(\frac{\hbar^2}{2m}\right) < \nabla\Psi.\nabla\Psi >$ and $-\left(\frac{\hbar^2}{2m}\right) < \Psi\nabla^2\Psi >$. Thus, it can be stated the difference between two forms of kinetic energy as proportional to the Laplacian (L) of the electronic density:

$$K - G = L - \left(\frac{\hbar^2}{2m}\right)\Psi^*\nabla^2\Psi - \left(\frac{\hbar^2}{2m}\right)\nabla\psi^*.\nabla\psi = -\left(\frac{\hbar^2}{4m}\right)\nabla^2\rho \tag{12}$$

Ruled by the Gauss's surface theorem over a spatial region $S(\Omega)$:

$$K - G = -\left(\frac{\hbar^2}{4m}\right)\int_\Omega \nabla^2\rho dr \qquad (13)$$

$$K - G = -\left(\frac{\hbar^2}{4m}\right)\oint dS(\Omega)\,\nabla\rho(r).n \qquad (14)$$

where $K(\Omega)$ and $G(\Omega)$ represent the kinetic energy densities, which are equivalent to the Laplacian of the charge density, $\nabla^2\rho_{(r)}$. If the surface $S(\Omega)$ is one of zero-flux at any point r where n is a normal vector, $K(\Omega) = G(\Omega)$ and becomes established the equation (1), whose meaning defines the surface by which the atom is delimited as zero-flux of charge density (Fig. 4). In other words, the value of the first electronic density derivative is zero, whereas the second derivatives go to a minimum or maximum of charge concentration.
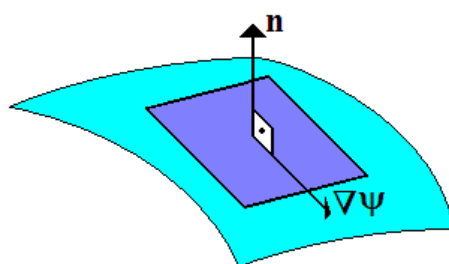

Fig. 4. Topology with representation of the zero-flux surface.

The relationship between surface conditions and high and low electronic density sites is ruled by the virial theorem. By assuming the contributions of the kinetic and potential energies, elevated and depressive charge density regions are modelled by the positive (kinetic energy density G is positive) and negative (electronic potential energy density U is negative) Laplacian values, as demonstrated by the equation (16):

$$2G + U = \left(\frac{\hbar^2}{4m}\right)\nabla^2\rho(r) \qquad (15)$$

$$U = \left(\frac{\hbar^2}{4m}\right)\nabla^2\rho(r) - 2G \qquad (16)$$

with $G = \frac{\hbar^2}{2m}N\int\nabla\psi*.\nabla\psi d\tau$, in which G is the gradient kinetic energy density and Ψ is an antisymmetric many-electron wavefunction (Matta & Boyd, 2007). By the action of the kinetic (G) and potential (U) energy operators, QTAIM identifies maximum and minimum of electronic density in the molecular surface and the chemical bonds are classified as closed-shell whether $\nabla^2\rho_{(r)} > 0$ or shared interactions when $\nabla^2\rho_{(r)} < 0$. As aforesaid, the negative Laplacian indicates high concentration of charge density (uphill) whereas depletion of charge density is motivated by the positive Laplacian (downhill). The Laplacian $\nabla^2\rho_{(r)}$ is defined by the sum of the eigenvalues of the Hessian Matrix H ($\nabla^2\rho_{(r)} \equiv \lambda_1 + \lambda_2 + \lambda_3$) (see Equations 17), whereas the electronic density $\rho_{(r)}$ is described as a set of critical points, such

as Cage Critical Points (CCP), Ring Critical Points (RCP), Bond Critical Points (BCP), and Nuclear Attractor (NA).

$$H = \begin{pmatrix} \dfrac{\partial^2 \rho_{(r)}}{\partial x^2} & \dfrac{\partial^2 \rho_{(r)}}{\partial x \partial y} & \dfrac{\partial^2 \rho_{(r)}}{\partial x \partial z} \\[2ex] \dfrac{\partial^2 \rho_{(r)}}{\partial y \partial x} & \dfrac{\partial^2 \rho_{(r)}}{\partial y^2} & \dfrac{\partial^2 \rho_{(r)}}{\partial y \partial z} \\[2ex] \dfrac{\partial^2 \rho_{(r)}}{\partial z \partial x} & \dfrac{\partial^2 \rho_{(r)}}{\partial y \partial y} & \dfrac{\partial^2 \rho_{(r)}}{\partial z^2} \end{pmatrix} \quad H = \begin{pmatrix} \dfrac{\partial^2 \rho_{(r)}}{\partial x^2} & 0 & 0 \\[2ex] 0 & \dfrac{\partial^2 \rho_{(r)}}{\partial y^2} & 0 \\[2ex] 0 & 0 & \dfrac{\partial^2 \rho_{(r)}}{\partial z^2} \end{pmatrix} \quad H = \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} \quad (17)$$

All these critical points are specific, and their internal formalisms are ruled either by the sum of the eigenvalues signs ($\lambda_1 + \lambda_2 + \lambda_3$) as well as by the number of non-zero eigenvalues. Therefore, it is obtained a coordinate pair (r, s), which can be used to classify the critical points above cited. For instance, the coordinates of CCP, RCP, BCP, and NA are (3,+3), (3,+1), (3,-1), and (3,-3). As explained above, r is a coordinate where a normal vector is aligned perpendicularly to molecular surface, but now r is interpreted as an intermediary point wherein two gradient paths of electronic density emerge from two bonded nuclei. Actually, this analysis is routinely applied in many investigations, in particular the application in systems formed by hydrogen bonds must be worthwhile. As widely established, these arguments have been also applied successfully to study π-systems (Oliveira & Araújo, 2011) and hydrogen-bonded complexes (Oliveira *et al*, 2009). As such, it can be seen critical points as extremes of electronic density, that is, maximum or minimum in each particular case. For instance, the BCP coordinates (3,-1) implies that the tridimensional (x, y, z) electronic density is extreme, whereas -1 is the summed result of two maximum (two -1 signs) and one minimum (one +1 sign) of electronic density. By the nature of the π⋯H hydrogen bonds, the proton donor is aligned perpendicularly to the π cloud, but in regards to QTAIM critical points, the BCP (3,-1) between the carbon atoms above mentioned is the attractor for the bond path linking the hydrogen to the C≡C, C=C, and C–C bonds. In this context, the coordinate (3,-1) is considered an able QTAIM source to accept protons along the CC bonds.

