# WORKSHOP DELLA DIVISIONE DI CHIMICA TEORICA E COMPUTAZIONALE - DCTC 2022 -

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April 8th 2022 | 10:00 – 17:30 |
Aula Magna del Rettorato dell’Università degli Studi di Firenze

**SCIENTIFIC COMMITTEE:**

**Prof. Isabella Daidone**
**Prof. Giovanna Fronzoni**
**Prof. Claudio Greco**
**Prof. Gloria Mazzone**
**Prof. Maria Cristina Menziani**
**Prof. Michele Pavone**
**Prof. Mirco Zerbetto**

**ORGANIZING COMMITTEE:**

**Prof. Carlo Adamo**
**Prof. Gianni Cardini**
**Prof. Marco Pagliai**

## Programma

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| 10:00 - 10:15 | Introduzione e saluti |
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| **I sessione** | Chair: Prof. Carlo Adamo |
| 10:15 - 11:00 | Conferenza Prof. Vincenzo Barone |
| 11:00 - 11:30 | Consegna medaglie e targhe ai vincitori dei premi Roetti, Scrocco e Del Re 2020 e 2021 |
| 11:30 - 11:45 | Giulia Dall'Ostio (Premio Nordio) |
| 11:45 - 12:00 | Edoardo Donadoni (Premio Nordio) |
| 12:00 - 12:15 | Davide Accomaso |
| 12:15 - 12:30 | Matteo Capone |
| 12:30 - 12:45 | Diego Sorbelli |
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| 12:45 - 14:30 | Pausa pranzo con sessione poster |
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| **II sessione** | Chair: Prof. Gianni Cardini |
| 14:30 - 15:15 | Conferenza Prof.ssa Elisabetta Venuti |
| 15:15 - 15:30 | Laura Gueci |
| 15:30 - 15:45 | Federico Coppola |
| 15:45 - 16:00 | Jacques Kontak Desmarias |
| 16:00 - 16:15 | Marco Mendolicchio |
| 16:15 - 16:30 | Michele Casoria |
| 16:30 - 16:45 | Edoardo Cignoni |
| 16:45 - 17:00 | Giacomo Salvadori |
| 17:00 - 17:15 | Jonathan Campeggio |
| 17:15 - 17:30 | Marina Macchiagodena |

La cerimonia di premiazione dei vincitori dei premi Roetti, Scrocco e Del Re 2020 e 2021 prevede la consegna delle medaglie e targhe. I vincitori esporranno in un flash talk di 5 minuti l'evoluzione delle loro ricerche.
I vincitori del premio Nordio 2020 e 2021 riceveranno l'attestato al termine del loro intervento.

# Premi

**Premio Del Re**

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| 2020 | Giovanni Di Liberto |
| 2021 | Eduardo Schiavo |

**Premio Scrocco**

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| 2020 | Lorenzo Cupellini |
| 2021 | Greta Donati |

**Premio Roetti**

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| 2020 | Nicola Tasinato |
| 2021 | Alessandro Erba |

# BOOK OF ABSTRACTS

# INVITED SPEAKERS

# *A four-pillar approach to computational chemistry: astrochemistry as a proof of concept*

*Vincenzo Barone*, SMART Laboratory, Scuola Normale Superiore, Pisa

A fascinating and complex chemistry takes place in the interstellar space and on exoplanets, where simple, small molecules start their evolution toward the key bricks of the life [1]. Although unbiased understanding of the involved systems and processes would shed light also on the origin of life in the primordial Earth, the processes that lead to the production of molecules are still a matter of debate; currently, knowledge is still at a rather primitive stage. The main goal of this presentation is to sketch a possible route for disclosing the secrets of the initial steps of chemical evolution in those unconventional environments by means of a "four-pillar virtual strategy" which integrates state-of-the-art quantum chemical methods (Pillar 1) with large-scale stochastic simulations (Pillar 2) relying also on artificial intelligence (AI) (Pillar 3) and virtual reality (Pillar 4) for further improving the reliability of the results and effectively cross widely different space and time scale [2]. The goal requires the development and integration of new models and algorithms and their implementation in a virtual infrastructure by which quantum chemistry [3], statistical mechanics [4], artificial intelligence [5] and visualization [6] tools can be deployed with the aim of selecting the most effective strategy for addressing key problems of astrochemical interest Starting from the already available technological backdrop (high-performance computing and virtual reality), a number of cutting-edge theoretical/computational advancements are needed, namely: (a) development and implementation of new quantum-chemical methods [7], (b) development/extension of multi-scale simulations and machine learning methods to model complex systems [8], (c) implementation of powerful kinetic models that balance accuracy and feasibility [9], and (d) integration with top-notch experimental data [10]. The integration of all the above items will create a new research paradigm of interest also for other scientific fields.

[1] C. Puzzarini, V. Barone, *A never-ending story in the sky: The secrets of chemical evolution*, Phys. Life Rev. **32**, 52-94 (2020).

[2] V. Barone, C. Puzzarini, G. Mancini, *Integration of Theory, Simulation, Artificial Intelligence and Virtual Reality: A Four-Pillar Approach for Reconciling Accuracy and Interpretability in Computational Spectroscopy*, Phys. Chem. Chem. Phys. **23**,17079-17096 (2021).

[3] C. Puzzarini, J. Bloino, N. Tasinato and V. Barone, *Accuracy and Interpretability: The Devil and the Holy Grail. New Routes Across Old Boundaries in Computational Spectroscopy*, Chem. Rev. **119**, 8131-8191 (2019).

[4] S. Del Galdo, M. Fusè, V. Barone, *The ONIOM/PMM model for effective yet accurate simulation of optical and chiroptical spectra in solution: camphorquinone in methanol as a case study*, J. Chem. Theory Comput. **16**, 3294-3306 (2020).

[5] G. Mancini,M. Fusè, F. Lazzari, B. Chandramouli, V. Barone, *Unsupervised search of low-lying conformers with spectroscopic accuracy: a two-step algorithm rooted into the island model evolutionary algorithm*, J. Chem. Phys. **153**, 124110 (2020).

[6] F. Lazzari, A. Salvadori, G. Mancini, V. Barone, *Molecular Perception for Visualization and Computation: The Proxima Library*, J. Chem. Inf. Model. **60**, 2668-2672 (2020).

[7] M. Mendolicchio, J. Bloino, V. Barone, *General perturb then diagonalize model for the vibrational frequencies and intensities of molecules belonging to Abelian and non-Abelian symmetry groups*, J. Chem. Theory Comput. **17**, 4332-4358 (2021).

[8] G. Mancini, M. Fusè, F. Lipparini, M. Nottoli, G. Scalmani, V. Barone, *Molecular Dynamics Simulations Enforcing Nonperiodic Boundary Conditions: New Developments and Application to the Solvent Shifts of Nitroxide Magnetic Parameters*, J. Chem. Theory Comput. **18** (2022), DOI:10.1021/acs.jctc.2c00046.

