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DDT - Drug Discovery Tool: a fast and intuitive graphics user interface for Docking and Molecular Dynamics analysis

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Computer-aided drug design plays today a central role in the identification of new drug candidates both in the industry and in the academia. Among the most successful approaches is docking-based virtual screening (VS), which is used to predict the interaction between a ligand, typically small molecules, and its protein or nucleic acid target (hereafter protein for the sake of simplicity). The resulting complexes are evaluated and ranked according to a scoring function, which estimates the strength of the binding interaction. However, the approximation of the docking sampling produces many false positives, then molecular dynamics calculations (MD) are often performed *a posteriori* to validate the docking poses. Despite the numerous software available for the analysis of the VS and MD results, none of them can manage simultaneously the many complexes coming from docking and the corresponding MD trajectories. As a result, the analysis of VS and MD can be time consuming and user challenging, delaying the drug design process.

The Drug Discovery Tool (DDT) was designed to overcome such limitations providing a fast and automated analysis platform for VS and MD calculations. DDT has a graphics user interface (GUI) implemented in the Visual Molecular Dynamics (VMD) software and allows analysing a large number of ligand/protein complexes obtained from AutoDock4 (AD4) docking calculations and MD simulations. The best complexes can be selected and saved using a number of filters based on chimico/physical properties of the system such as the number of ligand/protein contacts, localisation of the ligand in the binding site and clustering of the ligand binding conformations. Finally, we practically demonstrate how to use DDT in a drug design campaign.

Single-Hessian thawed Gaussian approximation: The missing rung on the ladder

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To alleviate the computational cost associated with on-the-fly ab initio semiclassical calculations of molecular spectra, we propose the single-Hessian thawed Gaussian approximation [1], in which the Hessian of the potential energy at all points along an anharmonic classical trajectory is approximated by a constant matrix. The spectra obtained with this approximation are compared with the exact quantum spectra of a one-dimensional Morse potential and with the experimental spectra of ammonia and quinquethiophene. In all cases, the single-Hessian version performs almost as well as the much more expensive on-the-fly ab initio thawed Gaussian approximation [2, 3, 4] and significantly better than the global harmonic schemes. Remarkably, unlike the thawed Gaussian approximation, the proposed method conserves energy exactly, despite the time dependence of the corresponding effective Hamiltonian, and, in addition, can be mapped to a higher-dimensional time-independent classical Hamiltonian system. We also provide a detailed comparison with several related approximations [5, 6] used for accelerating prefactor calculations in semiclassical simulations.

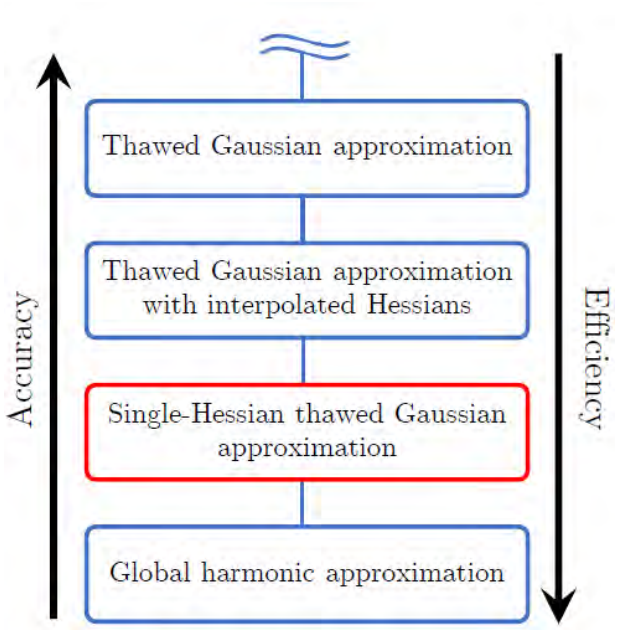

Figure. Hierarchy of several semiclassical wavepacket methods for simulating vibrationally resolved electronic spectra.

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Real-Time Spectroscopy in an Interactive Quantum Chemistry Framework

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A framework for interactive quantum chemistry established in our group allows for the interactive exploration of chemical reactivity along potential energy surfaces. [1,2] In order to facilitate the efficient spectroscopic identification of compounds, an extension of this framework has been developed. [3] We present a real-time spectroscopy tool that provides infrared and ultraviolet-visible spectroscopic information during the interactive exploration. Since very accurate *ab initio* electronic structure methods are too inefficient to be applied in an interactive framework, we rely on our open-source in-house semiempirical quantum chemistry program, Sparrow [4,5]. This allows for fast evaluation of the spectroscopic properties of interest with either NDDO or DFTB semiempirical models that may be later refined with more accurate methods if deemed necessary. Molecular properties of interest are, for instance, the dipole moment and its derivative (infrared spectroscopy) or the first roots of a linear response time dependent problem (ultraviolet-visible spectroscopy). Characteristic spectral signals may serve as diagnostic probes that do not require ultimate accuracy with respect to peak position and intensity. Such diagnostic bands from the interactive spectroscopy software can provide valuable hints on structures with characteristic spectroscopic properties.

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Self-Parametrizing System-Focused Models

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Relevant chemical processes take place in a vast variety of complex environments. In order to study chemical reactions in proteins, nanostructures or on surfaces, sophisticated and at the same time efficient methods to model nanoscale structures have to be developed. We combine [1] the ideas of an automatically parametrizable quantum-chemically derived molecular mechanics model [2, 3] with machine-learned corrections under uncertainty quantification. For a long time, classical force fields have been employed to obtain energies and forces for large systems, but recently, Machine Learning approaches [4, 5] have increasingly gained attention. Our approach generates an accurate physically motivated model from a minimum energy structure and its corresponding Hessian matrix by a partial Hessian fitting procedure [6] of the force constants. This model can be applied to generate a large number of configurations for which additional reference data can be evaluated on the fly. A Δ-Machine Learning model is trained on these data to provide a correction to energies and forces including uncertainty estimates. During the procedure, the flexibility of the Machine Learning model is tailored to the amount of available training data. Our approach [1] will be a starting point for the generation of system-focused electrostatic molecular mechanics embedding environments for any atomistic structure at the nanoscale.

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Implementation of linear-response TDDFT for X-Ray absorption spectroscopy in CP2K

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A new module for X-Ray absorption spectroscopy (XAS) based on linear response time-dependent density functional theory (LR-TDDFT) has recently been implemented in the quantum chemistry and solid state physics software package CP2K. It specifically targets excitations from a given set of core orbitals, which allows for solving a few decoupled problems of reduced dimensions instead of the usual really large LR-TDDFT one. Furthermore, the spatially localized nature of core orbitals is exploited in a resolution of the identity (RI) scheme which reduces the computational cost of the many four electron integrals typically needed in LR-TDDFT. This allows for simulation of large molecules and condensed phase systems alike.

Efficient geometric integrators for nonadiabatic quantum dynamics in the adiabatic representation

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Geometric integrators [1] of the Schrödinger equation conserve exactly many invariants of the exact solution. Among these integrators, the split-operator algorithm is explicit and easy to implement, but, unfortunately, is restricted to systems whose Hamiltonian is separable into a kinetic and potential terms. Here, we describe several implicit geometric integrators applicable to both separable and non-separable Hamiltonians, and, in particular, to the nonadiabatic molecular Hamiltonian in the adiabatic representation [2]. These integrators combine the dynamic Fourier method with the recursive symmetric composition [3,4] of the trapezoidal rule or implicit midpoint method, which results in an arbitrary order of accuracy in the time step. Moreover, these integrators are exactly unitary, symplectic, symmetric, time-reversible, and stable, and, in contrast to the split-operator algorithm, conserve energy exactly, regardless of the accuracy of the solution. The order of convergence and conservation of geometric properties are proven analytically and demonstrated numerically on a two-surface NaI model in the adiabatic representation. Although each step of the higher order integrators is more costly, these algorithms become the most efficient ones if higher accuracy is desired; a thousand-fold speedup compared to the second-order trapezoidal rule (the Crank-Nicolson method) was observed for wavefunction convergence error of 10^{-10}. In a companion paper [5], we discuss analogous, arbitrary-order compositions of the split-operator algorithm and apply both types of geometric integrators to a higher-dimensional system in the diabatic representation.

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An atomistic view over Mg^{2+} induced kinetic heterogeneity in the group II intron-exon recognition site

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The driving factors of nucleic acids folding are the stability of base-base and cation-mediated electrostatic interactions. In particular, Mg^{2+} ions strongly bind to RNA molecules promoting the formation of tertiary contacts and even specific functional motifs. As an example, a recurring tertiary contact of the group II intron family the 5′-exon–intron binding site interaction (EBS1-(d)IBS1), can only be stably formed upon addition of Mg^{2+} ion or under very high concentration of monovalent cations of the RNA cognate only. Although not in the same way, but the effect is observed for both RNA-RNA and RNA-DNA pairs. FRET and NMR studies suggest that cations interfere not only with the stability of the EBS1-(d)IBS1 interaction but also with the kinetics by inducing heterogeneity. In other terms, there is a multi-state folding regulated by Mg^{2+} specific binding site occupancy [1-4]. In this work we utilize molecular dynamics simulations powered by a combination of many state-of-the-art enhanced sampling techniques to characterize the structural and thermodynamics effects of Mg^{2+} and K^{+} binding on the homo and heteroduplex binding motifs. This simulation allows for the determination of relative binding affinities of divalent metal ions such as Mg^{2+} and the effects of ion competition. The highest affinity binding sites identified in the simulations corroborate with the proposed by NMR experiments. Preliminary results indicate that there are specific ion-induced conformational changes in the backbone of the RNA-RNA pair that further stabilize the tertiary contact formation while the same doesn't happen for its RNA-DNA counterpart. The combination of simulations and experiments provide a multi-lateral description in an atomistic level of the 5′-exon–intron binding ranging from its thermodynamics to the kinetics including non trivial effects arising from RNA-ions binding.

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Analytical implementation of atomic polar tensors in CP2K

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Current implementations to retrieve vibrational absorption spectra of molecular systems rely mostly on the double harmonic approximation. In this scheme a spectrum is calculated by carrying out a numerical differentiation of the system's electronic energy and electric dipole moment with respect to nuclear coordinates. The latter is called atomic polar tensor. This approximative routine relies on the appropiate choice of the displacement length in order to achieve a good trade-off between finite precision error and formula error.

Instead of relying on the numerical derivatives of the electric dipole moment, the atomic polar tensors $P^{\lambda}_{\alpha\beta}$ can be evaluated analytically by means of density functional perturbation theory. In the case of the Gaussian and plane wave method as implemented in the CP2K package, terms originating from the basis sets being centered at the nuclear positions as well as contributions from non-local pseudopotentials have to be considered in the derivation among others. We present their implementation and first applications thereof.

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CYP2D6 selectivity revised: deciphering reaction determinants by well-tempered metadynamics simulations and QM/MM calculations of variants with diverse enzymatic activity.

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Cytochrome (CYP) P450 monooxygenases are thiolate-ligated heme enzymes that have a crucial function in the detoxification of xenobiotics in our body. Catalytic reactions, including aliphatic and aromatic hydroxylations, epoxidation, and heteroatom oxidations, increase the solubility of potentially harmful compounds, thereby facilitating their clearance and limiting toxicity. Around 80% of the available drugs rely on this oxidation mechanism to reach bioactivation [1]. Computational techniques that provide information regarding the predominant site(s) of metabolism, mode of binding, or also binding affinities can be of high value to improve the lead compound and avoid any unwanted CYP-mediated adverse reactions [2]. However, the complete framework in which CYPs operate is complex. The better we understand the forces that dictate the catalytic reaction and their weight in the overall balance, the more accurate and reliable we can develop CYP-related modeling techniques.

In this work, we have investigated (i) the interplay between binding pocket environment and binding mode (shape complementarity) by performing well-tempered metadynamics simulation (WT-MTD) to obtain the free energy profiles of a well characterized and classical CYP2D6 substrate within normal (wild-type), increased, and diminished-to-non functional active CYP2D6 enzyme. The altered activity variants have both two mutations in close vicinity of the heme which will have an impact on the steric/electronic component of the catalysis. In a second step, we wanted to address (ii) the electronic complementarity of the substrate and the binding pocket. For each metabolic hot spot on the substrate, we deduced from the corresponding WT-MTD energy profile the binding mode that was closest to the preferred transition state geometry to determine the corresponding activation barrier by performing QM/MM calculations.

