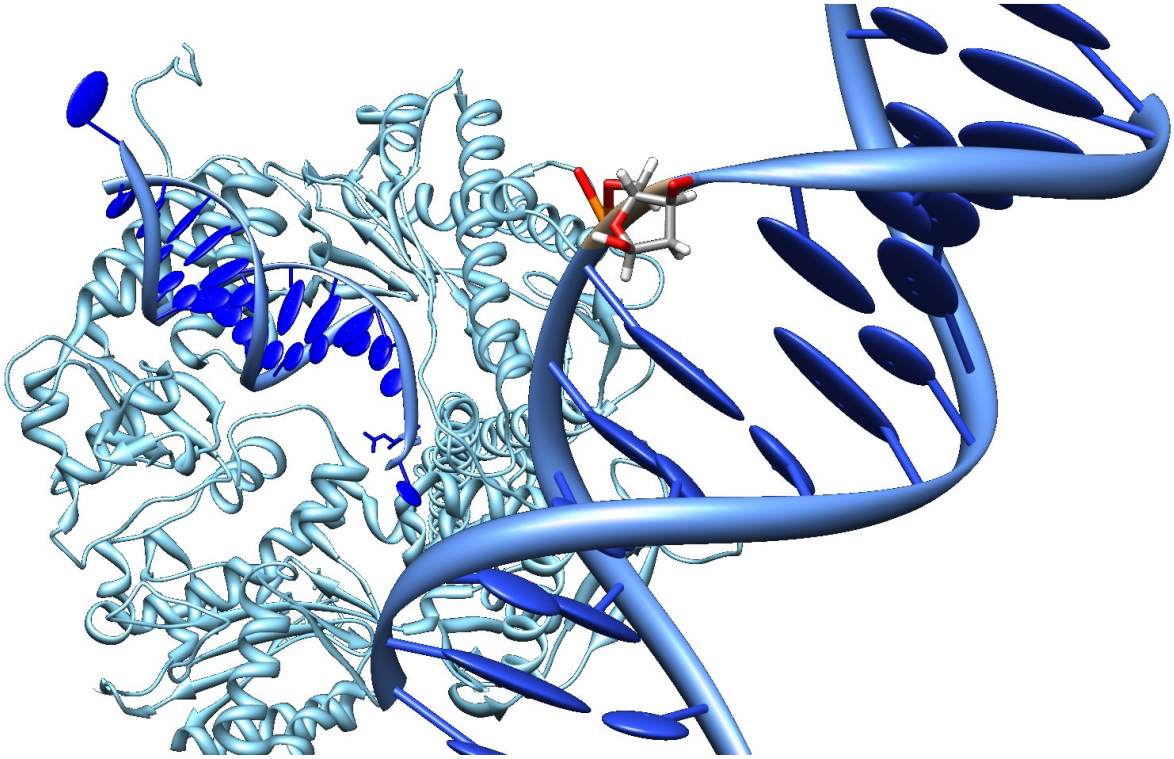
DNA damages:
modeling and rationalize structure and reactivity



CECAM Workshop
Lyon November 3rd – 6th 2015

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Centre Européen de Calcul Atomique et Moléculaire

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Elucidating the structure of damaged oligonucleotides as well as the mechanisms leading to lesions or conversely promoting repair is a fundamental challenge in chemical biology.

With this workshop we want to bring together leading experimentalists and theoreticians to give a most comprehensive picture of these processes, at a molecular and electronic level. We will also evidence how the structural modification of DNA, govern both the energy- and electron-transfer phenomena and the repair rate.

This scientific challenge needs to combine efforts from cutting-edge spectroscopies and molecular modeling. In particular multiscale modeling going from explicit quantum description of ground and the excited states, to mesoscale coarse grain simulations passing through an atomistic classical description is fundamental to get a clear comprehension of all these fundamental mechanisms.

That's why we are very happy to welcome all of you in Lyon, just one month after the discovery of DNA repair mechanism has been acknowledged by the Nobel Prize in Chemistry. We believe this workshop will allow very exciting and fruitful scientific exchanges and will possibly enforce future promising collaborations.

Obviously we would like to acknowledge and thank both CECAM and Centre Blaise Pascal who funded the workshop and all of you for participating.

The Organizing Committee
Elise Dumont, Lyon
Antonio Monari, Nancy
Filip Lankas, Prague
Célia Fonseca Guerra, Amsterdam