[9] V. Barone, J. Lupi, Z. Salta, N. Tasinato, *Development and validation of a parameter-free model chemistry for the computation of reliable reaction rates*, J. Chem. Theory Comput. **17**, 4913-4928 (2021).

[10] G. Ceselin, V. Barone, N. Tasinato, *Accurate Biomolecular Structures by the Nano-LEGO Approach: Pick the Bricks and Build Your Geometry*, J. Chem. Theory Comput. **17**, 7290-7311 (2021).

## The synergy between Raman experiments and computed crystal structures and spectra

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Different crystal structures may be conveniently identified by their Raman spectra in the region of the lattice phonon modes, where they display their own, unique features. Indeed, while the intramolecular vibrational spectrum of a compound probes its chemical identity, the lattice modes, associated to the weak dispersion forces of the inter-molecular field, probe the crystal dynamics, and are therefore sensitive even to slight structural differences.

Confocal lattice phonon Raman microscopy has proved to be a valuable tool for the investigation of a system solid state, to be used for non-invasive and prompt structure recognition at the micrometric scale, the effectiveness of which is greatly enhanced by the association with accurate solid state vdW-corrected DFT calculations. The accuracy and reliability of these methodologies to describe and predict not only crystalline structures, but also intermolecular vibrations will be addressed. A variety of polymorph identifications and recognitions both in the bulk and in thin film phases of organic systems, as well as applications to the study of photochemical reactions, will be presented.

# TALKS

# The Fascinating Multifaceted World of Chemistry

Greta Donati

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## ABSTRACT

The timescale of chemical phenomena strongly affects the choice of the theory level and the computational strategy employed to properly simulate the desired properties/processes. In this contribution three challenging case studies in which the timescale of the phenomena and the size of the systems under investigation determined the choice of three totally different theoretical-computational approaches, are presented.

1) The challenging case of Green Fluorescent Protein (GFP) excited state proton transfer. To understand the molecular driving forces of the photo-induced reactivity of GFP chromophore and the mechanism of the reaction, excited state ab-initio molecular dynamics simulations were performed and the whole protein was taken into account through a hybrid QM/MM approach.[1] *Picosecond timescale*
2) The plasmon excitations in noble metal nanoparticles are importantly affected by nuclear motion on the sub-picosecond timescale. The understanding of how nuclear dynamics influences the plasmon excitation decay in linear silver chain was carried out through non-adiabatic Ehrenfest dynamics.[2] *Femtosecond timescale*
3) Composite materials based on polymers filled with carbon nanotubes show peculiar electrical and thermal properties. The role of applied voltages, polymer matrix and filler concentration on Joule effect, characterizing these materials, was investigated by describing the systems at coarse grain level and simulating Joule effect through an in-house written code.[3] *Nanoscecond timescale*

Currently, I am focused on drug-discovery and investigation of drug-receptors interactions through classical MD and molecular docking simulations.[4] *Microsecond timescale*

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# Investigating ultrafast two-pulse experiments on single DNQDI fluorophore: a stochastic quantum approach

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## ABSTRACT

In the last decades, together with ensemble approaches, as two-dimensional electronic spectroscopy, single-molecule techniques have been recently developed.[1,2] In particular, ultrafast two-pulse experiments on single molecules are invaluable tools to investigate the microscopic dynamics of a fluorophore.[3,4] The first pulse generates electronic or vibronic coherence, the second pulse probes the time-evolution of the coherence. We set up a protocol based on a quantum mechanical description of the fluorophore coupled to the simulation of the real-time dynamics of the system wave-function. The vibronic structure of the molecule is included in terms of vibronic states energy and transition dipole moments. The dynamics of molecules interacting with pulses at ultrafast scale is influenced by quantum coherence decay induces by the presence of a surrounding environment therefore the fluorophore is considered as an open quantum system.[5] The molecule dynamics is computed through the stochastic Schrödinger equation (SSE)[6,7] within the Markovian limit.[8] In this model, dissipation and fluctuations due to the environment are included by means of stochastic terms in every realization of the wave function evolution. This protocol[9] has been applied to DNQDI fluorophore previously investigated experimentally.[10] The ground and first excited electronic states have been dressed with a manifold of vibrational states, whose energies and transition dipole moments have been computed with DFT/TDDFT methods. The dynamics has been computed with a homemade code, WaveT[8,11], including the experimental values of relaxation and coherence decay rate.[10] We find a good agreement with the experimental outcomes and provide a microscopic and atomistic interpretation.

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# Molecular dynamics simulations of doxorubicin in phospholipid membranes

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## ABSTRACT

Doxorubicin (DOX) is one of the most efficient antitumor drugs employed in numerous cancer therapies. Its incorporation into lipid-based nanocarriers, such as liposomes, improves the drug targeting into tumor cells and reduces drug side effects. The carriers' lipid composition is expected to affect the interactions of DOX and its partitioning into liposomal membranes. To get a rational insight into this aspect and determine promising lipid compositions, we use numerical simulations, which provide unique information on DOX-membrane interactions at the atomic level of resolution. In particular, we combine classical molecular dynamics simulations and free energy calculations to elucidate the mechanism of penetration of a protonated Doxorubicin molecule ($DOX^+$) into potential liposome membranes, here modeled as lipid bilayers based on mixtures of phosphatidylcholine (PC), sphingomyelin (SM) and cholesterol lipid molecules, of different compositions and lipid phases. Moreover, we analyze $DOX^+$ partitioning into relevant regions of SM-based lipid bilayer systems using a combination of free energy methods. Our results show that $DOX^+$ penetration and partitioning are facilitated into less tightly packed SM-based membranes and are dependent on lipid composition. This work paves the way to further investigations of optimal formulations for lipid-based carriers, such as those associated with pH-responsive membranes.

## REFERENCES

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# Shedding light on the ultrafast photochemistry of carotenoids: surface hopping simulations of lutein in condensed phase

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## ABSTRACT

Carotenoids are natural pigments synthesized by photosynthetic organisms. They are found in higher plants and in a wide variety of bacterial and algae. In these organisms, carotenoids serve several important functions[1]. They act as light-harvesting pigments by absorbing light in regions of the visible spectrum where the chlorophyll absorption is not efficient. Moreover, carotenoids play a crucial role in the photoprotection of photosynthetic organisms, and stabilize the structure of many photosynthetic pigment-protein complexes.