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Evolving a protein scaffold towards catalyzing tetrazol formation using QM/MM simulations and evolutionary computation

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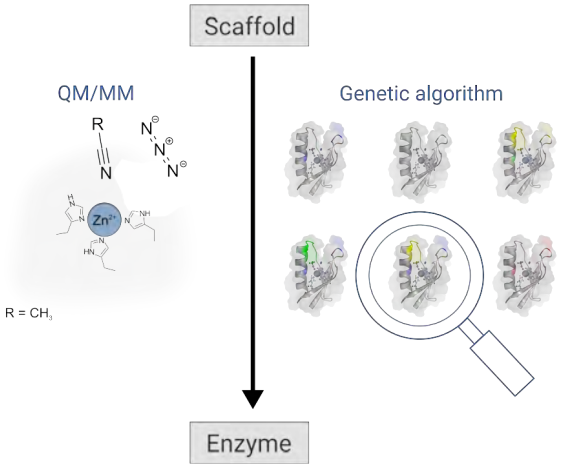
Computational enzyme design has garnered widespread attention in recent years to generate greener, cheaper and more proficient biocatalysts for new-to-nature reactions or natural reactions under non-natural conditions. In this work, we describe a combined approach of classical and first principles molecular dynamics simulations combined with a multi-objective genetic algorithm (GA) optimization to design a thermostable metalloenzyme that is able to catalyze the formation of tetrazoles. As a model reaction we use the formation of a tetrazole from acetonitrile and inorganic azide using zinc.



As a scaffold we use a thermostable variant of the 56 residue protein GB1 with zinc binding site [1]. From classical molecular dynamics, metadynamics as well as MM/PBSA calculations, it is evident that this scaffold can only bind the acetonitrile ligand and has no affinity for the azide, thus the catalytic rate likely is low.

We have determined the free energy barrier of the reaction in an unmodified version of the scaffold using QM/MM blue moon type simulations, which is 21 kcal mol^{-1} at ambient temperature (exp. 29.3 kcal mol^{-1} at 348 K for the $ZnBr_2$ catalyzed reaction). Subsequently, we have performed a multi-objective genetic algorithm optimization using the EVOLVE toolbox to optimize both the binding affinity of the azide ligand as well as the thermostability of the enzyme. We have already investigated the µs dynamics of this GA-optimized protein, and observed that the retention of the azide in the catalytic site is much improved due to better binding affinity. Further work will test the influence of the mutations that were made on the free energy barrier of the reaction using QM/MM blue moon type simulations to determine if the GA optimization produced a more proficient enzyme.

This work could open up the possibility to perform *in situ* click chemistry as a viable environmentally friendly and potentially regio- and stereoselective alternative to produce tetrazole derivatives by exploiting the power of biocatalysis and computational design.

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Machine Learning Approach with Molecular Dynamics Fingerprints to Predict P-Glycoprotein Substrates and Multidrug Resistance

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P-glycoprotein (P-gp) is a membrane transporter, responsible for the extrusion from the cell of a wide variety of molecules, such as metabolites, nutrients, and cytotoxic and xenobiotic compounds, including drug molecules [1]. As the P-gp mediated drug efflux limits the bioavailability of drugs in cancer cells, contributing to multidrug resistance, the identification of potential P-gp substrates in the early stages of drug discovery projects is highly desirable.

In this study, we combine molecular dynamics (MD) simulations with machine learning (ML) to classify small molecules in P-gp substrates and non-substrates. The information from the MD simulations are encoded in so-called MD fingerprints (MDFP), a concept previously used to predict physicochemical properties [2]. The workflow consists of three main steps. First, for every small molecule in the training and test sets MD simulations are performed both in water and in a POPC bilayer. Second, the MDFP is constructed using a combination of simple counts based on the topological structure of the molecules and distributions of properties derived from the MD simulations. Finally, the MDFPs are used to train different ML algorithms, such as for example gradient tree boosting and neural networks.

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Ab initio free energy computations with machine learning potentials and enhanced sampling

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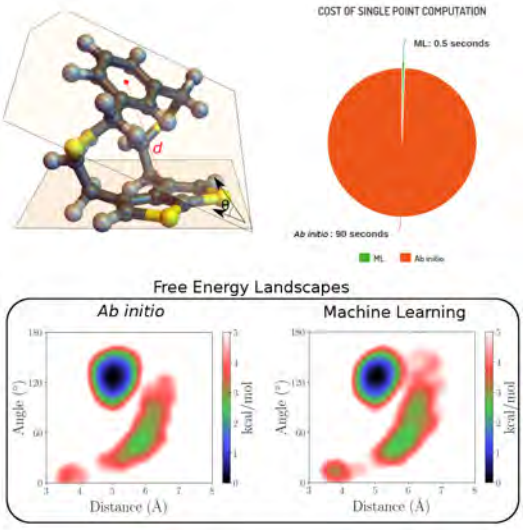
Machine learning techniques are increasingly used to generate fast and accurate predictors of molecular electronic properties, bypassing expensive first principle quantum chemical computations [1] and expanding the scope of what is feasible to perform. For instance, they can be used to access longer timescales in molecular simulations, which is crucial to obtain statistically converged thermodynamical properties of molecular systems such as relative free energies between multiple conformers. This is particularly important for flexible systems, whose stability is determined by a subtle interplay between variations in the underlying potential energy and conformational entropy. While significant steps have been made addressing this matter[2], the impracticality of obtaining both converged statistical sampling and accurate energetics has traditionally hindered the ability of describing the chemistry of flexible molecules. Here, we combine a machine learning potential energy function with an enhanced sampling scheme which allows us to perform cheap and accurate free energy computations. The machine learning potential is trained to predict DLPNO-CCSD(T)/CBS quality electronic energies [3] and we combine it with an enhanced sampling scheme that uses both Hamiltonian and *reservoir* replica exchange (Hres-RE). The developed algorithm dramatically speeds up free energy computations at a target level of theory by reusing canonical sampling generated under a different Hamiltonian. We have implemented Hres-RE in a python package that we name MOdular Replica Exchange SIMulator (MoRESim), which allows to design replica exchange simulations with a large degree of freedom, and which is available on demand (it will soon be posted online). We use this scheme to access the *ab intio* free energy landscapes of two prototypical systems with complex conformational spaces (a bridged asymmetrically polarized dithiacyclophane, incorporating a thieno[2,3-b]thiophene (40 atoms), and the cinchona alkaloid, a widely used organocatalyst (49 atoms)), both in gas phase and in solution (implicit solvent). In this way, we demonstrate the applicability of the implemented scheme to access the free energy landscapes of any middle sized molecule with an accuracy that would be unattainable otherwise.



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Where are our errors in Frozen-Density Embedding Theory coming from?

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We present Frozen-Density Embedding Theory (FDET)[1,2], a formal framework in which the whole system is described by means of two independent quantities: a. the embedded wavefunction $\Psi_{A;}$ b. the density ρ_B associated with the environment. The key aspect in FDET is how the embedding potential is constructed. For embedding system A: $H_A^{emb}=H_A+v_{emb}$. It should be mentioned that our embedding potential comprises both the electrostatic and nonelectrostatic DFT-based part. Generally, the errors in our embedding methods is relatively small. However, for certain systems, the error cannot be neglected. Error compensation and the lack of an immediate decomposition into physically interpretable energy components make it considerably difficult to ascribe the error to a specific phenomenon.

We have recently developed an extension of linearised-FDET for non-variational methods[3], particularly MP2. We analyse our embedded MP2 interaction energies via comparison with the supermolecular method and with SAPT0[4] (symmetry adapted perturbation theory). Since SAPT0 decomposes the interaction energy into four physically interpretable components (dispersion, induction, electrostatic and exchange), we were able to compare electrostatic and inductive contributions in our embedding protocol and in SAPT0. This allows us to attribute the overall error to one specific phenomenon and it also gives us insight about the validity of our embedding potential

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Computational Screening of Metal-Organic-Frameworks for Applications in Photocatalysis

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Among porous materials, metal-organic frameworks (MOFs) have been shown to be promising due to their structural tunability, adjustable topology and chemical functionality.[1-3] Those characteristics have been exploited recently in the development of efficient photocatalysts in order to address solar-driven chemical reactions such as hydrogen (H_2) evolution and CO_2 reduction.[4-8] Because of the modular nature of MOFs, an almost unlimited number of structures can be hypothetically anticipated, which makes the traditional trial and error strategy unfeasible. In this work, we propose a systematic scheme to evaluate property-descriptors of MOFs directly related with their potential performance as photocatalysts. Those descriptors assess (i) the UV-visible absorption capability, (ii) the redox and MOF/co-catalyst synergy, (iii) the electron-hole recombination lifetime and (iv) the photoconductivity. This procedure is envisioned to be applied in a high-throughput manner to large MOFs databases using cost-efficient methods previously tested and optimized in reduced test-sets to reproduce values based on highly accurate methods.

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State specific environment pre-polarisation of environment with point charges within Frozen-Density Embedding Theory

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Frozen-Density Embedding Theory[1],[2] (FDET) provides a system-independent formal framework for multi-level computational methods which describe the effect of a frozen electron density of the environment $\rho_B(r)$ on the chromophore. Within this framework, it is possible to treat either explicitly or implicitly the effect of the embedding species on the electron distribution in the environment in numerical simulations. In the state specific pre-polarization protocol[3], the response of the environment to the change of the electronic structure of the chromophore can be taken into account in the process of generating $\rho_B(r)$. In practice, due to some approximations made for the FDET potential, number of pre-polarization cycles and the choice of $\rho_B(r)$, this treatment is not exact.

The goal is to see how well the effect of polarisation is accounted for in the framework of FDET-ADC[4] in 2 ways of taking into account the environment response . The state specific pre-polarization with ESP-derived point charges[5] (ChelPG[6]) and Freeze-and-Thaw (each fragment enters alternatively as $\rho_1(r)$ or as $\rho_2(r)$ until $(\rho_1(r),\rho_2(r))$ self-consistency is reached) procedures are compared with supermolecular calculation with the Algebraic Diagrammatic Construction scheme (ADC)[7] for representatives cases of embedded chromophores.

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On the accuracy and efficiency of smooth Coulomb potentials

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The correct description of the correlation cusp represents a major challenge in electronic structure calculations. In particular, for orbital-based methods one requires a large number of basis functions with high angular momentum to obtain accurate results. One way to deal with this problem is the use of smooth, non-singular, potentials, constructed so that the electron coalescence at r=0 is finite. It has been shown that the employment of smooth potentials permits the use of smaller basis sets with fewer polarization functions [1, 2, 3].
In this work we explore whether one can construct models with smooth potentials, but without compromising accuracy. First, we present different strategies to obtain potentials of the *erfgau* form [4]. We then consider correcting the *erfgau* model in two ways, with short-range potentials and a first-order perturbation theory. Finally, the effect of the model potentials on the configuration interaction (CI) wavefunction expansion is analyzed.

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Gaussian Process-Based Refinement and Assessment of Dispersion Corrections

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We apply Gaussian process (GP) regression to correct for systematic errors[1] in noncovalent interaction energies derived from first principles. Compared to other established machine learning methods, GP regression does not only provide predictions/corrections but also estimates the associated uncertainty, which can be used to decide whether a correction for a new (supra)molecular structure is reliable or not.[2] By analogy with the popular class of semiclassical dispersion correction models,[3,4] our GP model[5] is trained on differences between approximate and reference interaction energies, here, obtained from PBE-D3(BJ)/ma-def2-QZVPP and DLPNO-CCSD(T)/CBS calculations, respectively. We generated a data set containing interaction energies for 1248 molecular dimers, which resemble those systems contained in the S66 database. Our systems do not only represent equilibrium structures, but also dimers at shorter and longer distances, and different orientations and conformations. We show that the GP correction after training on feature–energy pairs of about 100 dimers results in an up-to-10-fold improvement over our PBE-D3(BJ) interaction energies for the remaining dimers. We also find that our GP-corrected interaction energies are insensitive toward the actual parametrization of the D3(BJ) model, which is in clear contrast to DFT-D3(BJ)-corrected interaction energies. With a sampling method based on distances in kernel space the program advises the user for which structures a reference calculation should be made due to the overall uncertainty being above a user-defined threshold. This quality assessment, which established dispersion correction models lack, renders our GP approach suitable for an on-the-fly improvement of interaction energies.

