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Towards Reliable Materials Discovery with Foundation ModelsJ. Margraf¹

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The design and discovery of new materials from first principles has been a tantalizing prospect for computational chemistry for the past decades. Realizing this promise has been highly challenging due to several factors, including the vastness of chemical space, and the discrepancy between idealized crystal structures and real (potentially disordered) materials. In this context, machine learning interatomic potentials (MLIPs) have become an important tool, as they allow a more realistic description of materials due to their high computational efficiency. Until recently, MLIPs had to be developed from scratch for each class of materials, however, which is impractical for exploring large composition spaces. This has changed with the emergence of foundation models for atomistic materials chemistry, which are pre-trained for materials across the periodic table. In this talk, I will discuss how these foundation models are changing computational materials discovery, focusing on their potential for structure prediction in large composition spaces. We will also consider remaining limitations of the models and computational materials discovery more generally. For the former, we will discuss the need for electrostatics-aware and non-local models, for the latter we will discuss the role of crystallographic disorder when predicting new materials.

Non-Perturbative Vibrational Excitation by Explicit Pulses from Classical Phase-Space DynamicsS. UPADHYAYULA¹, J. VANICEK²¹SCIENTIST- LCPT, EPFL, ²PROFESSOR-LCPT, EPFL

We present a non-perturbative framework for vibrational excitation in molecular systems driven by electric fields with arbitrary time-dependence. For harmonic potentials with linear dipole coupling, the dynamics is exactly described by a displaced coherent state [1] whose evolution is fully determined by a complex phase-space coordinate [2]. Closed-form expressions for this coordinate reveal clear distinction between resonant and off-resonant regimes. At resonance, and within the rotating wave approximation, the dynamics yields a time-dependent phase-space displacement, leading to a Poisson distribution of vibrational populations at all times. Off-resonant driving results in an exponentially suppressed displacement due to finite detuning between the driving and vibrational frequencies. The approach reduces to time-dependent perturbation theory in the weak-field limit but remains valid in the strong-field regime, where perturbative treatments fail. Our results provide a transparent phase-space picture of vibrational control and establish a non-perturbative route to tailored state preparation in ultrafast spectroscopy.

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Exact Tunneling Splittings from Rotationally Projected Path-Integral SamplingY. C. Wang¹, L. Zupan¹, J. O. Richardson¹¹Institute of Molecular Physical Science, ETH Zürich, 8093 Zürich, Switzerland

Quantum tunneling between symmetry-related molecular structures produces characteristic splittings that sensitively probe rovibrational dynamics and the underlying potential energy surface. In this talk, I will present two recent advances in exact path-integral methods for such splittings. First, I will show how the previous symmetrized path-integral molecular dynamics (PIMD) framework for the rotational ground state^[1] can be extended to rotationally excited states by projecting onto selected J manifolds and symmetry subspaces with an Eckart spring, allowing rigorous rotationally resolved splittings for multiple J values to be extracted from a single set of simulations.^[2]

In the second part, I will introduce path-integral hybrid Monte Carlo with enveloping bridging potentials (PIHMC-EBP), a new path-integral sampling method based on the same rotational-projection formalism.^[3] In this approach, an EBP is constructed for direct free-energy sampling, and two tailored nonlocal updates are designed to enhance the sampling of slow collective motions. Compared with PIMD based on thermodynamic integration, this approach removes the need for quadrature and time-step convergence checks, greatly reducing manual effort in the analysis. Applications to malonaldehyde and the HCl dimer yield the most precise reported splittings while reducing the computational cost by several-fold and by roughly three orders of magnitude, respectively. Application to the water dimer provides the first numerically exact path-integral calculations for the ground-state splittings on three different PESs, all obtained simultaneously from a single set of trajectories by reweighting.

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A State-Space-View of Atom-Diatom Reactions Relevant to Rarefied Gas Flow

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Rarefied and hypersonic gas flows involve strongly non-equilibrium conditions in which energy transfer between translational, rotational, and vibrational degrees of freedom governs chemical reactivity. To investigate these processes at a microscopic level, quasi-classical trajectory simulations were performed for the $\text{O} + \text{O}_2$ [1], $\text{N} + \text{O}_2$ [2], and $\text{N} + \text{NO}$ [3] collision systems on full-dimensional reactive potential energy surfaces (PES) based on high-level electronic structure calculations. The full state space was characterized by analysing elastic, inelastic, atom-exchange, reactive, and atomisation channels over a broad range of initial rovibrational states. Distinct structure–reactivity relationships emerge from the simulations: low rovibrational excitation predominantly leads to elastic and inelastic scattering, rotational excitation enhances atom-exchange reactivity, and strong vibrational excitation promotes atomisation and complete dissociation. Final-state probability maps reveal significant vibrational-to-rotational energy redistribution during reactive collisions and highlight how different regions of the initial state space contribute to specific reaction outcomes. For the $\text{O} + \text{O}_2$ system, two independently developed reactive PES based on Reproducing Kernel Hilbert Space (RKHS)[4] and permutationally invariant polynomials (PIPs)[5,6] representations yield consistent state-resolved dynamics despite their different electronic-structure methodologies, demonstrating the robustness of the predicted trends. These results provide a comprehensive state-space description of energy flow in atom–diatom collisions relevant to hypersonic chemistry and offer a foundation for future state-specific and data-driven models of non-equilibrium gas dynamics.