Many of the natural functions of carotenoids are directly linked to the electronic excited states of such pigments. Thanks to a large number of spectroscopic and theoretical investigations it is now clear that in most carotenoids the lowest-energy optically allowed transition is $S_0 \rightarrow S_2$. The absorption from the ground state ($S_0$) to the lowest excited state $S_1$ is instead forbidden. Upon photoexcitation the generated $S_2$ state can decay to $S_1$, from which the transition to $S_0$ occurs. However, in the $S_1 \rightarrow S_2$ ultrafast decay the participation of a third state, called $S_x$, was detected[2-4], and the character of this intermediate state is still under debate[1,5]. The characterization of the aforementioned $S_x$ state is important to fully understand the light-harvesting function of carotenoids, since this state may be involved in the energy transfer towards chlorophylls[6].

Here, we present simulations of the excited state dynamics for a xanthophyll carotenoid, namely lutein, in methanol solution. The simulations were performed using the surface hopping method[7,8] and a quantum mechanics/molecular mechanics (QM/MM) scheme in which the QM lutein is embedded in a cluster of MM methanol molecules. The electronic states of lutein were computed using a semiempirical configuration interaction technique[7], with parameters specifically optimized for the system under study. Our simulations provide important insights into the ultrafast decay from the photogenerated $S_2$ state to $S_1$, including a clear characterization of the intermediate state $S_x$.

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# Primary Charge-Separation Heterogeneity in Photosystem-II

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## ABSTRACT

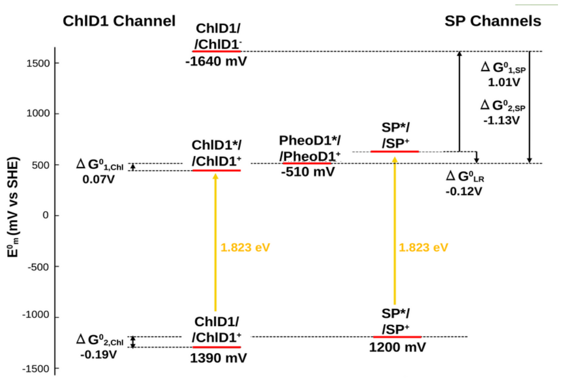
Photosystem II (PSII) is a multi-subunit protein complex that harvests sunlight to perform oxygenic photosynthesis. Light-driven charge-separation (CS) takes place at the reaction center, which consists of two paired chl-*a* called the special pair (SP), two accessory chl-*a* (ChlD1 and ChlD2) and two pheo-*a* (PheoD1 and PheoD2).

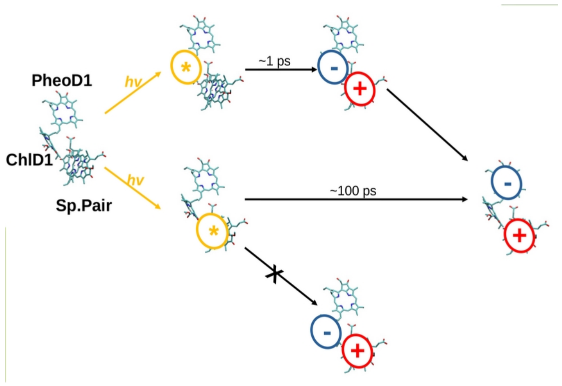
The kinetics of formation of the metastable radical pair within the reaction center (namely $SP^+/PheoD1^-$) after excitation of the primary electron donor shows several components [1]: a first, fast CS on the order of 1-5 ps, which is attributed to the formation of the intermediate radical pair $ChlD1^+/PheoD1^-$, and a second component on a timescale of tens of ps, which is assigned to the formation of the metastable $SP^+/PheoD1^-$ pair. Moreover, at least two other slower components associated to the formation of the $PheoD1^-$ anion have been observed, for which an unambiguous interpretation is still lacking.

Here, we employ a multi-scale approach based on molecular dynamics simulation, quantum chemical calculations and the Perturbation Matrix Method (PMM) [2,4] to study the thermodynamics and kinetics of the light-driven primary charge separation process. In particular, we compare the three most discussed charge separation pathways in the literature [1,3]:

(i) $ChlD1^*/PheoD1 \rightarrow ChlD1^+/PheoD1- \rightarrow SP^+/PheoD1^-$
(ii) $SP^*/ChlD1 \rightarrow SP^+/ChlD1^- \rightarrow SP^+/PheoD1^-$
(iii) $SP^*/PheoD1 \rightarrow SP^+/PheoD1^-$

The thermodynamic calculations indicate that only two of the proposed primary CS channels are feasible, namely (i) and (iii). The calculated time-constant associated to these two CS pathways highlight that (i) is compatible with the two fast components experimentally observed, while (iii) fits well with the slow components providing evidence for the presence of a long-range, secondary CS process in PSII at room temperature.





# REFERENCES

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# Natural Orbitals for Chemical Valence: a tool for an in-depth quantitative description of carbon dioxide activation processes

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## ABSTRACT

The intense research around carbon dioxide activation processes, which follows the dramatic increase of its concentration in the atmosphere, requires unequivocally a detailed knowledge of the factors that control its reactivity. From a chemical perspective, since carbon dioxide displays an amphoteric behaviour (having an acidic carbon and basic oxygen atoms), different interactions with the substrate used for its activation take place simultaneously and clearly disentangling these interactions is not straightforward task.

Computational chemistry is surely a valuable aid in this framework. There are a plethora of computational tools that would allow the analysis of the $CO_2$-substrate interaction. Among others, the Natural Orbitals for Chemical Valence (NOCV) approach[1] is probably one of the most powerful. Based on the electron density rearrangements upon interaction between two (or more) fragments, this tool decomposes the rearranged electron density in chemically meaningful contributions. This approach has been successfully used in a wide range of scenarios (analysis of metal-ligand interactions, covalent bonds in main group chemistry, hydrogen and halogen bonds,…).

In this contribution, we use the NOCV approach for an in-depth analysis of the activation and insertion of $CO_2$ in the Au-X (X=Al,Ga,In) bond of a series of gold-aluminyl, -gallyl and -indyl complexes,[2,3] which can be considered as a case study for cooperative $CO_2$ activation processes and serve as a model for both homogeneous and heterogeneous processes. The results show that the NOCV approach allows not only to decompose and analyse clearly each $CO_2$-substrate interaction taking place, but also the chemical bonds in the substrate that play a central role in activating $CO_2$. Furthermore, by coupling the NOCV method with other approaches, such as the Energy Decomposition Analysis (EDA)[4] and the Charge Displacement (CD)[5] analysis, it is possible to obtain a quantitative measure of the strength of each interaction. We show that such coupled strategies are fundamental in those cases where the Potential Energy Surfaces (PESs) have a peculiar topology or where, in general, an analysis based on simple parameters (such as bond lengths and bending angle deformations in carbon dioxide along the reaction path) may ultimately yield to a misleading interpretation of the observed reactivity.

