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Bridging the Gap: Integrating Machine Learning with Quantum Mechanical Calculations for Enhanced Molecular Electrostatics Modelling

Charlie Adams, Josh Horton, David Wright, Daniel Cole

Accurately modelling electrostatics interactions between small molecules and proteins is key to understanding affinity and selectivity of drug candidates. For many high-volume applications running expensive quantum mechanical (QM) calculations for each new system is deemed impractical, leading to the use of partial charge models built to compute charges at a fraction of the cost in molecular mechanics and snapshot complementarity methods. Until recently the use of semi-empirical calculations or heuristic models with limited applicability was commonplace. Newer generations of models exploit machine learning (ML) to front-load more accurate QM calculations to achieve greater accuracy while continuing to minimise the required computational costs. Here we present a comparison of a wide range of recent ML charge models with those available in popular simulation and cheminformatics packages and explore how improvements in electrostatic property modelling correlates with improved biochemical properties. An additional advantage of ML partial charge models is that they are able to be readily retrained with different QM methods depending on the problem at hand. In collaboration with OpenFF, we investigate how training the charge model to increasingly higher order properties, from partial charges to multipoles, influences the accuracy of the final model. As a discussion for future work, we also explore the possibility of training ML partial charge models using post Hartree–Fock methods for metal containing systems.

Protein dynamics and the temperature adaptation of enzyme catalysis: simulations of wild type and mutants MalL

Marvellous Arabambi , Carlin J Hamill, Vickery L Arcus, Marc van der Kamp, Frank Vollmer and Adrian J Mulholland

Understanding the temperature dependence of enzymatic reactions holds great promises for the design and engineering of enzymes with activities optimized for a specific temperature. This should aid in the development of biocatalysts. Growing evidence show that many enzymes express a curvature in Arrhenius plots, and a temperature of optimum activity, not caused by denaturation.1,2 This can be explained by macromolecular rate theory (MMRT) and is due to a difference in heat capacity (the activation heat capacity, ΔC‡) between the enzyme-substrate (ES) and the enzyme-transition state (E-TS) complexes. Previous work has shown that molecular dynamics (MD) simulations can be used to calculate ΔC‡ in good agreement with experiment for the glycoside hydrolase enzyme MalL.3 Here, further extensive MD simulations of the ES and a E-TS analogue of wild-type MalL were conducted to characterise the conformational landscape explored by these two states. ΔC‡ is calculated from the difference in fluctuations of the enthalpy and is negative. Principal component analysis (PCA) and clustering analysis show that the E-TS samples a more restricted conformational space than the ES. The latter samples conformations that overlap the former. The results indicate that there is a ‘transition state-like conformation’ (TLC) sampled by the ES before the chemical step.4 Experimental and MD simulation data for the MalL mutant S536R, designed to mimic a more conformationally restricted TLC, show a smaller magnitude in ΔC‡ compared to wild-type. This was due to both the ES and the E-TS complexes sampling similar conformational space.4 These results provide insight into the role of conformational changes on the ΔC‡ and shed light on the temperature dependence of enzyme-catalysed reactions.

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Multi-Scale Theoretical Investigation of the Linear and Nonlinear Optical Responses of Di-8-ANEPPS Embedded in Complex Environments: on the Way to Explore the Complexity of Cell Membranes

Charlotte Bouquiaux, Tarcius N. Ramos, Pierre Beaujean, Frederic Castet, Benoit Champagne

The aim of this work is to assess the effects of the environment on the nonlinear optical (NLO) responses of the di-8-ANEPPS chromophore by using newly-optimized theoretical chemistry methods. Two types of environments are considered: solutions for a general characterization of its NLO responses, and lipid bilayers to describe its sensor capacities. A two-step molecular mechanics-quantum mechanics approach is used and validated. It is shown that the di-8-ANEPPS NLO responses decrease with increasing the solvent polarity, in agreement with new experimental data. For biological systems, due to their enormous complexity, the strategy was to decompose the chemical diversity found in a plasma membrane (PM) into several one-component lipid bilayers, allowing to disentangle the effects of each lipid species. Starting from a pure DPPC bilayer, collections of systems varying either in the nature of the polar head or in the fatty acids were considered, showing that changes in the hydrophobic head modulate the NLO responses more than the variations in the hydrocarbon core. Mixed systems were then introduced by adding cholesterol molecules at different concentrations in DPPC bilayers, highlighting the condensing effect of cholesterol, inducing an increase in NLO responses. Finally, the system complexity was taken to a new level with the study of a multi-million atom PM. It showcases what is now possible to do in terms of computational resources and emphasizes the appeal of data mining tools in such complex investigations. These different contributions deepen our knowledge of the structural organization of increasingly complex systems. As this information is difficult to obtain experimentally, this work truly demonstrates the key role of computational chemistry in inferring structure-property relationships and in helping to unravel the complexity of biological systems.

Time-dependent study of light-induced hapticity changes in a ruthenium sandwich complex

Vera Brieskorn, Basile Curchod

The ruthenium sandwich complex [RuCpBz]+ (Ruwich) is an organometallic molecule that shows Ru-Bz bond destabilization when irradiated with light. As a consequence, the Bz hapticity is lowered from η6 to presumably η4 in the excited state, a phenomenon that could be exploited in photocatalysis. However, little is known about how the Bz binding mode in Ruwich is decreased, because hapticity changes of organic cyclic ligands are not often studied in a time-dependent perspective. Therefore, we simulated the excited state dynamics of Ruwich using adiabatic and nonadiabatic methods and developed a strategy to extract hapticity-related information from these simulations. To analyze the movement of Bz in Ruwich, we developed four geometry-based parameters and achieved a more rigorous definition of the concept of hapticity. From the hapticity definition, embodied by the parameter ά, and the three additional geometry parameters a more detailed view of the geometry changes occurring in Ruwich was obtained, showing that the hapticity of Bz fluctuates rapidly in the excited state.

Direct dynamics simulation of prospective PFAS molecules dissociation after electron impact of PPVE and C4H3F7O isomers.

Ryan Brook, Dmitry Makhov, Dmitry Shalashillin

The current search for replacement of environmentally harmful PFAS molecules used as the main ingredient in plasma used for etching procedures will only grow in importance as the need for semiconductors increases. In order to aid this search, we present Direct dynamics simulations of prospective molecules undergoing dissociation after electron impact(1), capturing trends of molecules found in experiment(2,3).

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Shapespyer: a Python driven toolchain for soft matter simulations

Andrey Brukhno, Michael Seaton, John Purton, Tim Snow and James Doutch

The Shapespyer project is a thriving collaboration between SCD, ISIS and Diamond (UKRI) under the overarching Ada Lovelace Centre (ALC) scheme, which supports and facilitates frontier interdisciplinary research by bridging between theoretical analysis, computer simulation and experimental studies. In particular, the primary goal of the project is to equip Small Angle Scattering (SAS) experimentalists with seamless simulation and analysis workflows allowing for verification of theoretical conjectures about complex molecular nanoaggregates by direct comparison between SAS experiments and detailed computer simulations.

To this end, we have developed Shapespyer - a Python-driven molecular structure generation API library with toolchains for simulation of multicomponent molecular nanostructures ubiquitous in soft matter and biomolecular systems. Taking a number of template molecules as inputs (one per solute species), Shapespyer automatically generates nanoscale aggregates that can be further used as inputs for molecular dynamics simulations carried out on any computing platform, including heterogeneous HPC. The outcomes include equilibrated structures and trajectories that can be analysed and compared with data from appropriate experiments, e.g. SANS, SAXS. The supported molecular arrangements include: 1 rings (flat discs); 2 spherical assemblies, e.g. micelles or vesicles; 3 cylindrical stacks, e.g. rods or worm-like structures; 4 pre-assembled aggregates arranged on 3D lattice(s); 5 bicontinuous 3D phases based on Schwarz minimal surfaces. The template molecule coordinates are taken from .pdb, .xyz, .gro (Gromacs) or CONFIG (DL_POLY / DL_MESO) files. Shapespyer automates the setup and batched runs of molecular dynamics (MD or DPD) simulations based on popular force-fields, e.g. CHARMM, OPLS, DPD, including the initialisation steps for adding ionic species and solvent. Specialised (Bash / Python) scripts are provided to perform equilibration and production simulations, with optional post-simulation analyses, executable on virtually any high performance parallel platform (HPC), including standard CPU systems and hybrid accelerated CPU/GPU systems (e.g. Scarf, ARCHER2, Baskerville). The supported analyses of the simulation results include: (i) cluster classification and size distribution analyses, (ii) radius of gyration and its principal components, (iii) hydration layer and cavity occupation analyses, (iv) mass and neutron-scattering-length densities.