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A multiconfigurational analysis of water oxidation catalysis

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In chemical reactions, correlation effects which can hardly be represented by a single determinant method (as e.g. density functional theory) may play an important role. Complete Active Space Self-Consistent Field (CASSCF) as a multiconfigurational approach has been widely-adopted in the analysis of such complex correlated wavefunctions. Nevertheless, it is difficult to select a "consistent" active space along the reaction pathway considering changes of the nuclear geometry. In this work, we present a simple systematic approach for the selection of active orbitals and the analysis of their correlation behavior during the water oxidation reaction of a Ru-based catalyst, which has recently successfully been used for efficient water oxidation and in silico design of new catalysts.

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Domain wall-defect interaction in $BaTiO_3$ by density functional theory.

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Some perovskites oxides are part of the class of ferroelectrics which contains interfaces separating regions of different polarization known as domain walls. However, very little is known about the interaction of defects with domain walls and the resulting properties of the material. We use density functional theory first principles calculations to study charged and neutral 180° domain walls in $BaTiO_3$ and calculate the formation energy of the apical and equatorial vacancies at both head-head and tail-tail walls. Our results show that energies are lower at tail-tail than head-head domain walls. Moreover, we found lower formation energies of equatorial oxygen vacancies than apical oxygen vacancies. This study forms the foundation to understand the interplay of oxygen vacancies and domain walls in the ferroelectric oxides and to predict the properties of defective materials. These results can be rationalized by the electric field and the bonding environment of oxygen ions in the domain structure respectively.

Effect of dispersion corrections on ab-initio free energy landscape by machine learning

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Atom pairwise dispersion-correction schemes are extensively used to correct the missing attractive term in standard density functional approximations.[1] These schemes are generally trained on a set of structures near equilibrium obtained from static quantum chemical computations. In fact, their suitability for describing free energy landscapes extracted from finite temperature simulations is much less explored. Accelerated sampling techniques combined with ab-initio potentials give in principle access to free energy landscapes. However, the computational cost of quantum chemistry is not compatible with achieving a converged statistical sampling.[2] Machine learning (ML) potentials [3] are seen as a promising alternative to beat the quantum chemistry cost without scarifying the sampling accuracy. In this work, we coupled machine learning corrected DFTB potentials with Hamiltonian replica exchange molecular dynamics to investigate the performance of dispersion correction schemes across the free energy landscapes. Instead of learning the forces, we derive the ML kernel in order to correct the DFTB forces across the dynamic simulation. In particular, we focus on fluxional organic molecules (e.g. including a photo-switchable catalyst and a molecular tweezers) featuring subtle non-covalent interactions. The use of ΔML [4] increases the achievable simulation time by several order of magnitude, while preserving the desired quantum chemical accuracy. This work demonstrates that the shape of the free energy landscape and the depth of its minima heavily depend on the dispersion-corrections and highlights the importance exploring the entire free energy landscapes of flexible medium size organic molecules.

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Exploiting artificial neural networks in simulation of complex ionic chemical environment

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Ab initio molecular dynamics of the condensed phase systems containing charged species represent challenging problem for computational chemistry. It requires an accurate description of complex chemical environment including various structural patterns, non-covalent interactions and charge transfer processes. The simulations of chemical reactions in the condensed phase are even more problematic. The reliable description of all these phenomena relies on the high-level computational methods *e.g.* hybrid DFT and post-HF methods. However, the converged statistical sampling of the potential energy surface (PES) of systems with such large number of degrees of freedom is hardly achievable. In recent years, the potentials based on machine learning and artificial neural networks were applied in various simulations of bulk materials, surface adsorption, gas phase reactions or aqueous solutions.[1] These methods are promising in the reproduction and prediction of high dimensional PES due their accuracy derived from the reference method and computational cost comparable to classical force field simulations.[2] One of the bottlenecks in the application of neural network potentials is to establish the optimal training set to characterize the system and compute reference energies and forces.[3] In the presented work, we apply artificial neural network potentials based on PBE and PBE0 to model a catalytic process in condensed phase. We focus on the description of subtle ion-solvent interactions and thermal fluctuations considering various compositions of the system. We utilize different simulation techniques to obtain suitable training set for reproduction of ab initio PES and reliable interpolation enabling stable simulation on the longer time scale. The simulation protocol discussed in this work can be further applied to describe the thermodynamic and structural properties of condensed phase systems and chemical reactions in a complex environment.

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Evaluating Force Fields Using Cross-Solvation Free Energies

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Pure-liquid properties (e.g. density and heat of vaporization) are one of the main targets of force-field calibration. However, for many applications, it is also important to ensure that the cross-interactions between molecules calibrated based on a liquid A (A-A interactions) and a liquid B (B-B interactions) are also well-balanced (A-B interactions). This can be investigated by analyzing the properties of liquid mixtures or, as in this project, the cross-solvation free-energies of A in B and of B in A. We have compared 6 force fields, namely GROMOS-2016H66, GROMOS-54A7, AMBER-GAFF, CHARMM-CGenFF, OPLS-AA and OPLS-AA/1.14*CM1A(-LBCC), using the experimental cross-solvation free energies of 25 organic compounds. Each compound is considered both as solute and as solvent, forming a 25x25 matrix of 625 cross-solvation energies.

A neural network based representation of state-to-state cross sections for atom-diatom collisions

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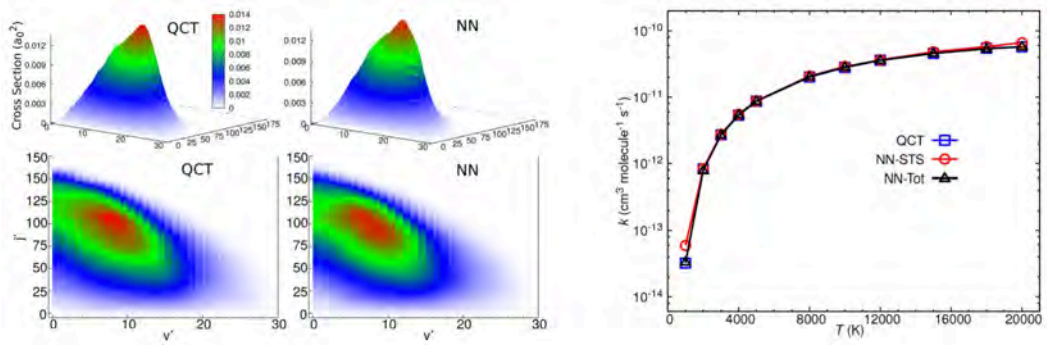
High-temperature, reactive gas flow is inherently non-equilibrium in terms of energy and state population distributions. Modeling such conditions is challenging even for the smallest molecular systems due to the extremely large number of accessible states and transitions between them. Here, neural networks (NNs) trained on explicitly simulated data are constructed and shown to provide quantitatively realistic descriptions which can be used in mesoscale simulation approaches to model gas flow at the hypersonic regime. As an example, the state-to-state cross sections for the $N(^4S)+NO(^2\Pi) \rightarrow O(^3P)+N_2(X^1\Sigma_g^+)$ are computed from quasiclassical trajectory (QCT) simulations. By training NNs on a sparsely sampled noisy set of state-to-state cross sections it is demonstrated that independently generated reference data is predicted with high accuracy. State-specific and total reaction rates as a function of temperature from the NN are in quantitative agreement with explicit QCT simulations and confirm earlier simulations and the final state distributions of the vibrational and rotational energies agree as well. Thus, NNs trained on physical reference data can provide a viable alternative to computationally demanding explicit evaluation of the microscopic information at run time. This will considerably advance the ability to realistically model non-equilibrium ensembles for network-based simulations.



Top: 3D surface and contour color map of QCT calculated and NN predicted state-to-state cross sections for N + NO(v=6, j=30) → O + N_2(v',j') at E_t = 2.5 eV. Bottom: Total rate coefficients calculated from QCT and predicted by the NN models for the N + NO → O + N_2 reaction between 1000 and 20000 K.

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Alternatives to conventional intermediate states in free energy simulations

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Free energy calculations require sufficient phase space overlap between the end states in order to converge. So far, this is achieved by dividing the free energy calculation into multiple substeps by introducing intermediate states along a user-defined reaction coordinate. The potential energy function of such states is usually generated by linearly mixing the potential energies of the end states, or using soft-core potentials. Multiple improvements have been proposed for this scheme, but a particularly promising approach is the use of specialized bridging ensembles, such as Enveloping Distribution Sampling. This removes the need for conventional intermediate states (and associated problems such as the van der Waals endpoint problem) by simulating a single reference state that is able to sample the relevant configurations of all involved end states at the same time. Instead of investing computer time to create phase-space overlap, transitions between conformations can then be enhanced by coupling reference states with different degrees of smoothing of energy barriers in a replica exchange scheme. The choice of smoothed reference states for replica exchange can be performed in a highly automatized fashion. We will illustrate this with several examples, starting from simple model systems and proceeding to biomedical applications.

Solvent scaling in MD simulations

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Adaptive resolution schemes in Molecular Dynamics (MD) simulations aim at eliminating the interface between coarse-grained (CG) and fine-grained (FG) subsystems, by making the particle resolution depend on a continuous switching variable s. However, the common schemes have two drawbacks in common: (1) an inherent lower limit on the resolution of one bead in terms of individual molecules and (2) the need for a (fitted) CG potential as an input. In this work, a new classical adaptive resolution method is being developed, which is formally related to the class of energy interpolation schemes. But instead of achieving a difference in resolution via interpolating different potentials, the resolution only affects the solvent dimensions (scaling) and molecular interaction parameters, while applying the same generic solvent potential to the whole system. So far, the scheme has been successfully applied to a liquid of diatomic dipoles, and its extension to water is envisioned as a future goal.

Self-ionization of water at aqueous platinum interface

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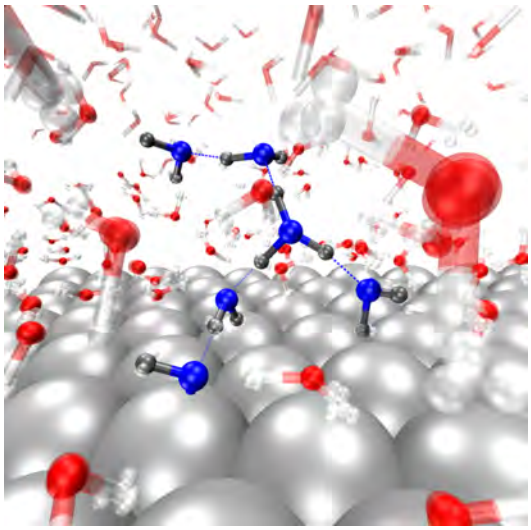
The dissociation of water into hydronium and hydroxide ions following their recombination is one of the most fundamental processes. The ionization of water at metal surfaces under the ambient condition is of immense importance to understand electrochemical possess. The hydronium and hydroxide species has been detected at water-platinum interface based on our quantum simulations. We elucidate the mechanism that how hydronium and hydroxide ions are formed and recombined at water-platinum interface with path integral ab-initio molecular dynamics simulations and it emerges as quite different from the classical ab-initio molecular dynamics and conventional view of water platinum interfaces.