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# Oxidation functionality of $MnO_x$ catalysts: a DFT study to unveil atomistic features

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## ABSTRACT

Manganese oxide-based catalysts ($MnO_x$) feature good activity and selectivity towards oxidation of a wide range of substrates, being preferred to noble metals due to great availability and low-cost. However, deactivation phenomena by over-oxidation and/or poisoning of active sites are generally recorded also for these catalysts [1-3].

Synergistic approaches involving experimental investigations and quantum chemistry calculations, mostly based on Density Functional Theory, showed to be important in highlighting the fundamental aspects of catalytic reactions enabling the development of effective catalysts and processes.

In this framework, a DFT study was performed on cluster-sized catalyst models, namely $Mn_4O_8$ and over-oxygenated $Mn_4O_9$ fragments, to predict the reactivity pattern of $MnO_x$ catalysts in the aerobic oxidation of benzyl alcohol to benzaldehyde, the consecutive formation of benzoic acid being also addressed. A systematic comparison of the oxidation mechanisms on the two fragments revealed some experimental strategies that could be used to design alternative catalytic routes and thus decrease undesired parasitic reactions leading to catalyst deactivation. In particular, the formation of water should be avoided, whose production on the surface seemed to be related either to the occurrence of Mars-van Krevelen mechanisms or to the presence of gas phase oxygen [1,2].

Further highlighting the role of oxygenated species in the reactions carried out on $MnO_x$ catalysts, the oxidation functionality of Mn(IV) sites towards CO and $H_2$ has been assessed through an analysis of adsorption and activation energies on the model $Mn_4O_8$ cluster, in presence and absence of $O_2$. DFT calculations indicate that Mn sites prompt an easy CO conversion to $CO_2$ via a reaction path involving both catalyst and gas-phase oxygen species, while much greater energy barriers hinder $H_2$ oxidation, in accordance with experimental data on the investigated $MnCeO_x$ catalyst [3].

Therefore, the present study corroborate the potential of $MnO_x$ materials as efficient, low-cost and robust catalysts fot the preferential oxidation of CO over $H_2$ and the selective benzyl alcohol oxidation to benzaldeyde, showing an effective sinergy between calculation and experiment.

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# Theoretical and Experimental Approaches to Understand Singlet Fission in Organic Semiconductors

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One of the greatest challenges that humanity is facing is the exhausting search for new energy sources that are clean, easy to use and that can avoid the worst consequences of climate change induced by the combustion of fossil fuels. Among the various forms of alternative energy to those based on petroleum products, the organic electronic has an exceptional potential in converting energy from sunlight to usable energy forms, that can lead to renewable, cheap and clean energy sources which are starting to become part of our everyday life. This pressing request to supplant fossil fuels has pushed modern research areas to advance in the field of organic electronics through the rational synthetic approach to get new electron-donor -acceptor molecules to be used in organic solar cells and photovoltaics. **[1]** The Shockley-Quessier limit **[2]** imposes a maximum conversion threshold (photon - exciton, 1→1) equal to 33% due to heat dissipation that decreases the potential of the photovoltaic cells. A valid strategy to overcome such theoretical limit is to exploit photophysical processes, known as *multiple exciton generation* as Singlet Fission (SF), that are able to give a 1→2 conversion, boosting the overall efficiency up to 100%. Indene-fused aromatic class of compounds have been recently proposed as potential candidate for Singlet Fission **[3]**. The molecular compounds that we investigated in this work belong to the asymmetrically substituted diarylindenotetracenes compounds, **[4]** which have been recently synthetized and characterized. In this contribution we show how a synergistic approach between theory and experiments (as vibrational and electronic time-resolved spectroscopies) allows one to understand the chemical-physical processes underlying SF. In the last few years accurate theoretical protocols were developed to interpret equilibrium and transient phenomena such as time-resolved fluorescence, reactivity in the excited states, polaron pair formation in organic polymers and photorelaxation in solution. **[5]** We provide, for the first time, the spectroscopic characterization of the crystals through UV-Vis spectroscopy and Raman spectroscopy for the ground state. The experimental results were interpreted with the help of DFT and TDDFT calculations. Thanks to time-resolved spectra, for the excited state we got some first insights about the SF event in these new molecules. The presence of features in the transient absorption spectrum could indicate that following photoexcitation triplet excitons or trapped excitons are generated. A preliminary analysis of the Femtosecond Stimulated Raman spectrum suggests that there is no charge transfer intermediate during the process, unlike as observed in previous cases. **[6]**

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# DFT Approaches for Spin-Orbit Coupling in Periodic Systems

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## ABSTRACT

The conventional Hohenberg-Kohn density functional theory, based entirely on the electron density, allows to express the total energy of a non-relativistic fermionic system in an external field described by a scalar multiplicative potential.[1] The theory may be generalized to include relativistic effects, such as spin-orbit coupling (SOC), by removing the restriction that the external field must be scalar and multiplicative. Unfortunately, the consequence of removing this limitation is that the energy becomes a functional of not only the electron density. It then depends on a much larger set of density variables (namely the magnetization or spin, the currents of the electron density and the currents of the spin), leading to the so-called spin-current DFT (SCDFT).[2] Although the SCDFT provides a formal route to including SOC in the DFT, the explicit parametrization of the energy functional in terms of such an extended set of density variables remains a formidable task.[3] Here we show how SCDFT can be made practical for calculations on molecules and infinite periodic systems through our *good old friend*, the hybrid exchange-correlation functional.[4,5] Practical computer implementations in the CRYSTAL code are discussed, based on the two-component self-consistent field approach and the coupled-perturbed Kohn-Sham approach.[6,7,8,9,10] A pilot application on the TaAs Weyl semimetal shows that inclusion of the extended set of SCDFT density variables in the energy functional is crucial for a correct quantitative comparison of the electronic band structure against available experimental data.[11]

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# General perturbative approach to vibrational spectroscopy employing curvilinear coordinates

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## ABSTRACT

Spectroscopies, such as infrared and Raman, are powerful tools for the investigation of the physical-chemical properties of molecular systems, providing detailed information related to their structure and dynamics. However, experimental spectra are tuned by several intertwined effects, which can make the interpretation of experimental data very challenging or even unfeasible without the support of reliable computational models.[1,2] Among the possible routes for the inclusion of anharmonic effects in the simulation of the vibrational spectra, the vibrational second-order perturbation theory (VPT2)[3-5] offers a good accuracy/cost ratio, giving the possibility to study also medium-to-large size systems.