Online resources:

https://www.scd.stfc.ac.uk/Pages/Shapespyer.aspx https://gitlab.com/simnavi/shapespyer

Exploring Cluster Surface Adsorption: A Proof-of-Concept Investigation of Phase Space Volume Using Nested Sampling

Thanawitch Chatbipho, Mingrui Yang, Robert B. Wexler, Livia B. Partay

Understanding the thermodynamic properties of complex systems often involves exploring phase space volume. In this study, we apply the Nested Sampling method to investigate simple Lennard-Jones cluster surface systems, aiming to determine the impact of adsorbate sizes and adsorption strength on phase transition properties. This is achieved by varying the sigma and epsilon Lennard-Jones parameters, respectively. A key advantage of Nested Sampling is its ability to derive the temperature-dependent partition function without prior knowledge of solid structures. Our findings reveal two significant phase transitions in these Lennard-Jones systems. At higher temperatures, condensation of adsorbates on the surface occurs, while a lower-temperature phase transition is associated with the rearrangement of adsorbates. Notably, increasing adsorption strength and adsorbate size leads to higher condensation temperatures, reflecting stronger and more extensive interactions that overcome the kinetic energy of the adsorbates. In addition, we observe distinct lowest-energy structures for different adsorbate sizes: smaller adsorbates tend to form multilayer adsorption, while larger ones tend to disperse around the cluster. When the interaction between adsorbates and the surface outweighs the interaction between adsorbates themselves, adsorption on the higher coordination number surface sites is favoured. In conclusion, our work demonstrates the efficacy of Nested Sampling in determining the thermodynamic properties of the simulated adsorption systems. Thus, this method becomes more promising to employ in more realistic systems where various applications such as the development of heterogeneous catalysis, gas containers, and filtration of toxic compounds are involved.

Simulating Nonadiabatic Dynamics Using the Meyer-Miller-Stock-Thoss Hamiltonian: A Comparison of Algorithms

Lauren E. Cook, Johan E. Runeson , Jeremy O. Richardson , and Timothy J. H. Hele

Mixed quantum-classical models are commonly used to simulate nonadiabatic dynamics. Often, these approaches use a mapping to describe the electronic dynamics by time-propagating a set of classical variables, where averaging over many trajectories allows the approximation of thermal equilibrium properties through correlation functions. Many integration algorithms exist to propagate the dynamics, but a through performance comparison appears to be lacking. Here, we compare three time-propagation algorithms for the Meyer-Miller-Stock-Thoss Hamiltonian: [1] the MInt, Split-Liouvillian (SL), and Degenerate Eigenvalue (DE) algorithms.[2–4] We determine that the MInt is the most accurate algorithm based on the symplecticity, energy conservation, computational cost, and accuracy of correlation functions. Despite not being symplectic, the SL algorithm obtains similar results for a lower computational cost and in some cases, better energy conservation. Approximations within the DE algorithm results in inaccurate dynamics, poor energy conservation and a higher computational expense for systems with weak electronic coupling. These results should guide future simulations utilising mapping variable approaches.

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Isolated cyanovinyl anion as a potential stable synthon

Adrianna Cyraniak, Iwona Anusiewicz, Sylwia Freza, Piotr Skurski

Retrosynthesis is a theoretical process of designing a chain of transformations from product to substrates. Successive disconnections of the target molecule result in simpler hypothetical units called synthons, which are usually unstable systems [1]. The search for sustainable synthetic equivalents of synthons is the greatest challenge of retrosynthesis. Verification of the thermodynamic and electronic stability of isolated synthons is important and can be carried out by suitably selected quantum chemistry methods.

Vinyl cyanide is a well-known organic molecule, and the stability of its radical form has been confirmed in the laboratory and the interstellar medium [2]. However, little is known about the stability of this compound in the cation and anion form. Verifying the stability of this system in ionic form will make it possible to determine whether there is a possibility of their potential use in retrosynthesis as synthons. It is important because of the broad use of compounds that contain cyanovinyl fragments in their structure.

To characterize (H2CCCN)0/+/- systems quantum chemistry methods from the DFT family and ab initio were used. The obtained findings led to the verification of the stability of neutral, cationic, and anionic α-cyanovinyl and β-cyanovinyl systems and to evaluate their potential use as stable synthons in the process of retrosynthetic analysis [3].

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Exploring Intermolecular Induction through Non-Orthogonal Pauli-Blockade Framework

Humahuti Dihingia, Bartosz Tyrcha, Piotr S. Zuchowski, Alston J. Misquitta

Improving Gaussian Basis Sets for Molecules with Machine Learning

Shaun T. E. Donnelly, J. Grant Hill

Gaussian basis sets are essential components of computational chemistry simulations, significantly affecting the accuracy and efficiency of electronic structure calculations. Traditional methods for generating these sets, approaches such as even-tempered, well-tempered [1], and Legendre polynomial expansion [2] basis sets, aim to prevent variational collapse and reduce problem dimensionality. However, these methods often involve complex optimisations and may not yield sets optimised for specific molecules.

This study introduces a novel approach to basis set generation, leveraging high-throughput calculations through the BasisOpt Python package [3]. Our objective was to develop high accuracy molecule-specific optimised basis sets for computational chemistry applications. We present a comprehensive comparison of our optimised sets against traditional basis set generation methods, demonstrating significant improvements in performance.

Furthermore, we detail the development of a machine learning model trained on these optimised basis sets. This model is designed to accurately predict basis set exponents for a wide range of molecules. Our findings suggest that integrating machine learning with high-throughput computational methods offers a promising avenue for advancing the precision and efficiency of Gaussian basis set generation.

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mol-CSPy: An open-source crystal structure prediction code

G. M. Day, J. Bramley, P. W. V. Butler, P. J. Bygrave, D. H. Case, C. Y. Cheng, R. Cuadrado, J. Dickman, J. Dorrell, J. Glover, R. Hafizi, J. Johal, D. P. McMahon, J. Nyman, P. R. Spackman, C. R. Taylor, J. Yang, and S. Yang

mol-CSPy is a Python 3 package developed by the Day Group for rigid-molecule crystal structure prediction (CSP). It has recently been made open source and is available under GNU General Public License v3.0 on GitLab[1]. mol-CSPy's key features include: CSP of rigid-molecules with quasi-random sampling[2], quasi-random search with basin hopping[3], and threshold simulations for characterisation of the lattice energy landscape of molecular crystals[4]. mol-CSPy utilises distributed multipole analysis and classical force fields via DMACRYS[4] for high-speed energy evaluations and geometry optimisations.

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Predicting Absorption and Emission Spectra of Solvated Nile Red with ESTEEM

Nicholas Hine, Jacob Eller, Panos Kourtis, Carlo Maino

Machine Learned Interatomic Potentials (MLIPs) offer a powerful combination of abilities for accelerating theoretical spectroscopy calculations utilising both ensemble sampling and trajectory post-processing for inclusion of vibronic effects, which can be very challenging for traditional ab initio MD approaches. We demonstrate a workflow that enables efficient generation of MLIPs for the solvatochromic dye nile red system, in a variety of solvents. We use iterative active learning techniques to make this process as efficient as possible in terms of number and size of DFT calculations. Additionally, we compare the efficacy of two methodologies: generating distinct MLIPs for each adiabatic state, and using one ground state MLIP in combination with delta-ML of excitation energies. To evaluate the validity of the resulting models, we compare predicted absorption and emission spectra to experimental spectra.

Spin-Dependent Nonorthogonal Generalised Wannier Functions for Linear-Scaling Density Functional Theory

Miguel Escobar-Azor, Ali Safavi , David O'Regan , Nicholas D. M. Hine

Density Functional Theory (DFT) has been essential in understanding the properties of magnetic materials, but the method must be solved with high precision to calculate the small energy differences between different magnetic states. Traditional DFT also faces challenges with large systems and strong correlations, both of which are often essential in describing magnetic properties. Nonorthogonal generalized Wannier functions (NGWFs) offer a solution by efficiently describing electron density matrices in linear-scaling DFT. ONETEP utilizes NGWFs for linear-scaling DFT with plane-wave accuracy. We describe enhancements to the ONETEP LS-DFT code, integrating spin-dependent NGWFs, PAW, and the Hubbard correction (DFT+U), enabling accurate and efficient calculations of spin-dependent properties across various materials. This poster validates the effectiveness of spin-dependent NGWFs by comparing the total energies of materials using ONETEP with and without the new SP-NGWFs implementation, alongside comparisons to results of other software suites like CASTEP and ORCA.

Contact Map Path Sampling for Protein Folding

Ziad Fakhoury, Gabriele Sosso, Scott Habershon

Recent advances in machine learning methods have had a significant impact on protein structure prediction, but accurate generation and characterization of protein-folding pathways remains intractable. Here, we demonstrate how protein folding trajectories can be generated using a path sampling strategy operating in the space defined by the residue-level contact-map. This double-ended strategy views protein folding as a series of discrete transitions between connected minima on the potential energy surface. Within this framework, varying complex paths can be sampled effectively circumventing the time-scale induced intractability.