One of the most usual types of interactions existing in DNA structure is the hydrogen bond. As already mentioned, the formation of a hydrogen bond claims by one center with high electronic density, such as those containing lone electron pairs. In this context, a lot of proton acceptors possessing great electronic density have been exhaustively examined, e.g., hydrogen peroxides (HP). The great insight to investigate the capability of hydrogen peroxide in genetic environment is due to its presence in human blood as a metabolic bioproduct. It is widely reported the formation of several interaction complexes at the DNA level, of which the adenine base is one of the most used in this regard. Thus, the work elaborated by Dobado and Molina (Dobado & Molina, 1999) display great informations about the formation of hydrogen complexes on the DNA structure, in particular those composed by adenine and HP. As depicted in Fig. 5, there are multiple hydrogen bonds formed, in general, they are mutual once HP is functioning either as proton acceptor or proton donor, and due to this it is not easy to estimate the real strengths of these hydrogen bonds. From the structural point of view, the values of the hydrogen bond distances vary
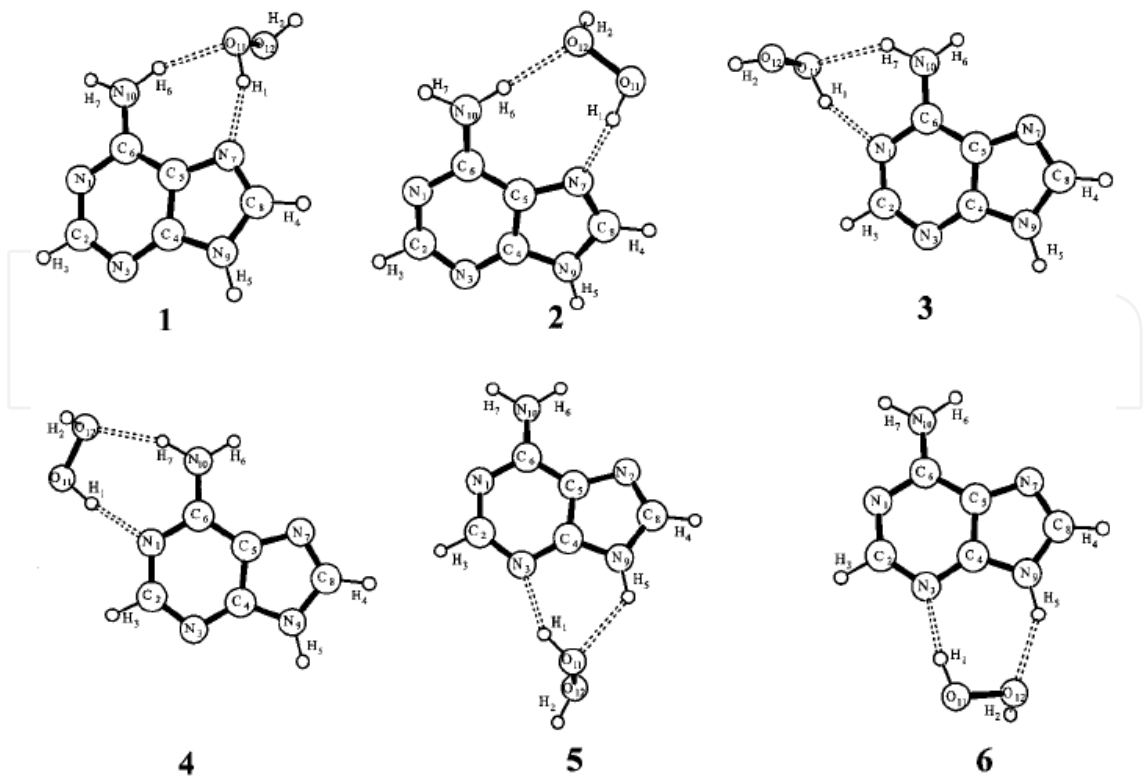
Fig. 5. The adenine⋯hydrogen peroxide complexes

between 1.8 Å and 2.1 Å. In terms of the QTAIM approach, by the topological contour plots of these geometries illustrated in the Fig. 6 became reliable to put in discussion the hydrogen bond profiles between adenine⋯HP.
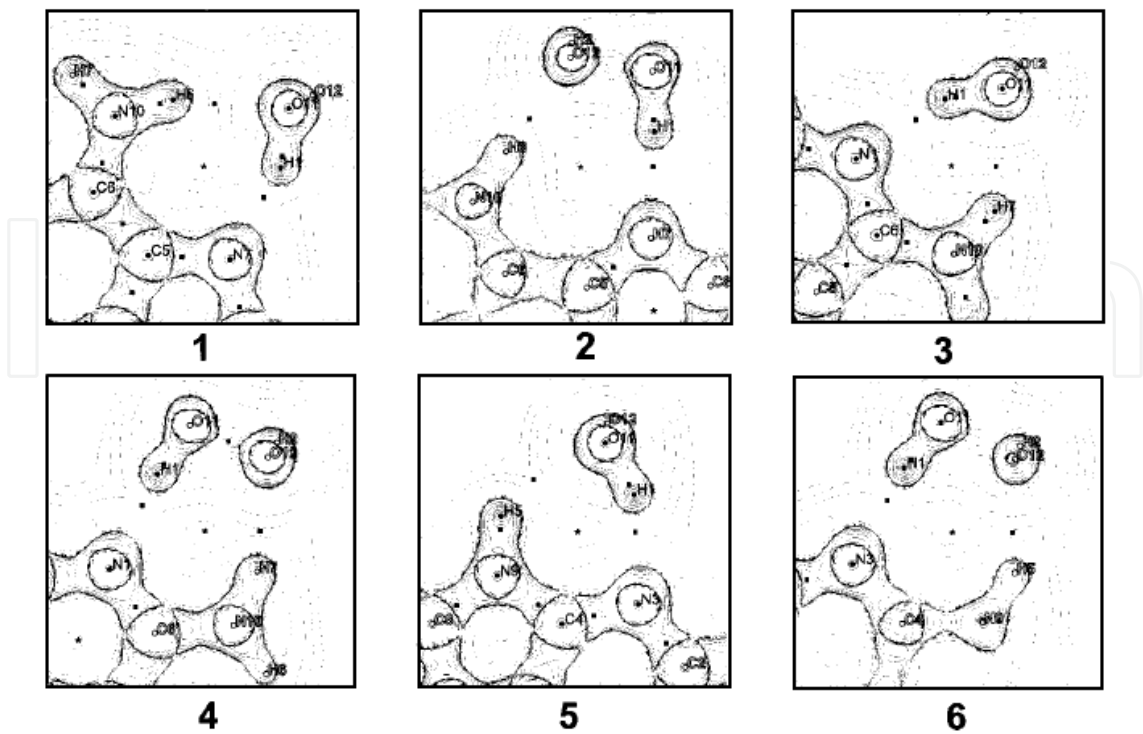

Fig. 6. $\nabla^2\rho_{(r)}$ contour maps for the hydrogen bonds.