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Data-driven reactivity design through generative modeling with quantum chemistry validationZ. Ivkovic^{1,2}, K. Jorner^{1,2*}¹Institute of Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zurich, Zurich CH-8093, Switzerland, ²NCCR Catalysis, Switzerland

Data-driven inverse-design is a new emerging field in chemistry, showing promising results in drug discovery^{1,2,3} but remains underutilized in the context of reactivity design. This gap is largely attributed to data scarcity and the lack of generative models explicitly tailored for reaction-centric applications. While existing 3D generative frameworks possess the capacity for conditional generation of molecules, they cannot handle conditional generation on reactive properties, limiting their impact on reactivity design.^{4,5} In this work, we present a specialized generative modelling approach aimed at scaffold elaboration for reactivity design. Due to data scarcity, we limit ourselves in this study to reactivity design through scaffold decoration. We construct a curated dataset of around 10,000 DFT-level calculated keto-enol tautomerization reactions by subsampling a combinatorial library sharing a common *N*-Salicylideneaniline core scaffold, and additional 90'000 reactions calculated at xTB-level. We train a 3D structure-generating model on these datasets to produce transition state geometries that exhibit desired reactive properties. The inherent advantage of our approach over existing 2D approaches is easy validation of model predictions due to generated transition states. Our approach demonstrates the potential of targeted scaffold elaboration to advance computational reactivity design and provides a foundation for future developments in structure-based reaction modelling.

Computational Insights into PFAS Recognition by Metabolite Receptors: A Data-Driven ApproachM. Nedyalkova¹, M. Lattuada¹¹University of Fribourg

Per- and polyfluoroalkyl substances (PFAS) are persistent synthetic chemicals widely used in industrial and consumer products. Because they resist degradation and accumulate in the body, PFAS exposure through contaminated water and food has been linked to immune suppression, thyroid and liver dysfunction, developmental and reproductive effects, and increased risk of certain cancers. Therefore, the ongoing research aims to clarify long-term health impacts and improve risk management strategies.

Nowadays, there is growing evidence for a link between PFAS and metabolite receptors. It was demonstrated that certain PFAS can interact with metabolite receptors that function as metabolite sensors. Through these receptor-mediated mechanisms, PFAS exposure may disrupt metabolic pathways, contributing to effects such as dyslipidemia, liver toxicity, insulin resistance, and other metabolic disorders.

In this study we used computational chemistry, chemometrics and machine-learning approaches to investigate the molecular level interactions between PFAS and key metabolite receptors. To shed light on the selectivity and binding affinity in the metabolite receptor-PFAS interactions, we have performed large-scale molecular docking screening with eight different metabolite receptors and several hundreds of PFAS. The trends in the binding affinity of PFAS toward specific receptors are interpreted by machine learning (ML) models. To train the ML models we have created dataset comprising structural, quantumchemical and chemometric descriptors for several hundred PFAS molecules. The study demonstrates the applied potential of data-driven approaches in rationalizing the health impact of PFAS and gives deeper understanding on the structural aspects of PFAS-metabolite receptors interactions.

Beyond the Hype: The Realities of End-to-End Data-Driven Chemistry in Agrochemical R&DE. Dapiaggi¹, N. Lopanitsyna¹¹Syngenta Crop Protection, Stein, Switzerland

Crop protection remains critical to global food security, with arthropod pests, fungal pathogens, and competing weeds together accounting for an estimated 20–40% of annual yield losses worldwide¹ - figures projected to worsen under climate change. Developing selective, effective, and sustainable solutions to control fungi, insects and weeds is therefore central to Syngenta's mission and drives the need for innovative approaches to accelerate the discovery of novel crop protection active ingredients.

New Artificial Intelligence-based approaches^{2,3} have garnered significant interest in how they can be integrated into commercial agrochemical discovery pipelines. In this talk, we describe Syngenta's journey in generative chemistry. Since pioneering its use in agrochemistry in 2019, we have accumulated substantial practical experience, and we discuss the realities of deploying generative chemistry in an industrial context: from the design of multiparameter scoring functions (e.g., biological activity, safety, sustainability, and IP novelty), to steering generative algorithms toward desired regions of chemical space, to efficient post-processing strategies.

Yet designing a molecule solves only half the problem - a promising candidate must also be synthesizable. By integrating retrosynthetic prediction^{4,5} and data mining⁶, we identify optimal synthetic routes in silico, transforming virtual designs into tangible chemistry. The convergence of generative design and synthesis planning compresses discovery timelines. Today, generative chemistry supports majority of our research projects.

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Perovskite-Chalcogenide Epitaxial Heterostructures: A Computational Study

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The commercialization of perovskite solar cells (PSCs) is still limited by common efficiency loss and long-term stability issues when scaling up solar cells. On the other hand, it has been observed that chalcogenides enhance the properties of PSCs when incorporated into transport layers.[1] However, despite evidence that such structures enhance perovskite growth,[2] research on epitaxial heterostructures in these two materials has been limited.[3] Recently, a CsPbBr₃/PbSe epitaxial nanocrystal was successfully synthesized, confirming its interesting decrease in hot carrier cooling.[3] This phenomenon could provide access to high-energy photons, which are usually lost due to thermalization, potentially exceeding the Shockley-Queisser limit.[4] My contribution aims to shed light on the physical and chemical mechanisms behind the optoelectronic properties of CsPbBr₃/PbSe epitaxial heterostructures. This will be achieved by performing accurate first-principles calculations based on density functional theory and ab initio molecular dynamics, and by analyzing the electronic and structural properties of the system. This study not only aims to characterize the CsPbBr₃/PbSe system, but also paves the way for broader research into perovskite-chalcogenide epitaxial heterostructures with different compositions, facilitating the rational design of high-quality interfaces in PSCs in the future.