Understanding Conformational Free Energy Surfaces through Enhanced Sampling Molecular Dynamics and Unsupervised Clustering Methods

Alexandre Ferreira, Matteo Salvalaglio, Ivan Marziano, Rui Guo

The understanding of the conformational free energy surfaces (FES) of flexible drug molecules is of crucial importance, considering the impact of molecular flexibility on a pharmaceutical molecule's key properties. Despite this, the conformational FESes of highly flexible molecules are complex and high-dimensional, and approaches suitable for handling these cases are lacking. Typical methods depend on the construction of histograms within the conformation space, at a cost which scales exponentially with dimensionality. Here, an approach which circumvents histograms and scales well with dimensionality is presented.

Utilizing concurrent well-tempered metadynamics molecular dynamics simulations, a physics-based dataset of molecular configurations can be constructed. The distribution of these configurations throughout conformation space are mapped by Density Peaks Advanced (DPA), an unsupervised clustering algorithm. DPA determines, for each configuration sampled from the simulation trajectory, a local density in conformation space, based on the distances between the configuration in question and its nearest neighbors in conformation space. From these local densities, local maxima in densities are identified. Due to the physics-based nature of the dataset, and the implementation of a reweighing scheme to correct for the effect of the metadynamic bias, these local densities can be transformed into each configuration's relative free energy. The resulting dataset is thus a per-configuration free energy surface in the full dimensionality of the conformation space.

The cost of this approach scales linearly with dimensionality and with the square of the number of sampled configurations; a significant improvement over the exponential costs associated with building high-dimensional histograms. We demonstrate that this approach recreates the well-studied conformational FES of alanine dipeptide, before exploring the conformational FESes of more flexible molecules.

Catalytic Partial Oxidation of Methane using an Yttria-Stabilized Zirconia

Erze Gao, Alexey Sokol, Richard Catlow

This project is about discovering the catalytic cycle for Catalytic Partial Oxidation of Methane (CPOM) via using Yttria-Stabilized Zirconia (YSZ). The partial oxidation of methane is an important industrial process for upgrading natural gas into syngas, a mixture of CO and H2 which is widely used in the industrial field. The reaction of CPOM occurs on the (111) plane of YSZ, in which the methane is physisorbed and oxidized into formaldehyde, before decomposing into syngas and other by-products. The surface model in this project is large symmetric slab model, which consists of 4*4 supercell with 96 ZrO2 formula units. The thickness, width and vacuum separation of the slab are respectively 16.36Å, 14.6 Å and ~15Å. The concentration of Y2O3 is 14.3 mol% on the surface, which fits the experimental observation of 10-14 mol%.

The surface was firstly pre-oxidized via the removal of one lattice oxygen and absorption of the oxygen molecule in the atmosphere. Thus, the pre-oxidized 'YSZ+O' model was prepared for further reaction. Then the research discussed the process of methane absorption and oxidation into surface formaldehyde on the YSZ, with various routes and reactions being analyzed. To be specific, the results mainly indicated a possible method which led to the decomposition of surface formaldehyde through H-Zr interaction. Proper structures were discovered with lower potential energy compared with the initial structure, which suggested that CO may be desorbed firstly. When the CO was abstracted at first, the remaining hydrogen could form a surface hydroxyl and an isolated proton located at the surface vacancy. The electronic structures are simulated based on the Density Functional Theory (DFT) via VASP, to achieve its configuration and polarization if possible. Besides, other routes such as abstracting H2 initially were also discussed, with higher energy barrier in the end.

Fast, accurate and spin-pure calculation of the electronically excited states of radicals

James D. Green, Jingkun Shen, Keith T. Butler, Timothy J. H. Hele

This project is about discovering the catalytic cycle for Catalytic Partial Oxidation of Methane (CPOM) via using Yttria-Stabilized Zirconia (YSZ). The partial oxidation of methane is an important industrial process for upgrading natural gas into syngas, a mixture of CO and H2 which is widely used in the industrial field. The reaction of CPOM occurs on the (111) plane of YSZ, in which the methane is physisorbed and oxidized into formaldehyde, before decomposing into syngas and other by-products. The surface model in this project is large symmetric slab model, which consists of 4*4 supercell with 96 ZrO2 formula units. The thickness, width and vacuum separation of the slab are respectively 16.36Å, 14.6 Å and ~15Å. The concentration of Y2O3 is 14.3 mol% on the surface, which fits the experimental observation of 10-14 mol%.

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Electron tunnelling and vibrational relaxation rates for chemisorbed hydrogen on metals from Projector Operator Diabatisation

Nils Hertl, Zuszsanna Konczor-Benda, Reinhard J. Maurer

The formation of a chemical bond between an atom or a molecule with a reactive surface is the elementary step that forms the foundation of heterogeneous catalysis. Yet, the successful adsorption along with the formation of a chemical bond is determined by both electronic coupling strength and efficient reaction energy dissipation into the substrate's phonons and electrons. For realistic simulations of the chemisorption process at metal surfaces, or light-driven desorption, accurate couplings between the adsorbant and the substrate's electronic states are essential. Yet, their acquisition and utilisation for molecular dynamics are not straightforward if one wishes to account for the spectral properties of the substrate. Hence, the energy dependence of these electronic couplings is often neglected which is referred to as the wideband limit. Here, we present a pragmatic protocol that is based on the projector diabatisation operator approach originally formulated for physisorption[1, 2]. We, however, will apply it to a strongly chemisorbed system, i.e., atomic hydrogen adsorbed on metal surfaces whose electronic states at the Fermi-level have different orbital character. Those extracted couplings can be translated into electron tunnelling rates between H atom and metal. We further provide a rigorous connection between these electronic couplings and the vibrational relaxation rate due to electron-hole pair (ehp) excitation. For chemisorbed hydrogen, vibrational relaxation triggered by ehp formation is an oft-observed phenomenon [3–5]. We can thus compare our acquired results to reflective IR measurements [3] and pump-probe experiments [5] along with relaxation rates obtained through density functional theory-based first-principles time-dependent perturbation theory calculations [6].

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Insight into the Correlated Disorder of Fumarate-Based MIL-53 Frameworks: A Computational Study of Free-Energy Landscapes

Chi Cheng Hong, Ross S. Forgan, Antonia. S. J. S. Mey, Claire L. Hobday

As the effects of climate change become more apparent in the form of rising global temperatures, the necessity for temperature control become more significant.1 Current refrigerants are low cost and work extremely efficiently but these materials possess very high global warming potentials.2 A greener alternative is a solid-state approach via barocaloric materials which exhibit large adiabatic temperature and isothermal entropy changes upon compression and decompression cycles.3 Several classes of materials have demonstrated the barocaloric effect but to compete with the efficiencies of current refrigerants, the magnitude of pressure required must be greatly reduced.

Metal-organic frameworks (MOFs) are porous, crystalline materials that are highly modular due to the many metal and linker combinations possible. Notably, certain combinations of metals and linkers have shown to result in a breathing effect wherein the adsorption and desorption of guest molecules are accompanied by a large reversible volume change.4 Hence, they have been recognised as potential barocaloric materials with the most well-known being MIL-53(Al) reporting a colossal entropy change of 311 J K−1 kg−1 under 16 bar of carbon dioxide gas.5 On top of the aforementioned combinations, another consideration is the correlated-disorder that can arise from the linker orientations which was previously shown to effect the mechanism in which a framework closes.6

My research focusses on unveiling the correlation between the transition metal centres of fumarate-based MIL-53 MOFs and the inherent flexibility of the framework as a result. Furthermore, a series of isoreticular MIL-53 frameworks from different synthetic pathways are being studied to understand how the linker induced correlated disorder affects the breathing mechanics of these frameworks. We gain insight on the flexibility of the frameworks by determining their free energy landscapes through first principles unbiased and biased molecular dynamics simulations.

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Point charge embedding approaches for simulating excited states in MOFs

Michael Ingham, Amir Sidat , Alex Aziz, Devis Di Tommaso, Rachel Crespo-Otero

Metal-organic frameworks (MOFs) have significant photocatalytic and optoelectronic applications, many directly dependent on their excited states. However, simulating the excited states of MOFs remains highly challenging due to their large and complex unit cells, the inherent dual molecule/crystal nature of MOFs, and the unfavourable scaling of quantum chemical methods.1 Crucially, this limits the application of traditional solid-state methods to MOF excited-state studies. For instance, band conduction is typically minimal in MOFs and transport follows a spatial-hopping scheme. Consequently, cluster models emerge as an effective approximation to take advantage of electronic structure localised on collections of sub-units at modest computational cost. By dividing a cluster model into multiple levels of theory, approaches such as ONIOM(QM:QM’) massively expand the spatial dimensions of cluster models, at minimal added cost.2,3 Point charge-embedding incorporates environmental electrostatics of the crystal into models, but must be carefully constructed to avoid overpolarisation artefacts.4 Despite advances in its application to solids, ONIOM(QM:QM’) with point charge embedding has rarely been utilised for MOF excited states. Here, we investigate the performance of the cluster, ONIOM(QM:QM’), and periodic approaches in the study of MOF excited states, with a special focus on the treatment of overpolarisation.