As can be seen, the structural nature of the hydrogen bond within these complexes is justly cyclic once two intermolecular BCP were located adenine and HP. According to QTAIM virial theorem of electronic energy, these BCP above mentioned are the source to obtain the Laplacian and electronic density quantities. It can be observed that the N–H···O (adenine···HP) and O–H···N (HP···adenine) hydrogen bonds were characterized not only in terms of the positive values of Laplacian fields and low amounts of electronic density, but also by the location of the RCP, what leads to the identification of large cyclic structures formed by seven or up to eight members. However, the charge concentration measurement on the RCP is valid to debate the hydrogen bond strength. As such, it was computed the higher $\rho_{(r)}$ value of 0.04 e/a_o^3 for O–H···N, whereas it was found 0.025 e/a_o^3 for N–H···O. In spite of this, the $\nabla^2\rho_{(r)}$ values of 0.1 e/a_o^5 and 0.06 e/a_o^5 also indicate that O–H···N is a pure closed-shell interaction albeit N–H···O cannot be one a typical one. In other words, the hydrogen bond is formed when HP is the strongest proton acceptor, what in this sense could be concluded that HP is a Lewis's base.

The formation of hydrogen bond is a quite diversified event and not occurs uniquely by means of independent species or isolated monomers, but also within the same structure whether the acceptor and donor of protons are located in appropriated molecular sites. This type of interaction is recognized as intramolecular, and its functionality on the DNA structure has been well examined. In this context, Hocquet (Hocquet, 2001) provided an explanation to the different conformations C3'-endo/anti and C2'-endo/anti of the deoxyribonucleosides, namely as 2'-deoxycytidine (dC), 2'-deoxythymidine (dT), 2'-deoxyadenosine (dA), and 2'-deoxyguanosine (dG) pictured in the Fig. 7 due to the formation of intramolecular hydrogen bonds between the purine base and the sugar group.
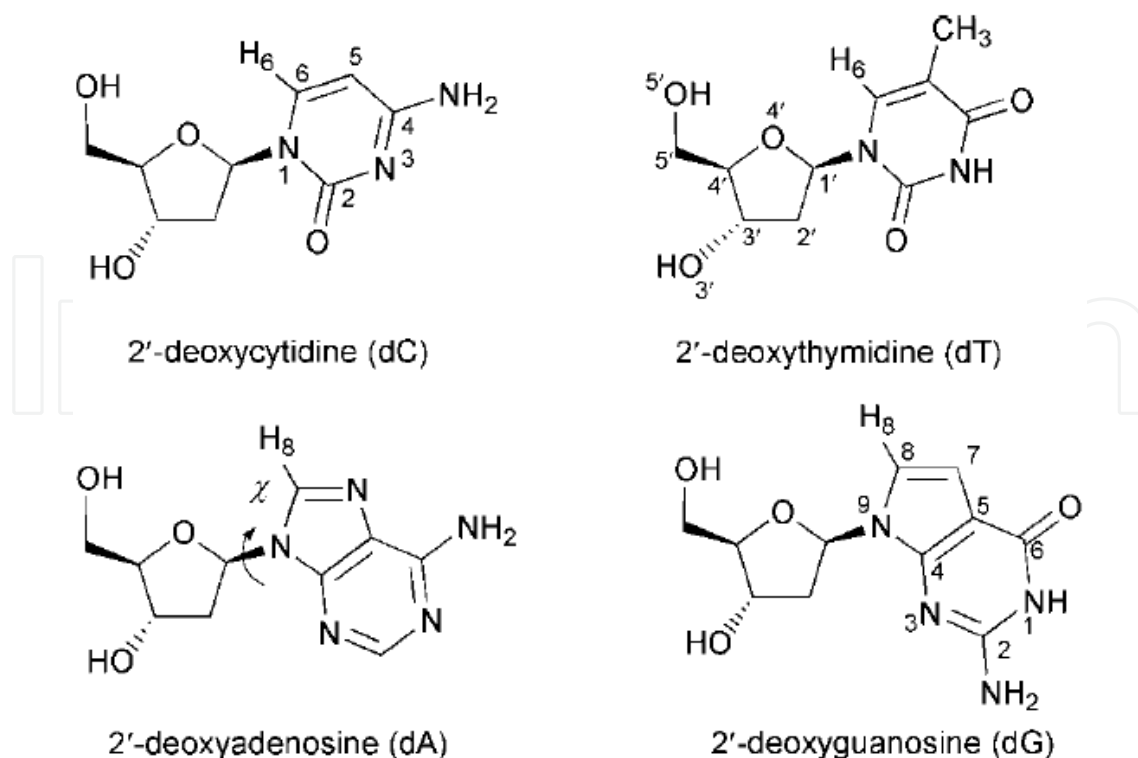