Scientific Program

	Tuesday 3	Wednesday 4	Thursday 5	Friday 6
		DNA Tandem Lesions. *Chair M. Sevilla*	**DNA Photosensitization** *Chair A. Monari*	**Photochemistry/ Photophysics** *Chair M. Garavelli*
9h00		A. Georgakilas	M. Barbatti	V. Lhiaubet-Vallet
9h40		E. Bignon	J. J. Nogueira	J. Segarra Marti
10h10		Coffee Break	Coffee Break	Coffee Break
10h40		J.-L. Ravanat	R. Improta	A. Francés-Monerris
				M. Marazzi
11h20		T. Drsata	F. Di Meo	
				Conclusive Remarks
11h50		Lunch Break	Lunch Break	
12h10				
14h00	Arrival & Welcome	Poster Session	Poster Session	
	G-quadruplexes *Chair C. Fonseca Guerra*	**DNA and Low-energy electrons** *Chair. E. Dumont*	**DNA lesions and reactivity** *Chair F. Lankas*	
14h20	G. Barone	M. Sevilla	I. Tunon	
15h00	G. Paragi	M. Mc Allister	E. Papaleo	
15h30	Coffee Break	Coffee Break	Coffee Break	
16h00	M. Pasi	T. Domratcheva	J. Ceron-Carrasco	
16h40	L. Espinosa	D. Roca Sanjuan	R. Suardiez	
17h10	F. Zaccaria		Round Table	

Duplex and G-quadruplex DNA-binding of synthetic molecules in the search of novel anticancer drugs: experimental and computational studies

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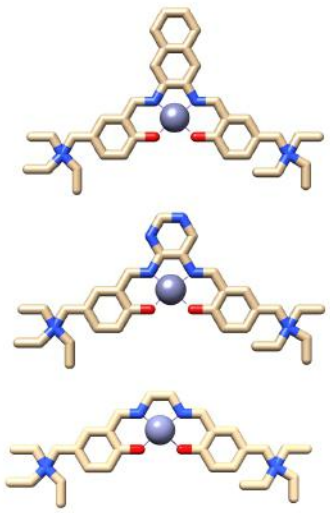
Nickel(II), copper(II) and zinc(II) complexes of N_2O_2 tetradentate Schiff base ligands strongly interact with B-DNA, usually by groove-binding and/or by intercalation [1]. It has been also shown that the presence of aromatic substituents on the N,N' bridge make them suitable G-quadruplex binders. In this context, we have recently investigated the binding toward duplex and G-quadruplex DNA of nickel(II), copper(II) and zinc(II) complexes of Salen derivatives (see Figure), by spectroscopic and computational approaches [2,3]. The compounds show also biological activity against human cancer cell lines.



Different substituents are currently considered on the N,N'-bridge, in order to increase their selectivity towards telomeric and oncogene promoter G-quadruplexes, targeting their grooves rather than their aromatic ends. The impact of the metal center on the quadruplex binding ability is also taken into account. The competitive binding toward duplex and G-quadruplex DNA in aqueous solution is addressed through circular dichroism, absorption spectroscopy and fluorescence resonance energy transfer (FRET) measurements. Atomic level details of the metal complex-DNA supramolecular systems are obtained through computational investigations, consisting of molecular dynamics (MD) simulations and by density functional theory/molecular mechanics (DFT/MM) calculations, providing support for the interpretation of the binding mechanism

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5-Substituted uracils: Another brick in the quad

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5-Substituted uracils (5sUs) are considered theoretically and experimentally as new building blocks in quadruplex structures. DFT calculations performed a-prior to experimental investigations and predicted the formation of 5sUs based tetrameric structures. Central cation binding as well as the stacking capacity of layers were examined similar to previous studies [1-3]. The stacking energy is very close to the interaction of two xanthine (Xa) layers, and 5sU tetrad cover almost exactly the same area as Xa or guanine tetrads. This latter property provides the possibility to combine Xa and guanine tetramers with 5sU based layer and form a common central channel within quadruplex structure.

Following the theoretical investigations, synthetic works has been started and the existence of 5sU complexes were pointed out by mass-spectrometry. Both homo 5sU and mixed (5sU with Xa) systems were found, as well as structures with 2,3,4, ... and 8 units. We are convinced that the suggested molecules can be used as new building blocks in many different applications including aptamers, bio-sensors or artificial ion channels.

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Sequence determines the structure and microsecond-scale dynamics of B-DNA and its bound cations.

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DNA-binding proteins specifically recognise their genomic target sites both by "reading" the base sequence and by probing the mechanical deformability of DNA. Specific protein-DNA interactions are fundamental in many important cellular processes, such as DNA replication, genome organisation and transcription regulation. The mechanical properties of DNA at the basis of these indirect recognition processes are highly sequence dependent, and as such can be regarded as a second genetic code. Understanding how the two layers of genetic information interact requires extensive structural and dynamical knowledge of B-DNA, currently unavailable from experiment. Using molecular dynamics (MD) simulations, an international consortium of laboratories combined efforts to obtain a large database of microsecond-scale MD simulations of a set of B-DNA oligomers with sequences designed to allow the comprehensive study of base-sequence effects. Our analysis of the MD trajectories elucidates in atomic detail how sequence affects the structure and dynamics of DNA, modulating the relative stability of its conformational substates and shaping the distributions of its tightly bound couterions. We expect these results will be instrumental in the study of how base sequence influences the interactions of DNA with proteins and other molecules.