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Nanoscale Non-adiabatic Dynamics Simulation of Charge Generation in Organic Solar Cells

Filip Ivanovic, Samuele Giannini, Jochen Blumberger

Organic solar cells (OSCs) have long been the subject of intensive research, as their easily processible constituent materials suggest a commercially viable alternative to their inorganic counterparts. In OSCs, excitation by light yields a tightly bound electron-hole pair, termed an exciton. Two-component cells, where two species are separated by an interface, constitute OSCs' greatest leap towards commercialisation, with their highest efficiencies exceeding 19%. Although such an interface is crucial for the dissociation of excitons into a sufficient yield of free charges, understanding the exact mechanism by which free charges are generated across the interface remains a formidable theoretical challenge, with contradictory results having been reported in the literature.

The complexity of such systems precludes a complete treatment by analytical theories, and instead requires first-principles quantum dynamics simulations, which must also be fast enough to access experimentally comparable time scales.

Here, we use an in-house non-adiabatic molecular dynamics package, termed X-SH, to simulate charge generation in an oligothiophene-perylene diimide interface, on experimentally relevant time and length scales. Our use of a DFT-parameterised Hamiltonian, which is updated on-the-fly, bypasses the need for explicit electronic structure calculations during the dynamics.

We elucidate the mechanism of charge generation in such an interface by modelling the excitons and charges with an explicit electronic wavefunction. This allows us to track their locations in real-time, on a microscopic scale that often cannot be resolved with photochemical experiments. We leverage the computational speed and flexibility of X-SH to identify key physical parameters affecting the efficiency of charge generation, and translate this into design rules to guide the synthesis of OSCs with yet higher efficiencies.

Electronic structure of the InAs-Al interface via DFT: using ZnTe and CdSe barriers for topological devices

Malcolm J.A. Jardine, Derek Dardzinski, Chris J. Palmstrom, Moira Hocevar, Vladimir N. Strocov, Sergey M. Frolov, Noa Marom

Understanding the effects of interfacing materials is pivotal to the design of semiconductor, spintronic, and quantum devices. We study the InAs/ZnTe,CdSe/Al interface via density functional theory (DFT).

InAs based systems are popular for Majorana setups for topological quantum computing. To supply the necessary superconducting affect this is interfaced with Al. However, this interfacing can lead to detrimental effects in the InAs, so the favorably lattice matched materials of ZnTe and CdSe are explored as a tunnel barrier between the InAs/Al interface.

The PBE+U method is used, with the Hubbard U parameters found via a machine-learned Bayesian optimization algorithm, allowing the simulation of large interfaces. We discuss effects such as band offsets at the interfaces, metal induced gap states (MIGS) and the effects of varying the barrier thickness. We also study the comparison of our CdTe and αSn DFT data with experimental ARPES data, utilizing the tools of bulk and z-unfolding to visualize our data.

L1 Metallo- Î² -Lactamase Antimicrobial Resistance Enzyme: A Computational Reaction Mechanism Study

Papu Kalita, Philip Hinchliffe, James Spencer, Adrian J. Mulholland

Antimicrobial resistance (AMR) poses a global health threat as the resistance of pathogenic bacteria to vital drugs. Particularly concerning is the widespread bacterial resistance to carbapenems, a class of "last resort" β-lactam antibiotics. An important and growing cause of resistance is L1, a metallo-β-lactamase (MBL) enzyme, which can break down nearly all types of β-lactam antibiotics, including carbapenems and penems. Notably, no clinical inhibitors have been discovered thus far that can effectively inhibit the hydrolysis process of L1. So, understanding the mechanisms through which these bacterial enzymes hydrolyse β-lactam antibiotics is crucial in combating this resistance. To gain insights into the hydrolysis mechanism of faropenem (a penem) by L1 MBL, we employed combined quantum mechanics/molecular mechanics (QM/MM) umbrella sampling simulations using DFTB3 and B3LYP/6-31G(d) QM methods, with umbrella sampling (US) and the adaptive string method (ASM). The simulations revealed that a zinc-bridging nucleophile, likely in the form of a hydroxide ion, plays a pivotal role in the hydrolysis process. The potential energy curves analysed using the DFTB3 1D-US method indicated the presence of a single transition state. Furthermore, the ASM analysis suggested a concerted pathway for faropenem hydrolysis by L1. These simulations provide an atomic level analysis of the reaction mechanism of antibiotic breakdown. These findings contribute to our understanding of how β-lactam antibiotics are hydrolysed by L1 and may aid in the development of strategies to prevent and combat AMR, including the development of MBL inhibitors.

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Modelling Excited State Dynamics of Organic Materials in the Condensed Phase

Karolina Kapusta, Rachel Crespo-Otero

Understanding the excited state dynamics in organic crystals is crucial for technological applications such as organic electronic devices, photovoltaic cells and organic light-emitting diodes. In the condensed phase, organic luminescence can often be quenched due to the presence of intermolecular interactions. Occasionally however, aggregation can enhance emission by stopping non-radiative energy dissipation pathways, leading to polymorph dependent luminescence. 1 This can be due to the presence of hydrogen bonds which play a significant role in processes such as excited state intramolecular proton transfers (ESIPT). 2

More work is needed to understand the competition of photochemical processes occurring such as ESIPT and charge transfer (CT). Moreover, the complexity of molecular aggregates poses challenges such as increased computational cost as well as the interactions between surrounding monomers. 3 We plan that our investigation will provide more insight into the photophysical processes that occur in molecular aggregates by excited state dynamic modelling.

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Covalent Organic Frameworks for Drug Delivery

Gregor J. Lauter, Alessandro Calzolari, Ganna Gryn'ova

Covalent organic frameworks (COFs) are highly ordered porous two- or three-dimensional polymers consisting of regularly connected nodes and linkers and characterised with diverse topologies, compositions, and properties. Voids inside the frameworks can be constructed to the desired dimensions and can accommodate a variety of guests: photons and excitons, electrons and holes, ions and molecules, enabling their uses as catalysts, chemosensors, and nanocarriers for biologically active targets. In this work we focus on capture, transport, storage, and release of drugs in/by COFs – a research avenue promising targeted delayed-release delivery of therapeutics by customisable, responsive, and biocompatible materials. We aim to develop a computational approach for predicting the encapsulation and uptake of drug molecules within the cavities of COFs, leveraging their structural characteristics. Our approach combines force field (FF)-based Molecular Dynamics, Density Functional Theory, and Grand Canonical Monte Carlo simulations. To further analyse the non-covalent interactions (NCIs) between the host COFs and the guest molecules, we are also developing dedicated NCI descriptors and structural fingerprints. Overall, these tools will allow not only the design of novel materials but also the rapid pre-assessment of their efficacy in applications related to the sequestration of small molecules.

Copper Nanowires for Electrochemical CO2 Reduction Reaction

Wuyang Lin, Azeem Ghulam Nabi, Matteo Palma, and Devis Di Tommaso

A promising carbon capture and utilization strategy is the electrochemical reduction of CO2 (eCO2R) to value-added chemicals. Critical to the success of this approach is the development of catalysts capable of selectively converting aqueous CO2 into a specific product. Copper (Cu) is considered the best pure metal candidate for eCO2R for its ability to catalyze the formation of several hydrocarbons, aldehydes, and alcohols. However, Cu lacks the required selectivity. In this regard, a fine-tuned control of its surface topology and nanostructuring could allow the enhancement of eCO2R catalysis. Here, we report a computational investigation of the growth tendency of Cu nanowires (NWs) as well as their ability to adsorb, activate, and convert CO2 to one- and two-carbon products to understand their potential application as eCO2R catalysts. Grand canonical Monte Carlo simulations of the growth of Cu nanowires with diameters between 0.8 to 2 nm showed the tendency to form regular nanowires with a facet center cubic unit cell pattern. Cu nanowires demonstrated a pronounced propensity to activate CO2, particularly those with a 0.8 nm diameter, owing to the markedly uncoordinated Cu atoms on the surface and higher d-band center, which effectively promotes CO2 interaction with the surface, molecule bending, C−O bond elongation, and charge transfer from the catalyst to CO2. Calculation of the CO2 conversion to C1 products shows the Cu NWs to be highly selective to carbon monoxide, a key intermediate ion in the generation of C2 products.