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Understanding the reaction mechanism of fluoroacetate dehalogenase for the design of enzymes that degrade “forever chemicals”

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Increasing concern over the environmental persistence and toxicity of per- and polyfluoroalkyl substances (PFAS), often referred to as “forever chemicals”, has necessitated technologies for their remediation [1]. Long-chain PFAS often degrade into smaller chain ones, such as tri-fluoroacetate (TFA), which extensively accumulate in the environment. No enzymes have yet been discovered to achieve the full degradation of short-chain PFAS, one reason that could explain their extraordinary persistence. It is therefore urgent to design a biomimetic system offering a cost-effective and sustainable solution to mitigate the environmental disaster of PFAS pollution.

The only known enzyme capable of breaking a carbon-fluorine bond is fluoroacetate dehalogenase (FACD), achieving the conversion of mono-fluoroacetate (MFA) into glycolate [2]. Yet, the enzyme fails at cleaving the C-F bonds of TFA, an analogue molecule to MFA where two hydrogens are replaced by fluorines. To shift the degradation ability of FACD towards polyfluorinated compounds, the first step was to better understand the reason for its current inactivity. To this end, classical molecular dynamics (MD), binding affinity MM/PB(GB)SA, and hybrid quantum mechanics/molecular mechanics (QM/MM) techniques were employed. Classical thermodynamic integration results showed that there was close to no thermodynamic barrier for MFA and TFA to enter the binding pocket of FACD. However, both substrates appeared to exhibit high conformational sampling and instability within the binding pocket, which seemed to hinder enzyme efficiency. Further, the QM/MM study of the reaction step with MFA and TFA highlighted key residues involved in the difference in reactivity between the two substrates.

A genetic algorithm (GA) model, based on random mutations from a library of amino acid conformers, was then used to optimize the wild-type FACD [3]. Based on our previous findings, the conformational flexibility of MFA and TFA in the binding pocket should be reduced to enhance reactivity. Therefore, multi-objective optimization was employed to optimize both the stability (force field-based descriptor) and binding (MM/PBSA calculation) of the enzyme. Best-performing mutants will be selected at the pareto front, tested with QM/MM and validated experimentally. The aim is also to now incorporate a reactivity descriptor in the multi-objective optimization, to lower the current activation barrier for C-F bond cleavage with TFA. Efforts to develop a fast yet accurate reactivity descriptor for the GA optimization will be discussed.

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Graph Theory Meets Shape Descriptors: Mining the Cambridge Structural Database for Monolayer-Protected Ag, Au, and Ag–Au Clusters

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Over the past years, the scientific community has increasingly invested in the systematic curation of large-scale, flexible, and continuously updated databases to support data-driven research. In crystallography, a key reference is the Cambridge Structural Database [1], which archives all published organic and metal–organic small-molecule crystal structures characterized by single-crystal X-ray and neutron diffraction. The database currently contains over 1.3 million experimental structures, with thousands of new entries added every year. From this database we retrieved, refined, and analyzed all deposited pure Ag, pure Au, and mixed Ag–Au structures.

To analyze these atomically precise nanoclusters, we developed a framework that combines topological analysis based on graph theory with geometrical shape analysis using rotationally invariant descriptors such as asphericity and prolateness [2,3]. Each nanocluster is modeled as a graph, where atoms are represented as nodes and chemical bonds as edges. Within this framework, we compute graph-based quantities, such as node degrees and canonical graph representations [4], to characterize structural connectivity. Because graph representations do not fully capture the three-dimensional arrangement of atoms, shape descriptors quantify ellipsoidal deformations and distinguish spherical, oblate, and prolate geometries. Additionally, we employ a graph-based chirality descriptor [5] that enables a quantitative estimate of chirality. This descriptor also allows us to localize chiral features to specific regions of the cluster, namely the metallic core, the metal–ligand interface, and the ligand shell.

We present a systematic comparison of graph- and shape-based descriptors for silver, gold, and mixed silver–gold monolayer-protected clusters, highlighting key similarities and differences in their structural connectivity, chiral properties, and shape trends. In particular, the shape analysis indicates that atomically precise nanoclusters predominantly occupy a spheroidal structural regime, in which two principal axes remain essentially equivalent. These insights contribute to a deeper understanding of the topological organization of metal nanoclusters and provide a basis for rationalizing their chemical behavior.