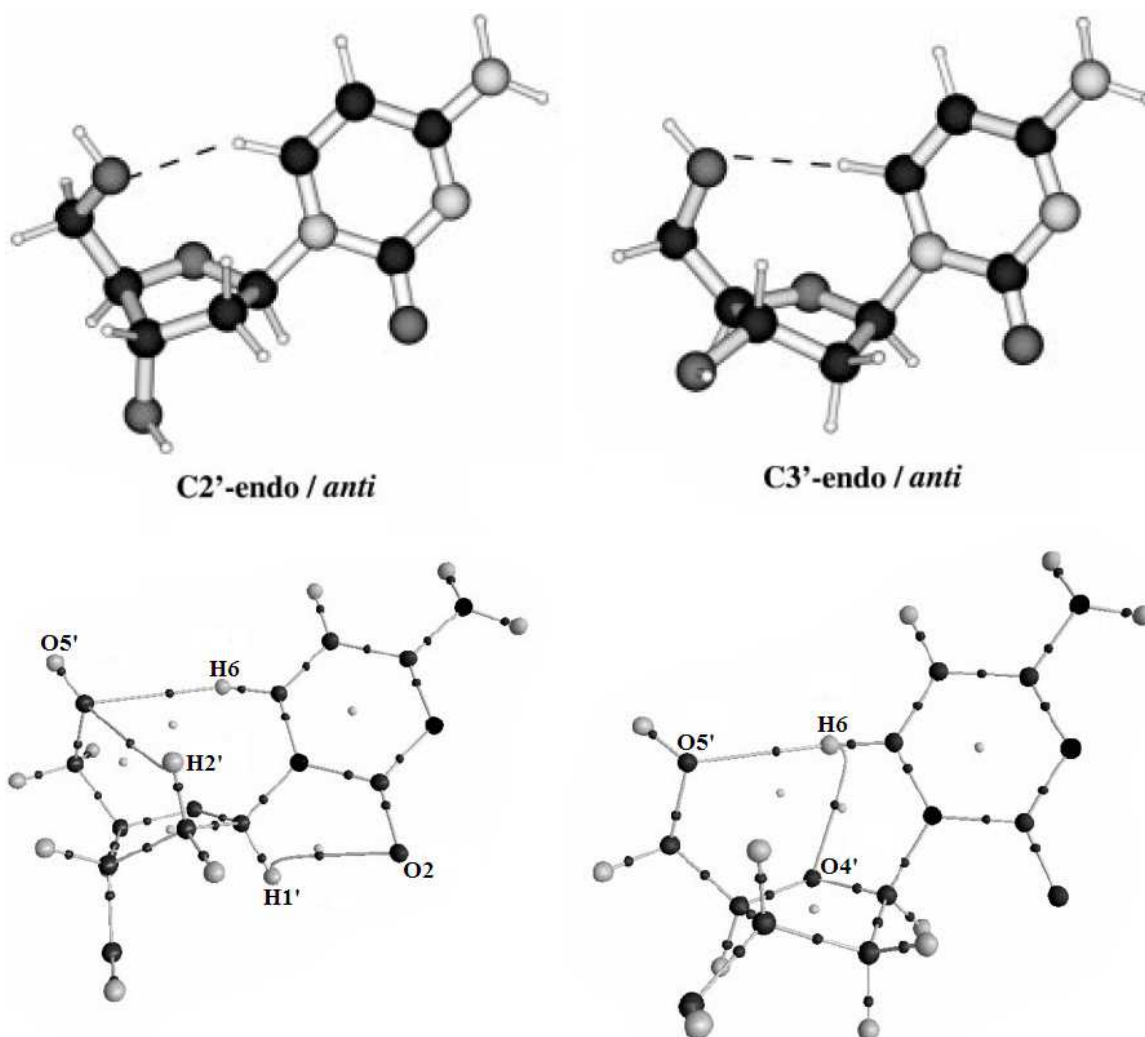Fig. 7. Chemical structure and atom numbering of the four 2'-deoxyribonucleosides.

Fig. 8. Geometry optimized structures of 2'-deoxycytidine (dC) and the molecular graph showing all BCP and RCP.

The QTAIM calculations used to examine the conformations of these deoxyribonucleosides revealed the existence of BPs and an intermediate BCP along them. In according to the molecular graph (see Fig. 8), it is quoted the formation of the O5'···H6, O5'···H2' and O2···H1' in C2'-endo/anti, whereas O5'···H6 and O4'···H6 interactions in C3'-endo/anti. In comparison with other traditional works, the values of the electronic density and Laplacian correspond to median hydrogen bond strength, although it should be mentioned that low $\rho_{(r)}$ values followed by positive $\nabla^2\rho_{(r)}$ provide a closed-shell interaction. In this scenery, we would like to say that the proton donor feature of H6 diminish as follows dT > dC > dA > dG. Nevertheless, it was demonstrated that dT shows higher electronic density in comparison to the remaining deoxyribonucleosides. In exception, the C2'-endo/anti conformation of dC presents an O5'···H6 hydrogen bond weak, but in other hand, the C3'-endo/anti conformation has a normal electronic density value but its Laplacian is very high, what signify the existence of closed-shell interaction.

Subramanian *et al* (Parthasarathi *et al*, 2004) have used QTAIM topological parameters, such as electronic densities, Laplacian shapes, and chemical descriptors to investigate the formation of DNA base pairs and which hydrogen bond profiles are formed among them. In

Fig. 9 is illustrated the bond paths, BCPs as red dots, and RCPs as yellow dots of the Guanine···Cytosine Watson and Crick (GCWC) and 2amino-Adenine···Thymine (2aminoAT) DNA complexes, which are formed by means of three stable hydrogen bonds.
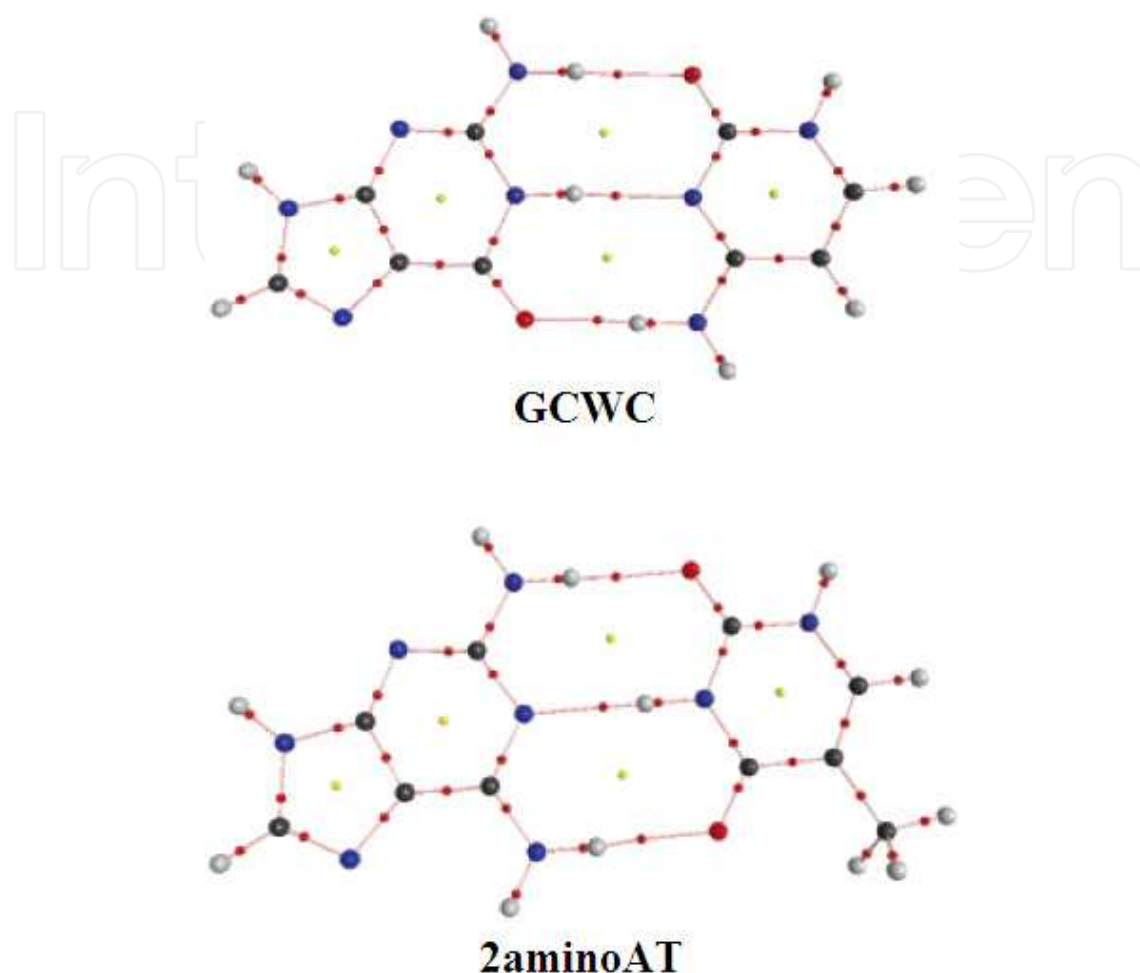