Unravelling the Structure of Silver-Mediated DNA Homopolymers using ab initio Computational Tools

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We present computational and experimental studies of highly stable silver-mediated DNA homopolymers with promising applications for DNA nanotechnology and biomedical sciences[1, 2]. Experiments with base replacements showed the stability of the silver-mediated cytosine (cytosine-Ag+-cytosine) in both parallel[3] and antiparallel[4] duplexes. Using Electrospray Ionization Mass Spectrometry in combination with different ab initio techniques we have found evidence of a novel stable guanine-Ag+-guanine conformation in a non-canonical Watson-Crick pairing[5]. Moreover, a direct comparison between experimental data and calculations of Electronic Circular Dichroism (ECD) spectra within the Time Dependent Density Functional Theory (TDDFT) framework has allowed us to elucidate the representative three-dimensional geometries for both stable mediated homopolymers. Through the analysis of the final structures, we report the presence of a new interplanar type of hydrogen-bond interactions[6].

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Ion Selectivity at the Internal Cavity Site of G-Quadruplexes: a Quantum-Chemical Approach

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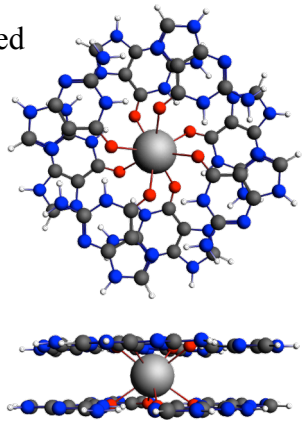
In the telomeric part of the chromosome, which is crucial for the protection of the genetic code,1 quadruplexes occur which are composed of stacked guanine quartets. The guanine bases in the latter are essentially coplanar and interact through hydrogen bonds. The quadruplexes are furthermore stabilized by the presence of monovalent ions, such as K+ and Na+, in between the layers of quartets with a preference for K+ under physiological conditions (see Figure).2

We report quantum-chemical calculations based on dispersion-corrected density functional theory (DFT-D)3 of bi-layered G-quadruplex (GQ) structures interacting in turn with K+, Na+, Rb+, Li+ or Cs+ at the channel coordination site. The model includes bi-layered GQs provided with sugar-phosphate backbone, interacting in turn with Li+, Na+, K+, and Rb+. The computational studies were performed for the conditions in the gas phase and in water described with an implicit solvent model. The simulations in water reproduced the consolidated experimental channel site cation affinity sequence4 K+ > Na+ > Li+.



With our quantitative Kohn-Sham molecular orbital (MO) and corresponding energy decomposition analyses (EDA), we have been able to understand the cooperativity of the hydrogen bonds.5,6 In this study, we analyzed the interaction of the alkali cation with the guanine bases and explain the experimental order of affinity in guanine quadruplexes.

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Studying the response to ionizing radiation (IR): An experimental and theoretical approach

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Exposure to ionizing radiation (IR) as a genuine exogenous stress induces a variety of responses in the cell initiated by the DNA damage response (DDR) and DNA repair, apoptosis and inflammatory or immune response[1]. Therefore, stimulation of this IR-response mega system especially at the organism level consists of several subsystems and submechanisms and exerts a variety of systemic effects[2]. Our group focuses on the study of the induction and processing of complex DNA lesions applying different methodologies. At the same, we are interested on the effects of low doses in the case of diagnostic examinations (<0.1 Gy). In this presentation, I will first present experimental evidence on how the mammalian cell or organism is expected to respond to complex DNA damage induction i.e. the signature of IR and primary 'danger signal'. At second, I will discuss the extremities of this response i.e. the phenomena of radiosensitivity and radioresistance in bacteria and human cells and insights gained by applying bioinformatics[3]. Last but not least and in the light of our recent work, I will present novel findings in the case of IR-low doses and expected levels of complex DNA damage calculated using Monte Carlo damage simulation (MCDS 3.10A) for DNA double strand break (DSB) induction and the general purpose Monte Carlo N-particle (MCNPX) radiation transport code system.

Acknowledgements
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Damaged DNA Structures Determination by Means of Molecular Dynamics