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Charge- and Spin-Aware Graph Neural Network with the Spin-polarized Charge Equilibration MethodD. Tang¹, S. Lubner^{1*}¹Department of Chemistry, University of Zurich

Machine learning interatomic potentials (MLIPs) provide an efficient and promising framework for atomistic simulations of complex chemical systems. Despite their strengths, further enhancements are still needed to expand their predictive scope across diverse chemical phenomena. This work presents an advanced equivariant graph neural network-based MLIP framework that incorporates charge- and spin-aware capabilities, enabling accurate predictions of energies, forces, atomic charges, and atomic spin moments in chemical systems. We introduce a novel spin-dependent charge equilibration (QEq) method,^[1] which extends the applicability of the QEq method^[2] to spin-polarized systems. The spin-polarized QEq-enhanced MACE^[3] models were thoroughly evaluated against density functional theory (DFT) reference datasets, demonstrating very good predictive performance for chemical systems, including organic molecules, metalorganics, and 2D/3D periodic systems. A key highlight is the model's ability to accurately capture polaron distributions on the TiO₂ (110) surface, showcasing its effectiveness in modeling spin-related properties. By addressing both charge and spin dynamics, this approach broadens the potential of MLIPs to tackle more complex phenomena in a computationally efficient manner. This development thus further promotes the accuracy and versatility of MLIPs, paving the way for more reliable and comprehensive atomistic simulations in materials science, chemistry, and related fields.

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Machine-Learning in NMR Crystallography: From Fast Predictions to Incorporation of Nuclear Quantum Effects

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Atomic-level structural insight is central to understanding chemical function in molecular solids, with chemical-shift-driven NMR crystallography serving as a key tool for three-dimensional structure determination.¹ Conventional approaches rely on predicting chemical shifts for static candidate structures using density functional theory (DFT), which imposes significant computational constraints on system size and the number of structures considered. Moreover, these methods neglect ensemble averaging over fast (sub-nanosecond) vibrational and thermal motions, as well as nuclear quantum effects, which are particularly important for light atoms such as protons.

Ab initio path-integral molecular dynamics (PIMD) has demonstrated improved agreement between predicted and experimental chemical shifts by incorporating thermal fluctuations and quantum delocalization.² However, such approaches remain computationally prohibitive and are often limited by approximations in the potential energy surface, including incomplete treatment of exchange effects and their functional dependence.

Here, we introduce QNC-NMR,³ a machine-learning-driven framework that overcomes these limitations by combining two models: PET-MOLS, which provides an accurate machine learning interatomic potential (MLIP), and ShiftML3,⁴ which enables rapid prediction of NMR shielding. PET-MOLS facilitates PIMD simulations at a computational cost reduced by several orders of magnitude relative to ab initio methods, while maintaining accuracy through training on hybrid-functional reference data. In parallel, ShiftML3 predicts chemical shielding with near-DFT accuracy at a speed approximately two orders of magnitude faster and without system-size limitations.

This integrated approach enables ensemble-averaged chemical shifts that explicitly incorporate thermal, nuclear quantum, and exchange effects. Benchmarking on crystalline systems shows a two-fold improvement in predicting of labile proton chemical shifts. Furthermore, QNC-NMR extends accurate chemical shift prediction to large and complex systems, including amorphous pharmaceuticals, which are beyond the reach of conventional DFT and classical force-field methods.

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High-performance polarizable embedding QM/MM implementation in the MiMiC framework

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Multiscale molecular simulations combining quantum mechanics and molecular mechanics (QM/MM) have become indispensable tools for studying complex chemical and biological processes. Among the available QM/MM schemes, polarizable embedding offers a more accurate description of the environment by accounting for the response of the classical region to the quantum subsystem. However, as of this day, it still remains far from widespread due to the reliance of existing implementations on proprietary software or their computational overhead that renders routine deployment in production simulations prohibitively expensive.

MiMiC [1,2] is a flexible framework for multiscale simulations in which independent programs handle individual subsystems at different levels of theory, which has been designed with performance in mind. It minimizes the overheads inherent to multi-program simulations, both in communication between concurrently running programs and in the computation of interaction terms between subsystems, to the point where they become barely noticeable. As a result, MiMiC is well-suited for modern HPC architectures, as already demonstrated by its electrostatic embedding implementation.

In this contribution, we present an implementation of the polarizable embedding QM/MM scheme within MiMiC, extending our earlier single-point proof-of-concept [3] based on the approach of Loco et al. [4]. Recent significant performance improvements in MiMiC, such as GPU offloading, were key to overcoming the longstanding computational barriers of molecular dynamics with polarizable embedding QM/MM. Aligned with the overall philosophy of MiMiC, the implementation will be open, compatible with multiple open-source QM and MM programs, and fully supported on modern HPC architectures, making polarizable embedding accessible to a broader community.

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Tripeptide-Dynamics from Empirical and Machine-Learned Energy Functions

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Molecular dynamics (MD) simulations provide a powerful route to connect molecular structure with spectroscopic observables, though their accuracy is often limited by the underlying energy functions. In this work, MD simulations of tripeptides in both the gas phase and in solution are presented using empirical and machine-learned energy functions. It is demonstrated that machine-learned potential energy surfaces (ML-PES), trained on MP2 reference data, enable quantitatively accurate and computationally efficient simulations. For the cationic AAA system, ML/MM-MD simulations in explicit solvent are shown to reproduce experimental infrared observables with high fidelity, including the splitting of amide-I vibrations. The predicted splitting of 20 cm^{-1} is in near-quantitative agreement with the experimental value of 25 cm^{-1} [1], and the relative ordering of vibrational bands is correctly captured. For the AMA tripeptide, an ML-PES capable of describing both zwitterionic and neutral forms is developed, enabling comprehensive exploration of its conformational landscape. In the neutral form, cyclization and intramolecular hydrogen bonding between terminal groups are found to lead to pronounced red shifts of NH- and OH-stretching modes to frequencies below 3000 cm^{-1} .