Charge Transport Behaviors of Oligoacene- and Fused-Thiophene- Based Amorphous Hole Transport Materials

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Amorphous organic hole transport materials (HTMs) have been widely used in various optoelectronic applications, such as perovskite solar cells (PSCs) and organic light-emitting diodes, due to their solution-processability and film-homogeneity.[1] Recently, searching for ideal HTMs incorporated into perovskite solar cells to enhance their power conversion efficiency and stability has attracted much attention.[2] It is well known that promising HTMs should possess a suitable ionization potential (IP) to enlarge the open-circuit voltage (V_{oc}) and high hole mobility to transport holes efficiently from the perovskite/HTM interface to the electrode [3]. In contrast to these well-known design principles, a comprehensive understanding of the structure-property relationship remains lacking, which hampers the discovery pace of new HTMs. As a result, investigating the non-trivial structure-property relation with the aid of computer simulations is beneficial. Here, we investigate two series of “linear” HTMs adopting an arm-core-arm design, which consist of oligoacene or fused-thiophene core and 4,4'-dimethyltriphenylamine arms. Our results show that increasing the number of units of oligoacene or fused thiophene, from monomer to pentamer, reduces reorganization energy and energetic disorder. Yet, it also increases the center-of-mass distance between molecules, leading to smaller electronic couplings. These two conflicting effects on hole mobility upon increasing the fused cores length indicate that optimizing the hole mobility can be fulfilled through fine-tuning the number of units. Furthermore, HTMs with oligoacene cores exhibit much smaller reorganization energy as compared to their fused-thiophene analogues, resulting in better hole mobility. Our results pave the way for future design of promising HTMs through optimization of the fused aromatic core. In addition, our computational protocols and our analysis will be useful for future investigations of structure–mobility relationships of amorphous organic semiconductors.

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Enhanced sampling and reweighting methods to understand rare-event kinetics of cyclic peptides

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Rare event kinetics dominate the mode of action of biological systems. For instance, the dissociation of a ligand from its binding pocket is a rare event, thus the majority of computer simulations would be trapped in the bound state without observing the rare unbinding process [1]. Therefore, so called enhanced-sampling simulations are needed that accelerate the relevant transitions. This comes at the cost of losing the underling kinetics. Subsequent reweighting of the enhanced-sampling simulations is therefore crucial to obtain the true kinetics, which has not been possible with standard techniques. Only recently, such reweighting algorithms have been proposed [2-4].

We use enhanced sampling and reweighting methods to analyze the conformational dynamics of cyclic peptides. Cyclic peptides can bind to large and flat binding sites with high affinity and are therefore promising therapeutic candidates for difficult, i.e. undruggable, targets [5]. We study the slow interconversion kinetics of cyclic peptides, which is crucial for their passive membrane permeability, and investigate optimal combinations of methods to obtain converged kinetic models. To validate the accuracy and speed of the methods, we use unbiased simulations of cyclic decapeptides that sufficiently sample between all metastable conformations [6]. The analysis of the conformational dynamics of cyclic peptides will allow us to rationalize the origin of their permeability and lead to more general insights and principles for the design of permeable cyclic peptides.

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Simulating Ion Diffusion in Solid-State Electrolytes using Deep Neural Network Potentials

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Novel solid-state electrolyte (SSE) materials with improved ion conductivity and stability properties are required for all-solid-state batteries to unfold their full potential and become competitive with standard commercial Li-ion batteries. High-performance computer simulations of the ion diffusion in the bulk of SSE materials are at the core of SSE screening algorithms that support experimental work *via* identification of promising candidates.

Traditionally, computational ion diffusion studies utilize classical molecular dynamics (MD) simulations with force field parameters that are fitted to *ab initio* forces computed at the density functional theory (DFT) level. In recent years, deep neural network (DNN) potentials have been proposed to be used in general MD schemes rather than classical analytical force fields.

In this work, we carefully compare the performance of the very recently published DeePMD DNN framework [1] for the study of ion diffusion in SSE materials against MD simulations based on state-of-the-art classical polarizable force fields. Emphasis is laid on the scheme to generate suitable training data sets for the fitting of the DNN potential. We discuss results of this comparison for a number of the most relevant Li-ion SSE materials.

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Spectroscopy with RT-TDDFT

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Time dependent density functional theory (TDDFT) is the work horse of theoretical spectroscopy due to its reasonable compromise between accuracy and computational cost. Complementary to linear response TDDFT (LR-TDDFT), like Sternheimer's or Casida's approach, a direct numerical integration of the time dependent Kohn-Sham equations is also viable for the calculation of spectroscopic properties. Distinct features of the real time TDDFT (RT-TDDFT) approach are an advantageous scaling for larger molecules, response beyond the standard linear response and the complete spectral range from just one simulation run.

Since the electronic response of the system to a perturbation is tracked in real time, a range of linear response functions can be calculated straightforwardly, giving access to purely electronic responses, such as UV/VIS and Xray absorption spectra, as well as electro-magnetic responses, such as electronic circular dichroism (ECD) spectra [1]. These applications of RT-TDDFT are discussed with respect to gauge invariance and origin dependence also in the presence of non-local potentials [2]. Moreover RT-TDDFT has been be extended to the calculation of Raman spectra in a short time approximation, using a Placzek type expansion of the electric-dipole electric-dipole polarizability [3]. This approach allows the simulation of full excitation profiles [4], including non-resonance as well as resonance Raman spectra.

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Non-covalent quantum machine learning corrections to density functionals

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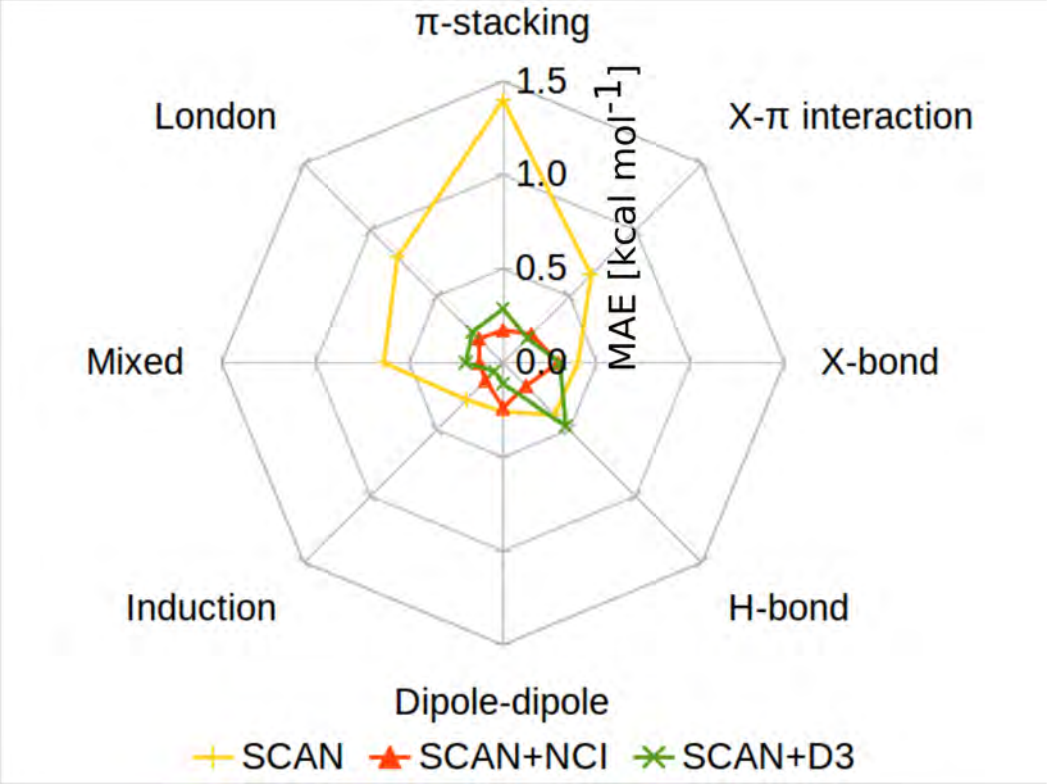
We present non-covalent quantum machine learning corrections (NCI) to six physically motivated density functionals with systematic errors. We demonstrate that the missing massively non-local and non-additive physical effects can be recovered by the quantum machine learning models. The models seamlessly account for various types of non-covalent interactions, and enable accurate predictions of dissociation curves. The correction improves the description of molecular two- and three-body interactions crucial in large water clusters, and provides a reasonable atomic-resolution picture about the interaction energy errors of approximate density functionals that can be a useful information in the development of more accurate density functionals. We show that given sufficient training instances the correction is more flexible than standard molecular mechanical dispersion corrections, and thus it can be applied for cases where many dispersion corrected density functionals fail, such as hydrogen bonding.



https://arxiv.org/abs/1903.09010

Concurrent Optimisation of Organic Donor-Acceptor Pairs through Machine Learning

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In the trial-and-error experimental exploration of materials to be used as Donors or Acceptors in Organic Photovoltaics, the chemical space is not explored uniformly, *i.e.* papers usually report variability either in the Donor or in the Acceptor only. The question that arises is whether this optimisation can occur separately, *i.e.* what is the efficiency of donor-acceptor pairs not experimentally investigated? This problem can be formulated as a matrix completion problem, in analogy to user recommendations on popular services such as social networks, YouTube and Netflix.

We face the matrix completion problem using Machine Learning to predict the efficiency of organic solar cells based on electronic and structural properties of both components, starting from experimental data we recently gathered from the literature and extending models we recently developed. We obtain excellent correlations to experimental data, with the advantage to enable predictions based on both components of a cell, while all other contributions in the field are limited to the analysis a single component. We validate our models on a small set of high efficiency pairs recently appeared in the literature and not included in our data set, predicting them as exceptionally efficient. We finally use the trained models to fill in the missing entries in the matrix of donor-acceptor combinations: our predictions reflect some results recently reported in the literature, and we propose new donor-acceptor combinations to be experimentally tested.

In general terms, the approach presented in our work is of wide interest for the scientific and chemistry community, because it is applicable to many multi-component optimisation problems, and shows how to use statistical and Machine Learning methods to test hypotheses relevant for experimental research.

Efficient geometric integrators for nonadiabatic quantum dynamics. II. The diabatic representation

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The first- and second-order split-operator algorithms are widely used integrators for solving the time-dependent Schrödinger equation. These two integrators preserve some important geometric properties of the exact evolution operator: both are unitary and symplectic while only the second-order split-operator algorithm is time-reversible [1]. Higher-order split-operator based integrators are not commonly used because they are thought to be inefficient due to the large number of Fourier transforms they require. The aim of this study [2] is to show that higher-order integrators based on the split-operator algorithm can be much more efficient (by orders of magnitude) if higher accuracy is desired.

For this, the first- and second-order split-operator algorithms were implemented. In addition, we also implemented several higher-order integrators by composing the second-order split-operator algorithm with different composition schemes [3-6]. To test the different integrators, we performed a convergence analysis by computing the photodissociation of NaI on a two-state one-dimensional [7]. The effect of dimensionality on the efficiency and accuracy of the integrators was also explored using a three-state three-dimensional model of pyrazine [8].

From the results, we observe that the higher-order integrators converge faster, in the time step, and are also more efficient than the first- and second-order integrators in both one- and multi-dimensional systems. We also confirm that, as long they are obtained using symmetric composition methods, the higher-order integrators preserve all the geometric properties of the second-order split-operator algorithm.

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Structural Dynamics of an Excited Donor-Acceptor Complex: Ultrafast Polarized Infrared Spectroscopy and Mixed Quantum/Classical Simulations

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In solution, particular combinations of donor and acceptor molecules can form ground-state pairs that exhibit a new, red-shifted, electronic absorption band not present in the individual donor or acceptor spectra. This new absorption is termed a ‘charge-transfer’ (CT) band and corresponds to excitation from the HOMO of the donor to the LUMO of the acceptor, effecting nearly instantaneous transfer of one electron from donor to acceptor. Charge-recombination (CR) then occurs in concert with solvent and vibrational relaxation and structural dyamics of the ion pair (IP). Due to the large distribution of ground-state complex structures, the excited state of the system is a composite of many different species. Although the thermodynamics and CR processes of such complexes have been the subject of intense study, the structural dynamics of the pairs and their relation to CR are still poorly understood.

We will present results of ultrafast visible (visTA) and infrared (TRIR) transient absorption experiments on the benzene/tetracyanoethylene (Bz/TCNE) pair in addition to a mixed quantum/classical computational study of the system. Population dynamics from the visTA and TRIR experiments reveal complex sub-10 ps dynamics followed by CR on a 55-60 ps timescale. Polarized TRIR anisotropy measurements reveal rich structural dynamics involving large-scale reorganization of Bz/TCNE radical ion pairs following excitation. A detailed computational study of the system combining quantum chemical calculations and classical molecular dynamics simulations was able to reproduce the experimental electronic absorption lineshape and TRIR anisotropy dynamics, allowing for a more detailed interpretation of the structural dynamics. We find that neither the ground nor excited state of the Bz/TCNE pair can be described using a single well-defined structure, and that the IPs convert from predominately face-to-face π stacks to edge-to-face T-shaped structures. Given the sensitivity of charge-transfer processes to donor/acceptor orientation, theoretical descriptions of the recombination dynamics must take into account the structural diversity and evolution of the excited state.