Fig. 9. Molecular graphs of DNA bases.

Initially, the QTAIM protocol indicates the existence of the hydrogen bonds N–H···O and N–H···N in conformity with their positive Laplacian values accompanied by low electronic density accounts, meaning the existence of a closed-shell interaction between these DNA entities. So, if we take into account the Koch and Popelier's criteria to ensure the characteristics of hydrogen bonds (Koch & Popelier, 1995), the alterations on the charge density of the proton donors are one of the most drastic events occurred after complexation. Of course that the QTAIM topological parameters are used in this insight, such as the appropriated values of electronic density and Laplacian values at the BCP, or even the mutual penetration between proton donors and acceptors.

Furthermore, one of the most important analyses in structures stabilized via hydrogen bonds is the measurement of its interaction strength, which can be obtained through the topological descriptors, e.g., electronic density, Laplacian, and electronic density energy, these in association with molecular parameters, such as interactions energies, structural distances, and vibrational stretching frequencies. In fact, these relationships have been very useful in studies of hydrogen-bonded complexes, but it was also used to investigate the

interaction strength between the DNA base pairs. Well, in Fig. 10 is plotted a relationship between the interaction energies and the electronic densities computed in each intermolecular BCP not only in regards to GCWC and 2aminoAT, but other DNA types are also included in this analysis, of which we can cite Cytosine···Cytosine (CC), two Thymine···Thymine configurations (TT1 and TT2), two Adenine···Adenine configurations (AA1 and AA2), as well as other ones.
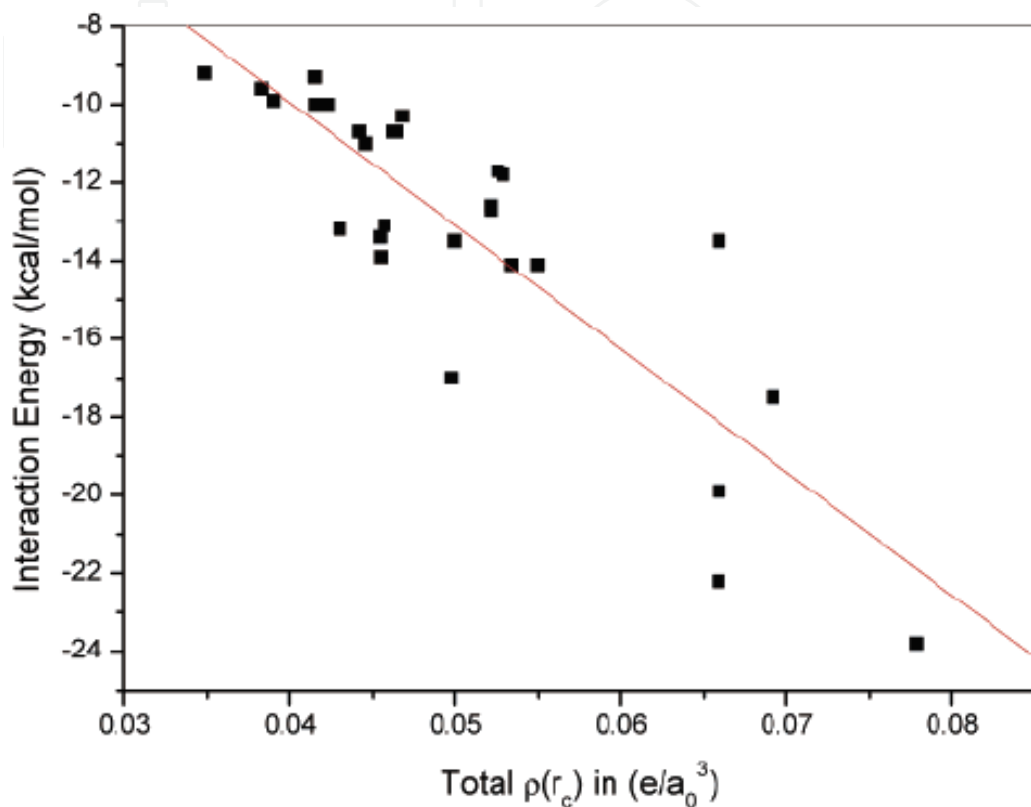

Fig. 10. Relationship between the interaction energy and total $\rho_{(r)}$ of the DNA base pairs.

Through the correlation coefficient value of 0.859 can be perceived a good and linear relationship between the electronic density in the range of 0.030 and 0.055 e/a_o^3 and the interaction energy between 9-15 kcal/mol. It can be seen that DNA pairing bases stabilized by three hydrogen bonds are most strongly bound, once the electronic densities of these systems are more than 0.05 e/a_o^3, and thereby they are not placed in the linear region. Notably, it is by the fact that the supermolecule approach is not accurate for determining the interaction energy in systems formed by three hydrogen bonds or higher, e.g. GCWC and 2aminoAT, we can assume that slight deviations in the linear adjustments should occur.