These results demonstrate that nanosecond-scale MD simulations with near-MP2 accuracy are feasible using machine-learned potentials, while maintaining close agreement with experiment. Beyond validating this approach, the potential of ML-driven simulations to bridge the gap between high-level quantum chemistry and experimentally accessible observables is highlighted. This framework enables predictive, atomistic modeling of biomolecular systems with high accuracy and is readily extensible to general tripeptide sequences (XYZ), providing a scalable and transferable strategy for investigating diverse peptide systems and their spectroscopic signatures.

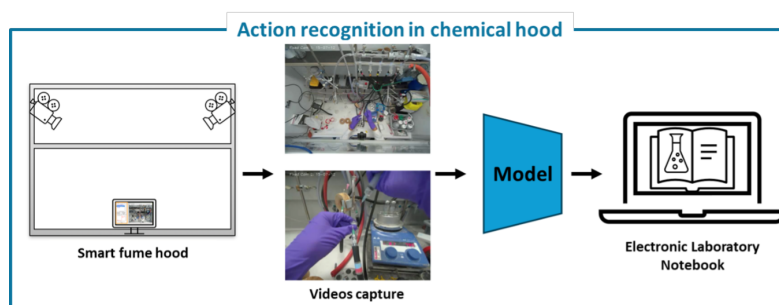
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Smart Labs: Enhancing Experimental Documentation through AI-driven Video Monitoring

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Modern experimental laboratories generate vast amounts of scientific data, yet traditionally only selected portions deemed immediately relevant are documented and published. Despite centuries of methodological refinement, the execution of chemical procedures remains largely manual, and critical details are frequently overlooked, incompletely recorded, or inconsistently interpreted.^{1–4} Systematic monitoring and comprehensive data collection through video recordings can substantially enhance reproducibility, deepen understanding of complex chemical processes, and enable advanced multimodal artificial intelligence applications.^{5,6} In this work, we introduce a smart fume hood, capable of performing action recognition and hands free documentation of experimental procedure. Thanks to a set of cameras, sensors and softwares, the system was employed for a data acquisition campaign, leading to the collection of about 7000 labelled video fragments. The dataset was used in the training of an AI model that achieved up to 84% accuracy over five action classes. The model was then integrated in the fume hood system and subjected to a prospective deployment, recognizing correctly approximately 70% of the experimental procedures in real-time and documenting the workflow from the video stream to the electronic laboratory notebook in a hands-free manner. This initiative represents an first step towards the realization of intelligent, data-driven laboratories where accuracy, reproducibility, and AI-powered analytics converge to accelerate scientific innovation and discovery.



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Nonzero-temperature vibronic spectra of polyatomic molecules from a zero-temperature classical trajectoryD. Barbiero¹, J. Vaniček^{1*}

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By combining coherence thermofield dynamics [1,2] with the single-Hessian approximation [3,4], we enable simulations of low- to medium-resolution vibronic spectra of weakly anharmonic systems at nonzero temperatures, at negligible additional cost relative to zero-temperature calculations [5]. In coherence thermofield dynamics, the von Neumann propagation of the coherence component of the density matrix is replaced by the Schrödinger evolution of a pure-state wavepacket in a doubled configuration space. Within the single-Hessian approximation to the thermofield potential, the evolution of the augmented wavepacket can be computed by propagating a single ab initio classical trajectory in the original phase space at zero temperature. Single-Hessian coherence thermofield Gaussian wavepacket dynamics is exact in any harmonic potential, provided that the reference Hessian is that of the final surface. When applied to Morse systems of increasing anharmonicity and varying temperature, this method successfully captures excited-state anharmonicity and key temperature-dependent spectral features, including hot bands and broadening. By combining the method with on-the-fly ab initio dynamics, we demonstrate its utility by computing the absorption spectra of naphthalene, aminocoumarin C450, and phenyl radical, and the photoelectron spectrum of SeO₂. Within the ab initio single-Hessian approximation, after the zero-temperature spectrum is obtained at the cost of classical molecular dynamics (on the order of hours), all nonzero-temperature spectra are computed in seconds.

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Machine Learning in Heterogeneous Catalysis: A Data-First Approach in Scarce Regimes

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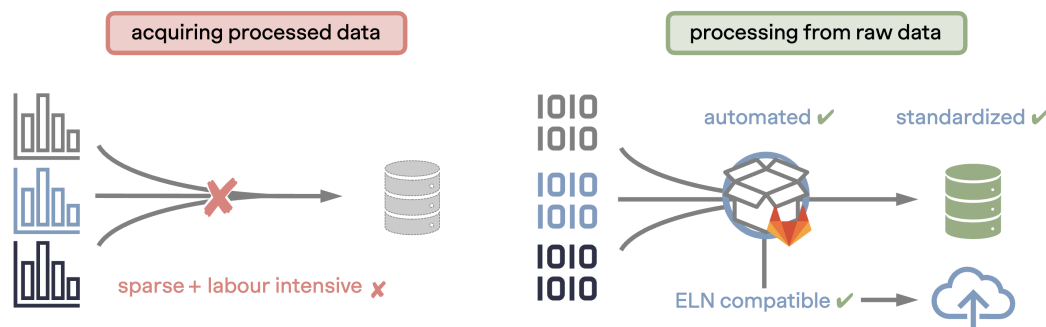
The ambiguous character of heterogeneous catalysts and the low-data regime they are found in continues to pose a challenge in leveraging the recent success of machine learning (ML) in fields such as spectra¹ and reaction predictions² in an area exploring a vast chemical space of materials.