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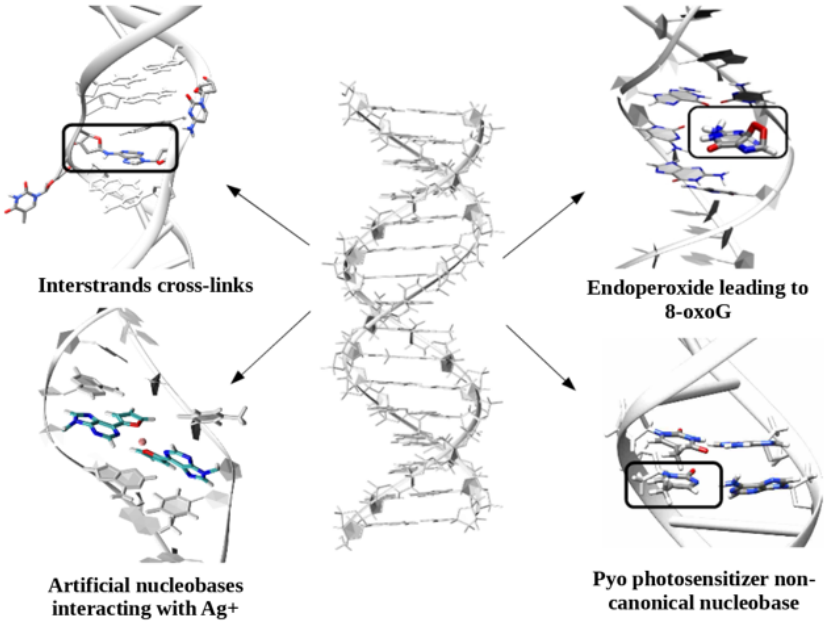
Molecular modelling allows chemical phenomena comprehension at the atomic scale. Nowadays, multi-scale approaches are widely used in the study of lesions formation mechanisms in DNA [1]. The knowledge of this kind of reaction is of capital importance in order to delineate the formation mechanisms of such damages and in a longer perspective, to design novel therapeutics. Molecular modelling can bring information in order to rationalize and characterize phenomena that take place in the DNA double-helix when this latter is the target of agents inducing chemical modifications on nucleobases.



We relied on this powerful tool in order to model the damaged DNA structural behaviour and understand in which manner the lesion can impact the double-helix structure. Molecular dynamics simulations allowed us to study the dynamical behaviour of differents damaged systems, and rationalize such damages formation by structural analysis. We studied many systems, such as the endoperoxide intermediate leading to 8-oxoG, inter-strand crosslinks [2], photo-induced damages on pyrimidine bases [3], and also some artificial systems inducing a metallic atom [4].

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Radiation-induced formation of tandem lesions: mechanistic aspect.

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During the last three decades considerable efforts have been made to determine the nature and quantify the amount of lesions produced in double stranded (ds)DNA exposed to oxidative stress. Nowadays, an almost complete decomposition pathway of the four DNA bases mediated by hydroxyl radicals and one electron-oxidation, the two damaging species of such a stress, is available. About 70 different DNA lesions have been identified and some of them have been quantified in cells exposed to ionizing radiations.
Regarding the chemical aspects of formation of these lesions, most of the reactions identified at the nucleoside level were also found to occur in double stranded (ds)DNA. However, differences exist and some modifications were found to be generated specifically in dsDNA. This highlights the fact that the 3D structure of DNA somehow plays an important role in the decomposition of the initially generated radicals.
Attention will be focused during the presentation on the formation of complex DNA lesions that could be significantly generated through a single oxidation event. Such damages are different to so-called locally multiple damage sites that are produced specifically by radiations as a consequence of multiple ionization processes. These include tandem DNA lesions generated through peroxidation reactions and also intra- and inter-strand crosslinks. These examples indicate that the described mechanisms of decomposition of the DNA bases could be different in dsDNA compared to that observed for free nucleosides. Moreover, this also indicates that in a cellular environment, biomolecules surrounding DNA could also play a role in the mechanisms of decomposition of initially produced DNA radicals.
To further delineate the mechanisms of radiation-mediated decomposition of DNA bases in dsDNA both experimental and theoretical approaches are required.

Applying a coarse-grained model to investigate structure and dynamics of oxidatively generated DNA lesions

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DNA in a cell is constantly subjected to oxidative stress which can lead to a formation of various complex DNA lesions. Important families of such lesions are intra- and interstrand cross-links (IaCLs and IeCLs) featuring two covalently bound nucleobases either within one strand or between the two DNA strands. These lesions are known to be highly mutagenic, thus playing an important role in carcinogenesis and aging.
IeCLs in particular can be formed from unrepaired abasic sites by oxidative processes. These sites constitue the most frequent DNA damage and have been extensively studied recently. However, the structural mechanism of IeCLs formation from abasic sites is only poorly understood. Detailed knowledge of structural and mechanical properties of DNA oligomers containing oxidized abasic sites is thus crucial. In case of IaCLs, no experimental structures are available, although the knowledge of their properties is important for interpreting the lack of repair of these lesions.
We employed a DNA coarse-grained model of rigid bases to asses structural and mechanical properties of oligomers containing either oxidized abasic sites or IaCLs. Parameters of the model were inferred from unrestrained explicit solvent molecular dynamics simulations.
Our results explain experimentaly proven high affinity of abasic site facing C base for the formation of IeCLs and suggest a mechanistic explanation of the phenomenon [1]. As for oxidative IaCLs, we observe that their structure significantly differs from photodimers and that the structure depends markedly on bases involved in the cross-link [2]. These differences may have specific implications for recognition processes.