Nevertheless, additional hydrogen bonds beyond than two previously identified are possible, mainly in GG3 complex but in GG1 not. Ideally it could be possible to identify a bifurcate hydrogen bond O6···H(C8) and O6···H(N2) in GG1, although it was not possible to characterize any BCP or RCP for these two interactions, what makes QTAIM unfeasible to be used in this regard. However, the application of the Laplacian instead of the electronic density as topological descriptor to predict the interaction strength is very useful in many situations. To the best of our knowledge, the hydrogen bond strength on the DNA bases is

also unveiled through the relationship between the interaction energy and the Laplacian computed in each intermolecular BCP, either those with two hydrogen bonds or even with three ones. This relationship is illustrated in Fig. 11, by which a correlation coefficient of 0.827 was obtained. We can observe that similar results were obtained in comparison to that presented for the electronic density. The low electronic density values as well as the depletion characteristic of the Laplacian corroborated themselves, and in this sense, these two QTAIM parameters show similar efficiency to predict the interactions strength of the DNA bases of pairs.
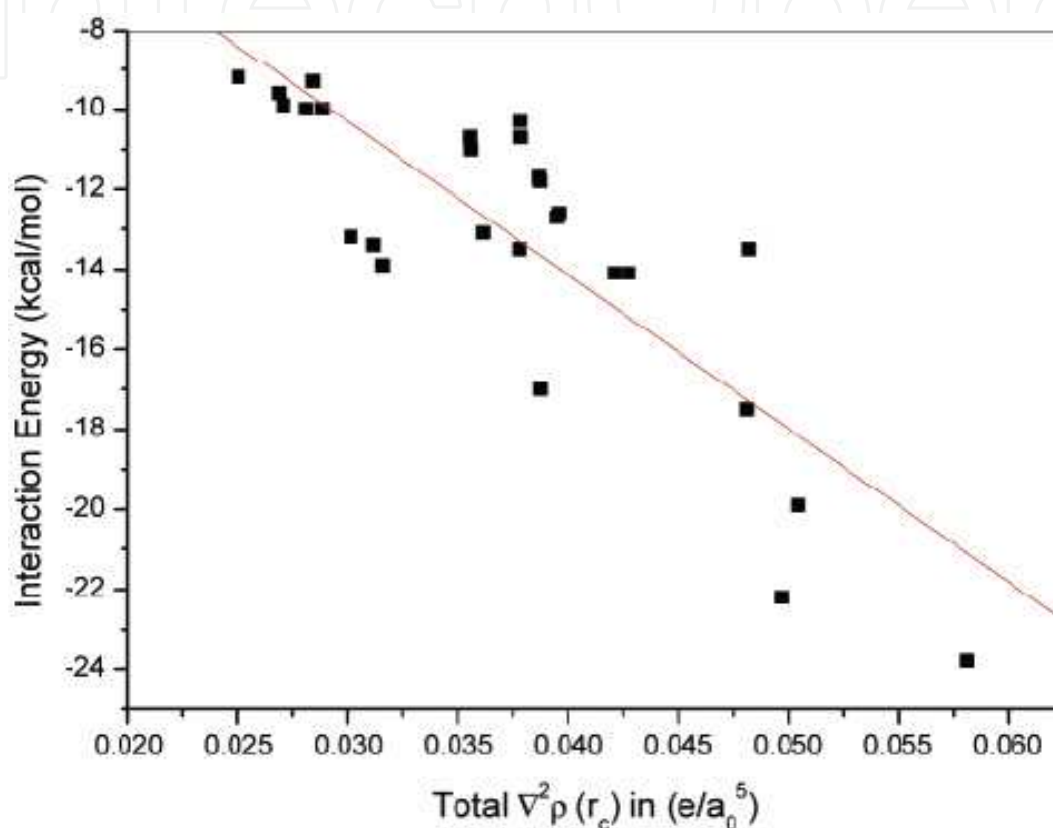

Fig. 11. Relationship between the interaction energy and total $\nabla^2\rho_{(r)}$ of the DNA base pairs.

As is widely known, the interaction strength is the cornerstone to preserve the molecular stabilization, and in the DNA scenery, it has been demonstrated that their nucleobases provide the molecular stability of the DNA chains due to the number of the hydrogen bonds to be formed, and indeed, their strengths are included in this context. Among the DNA structures well-known, it has been noticed that π stacking and hydrogen bonds are the most important types of interaction that retains the DNA helical structure with great influence of the guanine and cytosine nucleobases. In an overview, these nucleobases in olygonucleotides form are stabilized by distinct energies, i.e., 20 kcal/mol for hydrogen bonds whereas 2.40 kcal/mol for π stacking. In order to understand the connectivity between hydrogen bonds and π stacking, a symbolic model system was examined, in which the action of the benzene upon the formation of the $C_6H_6\cdots GC$ and $C_6H_6\cdots CG$ complex must be worthwhile (Robertazzi & Platts, 2006). In according to the Fig. 12, the bond paths and BCP of the $C_6H_6\cdots GC$ (a) and $C_6H_6\cdots CG$ (b) complexes can be analyzed. The QTAIM results show that no significant variation could be found between (**a**) and (**b**),
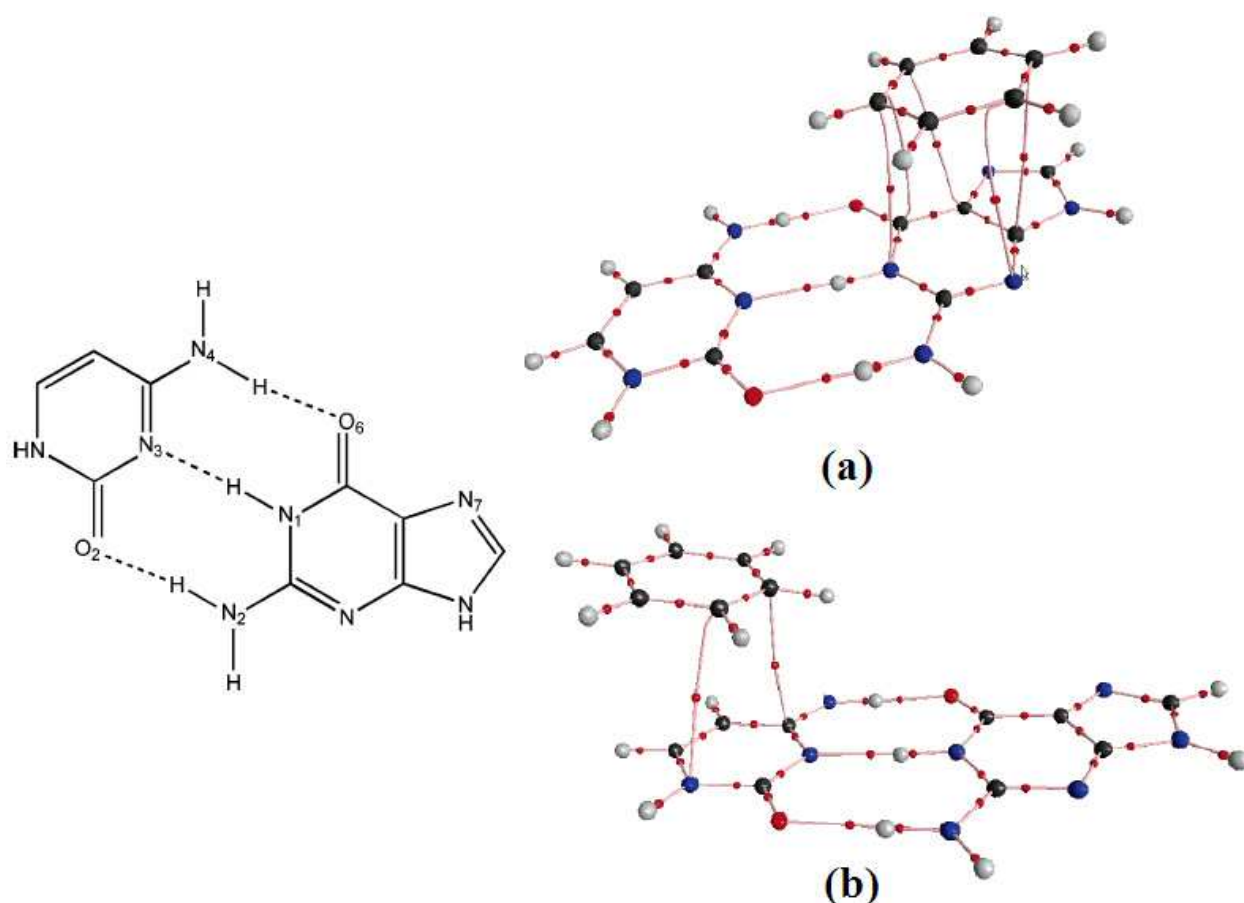
Fig. 12. Topologies of (**a**) benzene$\cdots$GC and (**b**) benzene$\cdots$CG.