Nonadiabatic Energy Loss During Hydrogen Scattering on Semiconductors

Xuexun Lu, Sara Oregioni, Nils Hertl, Reinhard J. Maurer

Ultrafast reactions at surfaces, either through hyperthermal scattering or light-driven processes, can involve electronic excitations. The molecular dynamics with electronic friction (MDEF) method is a simple effective approach to describe nonadiabatic effects that arise from electron-hole pair excitations in dynamics at metal surfaces. This method, however, breaks down in the case of reactions at semiconductors. Recent H atom scattering experiments on Ge(111) [1] and Xe(111) [2] have provided new insights on how scattering occurs on semiconductors, motivating the need for improving theoretical models.

Herein, we develop a simple model Hamiltonian for nonadiabatic hydrogen scattering on a semiconductor surface. The adiabatic potential energy surface (PES) is defined using a one-dimensional molecular potential parametrization of gas-surface scattering, along with a DOS discretized via the Gapped Gauss-Legendre method. Equipped with this model, we assess the performance of various mixed quantum-classical simulation methods such as surface hopping [3] and extensions of the MDEF method [4] to describe kinetic energy loss during scattering events. We explore a range of coupling strength parameters to assess the role of surface-adsorbate hybridisation in mediating energy loss and interpret our results in the context of the experiments. Through this work, we aim to explore scenarios where conventional wideband limit friction models fail and gain insights crucial for developing more comprehensive methods to study nonadiabatic dynamics at surfaces.

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Automating transition state search in metal catalysed reactions

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Finding transition states (TS) is a key step in elucidating the mechanisms underlying chemical reactions, facilitating the optimisation of synthetic procedures and the discovery of new catalysts. Traditional approaches to finding TSs employing DFT or similar methods have become routine. However, despite advances in the field, characterising TSs still requires significant human time and effort. Automation of TS search has the potential to address these challenges. Indeed, several advances have been made in this area using molecular graph-based methods[1,2] or by systematic exploration of the potential energy surface (PES)[3]; however, most of them have focused on organic reactions, and struggle to describe transition metal (TM) catalysed reactions, especially transition states and intermediate states. This is due to the complex potential energy surfaces (PES) of these systems, which arises from their complex electronic structure and flexible coordination ability. This also makes constructing molecular graphs challenging, consequently making it difficult to automate TS search for TM-catalysed reactions. Given the relevance of these reactions in pharmaceutical and materials industry, it is clear that automated in silico elucidation of reaction paths and their kinetics holds promise for optimising existing catalysts and designing new ones.

In this study, we present our efforts to design an automated workflow for TS search and reaction path elucidation for TM-catalysed reactions, building on our software autodE[2]. We discuss our implementation of recently published double-ended TS search method i-EIP (improved Elastic Image Pair)[4] in autodE. We then compare its robustness and efficiency against popular double-ended methods, including NEB-TS (Nudged Elastic Band – Transition State),[5] DE-GSM (Double-Ended Growing String Method)[6] and DHS (Dewar-Healy-Stewart)[7] across a series of TM-catalysed reactions. The results indicate that popular methods may not always be the most efficient. Additionally, we introduce a fast method of generating molecular graphs for metal complexes from low-level tight-binding calculations, which can improve the reliability of graph-based representations of reactions as used in autodE. We aim for this study to contribute to the broader application of automated reaction path-finding methods, paving the way for faster development of more efficient and selective catalysts.

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Machine Learning-Driven Virtual Screening for Antibacterial Design Targeting Enoyl-ACP Reductase (FabI)

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Multiresistant bacterial strains, as Staphylococcus aureus methicillin-resistant, are a growing challenge and a high priority for drug development, but no new antibiotic class has been introduced to the market since the 1980s. Computational methods, as molecular docking, are accelerating the development of new antibacterials with novel molecular targets, but predictability of molecular docking can be improved with machine learning (ML). The aim is to integrate ML models with molecular docking studies to improve prediction of ligand inhibitory activity against Staphylococcus aureus and Escherichia coli FabI enzymes. OEDocking was utilized to develop 1,522 docking protocols validated using redocking, crossdocking, and ROC curve. Eleven ML algorithms were applied to build 73,616,760 classification models relating inhibitory activity to LUNA interaction fingerprints. Best models were selected using internal and external metrics, including MCC, F1-Score, TPR, TNR, bACC, ROC- AUC, and Cohen-Kappa. Finally, the predictive ability of ML and docking were compared. For the best models of each algorithm, MCC 5-fold varied between 0.501 and 0.750, while MCC ext varied between 0.491 and 1.000. Support Vector Machine (SVM) and Multilayer Perceptron (MLP) produced the best models, outperforming docking studies in ROC-AUC and BEDROC-AUC (α=20.0) values. Furthermore, docking scores are binarized using thresholds determined by various strategies, and ML models outperform docking studies across validation metrics. Finally, a virtual screening was carried out and 33 compounds were selected for in vitro antibacterial studies. Nine of the tested compounds showed some activity against S.aureus and/or E. coli. These results suggest that machine learning-driven molecular docking studies are a promising strategy for improving the accuracy, sensitivity, and general predictive ability of virtual screening campaigns for the development of new antibacterial compounds.

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ichor: A Python library for computational chemistry data management and machine learning force field development

Yulian T. Manchev, Matthew J. Burn, and Paul L. A. Popelier

We present ichor, an open-source Python library that simplifies data management in computational chemistry and streamlines machine learning force field development. Ichor implements many easily extendable file management tools, in addition to a lazy file reading system, allowing efficient management of hundreds of thousands of computational chemistry files. Data from calculations can be readily stored into databases for easy sharing and post-processing. Raw data can be directly processed by ichor to create machine learning-ready datasets. In addition to powerful data-related capabilities, ichor provides interfaces to popular workload management software employed by High Performance Computing clusters, making for effortless submission of thousands of separate calculations with only a single line of Python code. Furthermore, a simple-to-use command line interface has been implemented through a series of menu systems to further increase accessibility and efficiency of common important ichor tasks. Finally, ichor implements general tools for visualization and analysis of datasets and tools for measuring machine-learning model quality both on test set data and in simulations. With the current functionalities, ichor can serve as an end-to-end data procurement, data management, and analysis solution for machine-learning force-field development.

Alchemical free energy calculations using machine learned forcefields

J. Harry Moore, *Gabor Csanyi*

Free energies play a crucial role in characterising the behaviour of chemical systems and are one of the most important quantities that can be estimated by molecular dynamics simulations. Solvation free energies are one of the most heavily optimised physicochemical properties of drug-like molecules and are commonly used to assess the accuracy of nonbonded parameters in empirical forcefields. However, machine-learned potentials (MLPs) are not readily decomposed into physically derived functional forms, making it challenging to apply standard alchemical methods that involve scaling individual pairwise interactions. In this study, we introduce an efficient alchemical free energy method suitable for many-body MLPs and evaluate the performance of the recently introduced MACE-OFF23 MLPs by calculating solvation free energies for a series of organic compounds. We propose that as MLPs become more capable and transferable, their ability to accurately predict condensed phase thermodynamic properties, including ensemble averages and phase-space integrals, will be a key criterion on which to compare them. Consequently, highly accurate, efficient and MLP-compatible free energy methods such as this form a key capability in application of MLPs for drug discovery.

Electrolyte dynamics with potential-induced charges on electrodes: Implementation and usage as a starting point for DFT calculations.

Sara Navarro, *Federico N. Pedron*, *Pablo Ordejón*

Understanding the electrode/electrolyte interface at the atomistic level is crucial for electrochemical processes such as those involved in corrosion and energy storage. The number of atoms the time scales involved, and the out-of-equilibrium situation forced by the external potential, are factors which make the simulation of such processes computationally prohibitive. Within the SIESTA DFT method and code [1], we already have a state-of-the-art approach to tackle some of these difficulties. The effect of the external potential is taken into account using non-equilibrium Green's functions (NEGF). The large number of atoms required in the simulation is handled using a hybrid QM/MM approach [2]. However, the time scales available in such NEGF-QM/MM simulations (up to ~0.1ns) are still insufficient to reach an equilibrated concentration profile for the electrolyte and its response to the external potential.

In this work, we present an implementation of the method of Siepmann and Sprik [3], based on a classical description of induced charges in the electrode. The method is used to equilibrate the electrolyte in the presence of the electrode potential, providing a much better initial configuration for subsequent DFT production runs. In combination with the current QM/MM approach, we can now achieve more realistic simulations within times affordable for DFT.

We present the first results of the implementation, by showing the density profile of water over gold electrodes. We compare these results to those achieved in (shorter) DFT simulations, and their impact in the subsequent production runs. Preliminary results on the ionic concentration profile of an electrolyte in contact with an electrified electrode will also be presented.