The VPT2 method, in the commonly-used framework of Cartesian-based normal coordinates is not able to describe correctly low-frequency, highly-anharmonic, large amplitude motions (LAMs), due to the truncated polynomial approximation of the potential energy. A possible solution to this issue is the separation of the normal modes in order to isolate LAMs. With the target of simulating vibrational spectra of small- to medium-sized molecules presenting some flexibility in the near future, the first step is then the choice of a suitable set of internal coordinates, in order to decouple LAMs from the other modes as much as possible. In fact, Cartesian-based normal coordinates are ill-suited for this purpose. Then, small-amplitude motions (SAMs) can be treated at the VPT2 level, while LAMs can be effectively described by low-dimension variational approaches. In order to reach this goal, the theoretical development of VPT2 framework in terms of internal-based normal coordinates is the first step. A purely VPT2 formalism in internal coordinates has been first presented by Quade[6] and more recently revisited by Isaacson.[7]

On the basis of the available literature,[8] the general expression of the vibrational Hamiltonian in internal coordinates has been derived, followed by the derivation of both energies and resonant terms, including the calculation of the variational correction required in the GVPT2 method. Interestingly, all quantities of interest (such as energies and resonant terms) can be written as generalizations of the corresponding Cartesian-based expressions, making the overall implementation far more manageable. The reliability of the new methodology will be illustrated through selected test-cases.

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# From a bioinformatic approach to synthetic conformational peptide epitopes to disclose molecular mechanism of aberrant immune response in auto-immune diseases.

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## ABSTRACT

Autoantibodies are relevant in many autoimmune diseases and may be the direct cause of lesions. Therefore, serum antibodies circulation in blood, can be used as biomarker for an early diagnosis. [1].

To this end, a 'chemical reverse approach' based on the use of patient' sera to screen focused libraries of synthetic modified peptides can lead to the identification of specific probes able to characterize specific and high affinity autoantibodies.

A structure-based designed type I' β turn glucopeptide structure, was the first antigenic probe in which an aberrant glucosylated asparagine (N-Glc) recognized the presence of specific IgM autoAbs in the sera of a Multiple Sclerosis (MS) patient population. [2]

With these considerations we performed molecular dynamics (MD) simulations to achive structural properties on different potential peptide epitopes using tree different solution 50:50 (w:w) of biomolecular solvent in water: Hexafluoroacetone (HFA), Hexafluoro-2-propanol (HFIP), 2,2,2-Trifluoroethanol (TFE).

The atomic charges of these solvent has been modeled by using both the standard GAFF protocol and DFT calculations.

It has been experimentally observed that these solvents were able to stabilize the secondary structure. [3]

MD simulations were initially performed using Gromacs 2021 on melittin, a membrane-active component of the venom of *Apis mellifera with a* stable α-helix in both fisiological environment and in biomimetical solvents, to verify the accuracy and reliability of the force fields (FFs).

These FFs have been applied in the study of glucopeptides, with the glycosil-moiety added thanks to the tool *doGlycans* developed by Reinis Danne *et all*. [4].

These preliminary results could provide insights useful to search structural homologies, through bioinformatic approaches, with different bacterial and human proteins (putatively glucosylated) with the aim to identify, design and synthesize new peptide sequences.

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# A different perspective for nonphotochemical quenching in plant antenna complexes

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## ABSTRACT

Photosynthesis is pivotal for almost every form of life on Earth [1]. Plants can carry out photosynthesis by collecting sunlight with dedicated “light-harvesting” complexes [2]. These complexes are densely packed with chlorophylls and carotenoids, and are responsible for the light absorption and the transport of excitation energy to the reaction centers, where the primary reaction of photosynthesis occurs. However, in excess light conditions, photosystems are not able to convert all the absorbed light into chemical energy. The excess energy, wandering within the photosystems, leads to the damage of the plants, for example by promoting the formation of reactive singlet oxygen. Plants are able to protect themselves by dissipating the excess light as harmless heat, a process known as “nonphotochemical quenching” [3,4]. It is widely accepted that carotenoids are involved this photoprotection process, accepting energy from nearby chlorophylls and dissipating it rapidly [5]. However, the precise identity of the quencher and the excitation transfer mechanism are not known. In this contribution we study a minor light-harvesting complex of plants, CP29, which is thought to be involved in nonphotochemical quenching [6,7]. We employ all-atom enhanced molecular dynamics simulations to widely explore the conformational landscape of CP29, gaining insights on the ensemble of conformations available to this light-harvesting complex. We combine our simulations with quantum chemical calculations of the excitonic interactions between carotenoids and chlorophylls embedded in CP29, linking the conformational ensemble to the functionality of the complex. With this work [8] we are able to understand the interactions that can distinguish between a light-harvesting and a quenched complex.

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# Photochemistry and transient intermediates in a bacteriophytochrome photocycle revealed by multiscale simulations

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## ABSTRACT

Phytochromes are photoreceptors responsible for sensing light in plants, fungi and bacteria[1,2]. Their photoactivation is initiated by the photoisomerization of an embedded chromophore, which triggers a large conformational change in the structure of the entire protein[3,4]. Although phytochromes have been subject of numerous studies, the photoisomerization mechanism and the following reaction path leading to the final active state remain elusive[5,6]. Here, we use an integrated computational approach that combines non-adiabatic surface hopping and adiabatic ground-state molecular dynamics simulations to gain atomistic details on the photoactivation mechanism of *Deinococcus radiodurans* bacteriophytochrome. Our simulations show that the ps-scale photoisomerization of the chromophore proceeds through a *hula-twist* mechanism that forces a counterclockwise rotation of the D-ring. The initial photoproduct rapidly evolves in an early intermediate which we characterize through IR spectroscopy simulation. The early intermediate then evolves on the ns-to-μs scale to a late intermediate, characterized by a more disordered binding pocket and a clear weakening of the aspartate-to-arginine salt bridge interaction, whose cleavage is essential to interconvert to the final active state.

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# Ethanol electro-oxidation reaction on the Pd(111) surface in alkaline media: insights from quantum and molecular mechanics

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**ORALE**

Fuel cells have emerged as a promising technology in facing the future environmental crisis to generate clean power. They can efficiently provide electric energy with negligible emission of polluting. [1-3]

Here, we report on a computational study of the ethanol (EtOH) electro-oxidation reaction catalyzed by Pd in alkaline media occurring in a direct ethanol fuel cell. This reaction leads to acetate as the final product and happens through several elementary steps involving adsorbed OH radical species. In particular, our work is focused on the first step of the reaction, namely the H-atom abstraction occurring at the Pd(111) surface

$$CH_3CH_2OH^* + OH^* \rightarrow CH_3CHOH^* + H_2O$$

This reaction has been investigated through ab initio and classical molecular dynamics simulations. The effect of solvation on the adsorption of $OH^-$ and EtOH on the Pd surface has been evaluated as well. We have found that both anion and radical OH are strongly adsorbed on the electrode, guaranteeing a significant surface coverage in this reactant. On the contrary, EtOH, despite a not negligible adsorption free energy in vacuum, shows a very modest affinity with the surface when solvation is accounted for. This implies that the role of the adsorbed EtOH could be almost irrelevant in the electro-oxidation reaction, at least from the point of view of thermodynamics, thus suggesting that the electrode coverage in EtOH is dominated by diffusion processes.