i.e., the electronic density for the hydrogen bonds and π stacking are in the range of 0.001 e/a_o^3.
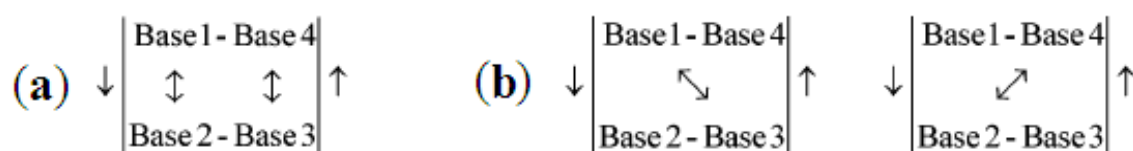
Likely, a decisive argument changes the conclusion highlighted above: inclusion of benzenic structures with the following substituents –NO_2, –F, –CH_3, –CHO, –OH, and –NH_2 into the ternary complexes (**a**) and (**b**). This action should be useful to demonstrate that the hydrogen bonds and π stacking can be affected by the hardness (n) of the substituted benzene, whose definition according to the Density Functional Theory (DFT) (Geerlings *et al*, 2003) is based on second derivative of electronic energy (E) with respect to the number of electrons (N) for a constant external potential $U_{(r)}$:

$$n = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)U_{(r)} \tag{18}$$

The great goal of this insight is the reduction of the charge transfer from guanine (G) to cytosine (C) with stacked substituted groups on the benzene structure. For example, changing –NO_2 by –NH_2 cytosine is a better proton acceptor with increase of the electronic density at the BCP of the hydrogen bonds H1$\cdots$N3 and H2$\cdots$O2, but otherwise, a worse proton donor causes an increase in the electronic density, what could lead to confirm surely that π stacking does influence the formation of hydrogen bonds between G and C. As can be

seen, hydrogen bonds and π stacking bring great deformations on the molecular sites of the DNA, but its ideal structure is preserved. In accord with Meggers *et al* (Meggers *et al¸* 2005), DNA polymer analogous formed by π stacking interactions in agreement with Watson-Crick pairing scheme of bases produces α-double helix with absence of the backbone sugar residues. Definitively, hydrogen bonds and π stacking interactions are not independent, as already discussed the influence between them.

The nucleobases dimers are formed by π stacking interactions, which can be also subdivided into intrastrand (**a**) and interstrand (**b**), as illustrated below. As widely-known, the formation of stacking interactions is closely compromised with the formation of the gene codes. In this context is that, in addition to the hydrogen bonds, the π stacking contacts should be carefully reliable to interpret the DNA structure and the α-helix formation.

$$(\textbf{a}) \quad \downarrow \left| \begin{matrix} \text{Base 1 - Base 4} \\ \updownarrow \quad\quad \updownarrow \\ \text{Base 2 - Base 3} \end{matrix} \right| \uparrow \quad\quad (\textbf{b}) \quad \downarrow \left| \begin{matrix} \text{Base 1 - Base 4} \\ \searrow \\ \text{Base 2 - Base 3} \end{matrix} \right| \uparrow \quad \downarrow \left| \begin{matrix} \text{Base 1 - Base 4} \\ \nearrow \\ \text{Base 2 - Base 3} \end{matrix} \right| \uparrow$$

Indeed, there is an intense discussion about the formation of hydrogen bonds on the nucleobases dimers. For instance, in recent years the triple hydrogen bonds occurrence on nucleobase has been evaluated through the application of high-level calculations, by which a slight difference in range of 3 kcal/mol between the dimer and the individual hydrogen bonds was discovered. Due to this, recently Matta *et al* (Matta *et al*, 2006) have developed a theoretical investigation of WC dimeric derived from the DNA fragments. It was quoted the existence of three types of hydrogen bonds, namely as N–H··O, C–H··O, and N–H··N. The first hydrogen bond type occurs between A and T as well as in G and C. The second hydrogen bond is recognized as triple between A and T. Finally, the last hydrogen bond model makes itself presents in a double format between A and T as well as G and C. Thus, it should be important to comment each one of these hydrogen bonds and their influence on the DNA structure.