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Free Radical Mechanisms of Radiation Damage to DNA: The role of the aqueous electron

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Radiation damage to DNA results from both roughly equal contributions of direct ionization of DNA including its first hydration layer (direct type effects) and indirect effects from attack of mainly hydroxyl radicals and aqueous electrons.[1] DNA damage from direct ionization results from formation of DNA-cation radicals (holes) and DNA-anion radicals (excess electrons) within DNA. Low energy electrons (LEE) produced during ionization have also been shown to lead to frank DNA strand breaks via dissociative electron attachment.[2] The role of the hydroxyl radical from the indirect effect has been well studied; however, the aqueous electron reactions with DNA have recently been called into questions by several workers. In this talk an overview of that status of our understanding of the effect of radiation on DNA will be given with special attention to the role and reactivity of the aqueous electron. A "new" model of the aqueous electron will be shown to account for its properties, such as, its free energy of solvation, VDE, as well as its redox potential.[3] Our work confirms that aqueous electrons will add to DNA; however, recent reports suggest interesting new pathways for subsequent reaction.[4] Supported by the NIH NCI under grant R01CA045424.

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Understanding the Interactions between Low Energy Electrons and DNA in Aqueous Solution

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Ionizing radiation can damage DNA in a cell directly, or it can excite molecules in the cellular surroundings. The Low Energy Electron (LEE) is one of the secondary species produced via this second process. It has been shown that this species can cause significant damage to DNA. In fact electrons with energies as low as 0eV have been shown to cause strand breaks in dry DNA. In the work I will present I discuss the work we have performed to investigate this damage mechanism using a combination of DFT and Molecular Dynamics. At variance with some previous works, in our simulations the interaction between the DNA and the surrounding water molecules are all modelled using DFT. Our results highlight the significant role that water molecules can play in DNA damage reactions and demonstrate that it is therefore important to incorporate explicit water molecules in any simulation of the DNA damage process. In the final part of the talk I will discuss more recent work in which we investigate the reaction between LEEs and a DNA-Cisplatin structure in an explicit water environment.

Intermolecular electron transfer in DNA damage and repair: insights from excited state calculations

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Redox properties of nucleobases are central in DNA damage by light and other agents and in enzymatic repair. Photoinduced interbase electron transfer leads to formation of asymmetric photoproducts between adjacent thymine bases such as 6-4 and spore photoproducts. Moreover, direct enzymatic repair of major photoproducts by DNA photoproduct lyases is ruled by forward and back electron transfer reactions. Contributions of the excited state calculations to the recent progress in these topics will be summarized. The focus will be on excited state calculations providing estimates of electron transfer rates. In the case of (6-4) photolyase, such calculations predict electron transfer rates in good agreement with those experimentally observed for the repair and futile electron transfer cycles. The impact of classical and quantum interactions of the active site system with its molecular environment will be highlighted.

DNA damage by UV light, OH/H radicals and low energy electrons: A theoretical insight form CASSCF/CASPT2 computations

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UV light, OH radicals, and low-energy (0-3 eV) electrons are frequent sources of damage to the DNA/RNA strands or its monomeric constituents.1 Even though the isolated nucleobases are known experimentally and theoretically to be characterized by ultrafast decay channels, which make them photo-stable against the UV radiation,[2] new photochemical paths arise in the DNA/RNA environment producing lesions. Thus, adjacent pyrimidine dimers may react via a [2+2] photo-cycloaddition giving rise to the cyclobutane pyrimidine dimers (CPDs). On the other hand, excited-state double proton transfer may also take place in the Watson-Crick base pairs producing tautomeric forms of the nucleobases. Meanwhile, one common lesion caused by reactive oxygen species (ROS) is the addition of the OH radical, and also ·H, to the ethylene bond of pyrimidines. Finally, low-energy ballistic electrons originated during the irradiation of the biological material produce dissociative electron-attachment processes in the nucleobases and might end in strand brakes.

During the last years, we have performed accurate photochemical reaction-path computations using multi-reference multiconfigurational methods to determine the mechanisms of the aforementioned DNA/RNA lesions. On the basis of the results obtained, we could rationalize the different quantum yields of formation of CPDs[3] and describe the thermal and photochemical inter-conversion between the canonical and tautomeric nucleobases.[4] In addition, we determined the absorption properties of the transient radicals formed by the addition of the ·OH/·H to the pyrimidines and we explored the photochemistry of these adducts.[5] In this context, we found photochemical paths which regenerate the canonical nucleobase. These channels might be accessible by irradiation of visible light and therefore might imply a photo-protection mechanism. For the DEA phenomena in nucleobases, we described the role of dipole- and valence bound anionic states of the bases and the distinct behavior of guanine as compared to adenine and the pyrimidines.[6] In this contribution, we will briefly summarize the findings obtained and comment on their relevance in the field of DNA/RNA damage.

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Photoinduced Processes in Nucleic Acids: From Prebiotic Synthesis to Stability of Genetic Code

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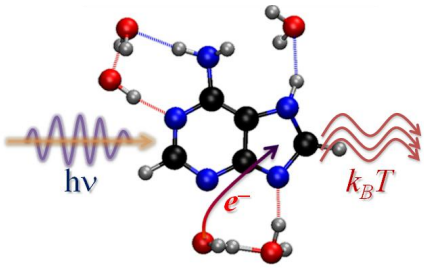
Nucleic acids are efficient UV chromophores and their exposition to solar irradiation may lead to deleterious photochemical reactions. Photoinduced processes in nucleic acids constitute a complex field of research [1], covering from photoexcitation of isolated nucleobases and base pairs, where ultrafast internal conversion dominates; to DNA *in vivo*, where enzymatic photo-repair efficiently fix photochemical impairments.