The thermocatalytic hydrogenation of CO₂ to methanol and other value-added products is a highly relevant reaction in the contemporary context and serves as a good example due to its frequent appearance in ML applied to heterogeneous catalysis. Case studies are often pivoted to a narrow elemental scope and rely on reaction parameters as part of the catalyst input representations³ which stems from the difficulty of establishing quantitative relationships between materials and catalytic activity across fundamentally different systems in case of scarce and costly data.

A common approach to overcome the bottleneck of few datapoints is to expand them through curation from literature. The acquired sets unfortunately suffer from missing values due to lack of standardized report formats as well as wide distributions of input domains e.g. space velocities or reaction pressures.⁴

The need for a data-first approach has been recognized for the leverage of data-science and machine learning in heterogeneous catalysis.⁵ It must focus on unified data processing pipelines guaranteeing fully standardized reports combined with adherence to FAIR principles for transparent processing methods as well as the data.

A software package is presented which is capable of integrating experimental parameters and raw measurements of catalytic tests in CO₂ hydrogenation into a FAIR, processed run controlled through a graphical user interface. The workflow is expandable to additional reactions as well as other research groups with diverging experimental setups and preprocessing workflows and is integrable into ELNs.



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An Explicit Machine-Learned Two-Body Potential Energy Surface for Molecular Dynamics Simulations of Molecular Clusters.

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Molecular dynamics simulations are often limited by empirical energy functions, which are parameterized near equilibrium regions and may fail to capture system-dependent interactions across a broad conformational space. QM/MM methods have paved the way for more accurate energy descriptions; however, this accuracy is achieved at a significantly higher computational cost.[1,2] Motivated by the need for faster alternatives that retain high accuracy, we introduce a new pairwise hybrid machine-learning/molecular mechanics (ML/MM) potential designed for application to large, heterogeneous condensed-phase systems. The PhysNet-based ML method describes short-range pairwise interactions,[3] whereas an empirical force field is used for pairwise interactions beyond a system-dependent switching distance. Models are fitted to MP2 dimer and pairwise cluster energies, and their quality is assessed at different switching distances. Dichloromethane and acetone are used as test systems to evaluate model accuracy, energy conservation, and radial distribution functions across different simulation ensembles.

The range-separated ML/MM models improve the description of pairwise cluster energies, with the best performance obtained at system-dependent switching distances. Using switching distance 7 Å, the ML/MM model achieves RMSE values of 0.40 kcal/mol for dichloromethane and 1.53 kcal/mol for acetone, comparable to or better than the corresponding two-body PhysNet description. Analysis of total cluster energies shows minimal many-body effects for dichloromethane, however pronounced for acetone, motivating future many-body corrections. NVE simulations of dichloromethane clusters show stable total energy conservation on the nanosecond timescale, with a σ of 0.147 kcal/mol and no observable drift. In the current implementation, the relative timings for MM, ML, and ML/MM are approximately 1:25:25, demonstrating that the hybrid approach remains computationally feasible. Simulations using thermostat further yield partial radial distribution functions in reasonable agreement with experiment[4], supporting the ability of the model to reproduce condensed-phase structural properties.

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Pushing Δ SCF to New Frontiers: Spin-Orbit Coupling in Gas and Extended Condensed Phase SystemsT. de Jong¹, M. Mališ¹, S. Lubert^{1*}¹University of Zurich

Almost all nonadiabatic (NA) processes encountered in nature happen in the presence of the condensed phase. Accurate in silico modelling of NA processes of photoexcited systems in the condensed phase, however, represents a significant theoretical and computational challenge.[1] Not only does the system increase its size due to additional environment molecules that have to be accounted for, but also the number of electronic states and the number of potential nonradiative deactivation (NRD) pathways increase. Consequently, the perturbative time-dependent density functional theory (TDDFT) method, widely used for NA molecular dynamics (MD), becomes computationally demanding. The variational delta self-consistent field (Δ SCF) approach offers a practical alternative. This approach not only renders excited state calculations computationally equivalent to their ground state counterparts, but also enables selecting individual excited states within the manifold, providing both efficiency and flexibility. Here, we report ongoing advances in the Δ SCF methodology and employ it to illustrate the importance of treating all atoms at the same level of theory. All methods were implemented in an in-house modified version of the CP2K code.[2]

The Δ SCF approach models excited states by modifying orbital occupation numbers according to a singly excited Slater determinant, whereby electron density is transferred from an occupied to a virtual orbital, followed by variational optimization of the electronic density under constrained orbital ordering and occupation numbers. Only recently has this framework been extended to incorporate multiple excited Slater determinants within a multi-reference Δ SCF formalism, thereby broadening its applicability to aromatic systems.[3] In the present work, we further extend multi-reference Δ SCF to include spin-orbit coupling (SOC)[4] capabilities, enabling the investigation of intersystem crossing events in fully periodic condensed phase aromatic systems. We present a benchmark comprising a diverse set of organic compounds. For a subset of these molecules, oxygen was systematically replaced by its heavier chalcogen analogues, sulfur and selenium, to evaluate the robustness and applicability of the multi-reference Δ SCF SOC approach. Additionally, one system was solvated in a fully periodic water box to demonstrate the applicability of the approach to condensed phase NA MD.