It is observed a slight higher concentration of $\rho(r)$ in the CG complex in comparison to AT, in which the values are 0.028 e/a_o^3 and 0.025 e/a_o^3, respectively. Moreover, the H··O hydrogen bond is sensitively weak in AT once the value of $\rho_{(r)}$ is 0.006 e/a_o^3. Furthermore, the ellipticity curvature λ_3 is smaller in AT rather than in CG, what indicates a less charge density accumulation in the intermolecular region of the AT system. Only for mention, the remaining λ_1 and λ_2 are perpendicular to the BP of the hydrogen bonds, what makes their negative results and then are not taken into account. In according to the Equation 15, the virial potential operator U is negative over the entire molecule, whereas G is positive. If U is the dominant term, a high electronic density concentration is assumed, as can be seen in shared interactions such as covalent or unsaturated bonds. In other words, the electrons are placed on the BCP. The same reasoning can be dedicated to G, although the kinetic contribution diagnoses closed-shell interactions, or in this current work, the hydrogen bonds N–H··O and H··O. Thus, it was suggested an alternative approach to the virial expression in order to propose a novel term so-called as electronic energy density H:

$$H = 2G + U \tag{19}$$

Well, it is by the contributions of G and U that H is estimated. It was observed negative values of H not for N–H···O, but actually to N–H···H. The main feature of the N–H···H hydrogen bond is its length, which is very short in AT than in CG. Thereby, the electronic density $\rho_{(r)}$ of 0.052 e/a_o^3 is AT is higher than CG, whose value is 0.038 e/a_o^3. Nevertheless, these hydrogen bonds exhibit positive value of $\nabla^2\rho_{(r)}$ as well as negative electronic energy density H, what is anomalous for closed-shell interactions, but it can be an indication of shared electronic density. However, Fig. 13 illustrates different π stacking interactions on DNA structure.
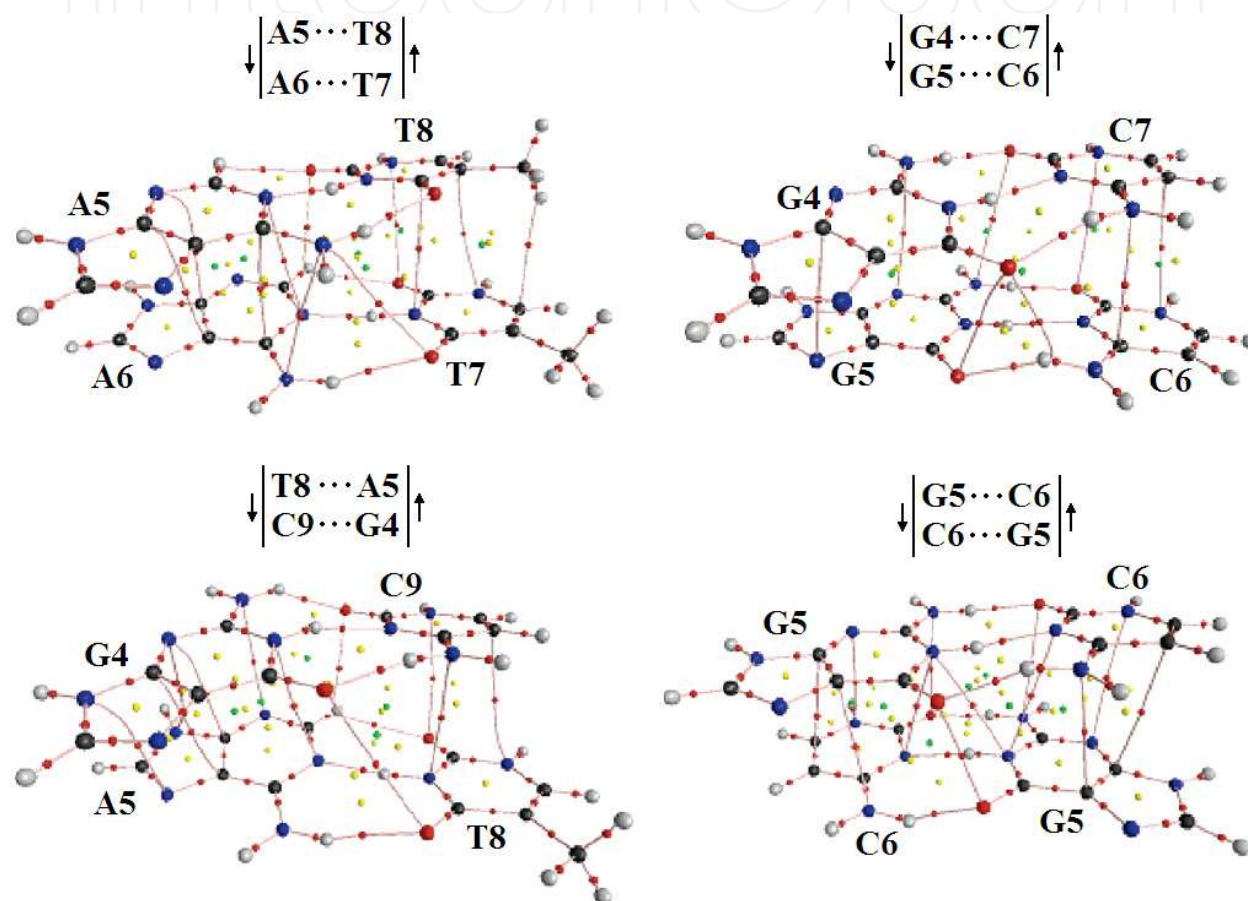
Fig. 13. Molecular graph of the nucleobase dimer duplexes.

It was discovered some diversity of π interactions formed by the N···N, C···C, C···N, and O···N contacts. These, some are intrastrand and other ones are interstrand. For the third structure, G4···C7 and G5···C6, in addition to the six hydrogen bonds, eight π stacking interactions are known, of which six are intrastrand whereas two are interstrand. As remarkably defined, the values of the electronic energy density H are positive due to the contribution of G accompanied by U with smaller negative amounts. By this relationship, the Laplacian fields are positive, and in this current analysis were obtained values of $\nabla^2\rho_{(r)}$ in range of 0.009-0.039 e/a_o^5, what no doubts in regards to the profile of closed-shell interactions remains about these interactions. In comparison with some typical hydrogen bonds formed, the $\rho_{(r)}$ values of the intrastrand and interstrand π-stacked contacts are very low, but the lowest charge concentration is found in intrastrand situations. In an overview,

it was quoted that albeit these π stacking interactions are weak, surely they can influence the geometry and stabilization of the DNA structure.

2. Acknowledgment

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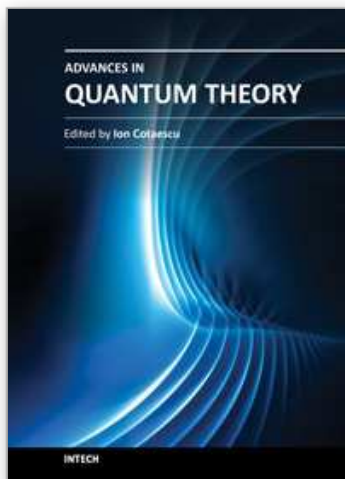
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