Furthermore, we have observed that the rate of the above reaction depends critically on the distance of EtOH and OH from the Pd surface. In particular, we noted a rate enhancement when the distance of the two reactants from the surface increases and hence the adsorption strength, especially that of OH, decreases. The picture emerging from our study is that of a electrode surface rich in the OH species, owing to the large adsorption free energy, but only a small amount of them, specifically those weakly bounded to the surface, are really active in the electro-oxidation reaction.

These results suggest that the exchange current in a fuel cell could be improved by modulating the interactions of the reactants, or of selected intermediates, with the surface of the electrode. In particular, a partial weakening of the adsorption energies could lead to an improvement of the fuel cell performances. Such an effect could be obtained by acting at a chemical or a physical level. From the chemical point of view, one may think, for example, to use specific cocatalysts designed to weaken adsorption interactions at the catalyst-cocatalyst interface. From the physical point of view, some effect on the adsorption energies, and hence on the reaction rate, could be obtained by warming up the electrode with some time-dependent protocol, or using electromagnetic radiation (probably UV) to weaken the reactant-surface interactions.

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# Virtual Double-System Single-Box: A Nonequilibrium Alchemical Technique for Absolute Binding Free Energy Calculations

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## ABSTRACT

In the last years various computational methodologies, based on molecular dynamics (MD) simulations with explicit solvent, have been devised to improve the calculation of absolute dissociation free energy in drug-receptor systems. In this context, the so-called alchemical approach[1] emerged as one of the best-automated and most widely used MD-based free energy methods. Here we present the fine-tuning of nonequilibrium (NE) alchemical transformations for absolute dissociation free energy (ADFE) calculations called NEW-vDSSB.[2] The acronym NEW stands for Non-Equilibrium Work. The work histograms, obtained by a swarm of rapid and independent NE alchemical trajectories connecting the target thermodynamic end-states, are related to the corresponding free energy via the Jarzynsk and Crooks theorems.[3] VDSSB stands for virtual double-system-single-box, a variant of the so-called double-system-single-box (DSSB) method.[4] NEW-vDSSB is implemented in ORAC and in GROMACS molecular dynamics packages.[5]

NEW-vDSSB has been applied to the calculation of the dissociation free energy of ligands of the SARS-CoV-2 main protease. The SARS-CoV-2 main protease, 3CL$^{pro}$, is a valid target for antiviral drug design. Its structure was known in February 2020 and several studies have tried to identify a candidate to inhibit the catalytic dyad formed by a cysteine and an histidine. In our case, some of the studied ligands have been identified using a previous docking study[6] and for others the activity for 3CL$^{pro}$ has been measured. The study allows to verify accuracy, precision, and efficiency of the NEW-vDSSB method with respect to the standard nonequilibrium approaches.

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# POSTERS

# Exact and approximate evaluation of transition rates for quantum-stochastic master equation dynamics

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## ABSTRACT

Simulations of the coupled dynamics of nuclei and electrons represent an important challenge in theoretical and computational chemistry to interpret measured quantum properties that can be modulated by nuclear motions. A possible solution is the quantum-classical master equation, the multiscale approach derived by R. Grunwald and R. Kapral from quantum-classical Liouville dynamics.[1,2] The key idea is to use the Liouville formalism to describe the coupled evolution of the classical probability density of the nuclei and the quantum density matrix of the electrons. The target system is partitioned into a quantum-classical subsystem that interacts with a classical bath. The nuclear coordinates are expressed in natural internal coordinates.[3] Finally, the degrees of freedom of the bath are projected out, leading to a stochastic Markovian evolution of the diagonal elements of the subsystem density matrix. The resulting system of equations can be interpreted as the adiabatic evolution of the classic probability density interspersed with transitions between two potential energy surfaces. An exact and an approximate protocol to calculate the transition coefficients are here presented and applied to a two-level model system, which resembles the behaviour of a photoswitching rotating molecule. Comparisons between the two results are illustrated, and the conditions under which the approximations hold are pointed out.

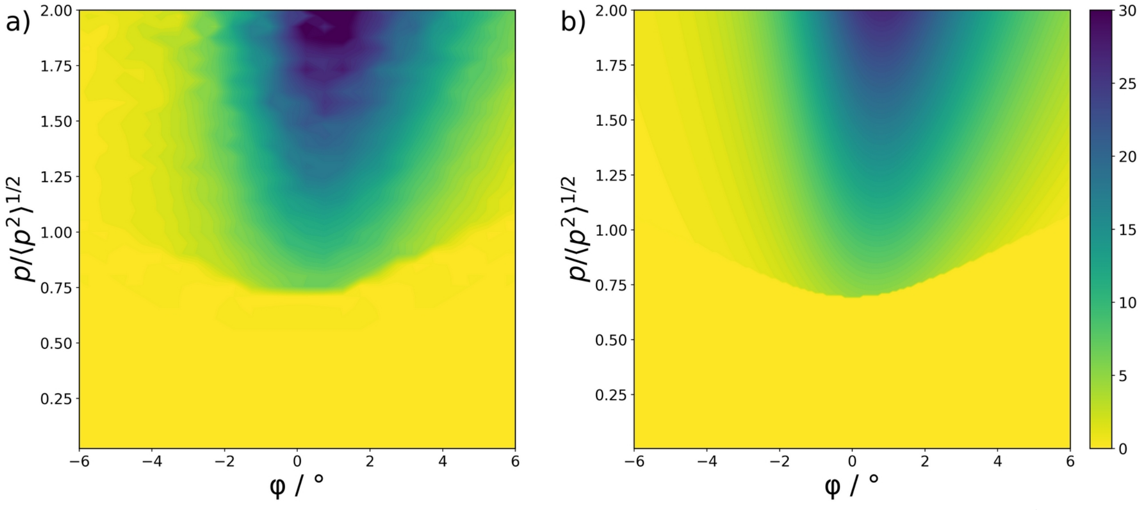

Figure 1. Plot of the transition rate coefficient from ground state to excited state (expressed in $ps^{-1}$) vs dihedral angle (φ) and conjugated momentum (*p*). In particular, the calculation is made by (a) the exact protocol, and (b) the approximate protocol.