The importance of accurately treating condensed phase environments has been highlighted in previous NA MD studies within the Δ SCF framework. Aqueous solvations of *cis*- and *trans*-diimide extends the first excited state lifetime relative to the gas phase, with the hydrogen bonding network acting as a barrier to N=N bond rotation.[5] In the case of cyclopropanone, while the NRD pathways remain similar upon solvation, the degree of photolysis is reduced in the condensed phase.[6]

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Identification of potential natural analgesic compounds through molecular docking-virtual screening, molecular dynamics simulation, MM/GBSA, DFT, and ADMET computations

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This study aimed to identify bioactive compounds from twelve medicinal plants known for their analgesic and anti-inflammatory properties using in silico approaches. The phytochemical components were subjected to cross-docking analyses against receptors implicated in pain and inflammation pathways. Based on binding energies, interaction profiles, and key amino acid residues within the receptor active sites, three compounds—apigenin, kaempferol, and quercetin—demonstrated the highest affinity for the cyclooxygenase-2 (COX-2) receptor. Notably, these compounds share similar structural scaffolds and exhibit analogous interactions with critical receptor residues. Furthermore, pharmacokinetic and toxicity assessments of the selected compounds indicated favorable oral bioavailability and an overall acceptable safety profile. Density functional theory (DFT) calculations revealed that these compounds possess relatively high softness. Molecular dynamics simulations of apigenin, kaempferol, quercetin, and the reference drug diclofenac complexed with COX-2 were performed over 100 ns. Analyses of root mean square deviation (RMSD), radius of gyration (Rg), root mean square fluctuation (RMSF), and ligand-protein interactions confirmed the stability of these complexes. Finally, MM/GBSA calculations estimated the binding free energies, with diclofenac and apigenin exhibiting the most favorable values. This study highlights pharmacologically active compounds potentially contributing to the analgesic effects of these plants. It underscores the value of such computational investigations in accelerating the discovery of specific bioactive agents responsible for therapeutic effects.

Incorporating rotational symmetry and quantisation into instanton theory

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Properly describing rotational symmetry of molecules is key for accurate simulations of quantum molecular dynamics. While Ring-Polymer Instanton Theory (RPI) correctly captures zero-point energy and tunnelling effects, the treatment of rotational partition functions in this framework has so far only been done classically. Our goal is to incorporate rotational quantisation of states into RPI from first principles in order to describe energy splittings between molecular rotational states (a spectroscopically observable quantity) and gas-phase reactions more accurately (i. e. beyond TST and standard RPI). Recently, we have extended RPI by introducing perturbative corrections (PC) [1, 2], which further improve its accuracy by describing anharmonic vibrational effects. We will describe further extensions of the perturbative approach to treat other anharmonic effects such as rotation-vibration coupling.

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Atomistic insight into structural transformations in Fe-rich smectitesM. Ernst¹, S. Churakov^{1,2}¹Institute of Geological Sciences, University of Bern, Baltzerstrasse 1+3, 3012 Bern, Switzerland, ²PSI Center for Nuclear Engineering and Sciences, 5232 Villigen PSI, Switzerland

Atomistic simulations of clay minerals provide detailed insight into the mechanisms governing transport, retention, and structural transformations. These processes are central to understanding the behavior of clays in environmental and engineered systems, where coupled structural and redox effects control ion mobility and reactivity. Smectites, a subgroup of 2:1 phyllosilicates, are of particular interest due to their high cation exchange capacity, compositional variability, and ability to incorporate both ferrous and ferric iron within their octahedral sheets.

In this contribution, we present results from ab initio molecular dynamics (AIMD) simulations of structural transformations and Fe reordering in Fe-rich montmorillonite with full Fe substitution in the octahedral sheet. We investigate dioctahedral-to-trioctahedral transformations at representative edge terminations of the most stable and symmetric surfaces, namely (010) trans-vacant and (011) cis- and trans-vacant configurations. To promote these transformations and to reconstruct the associated free energy landscapes, we employ metadynamics together with AIMD. The transformation mechanism is described by the migration of an Fe atom between neighboring octahedral sites, leading to a change in local coordination environment (Figure 1).