Vibrational Spectroscopy of N_3^- in the Gas and Condensed Phase.

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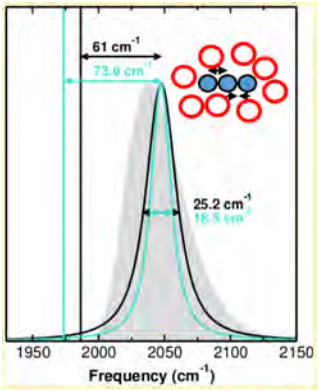
Azido-derivatized amino acids are potentially useful, positionally resolved spectroscopic probes for studying the structural dynamics of proteins and ;">macromolecules in solution. To this end a computational model for the vibrational modes of N_3^- based on accurate electronic structure calculations and a reproducing kernel Hilbert space representation[1] of the potential energy surface for the internal degrees of freedom is developed. Fully dimensional quantum bound state calculations[2] find the antisymmetric stretch vibration at 1974 cm^{-1} compared with 1986 cm^{-1} from experiment.[3] This mode shifts by 64 cm^{-1} (from the frequency distribution) and 74 cm^{-1} (from the IR-lineshape) to the blue, respectively, compared with 61 cm^{-1} from experiment for N_3^- in water.[4] The decay time of the frequency fluctuation correlation function is 1.1 ps, in good agreement with experiment (1.2 to 1.3 ps)[5] and the full width at half maximum of the asymmetric stretch in solution is 18.5 cm^{-1} compared with 25.2 $cm^{-1}$from experiment. A computationally more efficient analysis based on instantaneous normal modes is shown to provide comparable, albeit somewhat less quantitative results compared to solving the 3-dimensional Schrodinger equation for the fundamental vibrations.



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Mechanistic Origin of the Diverging Selectivity Patterns in Catalyzed Ethane and Ethene Oxychlorination

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In the context of vinyl chloride (VCM) production, a more sustainable oxychlorination catalyst that allows direct VCM formation from gas-derived ethane instead of expensive oil-derived ethene is intensively sought after. However, the catalysts that enable high VCM yields in ethene oxychlorination mostly form ethene when ethane is employed as the feed under equivalent conditions.[1,2] Here, we combine steady-state catalytic tests of ethane and ethene oxychlorination, as well as oxychlorination of a mixture of both hydrocarbons, temporal analysis of products, density functional theory, and kinetic modeling on an iron phosphate catalyst to identify the origin of VCM inhibition in ethane oxychlorination. We reveal the complete reaction network and, in particular, the sequential nature of ethane to ethene transformation, which would directly form VCM in a separate step. Yet, when ethane is present in the reaction mixture, ethene oxychlorination is inhibited due to competition between the alkane and the alkene for the same active sites on the surface (**Figure 1a**). This leads to the local depletion of active sites for ethene activation and thus ethene desorption instead of transformation to VCM. These observations are extended to other oxychlorination catalysts, such as europium and lanthanum oxychlorides, cerium oxide, and a reference copper-based system, exhibiting the same trend of VCM suppression (**Figure 1b**) due to the reaction energies of hydrocarbon activation (**Figure 1c**). This is a major hurdle in the transition to ethane as a feedstock for vinyl chloride production.

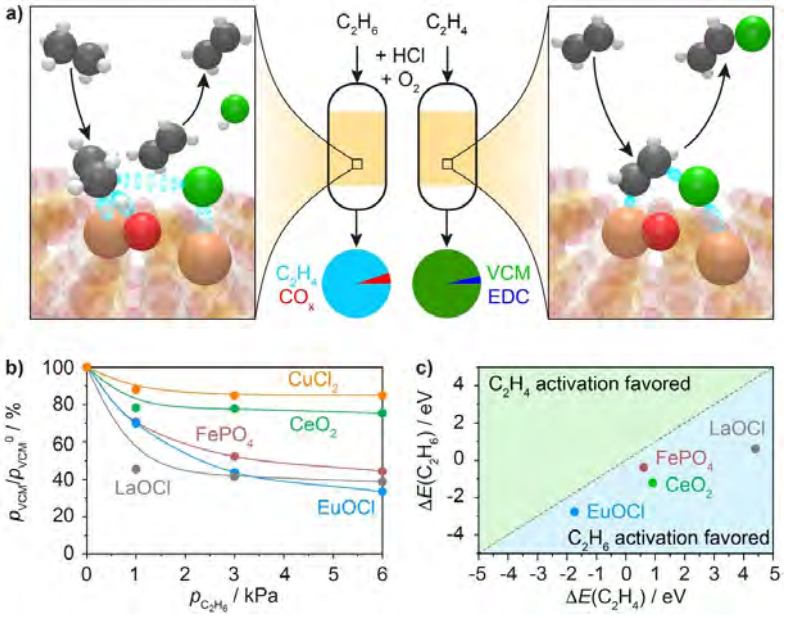

Figure 1 a) Typical diverging product distribution of ethane and ethene oxychlorination and the responsible steps in ethane (left) and ethene (right) activation. b) Suppression of VCM formation in ethene oxychlorination upon introduction of ethane to the feed. c) Reaction energies of ethane versus ethene activation over oxychlorination catalysts.

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Modeling Artificial Water Oxidation – Insights into Reaction Mechanism and Catalyst Design

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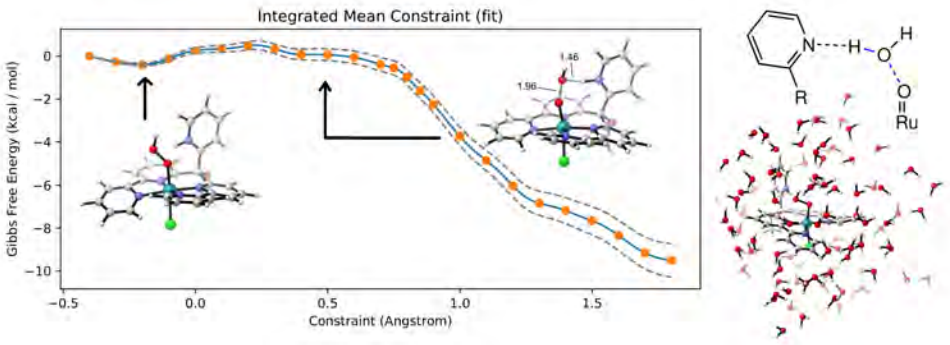
Burning fossil fuels has potentially contributed significantly towards man made climate change – reverting or at least limiting its effects is among the biggest challenges of the 21th century. The development of renewable energy sources such as solar light driven water splitting, a process inspired by nature's photosynthesis, promises to be a valuable source of renewable energy. While there has been considerable success in developing catalysts to facilitate this process, so far there is no commercial viable setup available. In order to further improve existing catalysts, as well as to design novel catalysts, an in-depth understanding of the underlying reaction network is necessary.

Recently we proposed a viable reaction mechanism for a mononuclear Ru-based water oxidation catalyst. A key feature of the latter is the non-coordinating covalently linked pyridine which was found to be in an optimal position to facilitate the oxygen-oxygen bond formation by interacting with the approaching nucleophile. Our theoretical study further showed that by tuning the basicity of the pyridine the barrier for the O-O bond formation could be significantly lowered. Moreover, ligand design was carried out *in silico* for the development of more active catalysts.

In the current study, we use forefront *ab initio* molecular dynamics simulations for a sophisticated inclusion of solvent effects. In order to get an accurate picture of the free energy surface, we apply enhanced sampling methods such as *Bluemoon* and *Metadynamics* – those allow us to characterize the reactive species under ambient conditions. Thereby we are not limited to the active site of the catalyst, but we are able to get a complete picture including the dynamics of the hydrogen bonding network. As a part of this study we also evaluated the applicability of well known protocols based on the *Bluemoon* ensemble to predict the pK_a value of the ligand of said transition metal based water oxidation catalyst.



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Efficient and Accurate Sampling of Reactive Events

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Molecular dynamics is a powerful tool to study the evolution of complex chemical reactions. However, reactants and products states are often separated by very large activation energy barriers. Due to the presence of these energetic bottlenecks, the typical time scales of a chemical transition cannot be reached in a standard simulation. These limitations can be overcome by applying a bias potential to the underlying potential energy surface, thus enhancing the fluctuations between reactants and product states. A very popular and widely used method to achieve this goal is Metadynamics[1]. At the core of a Metadynamics simulation lies the choice of the collective variables describing the essential thermodynamics of the process.

Recently we have introduced a new method named Harmonic Linear Discriminant Analysis (HLDA)[2,3] allowing to extract efficient yet physically meaningful collective variables from the local equilibrium fluctuations within the free energy basins. This allows extracting essential information without having any specific knowledge on the reaction mechanism and at the same time operating a drastic dimensionality reduction of the collective variables. Many interesting chemical reactions have been studied using this method, from fundamental organic chemistry textbook reactions to complex catalytic processes such as reactions in enzyme pockets.

Although enhanced sampling methods allow reaching long time scales the convergence of the free energy surfaces associated to the process of interest often requires sampling of millions of different configurations. This limits the affordable accuracy of the method used to describe the potential energy and forces and restricts the applicability of high level ab initio methods to very few examples. Due to this fact the conclusions derived from these kind of simulations can only be qualitative. To overcome this problem we introduce a new method combining Metadynamics and Free Energy Perturbation (FEP)[4]. This new approach to enhanced sampling allows the perturbative estimation of accurate ab initio free energy surfaces starting from a trajectory obtained using a lower level of theory with a computational cost of several orders of magnitude less than traditional approaches.

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Highly efficient Kr/Xe separation from poly(triazine imide) nanopores

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The noble gases, krypton and xenon, have several crucial applications including in illumination, lasers, insulation, analytical chemistry, etc. Currently, krypton and xenon are separated by cryogenic distillation, which is highly energy intensive, and the energy-efficient separation route is desired. [1]. In this context, size-sieving based separation of Kr and Xe across a nanoporous film, based on the difference in their size and van der Waals interactions, is highly attractive. Two-dimensional nanoporous material, that can be synthesized readily, for Kr/Xe separation is especially appealing because one can achieve a high Kr crossover rates across the nanopores. Poly(triazine imide) or PTI, one of the most crystalline layered g-C_3N_4, has been recently exfoliated to atom-thick single-layer in our and other laboratories [2][3], and appears to be suitable for Kr/Xe separation attributing to the triangular nanopores formed by imide bridged triazine rings (Figure 1a).

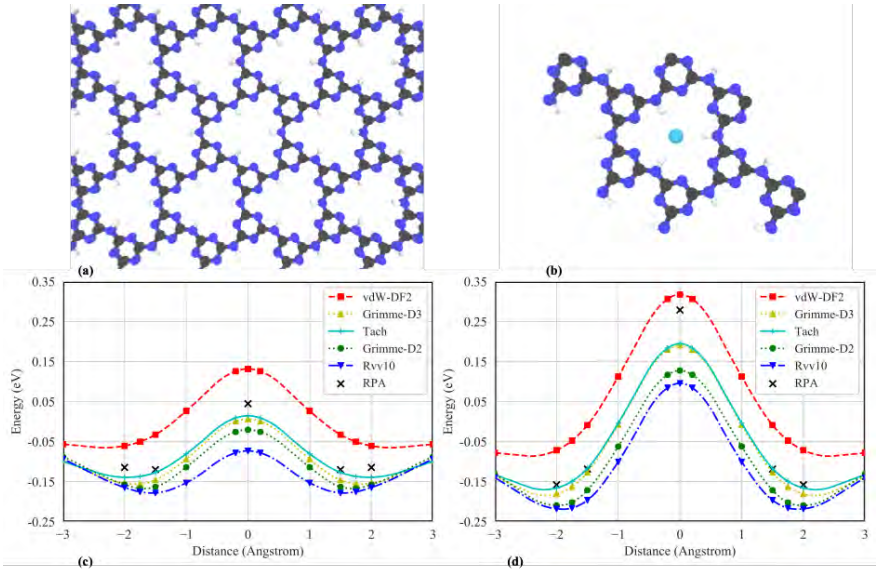

Figure 1. a) The structure of PTI lattice. b)Kr molecule at the center of PTI pore membrane.Potential energy surface for c) Kr, d) Xe on a PTI monolayer using different van der Waals approximation.