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Unravelling nucleation in Ferritin nanocages from atomistic molecular dynamics simulations

Matteo Paloni, Johanna Galloway, Aaron R. Finney, Fiona Meldrum, Matteo Salvalaglio

Ferritin nanocages are large protein complexes formed by 24 subunits that assemble into a nanoreactor with an 8nm lumen. They store iron ions in a bioavailable form as ferrihydrite, a ferric oxyhydroxide within the cavity. Ferritin nanocages are formed by two types of subunits, namely H- and L-chain ferritins, which are characterized by a different ability to form nuclei of ferrihydrite and grow mineral structures [1]. The different role of the two types of chains in the nucleation and growth of the minerals is not yet completely understood. In particular, the confinement of the ferritin cages and charges on the surface of the lumen templates and stabilize ferrihydrite for iron storage.

Molecular dynamics (MD) simulations are a powerful tool to characterize with atomistic detail the formation and growth of minerals inside the ferritin lumen. We performed unbiased microsecond-long atomistic MD simulations in presence of sodium chloride to investigate the transport properties of ions across the protein and their implications on the nucleation and growth mechanisms. These simulations also provide a first insight into the properties of the sites that promote nucleation of minerals inside the cavity which are used to rationalize experimental observations on the location of formation of the minerals and the differences between subunit types.

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Investigating conductive properties of a single-heme cytochrome

András Pethő, Jochen Blumberger

Multi-heme cytochromes are fascinating compounds which play a part in the survival of bacteria in anerobic environments by exporting electrons out of the cells. As such they possess magnitudes larger conductivity compared to non-heme proteins, even rivaling that of certain inorganic semi-conductors. This property means that these proteins show exciting potential for constructing biological wires. The reasons behind this increase, despite being observed many times, are unknown. The goal of this project is to shed light on a possible mechanism of conductivity by looking at how the heme number influences this property. To do this the project will examine proteins with varying number of heme cofactors. This will be done in tandem with two experimental groups measuring the conductive properties of the proteins in vacuum and in an aqueous environment. Thus, the project will allow a detailed insight into the molecular configurations behind the experimental results. This poster reports the initial results of the project which were acquired from the single-heme MtoD. The results reported here are from the initial junction creation process along with the first results of the electronic structure calculations for the gold-protein-gold system. The theory behind acquiring the I-V curves is also introduced. The results show that the process of junction creation using molecular dynamics is reliable, while highlighting the influence of the protein orientation for the conductivity. With the latter causing a magnitude of difference in terms of the simulated current through the junction for a given voltage. These findings highlight the need for careful consideration when analyzing the results to make the different systems comparable. Nevertheless, the data presented here shows great promise in furthering our understanding of multi-heme cytochromes and their potential for use in the field of bioelectronics.

In search of enzyme activation: A steered molecular dynamics/Markov state model workflow for evaluating allosteric drug candidates

Frederick Powell, Adele Hardie, Dr Graeme Barker, Julien Michel

We have developed a computational workflow using steered molecular dynamics (sMD) and Markov state models (MSMs) to assess the allosteric potential of small molecule modulators of enzyme activity.[1] Our workflow uses sMD to explore the conformational space of the target system.[2] By employing sMD, we can sample conformational space that is inaccessible under routine MD timescales. Subsequently, we utilise intermediate conformations arrived at via sMD as the starting point for multiple short, equilibrium MD simulations. The resulting data is pooled and used to construct MSMs,[3] affording us insight into the metastable conformational states of the target protein, as well as the probability of the protein occupying such states with and without an allosteric modulator in situ.

We have applied our workflow to investigate small molecule activators of the cell signalling enzyme, Epac1. Epac1 is endogenously activated by the ubiquitous secondary messenger, cyclic AMP (cAMP),[4] whereupon it plays a key role in regulating inflammation response in cardiovascular and pulmonary endothelial cells.[5] As such, it was identified as a key target for pharmaceutical intervention and a drug discovery project has ensued.

We first used protein-ligand docking modelling and accompanying synthetic studies to advance our hit compound, I942 (a partial Epac1 activator),[6,7] into a promising lead compound. We have since successfully employed the above workflow to model Epac1 in the apo form and with a selection of known activators, with our model successfully reproducing experimental Epac1 activation data. We are now modelling novel drug candidates resulting from the earlier protein-ligand docking assay in hopes that our workflow accurately predicts their allosteric potential.

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The comparative assessment of linear and nonlinear Hamiltonian models

Chen Qian, Reinhard Maurer

Density Functional Theory calculations are pivotal for analyzing the electronic structures of the material, yet the iterations of the self-convergence field to obtain the Hamiltonian matrices during the calculation require extensive computational resources. Boosted by the recent advances in machine learning, innovative paradigms for Hamiltonian and overlap matrix prediction emerged, significantly enhancing computational efficiency. This study evaluates several typical mainstream machine learning models tailored for this purpose, including the linear ACEHaniltonians model and the deep equivariant graph neural network DeepH-E3. For the Hamiltonian and overlap matrices, we compared the data efficiency (i.e., the requirement for the training data size), tested the performance for larger-scale systems, and assessed the model representation capability for multi-element systems across these models. To address the large file size of the dataset, which increases exponentially with the number of orbitals and is usually not storage-friendly, we also explored approaches to train the Hamiltonian model using nonlinear loss and datasets other than the Hamiltonian matrix itself.

Investigating allosteric inhibitory mechanisms of the soluble epoxide hydrolase

Qiongju Qiu, Franca Fraternali and Maria R. Conte

The soluble epoxide hydrolase (sEH) is a bifunctional enzyme with its C-terminal domain (CTD) responsible for hydrolysis of epoxy fatty acids (EpFAs). sEH is an attractive therapeutic target for many diseases such as cardiovascular diseases and pain as inhibiting sEH could restore higher levels of beneficial EpFAs. The majority of sEH inhibitors studied to date are orthosteric inhibitors that directly occupy the enzyme catalytic pocket. Although some of them have entered clinical trials, none has thus far been successful. Recently, the endogenous 15-deoxy-Δ12,14-Prostaglandin J2 (15d-PGJ2) were found to allosterically inhibit sEH activity through covalently binding to C423 and C522 sites1,2; however, the underlying mechanism of this allosteric inhibition remains unclear. This project aims to explore the allostery of sEH inhibition through a combination of experimental and computational approaches.

Replica exchange molecular dynamics (REMD) simulations were conducted, suggesting that the binding of 15d-PGJ2 to C423 and C522 sites lead to changes in protein properties including protein conformation, residues flexibility and accessible surface. Further analysis performed with AlloHubMat3 highlighted several regions that may be potentially involved in the allosteric signalling pathway. Further simulations and experimental work have been planned to understand the complex allosteric communications of sEH inhibition. This would provide valuable information for design of new drugs that inhibit sEH using allosteric mechanisms.

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Tuning Zeolite Catalysts using Organic Additives

Matt Robinson, Andrew Logsdail

Zeolites are porous aluminosilicate frameworks commonly used in industry as catalysts due to their high acidity, low environmental impact and high thermal stability. Typically, zeolite catalysts must be fine-tuned for application to a given process, but it has been shown that flexibility can be introduced by adding organic additives to some zeolite catalysts.

In the domain of renewable chemicals, protonated mordenite (H-MOR) has been identified as a strong candidate for catalysing the dehydration of ethanol to ethylene, a potential green route from bio-ethanol to a highly-demanded chemical feedstock. When catalysed by H-MOR, the reaction produces side products such as diethyl ether, which are thought to originate only from Brønsted Acid (BA) sites in the larger 12 membered ring (MR) and not the smaller 8MR side pocket (SP). Pyridine has been shown to selectively titrate BA sites in the 12MR, particularly at industrially-relevant temperatures, allowing the catalyst porosity to be controlled through molecular doping. Therefore this project aims to investigate the application of pyridine-based additives to tune the selectivity of the H-MOR-catalysed ethanol dehydration reaction.

Our work uses Density Functional Theory (DFT) to calculate adsorption free energies, kinetic barriers and to study the dynamic behaviour of the various reaction species to investigate the favourability of each species in each H-MOR pore. The pyridine additive can be decorated with other functional groups, which can further enhance or diminish the additive's adsorptive behaviour to the zeolite. The choice of tailor-made additives could open up wider applications and higher selectivities for zeolite-catalysed reactions.