In the last years, we have worked on diverse topics within this field, including internal conversion mechanisms in isolated nucleobases in the gas phase [2] and in water [3] (figure), isomerization effects [4], damage and repair of thymine dimmers [5], and the impact of UV radiation on prebiotic synthesis of nucleotides [6]. This research has been based on quantum chemical methods, including nonadiabatic dynamics simulations.

In this talk, I will discuss our most recent results and critically appraise the strengths and limitations of the available theoretical methods [7] to deal with these phenomena.



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Tuning Excited State Properties of Photosensitizers by Rational Functionalization

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Photosensitizers are usually employed as anticancer drugs by inducing DNA damage into cancer cells in photodynamic therapy. Methylene blue is a type II photosensitizer, which has shown promising results for tumor treatment [1]. The mode of action of type II photosensitizers is related to the generation of triplet excited states by intersystem crossing, and further energy transfer to the molecular oxygen present in the environment. Thus, rationalizing the factors that influence intersystem crossing in biological environment is crucial to improve the efficacy of photodynamic therapy.
Laser flash spectroscopic experiments have shown that the triplet generation quantum yield of methylene blue drastically decreases upon addition of different amounts of DNA [2]. This was explained by the quenching of the bright state of the dye by electron transfer from the guanine and adenine residues. Although electron transfer reactions between the photosensitizer and DNA can be considered as DNA damage by themselves, the degradation of the photosensitizer by electron transfer avoids further excitation of oxygen by energy transfer from the triplet state of the dye, lowering the efficacy of the photodynamic treatment. Electron transfer from the nucleobases to methylene blue can be suppressed by a suitable functionalization of the dye with electron donors groups, as was suggested recently by us [3]. The insertion of electron donor substituents on the aromatic system of methylene blue red-shifts the electronic states involved in intersystem crossing. This way, the charge transfer state, which inhibits the triplet state generation, is not energetically accessible and does not participate in the deactivation mechanism of the drug. Here, we show how a rational functionalization of methylene blue was carried out based on QM(CASPT2 and TD-DFT)/MM(Amber) calculations and simple molecular orbital theory concepts, and how the charge-transfer excited state can be easily identified by calculating the charge transfer numbers [4] from the one electron transition density matrix.

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Photophysics and Photochemistry in DNA: How little we know, How much to discover

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By discussing some of the results obtained in the theoretical study of the excited state behavior of realistic oligonucleotides, we shall give some insights in the complexity of the dynamical processes triggered in DNA by absorption of UV light, pointing out some of the open issues and of the challenges to be tackled. We shall focus mainly on oligoAdenine,[1,2], dipyrimidine[3-5] and dipurine[6] steps, GC and AT double strands [7,8] and Guanine Quadruplex helices[9]. Our studies show that different kind of excited states, each one often responsible of a different spectral signature and in dynamic equilibrium, are involved in the deactivation pathways.

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DNA Electronic Circular Dichroism Spectra at the Inter-Base Pair Scale

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DNA is the central molecule of life. While it is mainly known for its storage of genetic information, DNA is also involved in a myriad of molecular recognition events and activities of DNA-protein complexes and is capable of maintaining its supramolecular structures. These functions may be significantly affected by slight structural modifications of DNA, and the development of tools to predict its conformation is thus crucial to understand DNA biochemical processes.

Over the past years, circular dichroism (CD) has been widely used to elucidate the several conformations of DNA in solution (e.g., A-, B-DNA or G-quadruplexes).[1] Theoretical CD calculations are relevant to rationalize and forecast DNA chirality at the nanoscale. However, computational cost appears as a bottleneck for calculating the entire DNA CD-spectra regarding the size of the system. This may be bypassed by using a building-block approach based on base-pair dimers, i.e., by evaluating and summing two-body ECD contributions between direct neighbours. By reducing an entire double strand (ds) DNA to multiple base-pairs, each ECD two-body contribution can then be calculated using the complex polarization propagator (CPP) approach[3] in conjunction with DFT. This is successfully applied here to rationalize the ECD spectra of B-DNA dsDNA (dA)20(dT)20 case study as well as a nucleosomal DNA.[4]

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Simulations of Complex Chemical Reactions. The Case of the Enzymatic C5-Methylation of DNA

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Analysis of complex chemical processes in condensed phases usually implies the exploration of multidimensional free energy surfaces. This goal may require an unaffordable computational cost because of the size of the system and the number of coordinates that need to be explored. This is the case of the enzymatic C5-Methylation of DNA, a chemical process that involves several chemical events that can happen concertedly or sequentially. A convenient strategy is to combine hybrid QM/MM descriptions with methods that focus on the relevant regions of the free energy surface, such as the string method. Here we will show that this strategy gives a complete description of the molecular mechanism of this complex chemical reaction in good agreement with experimental findings. Our proposal clarifies the role of Glu119 and identifies the nature of the base in charge of proton abstraction, two issues that have been the subject of a long debate in the literature.