In this study, the potential energy surfaces of Kr and Xe on a PTI monolayer have been investigated with density functional theory (DFT) with different van der Waals approximations. Due to the large difference among them, more advanced technique, random phase approximation (RPA), was used to validate the potential energy profiles. DFT calculations on PTI monolayer exhibit different energy barriers for Kr and Xe, which results in an extremely interesting selectivity for Kr/Xe separation. Classical molecular dynamics (MD) simulations proved that PTI monolayer yields a high Kr permeance (pressure normalized flux). Such a promising membrane could have ubiquitous impacts on energy-saving for separation of this challenging and important gas mixture.

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Machine learning of accurate spin splittings in a large carbene chemical space

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Accurate singlet and triplet ground state calculations of a machine-generated carbene chemical space with >8k molecules are presented. Spin splittings are computed at high-order multi-reference level of theory (MRCISD+Q) for this systematically constructed chemical space. We show that with kernel ridge regression-based quantum machine learning (QML),[1] using the aSLATM[2] representation, the out-of-sample error of the predicted singlet-triplet splittings can be systematically controlled. The performance of different frequently used DFT methods in the context of diradical and strongly correlated systems (B3LYP, TPSS, broken-symmetry B3LYP, finite-temperature TPSS) is investigated. Somewhat surprisingly, it is found that broken-symmetry B3LYP and finite-temperature TPSS perform comparable to the semi-empirical CASCI-PM6 method and much worse than conventional B3LYP. Furthermore, the performance of these methods' baselines for predicting MRCISD+Q spin splittings with Δ-machine learning (ΔML)[3] is investigated and used to quantify a form of unsystematic error over chemical space. In this context, we show how ΔML with a state-averaged-CASSCF(2e,2o) baseline enables the chemically accurate prediction of MRCISD+Q spin splittings with only a few hundred training molecules. Finally, the data set gives insight into new carbene chemistry of mostly unknown structures with singlet-triplet spin gaps ranging from -100 kcal/mol to +50 kcal/mol.

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On water slip confined between two-dimensional materials from ab initio molecular dynamics.

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Water slip under confinement has received increased attention in the recent years, driven by the interest to develop efficient desalination membranes, as well as nanoscale osmotic power generators [1,2]. The electronic and chemical nature of materials has been suggested to be highly relevant to slip [3,4]. In this work, we present results on the structure and collective dynamics of liquid water confined between graphene, hBN, and MoS2 sheets from ab initio molecular dynamics simulations. We find that the friction coefficient changes dramatically between the three materials, due to their strikingly different underlying energy landscape. We also report on an intriguing mechanism driving slip under confinement, where stronger confinement regimes give rise to an enhanced slip, due to a reduced friction relaxation time.

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The Effects of S-Nitrosylation on the Conformational Dynamics of Myoglobin

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S-Nitrosylation is a a type of post-translational modification that occurs in a variety of proteins by the covalent attachment of nitrogen monoxide (NO) group to the thiol side chain of a cysteine or to transition metal center of broad spectrum of proteins. Further, it is known that S-nitrosylation directly impact the regulation of numerous signal transduction pathways in cellular systems. [1] However, effects of the modification to the conformational dynamics in protein structure, the reaction mechanism that produce S-nitrosothiol on the cysteine residue and kinetic rates with respected to intermediate states yet to be fully understood.

Herein, the main aim of the study is understanding the effects of S-Nitrosylation of Cys-10 to conformational behavior of myoglobin. Therefore, two different complexes based on wild-type myoglobin (PDB entry 2NRM) [2] and S-Nitrosylated Myoglobin been prepared; both systems have been solvated in water with a buffer region of 15 Å to edges of cubic box which has dimensions of 74Å x 74Å x 74Å. Important bonds (S-N, N=O) and torsion angle (C-S-N=O) have been parametrized by the means of density functional theory at B3LYP/aug-cc-pVDZ level. Molecular dynamic simulations carried out with CHARMM [3] software package via utilization of CHARMM36 force field. [4]

Also, in the application site, S-nitrosothiol can be used as a probe in spectroscopy. Since, N=O bond vibrates out of protein absorption band, probe can provide structural fingerprint by which target protein can be identified. In this study, S-Nitrosylated myoglobin and Cys-NO ligand have been simulated with conventional MD as well as fluctuated point charge model (FPC) and distributed charge model (DCM). Normal mode analysis have been performed with ab initio methods. IR and Power spectra of the protein have been calculated with conventional MD and multipole expansions.

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Exploring the Connections Between Quantum and Semiclassical Instanton Reaction Rate Theories

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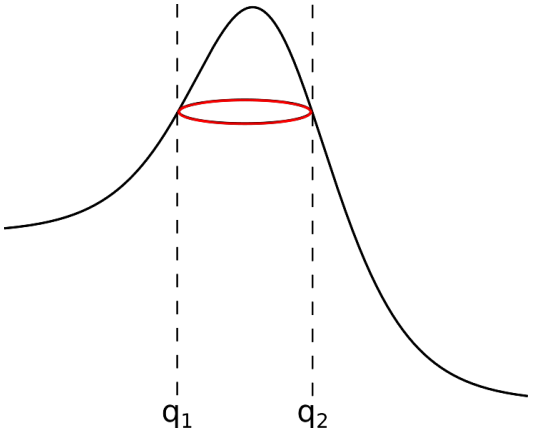
We present a derivation of the quantum and semiclassical instanton expressions for the calculation of reaction rates. Starting from the exact expression for the reaction rate in terms of the flux-flux time correlation function, we use the steepest-descent approximation to obtain the quantum instanton expression, complete with the prescription for finding the optimal dividing surfaces. From the resulting quantum instanton expression, we show that making a standard semiclassical approximation results in the well-known semiclassical instanton expression. The full derivation allows us to examine the links between the two methods, as well as develop an understanding of the breakdown observed in the quantum instanton rate for highly asymmetric barriers in terms of semiclassical paths.



Exploring the Chemical Space in the search for improved Azoheteroarene-based photoswitches

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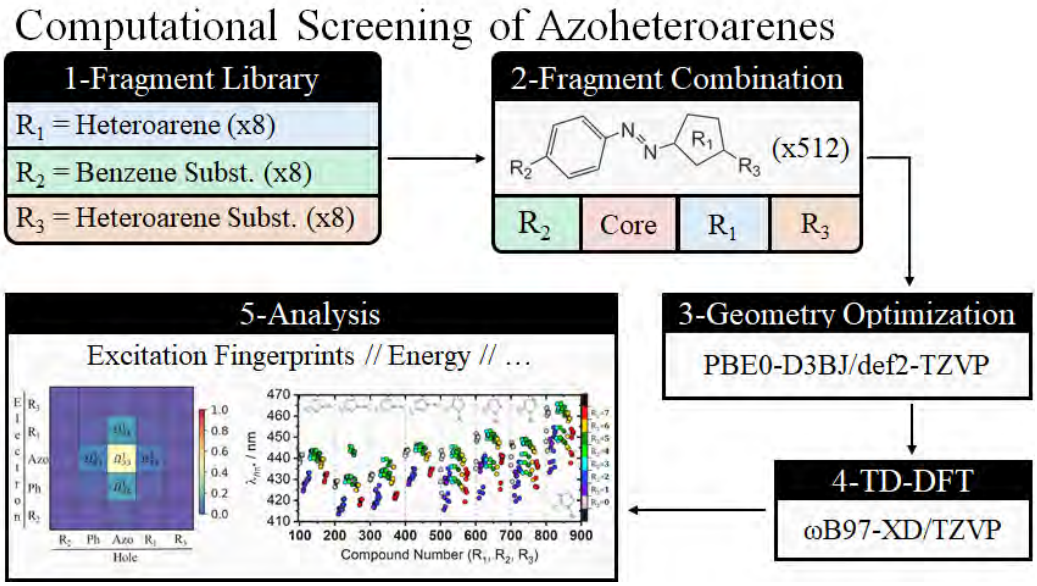
Azoheteroarenes have recently emerged as an interesting alternative to azobenzene in the quest for better molecular photoswitches. [1,2] Both families display similar photochemical properties: they undergo a reversible photo-isomerization between the E- and Z-isomers after irradiation of either the nπ* (S_0-to-S_1) or the ππ* (S_0-to-S_2) bands. The greatest advantage of azoheteroarenes is their structural diversity, which implies a larger potential towards exploiting chemical functionalization to tune the nπ* and ππ* bands and other relevant properties such as the thermal stability or the half-life times. At this stage, however, the exploration of azoheteroarene derivatives is still rather limited, and the potential of such tuning is unclear.

With the aim at improving this situation, we present a computational screening of azoheteroarenes derivatives. It includes the analysis of the photochemical properties of the E- and Z-isomers of 512 compounds, representing 64 different substitution patterns for eight different heteroarene families based on pyrazole, pyrrole and imidazole. The effect of functionalization on the energy, intensity and character of the nπ* and ππ* bands is discussed. An approximation to the thermal stability and the half-life times is also given, based on the isomers relative energy difference, and the strength of the azo N=N bond. Beyond the in-depth analysis of the relevant transitions, our screening clearly identifies the main characteristics of each of the azoheteroarene families, and the best substitution patterns in order to design better photoswitches.



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Electron correlation effects and quantum entanglement measures from multi-configurational wave functions

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The accuracy of a quantum chemical calculation relies on the correct description of electron correlation, which is traditionally divided into static and dynamic contributions. Single-reference methods such as Density Functional Theory or Coupled Cluster can reliably account for dynamic correlation but the presence of static correlation necessitates a multi-reference description as provided by the Complete Active Space Self-Consistent Field [1] or the Density Matrix Renormalization Group [2] methods. To assess the reliability of a certain method for a given system, it is therefore crucial to have an estimate of the degree of static correlation present. We have suggested to assess the multi-configurational character *via* entanglement measures such as the single-orbital entropy $s_i(1)$ [3-6] from a multi-configurational wave function and proposed the $Z_{s(1)}$ diagnostic [7] which condenses this information into a single value. Here, we evaluate $Z_{s(1)}$ for a range of systems including transition states of transition metal catalyzed reactions and discuss its reliability as a multi-configurational diagnostic as well as its transferability between different systems. To indicate the presence of static correlation, strongly correlated orbitals have to be identified from which $Z_{s(1)}$ is to be evaluated, and we find that this identification is crucial for the success of the diagnostic. Yet it is difficult to pinpoint due to the ambiguity underlying the separation of electron correlation into static and dynamic. We address possible extensions to our previously proposed definition of $Z_{s(1)}$ that account for this difficulty.

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Automated Force-Field Refinement From Experimental Data for Compound Families: Automated Setup of Molecular Topologies

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Molecular dynamics (MD) simulations are central to the fields of computational biology, chemistry, and physics, as they form a powerful tool for modeling molecular systems and investigating their properties. In order to achieve accurate results for these properties, the quality of the underlying force-field parameters is essential. Owing to computational and methodological advances in the field over the past few decades, the last few years have witnessed a massive explorative effort towards the automation of these simulations and, in particular, of the force-field development procedures. An empirical parametrization procedure achieves the optimization of the force-field by systematically adapting its parameters and comparing the corresponding simulation results to experimental data. The CombiFF project, developed in the CSMS group at ETH Zurich, aims at taking a major step forward in the area. Its goal is the design, implementation and application of an integrated scheme for the automated refinement of force-field parameters against experimental condensed-phase (predominantly thermodynamic) data, considering entire classes of organic molecules constructed using a fragment library via combinatorial isomer enumeration.