Understanding Organic Cocrystals for Room Temperature Phosphorescence

Kanyarat. Rueangboon, Maria Eugenia. Sandoval-Salinas, Rachel. Crespo-Otero

Organic co-crystals offer a versatile platform for designing efficient room temperature phosphorescence (RTP) materials. Despite the growing number of reported organic co-crystals with RTP, there is a lack of understanding regarding how to exploit specific intermolecular interactions to achieve and enhance phosphorescence. Different strategies such as crystallisation, H-aggregation, and the heavy atom effect allow obtaining organic RTP with significant excited state lifetimes [1]. Recently, Abe et al. used the heavy atom effect and rigid environment strategies to modulate the RTP in co-crystals of DITFB with Chry, Pyr, and Phen [2]. To understand how specific intermolecular interactions and crystal packing affect the excited state mechanisms, we investigated the nature of the electronic transitions and the effects of the spin-orbit couplings in these co-crystals. Our calculations provide information about how to control photophysical properties in these systems through specific intermolecular interactions, which have an impact on the rational design of organic materials with a broad range of applications.

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Theoretical Electronic Structure of Iron(III)-Oxo Clusters

Ali Safavi, Nicholas Hine

We have investigated the theoretical electronic structure and spectroscopic properties of iron(III)-oxo nanoclusters. We use a variety of methods, spanning density functional theory (DFT), hybrid DFT (HDFT), DFT plus a Hubbard correction (DFT+U), time-dependent DFT (TDDFT) and linear-scaling DFT (LSDFT). The wider application of these hematite-based nanoclusters is in solar fuels. Bulk hematite is abundant, stable and is a low-cost system. Hematite also benefits from having a band gap of 2.2 ± 0.1 eV, which places it in the visible region. Despite these benefits, practical hematite-derived solar fuels have not been achieved due to limitations such as a low absorption coefficient because of an indirect band gap, an excited state lifetime of about a picosecond as well as a short charge carrier diffusion length. Use of smaller hematite-like nanocluster systems can improve on these limitations given their differing properties to bulk hematite as a result of quantum confinement effects.

The clusters we have studied include straightforward single-iron systems like [Fe(H2O)6]3+ and [Fe(EtOH)3]3+ as benchmarks, as well as more challenging multi-iron systems like Fe2(OtBu)6 and Fe5O(OEt)13. We present benchmarking of the computational approaches other and present a comparison of energetics and spectra as a function of size and ligands.

The role of structural isomers in the photophysics of organic crystals

Maria Eugenia Sandoval-Salinas, Federico J. Hernandez, Rachel Crespo-Otero

The synthesis of organic materials exhibiting room temperature phosphorescence (RTP) is, nowadays, a hot research area due to the broad range of applications of these materials in optoelectronics. In this sense, carbazole derivatives have been used as one of the main chromophore building blocks to produce organic RTP materials for over a decade. However, it was not until 2021 that Chen et. al. detected that the RTP of carbazole is not an intrinsic property of the material but caused by an impurity present in the crystal [1]. Also, in 2021, Ding et al reported the effect on RTP properties by systematically doping an organic crystal with a series of structural isomers [2]. In this work, we present a full characterisation of representative dimers formed by a structural isomer for different organic materials. We model our materials using embedding cluster models within an ONIOM(QM:QM') formalism [3,4]. Special attention is paid to the intermolecular interactions and the access to charge transfer states as well as their role as mediators to enhance or prevent the population of the triplet manifold.

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Exploration of Defect Superstructures in Graphene

Benedict Saunders, Lukas Hörmann, Reinhard J. Maurer

Graphene has been meticulously studied due to its remarkable mechanical, electrical, and thermal properties. It is well documented that introduction of various dopants and defects in the lattice can be used to tune the material's properties for a specific application, such as for electronics, sensors, or catalysis. In order to design graphene with specific properties, one must achieve control over the composition and concentration of defects. This requires a fundamental understanding of the stability of defects and their interaction in a superstructure. We present a comprehensive surface structure determination approach using the SAMPLE[1] structure search code, extended to enable the systematic generation of defective superstructures, using a combination of Density Functional Theory and machine learning. Henceforth, we show the capabilities of our approach for a proof-of-principle application on free-standing graphene with heteroatom, vacancy, and topological defects. Finally, we use the SAMPLE code to gain physical insight into the interactions between these defects, paving the way for effective and rational growth models of topologically designed defective graphene.

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Non-equilibrium electrons generated from the extended two-temperature model to drive chemical dynamics at surfaces

Henry T. Snowden, Reinhard J. Maurer

A mechanistic understanding of ultrafast light-matter interactions with surfaces and nanoparticles is invaluable for the study of ultrafast dynamics at surfaces. The two-temperature model (2TM) represents the most common approach to model light-matter interaction. It assumes that electrons remain in a Fermi-Dirac distribution, which is heated by a laser source term. This assumption is invalid immediately after a laser pulse, where a short-lived population of non-equilibrium electrons is generated. Here we will explore the extended two-temperature model (e2TM), proposed by Carpene [Phys Rev B 74, 24301 (2006)], including further extensions from Uehlein et al. [Nanomaterials 12, 1655 (2022)]. We will show that the e2TM captures information consistent with simulations based on the Boltzmann transport equation while maintaining much of the simplicity and computational efficiency of the 2TM. We incorporate many parameters directly calculated from first principles, such as the density-of-states (DOS) and properties derived thereof. We present a systematic assessment of the dependence of the e2TM on the type of metal and surface termination and directly relate our results to time-resolved spectroscopy results. Finally, we will examine the necessary properties of a material required to generate long-lived non-equilibrium electrons and suggest possible material candidates.

Molecular dynamics investigation of the role of lattice heating in laser-driven hydrogen evolution at copper surfaces

Alexander Spears, Wojciech G. Stark, Reinhard J. Maurer

Light-induced ultrafast dynamics entail the energy transfer between light, electrons, and phonons at interfaces. Whether or not this energy transfer can be harnessed to selectively drive photocatalytic processes remains an open question. Molecular dynamics with electronic friction (MDEF) provide a fully anharmonic mixed quantum-classical description of electron-phonon coupling, whereby electronic friction is usually approximated with a homogeneous electron gas model. While this method has previously been used to model state-resolved scattering experiments or to determine vibrational lifetimes after femtosecond laser pulses, its validity has yet to be fully assessed. We compare the dynamics of laser-driven hydrogen recombination across different copper surface facets using machine-learning interatomic potentials based on electronic structure theory to enable the efficient statistical sampling of chemical dynamics. Using this approach, we compare results from thousands of simulations based on electronic friction using first-order response theory and the homogeneous electron gas model and analyse the ability of different approximations to accurately describe the non-adiabatic energy transfer between the surface and adsorbates. These methods also allow us to investigate the influence of lattice heating after an ultrafast laser pulse.

Nonadiabatic effects in reactive hydrogen dynamics at Cu surfaces

Wojciech G. Stark, Connor L. Box, Reinhard J. Maurer

The complexity of the dynamics of molecules at metal surfaces often causes discrepancies between classical methods and experiments. This has been credited mainly to the continuum of electronic states at metal surfaces. Classically, molecular dynamics methods are simplified by using Born-Oppenheimer approximation, which assumes that light electrons instantly follow movement of heavy nuclei. Nevertheless, dynamics of the molecules at metal surfaces can be much more complex due to electron-hole pair excitations. There are many methods to include such nonadiabatic effects, with one of the most efficient being molecular dynamics with electronic friction. In this study, we construct unified ML-based electronic friction models for H2 dynamics at multiple Cu facets. Furthermore, we use the models to assess the impact of nonadiabatic effects on state-to-state scattering dynamics.

Effective Harmonic Potential Study of Mg Interstitials Using Neural Network

Zhuoyang Ti, Georg K. H. Madsen

Lattice anharmonicity exerts a substantial influence on the concentrations of defects in compounds at high temperatures. Although phonon-based methodologies and molecular dynamics provide valuable perspectives on the temperature-dependent properties of materials, directly integrating these effects through density functional theory remains challenging. In this study, we examine the defect thermodynamics of magnesium by employing an effective harmonic potential, derived from a neural network force field. This surrogate model facilitates precise calculations of anharmonic interstitial formation free energies over a range of temperatures.

Developing Standardised Modelling Workflows for QM/MM Studies of Metal Oxides

O. van Vuren, G. A. Bramley, A. J. Logsdail

Modelling plays a key role in advancing our understanding of materials, assisting in both the discovery of novel condensed phase systems and development of their applications. Thus, models of solid state materials need to be both accurate and efficient, yet there is often a compromise between accuracy and computational cost. QM/MM (Quantum Mechanical/Molecular Mechanical) simulations achieve high accuracy with good computational efficiency by limiting the full quantum mechanical calculation to a small region of interest where preserving physicality is critical; the interactions with the quantum region are then modelled though coupling to an environment of classical charges.