Structural communication in DNA binding domains of transcription factors: how interactions with DNA, mutations or post-translational modifications reshape the interfaces for cofactor recruitment.

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Little is known about the molecular mechanisms related to the conformational changes induced at distal sites in many transcription factors, which are often related to cancer disease, such as p53 and the family of ARID domains. Thus, my group is focusing on the characterization of their structural dynamics to enrich the knowledge on this important group of regulatory proteins. In particular, we are employing a combined approach that integrates atomistic microsecond molecular dynamics simulations, enhanced sampling techniques, methods inspired by graph theory [1,2] and cross-validation of the simulated ensembles with NMR data [3]. To relate these properties to protein function we studied both the free and DNA-bound forms of wild type, mutated and phosphorylated variants of p53, ARID proteins [4] and other domains of transcription factors. The interaction with DNA not only stabilizes the conformations of the DNA-binding loops, but also strengthens pre-existing paths in the free
protein for long-range communication to potential interface for cofactor recruitment. Conformational states of these distal regions that are only a minor population of the free ensemble are promoted by DNA interactions, altering the preferences for certain classes of biological partners and thus influencing the signaling pathways mediated by these proteins. Moreover, mutations or post-translational modifications can also contribute to reshape the population of these interfaces. One future direction of our research will be to apply the same methods to the study the DNA-protein interactions of proteins involved in DNA mismatch repair, a crucial pathway for cellular control of DNA damages.

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Revisiting Rare Tautomeric Forms in DNA: A Theoretical Model for Predicting Genetic Mutations

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As already noted by Watson and Crick by 1953, the correct replication of DNA rests on the assumption that the original genetic sequence of the adenine-thymine (AT) and guanine-cytosine (GC) base pairs is fully preserved during the process [1]. However, protons along the interbase hydrogen-bond network are not static entities but they can be exchanged through proton transfer (PT) reactions. The resulting non-canonical A*T* and G*C* structures are the so-called rare tautomers. In Watson and Crick's words: "It would be of interest to know the precise difference in free energy between the various tautomeric forms under physiolog- ical conditions". Unfortunately, rare tautomeric forms are very difficult to detect [2], so no direct and accurate free energy measure has been discerned. In contrast, theoretical chem- istry could provide an accurate quantification of PT reactions in DNA and their biological consequences [3]. In this talk, we overview the literature as well as part of our current work devoted to assess the importance of rare tautomers as promoters of mutations in DNA [4].

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Structural and mechanistic study of dUTPases reveals the catalytic roles ofan arginine finger-like residue

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The dUTPase enzymes catalyse the hydrolysis of dUTP to dUMP. In this way dUTPase removes dUTP from the deoxynucleotide pool, avoiding U to be misincorporated in DNA, and produces dUMP that is a precursor of dTTP. Inhibition of dUTPase produces an increment of the dUTP/dTTP ratio in the nucleotide pool resulting in increased uracil content of DNA that activates a hyperactive futile cycle of DNA repair.

dUTPase is a trimer of identical subunits containing one active site each. The C-terminal arm of each monomer determines the catalytic efficiency and contribute to selectivity of the enzyme. This segment contains a conserved Arg directly preceding a glycine-rich P-loop-like motif. Numerous studies demonstrated that the presence of this conserved arginine together with the P-loop-like motif are critical for optimal catalytic efficiency.

In the present study, we focus on the role of the conserved Arg in the mechanism of the trimeric dUTPase from Mycobacterium tuberculosis. As this Arg governs interprotomer catalysis while being located on a distant loop, we propose that it conceivably meets the requirements established for Arg fingers. We address its contribution to the catalytic mechanism of Mycobacterium tuberculosis dUTPase by investigating constructs of with either deletion of the P-loop-like motif or exchange of the conserved arginine. The structural data from crystallography and molecular dynamics simulations together with kinetic and ligand binding analyses reveal the unique role for the Arg in active site organization and providing optimal ligand geometry for catalysis. QM/MM calculations are performed to quantitatively assess the structural and electrostatic contributions of the Arg in catalysis.