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# Static and dynamic properties of fluorescent probes with computational methods

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## ABSTRACT

In recent years, several computational approaches have been developed for computing electron absorption spectra [1]. These are usually used for molecules with a rigid or partially rigid structure [2], while for flexible molecules precautions are necessary for a comparison with experimental data. For the latter, a sampling of the configurational space is required to successfully reproduce the spectroscopic properties. To try to describe the electron absorption spectrum of flexible molecules in aqueous solution, the problem is further complicated when it is necessary to carry out a sampling that explicitly considers the presence of the solvent. Generally, two strategies are employed: one based on the Monte Carlo method [3] and one on molecular dynamics (MD) simulations [4]. The purpose of the master thesis is to determine the absorption spectrum of the fluorescent probe 9-(4-((bis(2-((2-(ethylthio)ethyl)-thio)ethyl)amino)methyl)phenyl)-6-(pyrrolidin-1-yl)-3H-xanthen-3-one (PET probe) and to study the behavior of azobenzene during MD simulations. The computational strategy chosen involved the use of classical molecular dynamics simulations for the sampling of the configurational space, which was followed by a series of Time Dependent Density Functional Theory (TD-DFT) calculations to simulate the absorption spectrum. The TD-DFT calculations on the PET probe were performed both for the gas phase system and in the aqueous solution. The procedure followed consists of a systematic extraction of the molecule structures generated by the MD simulation, on which TD-DFT calculations of vertical transitions with four different exchange and correlation functionals (PBE, BLYP, PBE0, B3LYP) were carried out, from which absorption spectra were determined. The latter were compared with the spectra generated by the molecule with an optimized structure, to verify the effect of the molecular conformation on the spectral profile. The absorption spectra in water of the fluorescent probe were also compared with the results of experimental measurements of the derivative structurally more like the model compound studied [5]. It has been observed that the PBE0 and B3LYP functionals faithfully reproduce the wavelength of the experimental absorption maximum. About azobenzene, we observed the necessity to pay particular attention in modeling the torsional potentials of the molecule using classical force fields [6]. In fact, it has been noted that the force fields usually used do not properly consider the conjugation of the system, generating a non-planar structure, unlike what was expected for the ground state of azobenzene. Appropriate modifications to the standard force fields allowed the correct reproduction of the molecular structure in classical dynamics simulations. Solving this problem on azobenzene, a precursor of numerous dyes, is a necessary step to be able to simulate absorption and emission spectra of this molecule or its derivatives. The correctness of the force field produced was verified through molecular dynamics simulations on a water-soluble azobenzene derivative: the fluctuations of the dihedral angles are perfectly consistent with those found for azobenzene. In conclusion, the

study conducted made it possible to evaluate the importance of correct sampling of the configurational space of fluorescent probes, to be able to accurately determine both structural and dynamic properties.

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# Chemical effect in the SERS spectra of piperidine adsorbed on silver colloidal nanoparticles

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## ABSTRACT

We have studied the SERS (Surface Enhanced Raman Scattering) [1,2] spectra of piperidine adsorbed on silver/chloride colloids by means of a combined DFT (density functional theory) and TD-DFT (time-dependent DFT) approach, analyzing the chemical effect on the Raman enhancement of the molecule [3].

This effect is due to at least two contributions, both related to the formation of molecule/metal complexes.

(1) The first contribution derives from the changes in both the molecular force constants and the dynamic polarizabilities of the normal modes, when the molecule is chemisorbed, provoking sizeable differences in the band frequencies and intensities. In this respect, the DFT calculations satisfactorily simulate the SERS spectra of piperidine adsorbed on silver, and suggest that the most probable species formed on the silver particle surface is a complex formed by a deprotonated piperidine molecule linked to a silver ion.

(2) (2) A second contribution to the SERS enhancement is due to a Raman resonance effect that occurs when the wavelength of the Raman excitation falls within the electronic excitation band of the molecule/metal complex.

Indeed, the SERS spectra of piperidine show a significant dependence on the wavelength of the laser lines employed in the Raman excitation, with a marked enhancement in the region of the green radiation.

TD-DFT calculations on the most-probable surface complex explain this spectral behavior, because a strong excitation band of the complex is predicted in the green spectral region.
This pinpoints that a Raman resonance effect can be held responsible for this enhancement.

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# Computational Investigation of Isoeugenol Transformations on a Platinum Cluster: Hydrodeoxygenation to Propylcyclohexane

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## ABSTRACT

In a scenario of declining fossil resources and increasing demand for renewable and sustainable alternatives, biomass offers a great potential to complement the depleting energy reserves and significantly decrease anthropogenic greenhouse gas emissions into the atmosphere [1, 2]. Biomass represents a promising energy source profusely obtainable everywhere in the world. Its conversion to liquid fuels has oriented this work towards catalytic hydrodeoxygenation (HDO), which is currently considered one of the most challenging routes for the upgrading of biomass-derived bio-oils [3]. For this purpose, a subnanometric platinum cluster [4] was chosen as the catalyst model, this being a computational reference element for catalytic hydrogenation [5], and isoeugenol as a model monomeric compound of bio-oils.

Clarification of the HDO mechanism of isoeugenol on platinum cluster, by means of an atomistic approach based on density functional theory, is the aim of this computational investigation that can be considered as the starting point to investigate possible different reaction paths on different metal clusters, in order to provide experimental chemists with useful tools for large-scale process optimization. This study therefore, through the analysis of one of the possible mechanisms for the reaction that converts isoeugenol to propylcyclohexane, aims to identify the most significant elementary stages and intermediates of the process in order to use them as descriptors for future mechanism investigations.

After a short subsection concerning the preliminary study on the ease of hydrogen molecule fragmentation and hydrogen diffusion on platinum cluster, HDO was investigated following a DDO (direct deoxygenation) type mechanism which involves the saturation of the allyl double bond, the removal of the methoxy group, the removal of the hydroxy group, and finally the saturation of the benzene ring. DFT calculations revealed that the formation of the 4-propylphenol intermediate represents the step which mainly determines the rate of the process and the intermediate therein involved the pivotal point for ramifications, possibly leading to undesirable or secondary products such as propylcyclohexanol.

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# A New Self-Consistent Empirical Potential Model for Multicomponent Borate and Borosilicate Glasses

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## ABSTRACT

A new self-consistent empirical potential model based on the recently developed BMP potential has been developed for the simulation of multicomponent borate and borosilicate glasses. The BMP potential is based on the PMMCS force field (a pair-wide interatomic potential where the cation – oxygen and oxygen – oxygen interactions are described by Morse functions) with the addition of T-O-T (T = Si, P, and B) three body interactions and network former – network former repulsive interactions. We exploited the Bayesian Optimization approach to create a model which provides the *D* parameter for the B-O interaction as a function of the composition, and in particular of R = [$Na_2O$]/[$B_2O_3$] and K = [$SiO_2$]/[$B_2O_3$] ratios, which allows to better simulate the glass properties in a wide range of compositions. The obtained force field (FF) has been applied to several borate and borosilicate glass series containing, as modifier oxide, $Na_2O$, $Li_2O$, CaO, and MgO, and tested on experimental data such as the fraction of $BO_4$ ($N_4$), density, non-bridging oxygen (NBO) speciation, neutron diffraction spectra, $^{11}B$ and $^{17}O$ MAS NMR, and elastic properties. A comparison with other interatomic potentials found in literature has also been performed. Our force field reproduce well almost all the above-mentioned properties, showing excellent agreement with experiment for what concern the $N_4$ and NBO fraction, density, neutron diffraction and NMR spectra, while giving a systematic overestimation of the elastic properties values, for which the trend is anyway well reproduced.