We have performed calculations on point defects in bulk MgO, employing QM/MM simulations (validating these against periodic DFT calculations) to develop a full workflow for producing accurate and realistic simulations. Our initial methodology is based on the simple system of bulk magnesium oxide to facilitate accurate model development, allowing us to design heuristics for easily setting up embedding simulations. Currently, we have been exploring how to best define an optimal size/shape of the QM and MM regions for accurate and efficient simulation, building on previous work in this area that suggests a unit cell based partitioning approach is superior to the simpler radial partitioning method. Our investigation into MgO is now being extended into surface models to achieve this goal, utilising the same methodologies as seen in the bulk studies, observing the efficacy of this methodology for modelling point defects in the solid state.

In the future, we hope to use this work to investigate species that are more challenging to model for their applications in catalysis such as rocksalt structure MnO and CoO as well as expanding the scope to materials for photocatalytic hydrogen production such as TiO2.

Computational Approach for Targeting Serine Protease Inhibitors in Oral Cancer: Insights into Serpin Expression Dynamics and Drug Design

Soujanya Jagadish Vastrad, Saraswathy Ganesan Rajalekshmi, Ashok Madarkhandi

The Serine Protease Inhibitors (Serpin) superfamily exhibits diverse biological roles, ranging from regulating the fibrinolytic system to influencing angiogenesis. Certain serpins have been associated with both the progression and regression of cancers, highlighting their potential significance in therapy and diagnosis. For instance, plasminogen activator inhibitor-1 (PAI-1), a key regulator of thrombolysis, can have dual effects by either promoting or inhibiting tumor growth. Additionally, maspin, another serpin, enhances cancer cell sensitivity to apoptosis while inhibiting migration, effectively impeding tumor progression [1] [2]. In this study, we aimed to examine the expression patterns of Serpin family members (A, B, C, D, E, H) in oral cancer, aiming to advance their potential as drug targets and develop treatment strategies for the disease. Our analysis utilized filtered oral tissue transcriptomic data obtained from cBioPortal (TCGA-HNSC Firehose) [2]. The normalized profiles were subjected to Kruskal-Wallis tests to assess the significance of expression differences between normal and disease groups [3]. Serpin family E members 1, 2, and 3 demonstrated significant differences, with respective p-values of 1.399e-09, 1.414e-07, and 0.006197. The overall survival analysis by Kaplan-Meier, using the R packages [4], revealed SerpinE1 as the most clinically relevant target protein associated with the disease, with a corresponding p-value of 0.0006. SerpinE1, also known as plasminogen activator inhibitor-1 (PAI-1), is the main physiological inhibitor of plasminogen activators (PAs). To provide insight into potential drugs targeting this protein, three primary ligands—Oxametacin, Talmapimod, and Indibulin, which exhibited a Tanimoto similarity index above 0.3 with the established small molecular inhibitor TM5484, were chosen for further docking and dynamic analysis [5]. The ligand-binding domain of SerpinE1 was obtained from the Protein Data Bank, and ligand-protein docking was performed using Schrodinger Glide. Among the ligands, Indibulin exhibited a comparable score of -3.5 to that of TM5484's score of -3.8. Molecular dynamics conducted using DESMOND revealed stable complex formation between the protein and ligand, with hydrogen bonds and water bridges observed, particularly at the Gln-123 residue, which exhibited stronger interactions compared to other bonds.

The analysis mainly highlights the potential interaction of Indibulin at the Gln-123 residue, specifically located at the flexible joint region adjacent to the vitronectin (Vn) binding site on PAI-1. This restriction of flexibility may induce a conformational change in PAI-1 [7]. Thereby suggesting the potential utility of Indibulin against SerpinE1.

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Modelling the Dermal Absorption of Agrochemicals

Callum Ward, Conor Whitehouse, Jennifer Webb and Rebecca Notman

It is estimated nearly one third of the global population face food insecurity.(1) To meet the growing global demand for food, crops of the future need to be sustainable, high quality and safe. Crop protection products help to achieve this by protecting crops from insects, weeds and disease; however, it is crucial to ensure that exposure to the product is safe to the farmer, community and environment. One route of exposure is through contact with skin. Accordingly, dermal absorption is routinely assessed during the testing and registration of new product formulations and is strictly regulated. Understanding how substances interact with the stratum corneum skin barrier lipid layers is key to understanding and predicting dermal absorption. We aim to develop models using molecular simulation that can rationalize and predict agrochemical dermal absorption rates, beginning with a well-known test case, glyphosate.

We use molecular dynamics simulations to explore the dermal permeation process through a model stratum corneum lipid bilayer. We have optimized umbrella sampling with the dynamic histogram analysis method (DHAM) (2) to sample the free energy landscape of agrochemical skin permeation and calculate the skin permeation coefficient (Kp) in order to relate our simulated systems to experimentally derived quantities. To explore the mechanism of dermal absorption we relate the dynamics of agrochemicals within our model bilayer and the physical properties of the simulated membranes to calculated Kp's. To the best of our knowledge, molecular simulations of the permeation of agrochemical formulations through model skin membranes is entirely novel.

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Elucidating the role of potassium in methane steam reforming using first-principles-based kinetic Monte Carlo simulations

Sai Sharath Yadavalli, Carlo Fonte, Glenn Jones and Michail Stamatakis

In the chemical industries, potassium is commonly employed as a promoter to reduce coke formation on the Ni catalyst surface and has been demonstrated to significantly improve the productivity of the MSR reaction [1]. Despite numerous theoretical/experimental studies, there is a lack of detailed understanding on the potassium effect at steam reforming conditions. In this contribution, we developed a first-principles-based KMC model of MSR on Ni(111) and potassium-doped Ni(111) surfaces. The cluster expansion (CE) methodology (implemented in graph-theoretical KMC [2]) was employed to systematically capture the adsorbate-adsorbate interactions of MSR species on Ni and potassium sites. We performed KMC simulations with different loadings of potassium (0.5-3%) on Ni(111) to understand its effect on macroscopic coverages and net MSR turnover rates. A thorough examination of the KMC process statistics was carried out to rationalise the effect of potassium on MSR kinetics. At high operating conditions, we found that the potassium strongly promotes the oxidation of CH and carbon adsorbates. For instance, at 1273 K and 10 bar, we observe that the net MSR turnover rate on potassium-doped Ni(111) system is 3 times higher than Ni(111). The KMC process statistics analysis reveals that the key oxidation events/steps such as CHO formation, CHOH formation, COH formation and CO formation occur significantly faster on the potassium sites than Ni(111). Furthermore, a detailed flux analysis has been performed to identify the dominant MSR pathways on Ni(111) and potassium-doped Ni(111) surfaces. At high temperatures, the CHO pathway and CO pathway occurring on the potassium sites contribute substantially to the net flux of MSR (these pathways constitute around 33% of the net flux). The aforementioned results provide a deeper mechanistic level understanding of the role of potassium in MSR. Overall, our KMC simulations can potentially aid in the design of next-generation Ni-based catalysts that exhibit high activity and stability at MSR conditions.

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Elevating Photocatalysis: Unleashing the Potential of Titanium-Oxo Clusters through HOMO/LUMO Gap Engineering for Sustainable Transformations

Ashwani Ashwani, Stephen E. Brown, Bin Wang, Frederik Tielens, Frank D. Proft, Sebastian D. Pike

Titanium-dioxide is an important semiconductor material used in applications such as self-cleaning windows and photocatalysis[1]. Nanoscale titanium-oxo clusters serve as a link between molecular and materials chemistry[2]. Photocatalysis has emerged as a potent method for sustainable chemical transformations[3]. Titanium-oxo clusters have received interest as photocatalytic materials because of their distinct structural and electronic characteristics[4]. The photocatalytic properties of titanium-oxo clusters may be optimised by engineering the HOMO/LUMO gap, which is analogous to the band gap in (nano)materials, enabling a wide range of applications in energy conversion, environmental clean-up, and chemical synthesis[5]. In this study, we explore the electronic structure and photochemical properties of a series of Ti6-oxo clusters and their influence on photocatalytic performance. TD-DFT calculations revealed that the ligand based energy level could effectively alter the band structure of titanium-oxo clusters. It also shows a trend between the dye and non-dye ligands. References 1. Haider, A. J.; Jameel, Z. N.; Al-Hussaini, I. H. M., Energy Procedia 2019, 157, 17-29. 2. Schubert, U., Chemistry – A European Journal 2021, 27 (44), 11239-11256. 3. Chen, X.; Mao, S. S., Chemical Reviews 2007, 107 (7), 2891-2959. 4. Krämer, T.; Tuna, F.; Pike, S. D., Chemical Science 2019, 10 (28), 6886-6898. 5. Brown, S. E.; Mantaloufa, I.; Andrews, R. T.; Barnes, T. J.; Lees, M. R.; De Proft, F.; Cunha, A. V.; Pike, S. D., Chemical Science 2023, 14 (3), 675-683.