In order to run the MD simulations necessary for force-field parametrization with software packages such as GROMOS, the desired molecules needs to be specified in a topology file which contains information on the atoms, as well as the nonbonded and the covalent interaction parameters of the molecules. The essential task of setting up such topologies is often tedious and repetitive when done manually. The first aim of the CombiFF scheme is to automatize this step of force-field parametrization. To this end, two pieces of software have been written : an isomer enumerator and a topology builder. When used in combination, these two pieces of software are able to create the molecular topologies of all possible constitutional and stereoisomers of a given class, or *family*, of small organic molecules, specified by properties such as molecular formulas, number of cycles or multiple bonds, occurrence of substructures *etc,* in a format that can be used by MD simulation engines. Additionally, each molecule in the family is described by a unique identifier, a canonical SMILES string, in order to gather the experimental data necessary for the subsequent (automated) force-field parametrization.

Error-Propagation by Increments

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For many practical applications, it is important to know how large the error of a given quantum chemical method is [1]. Unfortunately, a simple comparison to a reference calculation of high reliability is often not possible, especially for large molecules. We propose an approach to tackle this problem based on a many-body expansion utilizing the Bethe–Goldstone equation [2]. Many popular approaches in quantum chemistry are based on this idea, for example, the method of increments [3], the kernel energy method [4], many-body expanded full configuration interaction [5], and the fragment molecular orbital method [6].

In our specific case, we do not rely on a partitioning of the orbital space (as is done, e.g., in the method of increments) but instead directly fragment the molecular structure. Then, for each of these fragments, a reliable but computationally demanding reference calculation is carried out (our approach is general enough to allow any quantum chemical calculation). To be flexible regarding the choice of fragmentation, it is often necessary to separate strongly interacting parts (e.g., cutting through a covalent bond). We rely on the embedding approach proposed by Manby, Miller, and coworkers [7] to take such parts into account by a computationally less expensive method (see also Ref. [8]).

We find that our many-body expansion is quickly converging for the cases studied; in fact, it is often sufficient to truncate it at third order. Therefore, this method provides a viable way to reliably propagate errors calculated on smaller fragments to larger molecules [9].

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In Silico Photochemistry using Ab Initio Nonadiabatic Molecular Dynamics

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What happens to a molecule once it has absorbed UV or visible light? How does the molecule release or convert the extra-energy it just received? Answering these questions clearly goes beyond a pure theoretical curiosity, as photochemical and photophysical processes are central for numerous domains like energy conversion and storage, radiation damages in DNA, or atmospheric chemistry, to name a few. Ab initio multiple spawning (AIMS) is a theoretical tool that aims at an accurate yet efficient *in silico* description of photochemical and photophysical processes in molecules. AIMS describes the excited-state dynamics of nuclear wavepackets using adaptive linear combinations of traveling frozen Gaussians [1].

In this talk, I intend to survey some recent developments and applications of the AIMS technique. A significant feature of the AIMS framework – besides its controlled approximations [2,3] – is its adaptability, which permits the addition of critical physical processes for a realistic simulation of photochemical processes. For example, we recently included spin-orbit coupling in AIMS [4] and the effect of an external electric field [5], leading to two new schemes called Generalized AIMS (GAIMS) and eXternal Field AIMS (XFAIMS). We also proposed a simple yet rational approximation to AIMS termed Stochastic-Selection AIMS (SSAIMS), which allows decreasing the computational cost of an AIMS dynamics substantially [6].

Also, we also interfaced AIMS with the GPU-based electronic structure code TeraChem to study the excited-state dynamics of large molecular systems. Combining the accuracy of AIMS with the efficiency of GPU-accelerated electronic structure calculations (LR-TDDFT or SA-CASSCF) allows indeed for a significant step forward in the simulation of nonadiabatic events, as it pushes the boundaries of the well-known compromise between efficiency and accuracy imposed by the computational cost of such dynamics. Thanks to this new interface, we could investigate the nonadiabatic dynamics of different medium-size organic molecules important in biological chemistry, organic electronics, and atmospheric chemistry [7-9].

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An approach for calculating the logarithmic derivative of the time-dependent wavefunction

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Computational treatment of quantum dynamics in molecules is often based, in one form or another, on the solution of the time-dependent Schrodinger equation. Due to extreme complexity of this problem, a lot of efforts were directed on the development of efficient approaches which allow to tackle dynamics in realistic systems. One of the most promising recent ideas is to use a specific ansatz for the full molecular wavefunction which is known as the exact factorization approach [1,2]. Within this formalism the correlated motion of nuclei and electrons in a system is represented by the two coupled equations containing terms responsible for the electron-nuclear couplings. Despite the bright promise of the exact factorization, the appearing equations of motion are extremely complicated to solve [3]. Namely, one of the key complexities is the necessity to calculate the logarithmic derivative of the time-dependent nuclear wave packet. Although at first glance the logarithmic derivative seems to be a straightforward quantity to calculate, it becomes clear upon closer inspection that its direct numerical evaluation is ill-defined. Here we present a new approach for the explicit propagation of the logarithmic derivative in time. The developed methodology combines Schrodinger picture with de Broglie-Bohm formulation of the quantum theory. In particular, we show how the polar representation of the wavefunction can be used to propagate the logarithmic derivative utilizing the topological phase of the wavefunction. Although the developed approach were initially designed to calculate the logarithmic derivative, it turned out to be an interesting tool to explore connections between Schrodinger and Bohmian mechanics. We hope that our study will stimulate further theoretical research aiming at developing computational approaches based on the factorized form of the molecular wavefunction.

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Nonadiabatic molecular dynamics simulations

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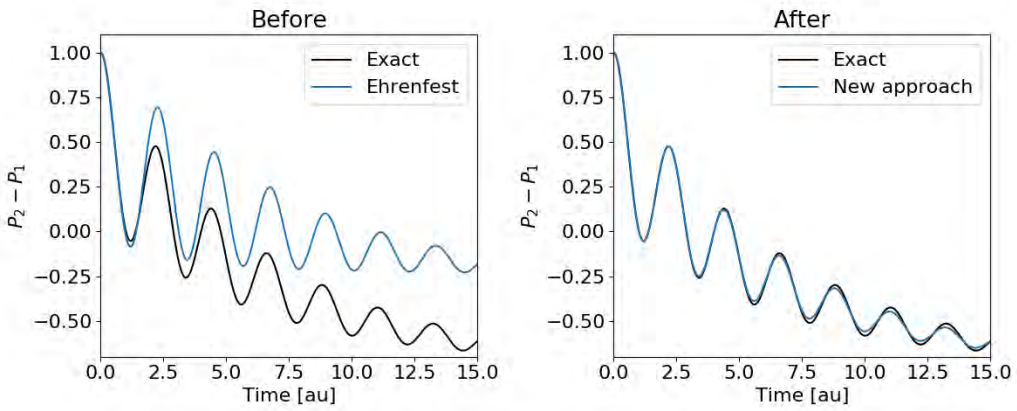
[1] ETH Zurich, Lab. für Physikalische Chemie

A long-standing goal in computational chemistry is to combine the quantum description of nonadiabatic processes with the simple classical trajectories in molecular dynamics (MD). In classical MD one calculates molecular properties via an average over many particles that follow Newtonian mechanics on a potential energy surface, which emerges from the famous Born-Oppenheimer approximation. This approximation is however no longer valid for nonadiabatic processes, such as interaction with light, internal conversion and ultrafast electron transfer. To describe these phenomena one has to include multiple potential energy surfaces, which raises the question: is it possible to combine classical MD trajectories with nonadiabatic dynamics on multiple surfaces in a rigorous way?

In my talk I will show a simple way to achieve this for a two-surface problem, without invoking the surface-hopping ansatz. The key idea is to assign an additional pair of variables to each trajectory to describe the electronic states, in addition to the nuclear coordinates and momenta. These variables are encoded as the orientation of a unit vector on a sphere, where the north pole represents the ground state, the south pole represents the excited state, and other points on the sphere represent general superpositions of both surfaces. We have showed[1] how to derive a mixed quantum-classical method in this way, which shares the same equations of motion as in Ehrenfest dynamics, but differs in an important way in how initial distributions and observables are defined.

I will show benchmark results for the approach applied to population transfer in various model systems. The figure shows an example of the population difference between two electronic states for a condensed-phase system that is initially in its excited state. Ehrenfest dynamics predicts completely wrong final state populations, whereas our method is in almost perfect agreement with the exact result.



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Self-consistent DFT+U+V study of oxygen vacancies in $SrTiO_3$

C. Ricca[1], I. Timrov[2], M. Cococcioni[2], N. Marzari[2], U. Aschauer[1]*

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Neutral oxygen vacancies are known to determine the physical properties and in particular the conductivity of $SrTiO_3$ (STO). Despite a great deal of effort, the nature of these defects in STO is still widely debated, and results are contradictory, especially in regards to the nature of the associated electronic states. This ambiguity has often been related to STO's peculiar electronic properties: STO is a d^0 transition metal oxide with a mixture of ionic and covalent interactions, leading to a competition between trapping electrons associated with the defect in the vacancy or to localize them on Ti-3d orbitals. This particular situation may not be properly described by standard density functional theory (DFT) approaches or even by Hubbard corrected DFT+*U*, both providing largely underestimated bandgaps and inaccurate crystal field splitting compared to experiments. Here, we apply, for the first time, a novel DFT+*U*+*V* method in which the Hubbard *U* and *V* parameters are computed self-consistently to oxygen deficient STO. This extended Hubbard model combines the conventional on-site Coulomb interaction for *d* electrons on Ti sites (*U*) together with inter-site electronic interactions between Ti-d and O-p states (*V*). Compared to DFT+*U*, this approach increases the predictive accuracy for weakly correlated transition metal oxides and systems where hybridization plays a major role, as is the case in STO. Results show that self-consistent DFT+*U*+*V* is able to provide a picture of V_O defects in STO similar to the one given by hybrid DFT functionals but at a much lower computational cost.

Calculating electronic excitation spectra for large-scale applications

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Time dependent density functional theory (TDDFT) has proven to be a powerful standard approach enabling the calculation of excitation energies and excited state properties for medium-sized systems of about 100 atoms. Large-scale applications aiming for broad-band electronic spectra of systems in the size range of several hundreds of atoms are however not routinely feasible within standard TDDFT. In 2013, Grimme therefore proposed a simplified Tamm-Dancoff (sTDA) density functional approach approximating two-electron repulsion integrals using Löwdin monopoles and a semi-empirical Coulomb operator [1]. The sTDA ansatz was assessed for a variety of test sets proving that accuracy loss for excitation energies in comparison to standard TDDFT is negligible while computational savings are increased by two orders of magnitude [2,3]. Based on the original implementation by Grimme, we present an sTDA implementation in the Gaussian and plane waves (GPW) framework of the CP2K program package [4], broadening the application range from molecules to periodic systems. We show benchmark results comparing to standard TDDFT and the original sTDA implementation.

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The relationship between physical conditions for ρ_B and the error within Frozen Density Embedding Theory.

N. Ricardi[1], A. Zech[1], Y. Gimbal-Zofka[1], T. Wesolowski[1]*

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Frozen Density Embedding Theory (FDET)[1],[2] is a multi-level method which describes the effect of a frozen electron density of the environment, ρ_B (**r**), on the wavefunction of the system of interest (Ψ_A), maintaining a quantum-mechanical description for the whole supermolecular system.
FDET exhibits large flexibility: any choice of methods for the subsystems A and B is possible, including for instance the generation of ρ_B(**r**) as a superposition of densities or time-averaging[3]. Additionally, the multi-level approach of this formalism can be further extended by combination with other environment models (e.g. PCM, MM).
Three factors determine the accuracy of FDET-based embedded wavefunctions[4],[5]:
• the basis set expansion which may excessively localise the wavefunction
• the approximate nature of the DFT functionals used for exchange-correlation and kinetic component of the interaction
• violations of the condition ρ_B^{frozen} (**r**) ≤ ρ^{I}_{TOT} (**r**)
In particular, the latest relates to chemical phenomena such as polarisation and environment response. In order to investigate the influence of such phenomena on the quality of the FDET results, we selected embedding protocols which differ in the way ρ_B(**r**) is generated, resulting in different manners of accounting for polarisation effects. Then errors in measured quantities have been compared to parameters obtained from the direct analysis of the violations of the last condition.