Reactivity of the triplet excited state of thymine and its derivatives

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Thymine (Thy) triplet excited state, populated either directly or through photosensitization, is an essential species in the processes involved in DNA damage. Its photochemistry has been related to the formation of dimeric lesions like the well-known cyclobutane dimers (CPD). By contrast, and according to the generally accepted paradigm, the (6-4) photoproducts (6-4PP) formation only occurs upon direct irradiation from a singlet excited state. First, the attention will be centered on the CPD photosensitization by exogenous and endogenous photosensitizers. Indeed, the triplet energy of thymine in DNA is a critical parameter as the feasibility of triplet-triplet energy transfer is linked to the excited state energies of the donor (photosensitizer) and acceptor (thymine) compounds. Its precise value has been established through combination of laser flash photolysis experiments and agarose gel electrophoresis.[1] Next, the ability of 64PP to play the role of an intrinsic UVA-photosensitizer will be addressed through the study of their 5-methyl-2-pyrimidone chromophore.[2] The overall results reveal that 64PP can act as a Trojan horse promoting DNA lesions in its neighbourhood. This result is of particular importance in relation with clustered DNA damages, which are hardly repaired and are responsible for critical biological events. Finally, the photochemistry of Thy from upper triplet excited states will be explored by considering the Norrish−Yang photocyclization as typical nπ* photoreaction. From the obtained results, it is proposed that part of the assumed "singlet" Thy photoreactivity, like the Paternò-Büchi photoreaction leading to 64PP formation, can proceed instead from an upper triplet excited state with the appropriate electronic configuration.[3]

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Monitoring the UV-photoinduced events in solvated nucleosides: first steps towards accurate time-resolved non-linear electronic spectroscopy

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Photoinduced events occurring in the genomic material upon UV-light irradiation are of paramount interest as they relate directly to the intrinsic photostability of the DNA/RNA,[1] as well as to the triggered photochemical pathways leading to photo-damage.[2] These deactivation channels are often coupled and cannot be directly resolved with standard pump-probe spectroscopic techniques.[3] In order to tackle the problem from a bottom-up approach, the photophysics and photochemistry of water-solvated nucleosides,[4] adenosine in particular, are here characterised within a CASSCF/CASPT2 QM/MM protocol.[5] The photoinduced events are described in terms of both static and dynamic approaches, featuring conical intersection characterisations and minimum energy path computations, together with semi-classical excited state trajectories yielding a time-resolved estimate. Novel bidimensional optical spectroscopic techniques, recently introduced by coupling the QM/MM scheme with non-linear response theory,[6-8] are then used on top of the static and dynamic pathways characterised. Monomeric species and their fingerprints are firstly tackled and their main fingerprints characterised yielding a robust approach to differentiate the monomer-localised processes. The model is then extended to deal with dimeric diribonucleotide systems,[9] comprising a range of π- and T-stacking interacting motifs enhancing a variety of intermolecular interactions with overlapping spectroscopic fingerprints requiring novel approaches for their accurate characterisation. Theoretical bidimensional electronic spectroscopy methods are then employed to provide state-specific fingerprints to unequivocally disentangle the diverse photo-excited decay channels populated upon UV-light absorption and their concrete contributions as well as their dependence on relative conformation.

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A theoretical study on the OH/H radical addition to DNA/RNA pyrimidines and the photochemistry of the adducts

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Cellular DNA is constantly exposed to reactive species that can alter the natural structure of the DNA/RNA nucleobases.[1] It has been demonstrated that an unbalanced oxidative stress can cause DNA-protein crosslinking and/or DNA/RNA strand breaking, producing mutations in the genetic material. These modifications may ultimately lead to cell death or even serious diseases like cancer or neurodegeneration, among others.[2] Understanding the complex mechanisms behind this important processes at the molecular level requires the contribution of both experimental and theoretical approaches.

In the present communication, we will discuss on recent findings obtained in the theoretical study of the OH/H radical addition to the C5=C6 double bond of DNA/RNA pyrimidines.[3,4] The ground-state reactivity between the free radicals and the nucleobases, as well as the absorption properties and photochemistry of the formed adducts have been determined by means of the CASPT2//CASSCF protocol. The findings help to interpret the experimental observations recorded during the last decades and shed light into the molecular mechanisms of the DNA/RNA damage.

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Ultrafast Population of the Benzophenone Triplet Manifold: a Photochemical Study for an Improved Understanding of DNA Photosensitization

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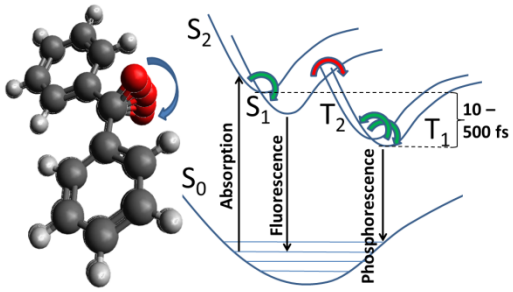
The photochemistry of benzophenone, a paradigmatic organic molecule for photosensitization processes, was investigated by means of extensive surface-hopping excited-state molecular dynamics and compared with the available experimental and theoretical data [1]. Different mechanisms were found to be relevant in the femtosecond time scale, from 10 to 600 fs: the long debated direct ($S_1 \rightarrow T_1$) and indirect ($S_1 \rightarrow T_2 \rightarrow T_1$) mechanisms for population of the low-lying triplet state are both possible, eventually allowing a kinetic equilibrium between T_1 and T_2 states never observed before, and of particular interest for benzophenone-mediated photo-induced energy transfer towards DNA [2].



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