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# Computational modelling of a reaction in confined environment: partition of reactive species between surfactant aggregates and aqueous solution

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## ABSTRACT

Many organic reactions catalyzed by metals cannot be carried out in aqueous solution since the organic substrates are generally insoluble. However, the presence of amphiphilic surfactants, which spontaneously form micellar aggregates in water, makes it possible to carry out reactions in the inner lipophilic core of the micelles, where substrates and catalysts can interact [1]. For example, the condensation reaction of an aryl boronic acid with an aryl halide catalyzed by $Pd(PPh_3)_4$ (Suzuki-Miyaura reaction) occurs at room temperature in basic aqueous solution with a small amount (≤5 wt%) of a suitable surfactant agent. Objective of the study is the characterization of the partition of the species involved in the Suzuki reaction between the aqueous and the micellar phase. The polyethoxylated glycerol triricinoleate, the principal component of the non-ionic surfactant Kolliphor® EL (KOL), was selected as the constituent of the micellar phase. The aggregation process of the KOL monomers in aqueous solution was previously studied by Molecular Dynamics (MD) simulations carried out using the *united-atom* 2016H66 force field specifically refined for the description of polyethylene oxides [2,3]. The simulations showed the spontaneous formation within 50 ns of stable micellar aggregates, consisting of about 20-24 monomers each, with radii of gyration of approximately 2.5 nm. For checking the reliability of the force field parameters, the free energies of solvation in water and n-octanol of the different species involved in the reaction were calculated by the Free Energy Perturbation approach, using the 2016H66 and the *all-atom* OPLS force field parameters; the atomic charges were obtained by fitting to the molecular electrostatic potential calculated at DFT level (M06-2X/6-31G*). The obtained solvation free energies values have been compared with those calculated *ab initio* by using the SMD model [4]. For reproducing the QM solvation free energies of the anionic species, it was necessary to scale the atomic charges by a factor $1/\sqrt{\varepsilon_e}$ and to add the electronic polarization term calculated with PCM, using the non-scaled atomic charges, and describing the continuum medium with the dielectric constant $\varepsilon_e$ [5]. The interaction between the different species and the micellar aggregate has been investigated by means of Steered MD simulations followed by Umbrella Sampling. To assess the reliability of our protocol, the partition free energies between water and n-octanol for molecules for which experimental values are available have been calculated. Results have shown that the aryl halide reactant and the product both accumulate in the micellar phase at around 2 nm from the center of mass of the aggregate. Calculations for aryl boronate and the catalyst are in progress.

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# Computational study of ATP-$Zn^{2+}$ interaction in water

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## ABSTRACT

In nature divalent cations, such as $Mg^{2+}$, $Ca^{2+}$ and $Zn^{2+}$, regulate ATP hydrolysis by structural and catalytic action [1]. The interaction of the formers with ATP have been widely investigated, whereas less is known about $Zn^{2+}$. Special interest for this cation is related to its use in artificial nucleases, whose aim is to mimic the performance of natural enzymes in releasing ATP chemical energy [2,3]. Mechanistic aspects are influenced by solvent-ion interactions and conformational flexibility of ATP, which can be investigated by molecular dynamics simulations. However, the time scale of ligand and water exchange with metal are not accessible by ab initio approaches and, even resorting to classical force field, sufficient sampling of free energy surface would be unfeasible through standard simulations.

We have addressed this problem with metadynamics [4] using collective variables that describe the coordination of $Zn^{2+}$ with triphosphate of ATP. We found that, even for this relatively simple system, obtaining a satisfactory description is challenging and we explored the performance of different collective variables to sample the relevant region of the configuration space. Through intensive simulations, for a total length of 10 microseconds, we successfully reconstructed the free energy surface as a function of the coordination number of $Zn^{2+}$ and oxygen atoms of triphosphate for $Zn^{2+}$-methyl triphosphate and $Zn^{2+}$-ATP. Moreover, we considered a system made of ATP and a complex of $Zn^{2+}$ with a macrocyclic ligand ($CH_3$TACN) [5], which was employed also in dissipative self-assembly [6]. The behaviour of the system is rationalised in terms of enthalpy gain, from direct ion-ion and ion-water interactions, and entropy penalty on conformational freedom of triphosphate upon binding.

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# Water in hydrogels: from solvent-monomer interactions to water states in poly-HEMA systems

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## ABSTRACT

Despite the numerous experimental papers devoted to hydroxyethyl methacrylate (HEMA)-based physical and chemical hydrogels, literature lacks theoretical studies on both the HEMA monomer and on poly-HEMA systems. Due to their wide application in biomedical fields, transport properties of such hydrogels and the system dynamics might deserve deeper investigations. [1,2] In this context, we focused our attention on the monomer-solvent interactions and water state in poly-HEMA hydrogels. In the case of the monomer, we decided to study (i) its structural and spectroscopic properties through Density Functional Theory (DFT), to confirm *cis*- and *trans*- conformers coexistence[3]; (ii) hydrogen bonding description through molecular dynamics (MD) simulations with various water models (TIP3P, SPC/E, TIP3P-FB, TIP4P-FB). As a result, the HEMA conformation (*cis* or *trans)* does not affect solute-solvent interactions, occurring mainly through the C=O and C-OH groups in the T range between 230 and 360 K. When considering the poly-HEMA systems, the water role was investigated differentiating between three states in physical systems for water content (WC) from 10 to 40%wt. The distinction was performed based on geometrical considerations, defining: (i) "bound" water, the solvent molecules within 3.5 Å from the polymeric chains; (ii) "intermediate" water, the ones in the 3.5 and 6 Å range and (iii) "free" water, all the rest. Radial distribution functions were calculated for evaluating the solute-solvent and solvent-solvent interactions. Water diffusion coefficients were computed at various T (273, 298, 360 K, respectively). Moreover, pairwise distances were calculated to verify which molecules were effectively remaining in the same shell during the diffusion coefficient evaluation time. Our results show that free water fraction is negligible up to WC 20% w/w in agreement with experimental findings [4]. From WC 20 to 40%wt, about 2 water molecules coordinate each C-OH group and 1 interacts with the C=O group at 1.8 Å distance. The average diffusion coefficients get larger while increasing WC (from 0.05 +/- 0.03 at WC 10% to 0.36 +/- 0.11 $*10^{-5}$ $cm^2/s$ at WC 40%, at T 298 K); this is in compliance with the increase of the free water fraction, which presents a bulk-like water behaviour, as shown by its individual diffusion coefficient.

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