With this, we aim at understanding the sources of error in different type of interactions, and to guide the selection of an appropriate protocol for the system at hand.

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Molecular modelling in crop protection: current technologies and applications

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Computational chemistry is a well-established discipline in the pharmaceutical industry and in recent years it’s been growing fast in the crop protection field too. A number of diverse molecular modelling techniques, ranging from quantum mechanics calculations to molecular dynamics simulations, can be effectively applied to many aspects of agrochemical research and contribute to the elucidation of modes of action and the design and optimization of novel active ingredients, while addressing resistance and selectivity issues. This talk will discuss, through a selection of case studies, the contribution and impact of molecular modelling in different fields of agrochemistry, aiming at the development of selective, safe and resistance-breaking products.

Using RE-EDS to calculate relative binding free energies for ligand scaffold hopping

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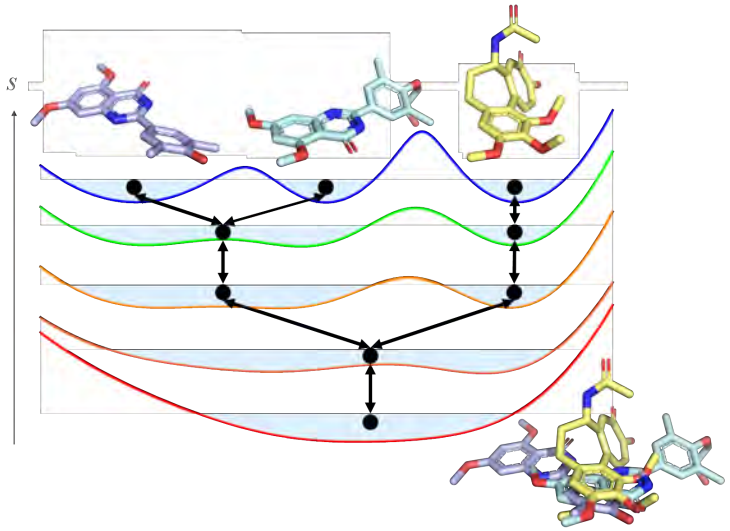
Calculating the relative binding free energies of a set of ligands to a particular protein is a key application of computational chemistry, facilitating the design of new drug candidates, or explaining experimental results. We have developed the molecular-dynamics (MD) based free energy method RE-EDS [1,2], which is a combination of Hamiltonian Replica Exchange (RE) [3] and Enveloping Distribution Sampling (EDS) [4,5]. RE is a standard approach to enhance sampling in MD simulations. A major advantage of EDS over other free energy methods is the possibility to calculate free energy differences between multiple end states (e.g., multiple ligands) from a single simulation [5]. This feature improves efficiency by up to an order of magnitude compared to pairwise methods. To enable sampling of all end states in a simulation, EDS uses a reference state Hamiltonian.



This reference state envelops all ligands in the system and can be modified by two parameters for optimal sampling. The first parameter is the smoothing parameter *s*, which can lower the energy barriers between the ligands such that transitions from one state to another occur. The second parameter is a vector containing the so-called energy offsets, which are used to align the potential-energy landscapes of all ligands, and, therefore, allow equal sampling of all ligands. However, the determination of the optimal reference-state parameters is challenging and time-consuming for more than two end-states. This issue can be addressed with RE-EDS. In RE-EDS, replicas of the reference state are simulated with different smoothness parameters. At regular time intervals, exchanges of the configurations between replicas are attempted, which enables transitions between end states. This simplifies the choice of the reference state parameters and allows the simulation of ligands with more diverse structures compared to conventional free energy methods. Here, we explore the possible structural diversity of ligands in relative binding free energy calculations with RE-EDS.

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Molecular Dynamics simulations with RKHS based potentials

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Molecular Dynamics (MD) simulations are a necessary tool for interpreting experimental results and engineering new materials with desired properties. Compromises between the size of simulations and its accuracy are usually necessary. Classical simulations can explore systems of the size of million of atoms for microseconds, but are unable to describe bond formation/cleavage and the accuracy is intrinsically limited by the functional form of the Force Field used. Quantum Mechanical (QM) simulations can be extremely accurate, but they are tremendously limited in size and time.

Interpolation methods on *ab-initio* data, as the ones based on Reproducing Kernel Hilbert Space (RKHS)[1], can be implemented in classical MD packages. At a price of a small overhead respect to classical simulations, the wise choice of kernels are able to reproduce quantum-mechanical results for the interested properties. The one and three dimensional models, based on a previous work in our group [2] , are respectively in release and development in CHARMM [3].

The mono-dimensional case is successfully used for describing 2O -> O_2 recombination, on top and inside of a grain of amorphous solid water at 50 K [4]. The high rate of reactive events (~80% over 1000 simulations of 100 ps) confirms that the oxygen atoms have sufficient energy for overcoming the average encountered diffusional barriers (0.6 kcal/mol over a 0.1 kcal/mol temperature) [5] . The scarce coupling between O_2 vibration and the other modes can explain the reduced number of observations of O_2 gas in space, that will be trapped in the grain and possibly reacts with other incoming species.

The inclusion of multiple Potential Energy Surfaces via different kernels allows the study and implementation of non adiabatic effects during simulations. Recombination on O_2 is performed, including Spin Orbit Coupling effects between the $^1\Sigma_g$ excited state and $^3\Sigma_g$ ground state. Preliminary results show that the $^1\Sigma_g$ state is the favourite formation channel (66% of 1800 reactive events).

The three dimensional case is tested for the CO + O -> CO_2 formation in the same environmental conditions used for O_2. Compared to the previous simulations, a better coupling between the molecular modes and the water is observed, that has as a consequence a more efficient relaxation mechanism and higher diffusivity for the recombined molecule.

This study shows that RKHS is a powerful tool that allows the inclusion of reactive events and enhance the accuracy of calculations using classical MD packages.

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Automated force-field refinement for compound families

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Nowadays, classical (force-field based) atomistic simulations of condensed-phase systems play a key role in all areas of natural sciences. Owing to computational and methodological advances in the field over the past few decades, and to a resulting increase in the usefulness of the simulation approach in e.g. material and drug design, the last few years have witnessed a massive explorative effort towards the automation of these calculations and, in particular, of the force-field development procedures. In this context, our goal is the design, implementation and application of an integrated scheme for the automated refinement of force-field parameters against experimental condensed-phase (predominantly thermodynamic) data, considering entire classes of organic molecules constructed using a fragment library via combinatorial isomer enumeration. The main features and objectives of the proposed approach can be stated as follows: (i) keep the force-field design focused on the central building blocks of physical organic chemistry, the chemical functional groups; (ii) treat the force-field parameters as empirical quantities, to be optimized primarily against experimental data rather than against the results of quantum-mechanical calculations; (iii) enable a complete automation of the topology-construction and parameter-optimization procedures; (iv) construct force fields with a broad (though not exhaustive) coverage of the chemical space, optimized against an extensive experimental dataset; (v) enable the comparison of different choices in the force-field functional form at optimal parametrization level, so as to guide the refinement of this functional form towards the most relevant improvements; (vi) provide chemical insight into the specific properties of the classes of organic compounds considered. As a first application, this workflow is illustrated here in the context of two molecule families, saturated haloalkanes and non-hydrogen-bonding oxygen-containing compounds (ethers, esters, aldehydes and ketones) up to 6 carbon atoms. Considering 300 and 123 molecules, respectively, in the two families, the force-field parameters (based on the GROMOS force-field functional form) are systematically optimized against a total 607 and 233 experimental values, respectively, for the liquid density and vaporization enthalpy. After 10-25 refinement iterations for the non-bonded interaction parameters (about 2 weeks calculation time using 400 CPUs), the final RMSD's against experiment are 55.65 kg/m^3 and 3.48 kJ/mol for the haloalkanes, and 24.87 kg/m^3 and 4.62 kJ/mol for the oxygenated compounds. Further sets of 320 and 444 molecules (600 and 726 experimental data points) are used for validation, with only slightly larger RMSD's relative to experiment.

Learning (from) the electron density: focus on non-covalent interactions and transferability

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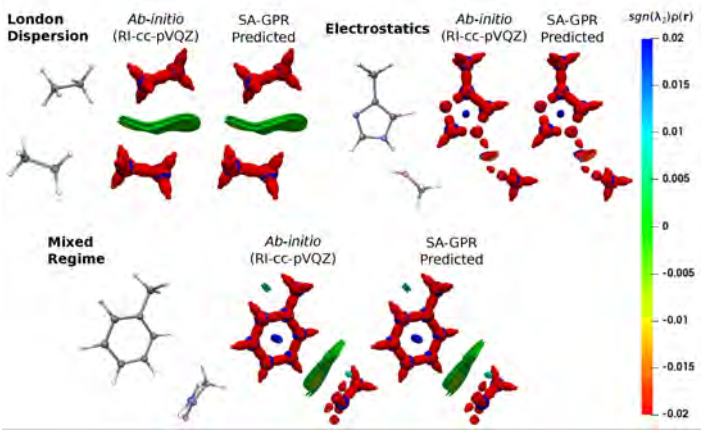
Intermolecular interactions are the cornerstone of chemistry beyond the single isolated molecule. Their undisputed importance is readily demonstrated by the intensive research effort spent achieving ever more accurate quantification of their magnitude and a chemically more intuitive characterization of their spatial behavior. Among all the molecular properties that encode the relevant information needed to fully characterize both intra- and intermolecular interactions, the molecular charge density occupies a preferential place due to its observable nature and its dependence only on three spatial variables. While, ρ(**r**) can be accurately obtained solving the electronic structure problem through *ab-initio* computations, this approach can become rapidly demanding if the electron density has to be evaluated for thousands of different molecules or for the very large chemical systems, such as peptides and proteins. To address this problem, we present a transferable and scalable machine-learning model of the electron density, able to predict the full density field directly from the atomic coordinates.[1] Additionally, we show how the regression model can be applied to access the information about intermolecular interactions in a chemically diverse ensemble of molecules derived from the BioFragment database (BFDb).[2] Finally, we demonstrate the transferability of the model to new chemical situations, by predicting and analyzing the electron density field of a complex polypeptide.



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Alchemical Perturbation Density Functional Theory (APDFT)

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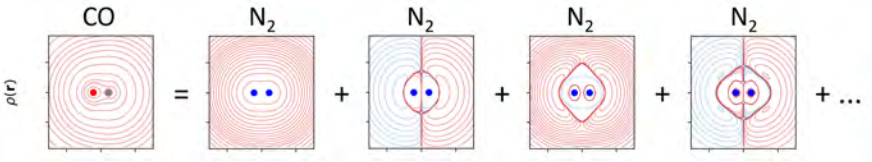
We introduce an orbital free electron density functional approximation based on alchemical perturbation theory. Given convergent perturbations of a suitable reference system, the accuracy of popular self-consistent Kohn-Sham density functional estimates of properties of new molecules can be systematically surpassed - at negligible cost.

For example, using the CCSD solution for N_2, APDFT calculated properties of CO are more accurate than PBE already at 1st order (energies and dipole moments) and 2nd order (quadrupole-moments and forces). The associated energy functional is an approximation to the integrated energy derivative, requiring only perturbed reference electron densities: No self-consistent field equations are necessary to estimate energies and electron densities. Instead, our approach relies on the electron density response w.r.t nuclear charges and treats changes of nuclear charges at any sites as perturbations to the system. We show that the resulting expansion in perturbation orders converges quickly by analytical proof for the hydrogenic atom and for any free atom. Numerical convergence is shown for alchemical perturbations of H_2, N_2, and benzene.
APDFT based estimates of the electron density of a target molecule are obtained for the same perturbations.
Estimated electronic ground state properties considered include covalent bonding potentials, atomic forces, as well as dipole and quadrupole moments.
APDFT is widely applicable to any level of theory that makes electron densities available and allows to assess a combinatorial number of molecules with one fixed set of calculations rather than calculating molecules one-by-one.

If the perturbation series converges and if the reference level of theory is of sufficient quality, APDFT represents a systematically improving DFT approximation of hierarchies of accuracy.



G. F. von Rudorff, O. A. von Lilienfeld, **2019**, arXiv:1809.01647