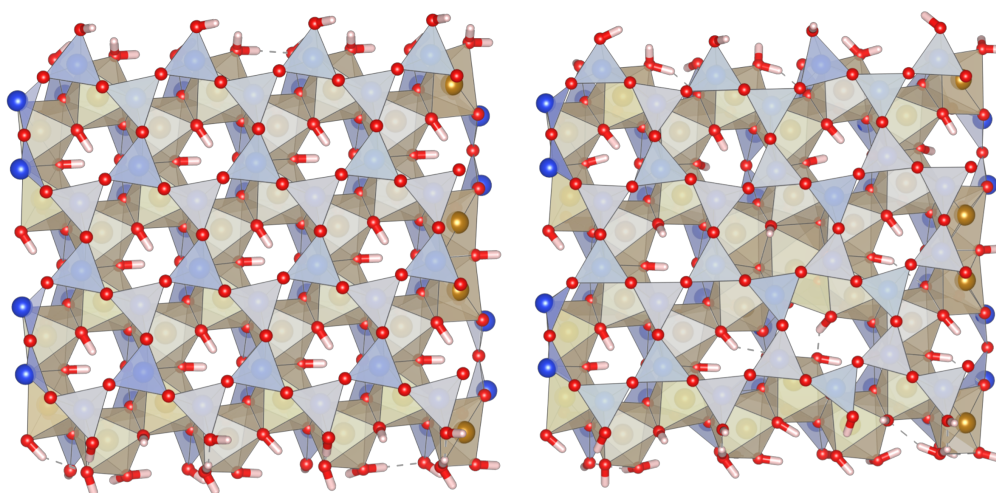


Figure 1: Initial dioctahedral structure (left) and resulting trioctahedral structure (right).

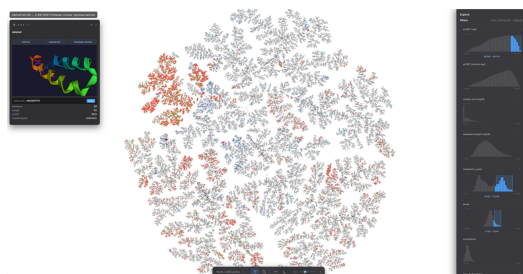
From Proteins and Molecules to Cats and Dogs: Visualization as Scalable Minimum Spanning Trees

A. Flores¹, J. Reymond²

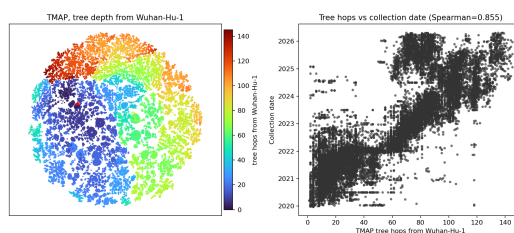
¹University of Bern, ²University of Bern

Here we present TMAP2 for visualizing large and complex datasets as minimum spanning trees. Each point is connected through real nearest-neighbor relationships, so the map can be explored as a network of meaningful paths. This makes it possible not only to see clusters, but to identify relationships across the data.

A map of data should not only show where things are. It should also show how one thing is connected to the next. TMAP2 was built for this problem in chemistry. Large molecular libraries contain thousands or millions of compounds, and chemists often want to see more than clusters. They want to follow chemical series, find bridges between scaffolds and understand how one region of chemical space connects to another. TMAP2 turns those relationships into a tree: each compound is connected through nearest-neighbor links, so the map can be searched, filtered, and followed like a route through chemical space. It builds a readable structure, where each edge has a meaning and each path tells a story. The question then becomes which story you want to tell.



TMAP2 can also recover stories that are not given to the algorithm. We built a tree from SARS-CoV-2 spike protein sequences using only the sequence content. The method was not told when each virus was collected. It only compared sequences by similarity and connected them through nearest-neighbor relationships. Yet when we count the number of tree steps from the original Wuhan-Hu-1 sequence (i.e. how far in the tree they are), the map follows the real calendar history of the pandemic. Early variants stay close to the root, while later variants move farther away along the tree. This shows why topology matters. For evolving systems, developing cells, chemical series, or image collections, those paths can become simple, readable stories.



Photodissociation of molecules using semiclassical nonadiabatic molecular dynamic methodsD. Furlanetto¹, J. O. Richardson^{1*}¹ETHZ

The photodissociation of molecules can be simulated through nonadiabatic molecular dynamic methods. Semiclassical methods allow on-the-fly simulations of molecules in full dimensionality at low computational cost. The mapping approach to surface hopping (MASH) is a novel deterministic method that ensures consistency and time-reversibility.

MASH and standard fewest-switches surface hopping (FSSH) are compared to full quantum-mechanical results on model systems. The simulation of the photodissociation of ammonia with on-the-fly electronic structure shows the limitations of standard surface hopping. MASH solves the inconsistency between the active state and the electronic coefficients, showing improvements in all the systems studied. The electronic populations after dissociation are compared for the different methods. The standard surface hopping can fail to describe the long-time limit distribution of the active state, while MASH describes the correct limit thanks to internal consistency and detailed balance at the same computational cost. In this way, MASH appears to be an excellent simulation method that correctly describes without further corrections the electronic populations after photodissociation.

Evaluating vibronic spectra beyond the Herzberg-Teller approximation with Hagedorn wavepacketsM. Gandolfi¹, J. Vaniček^{1*}¹Laboratory of Theoretical Physical Chemistry, Institut des Sciences et Ingénierie Chimiques, École Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

In most calculations of vibrationally resolved electronic spectra, the transition dipole moment is assumed to be either a constant or a linear function of nuclear coordinates. We describe an efficient method, which goes beyond these so-called Condon and Herzberg-Teller approximations and allows for an arbitrary polynomial dependence of the transition dipole moment on nuclear coordinates. To propagate a wavepacket in the form of a Gaussian multiplied by an arbitrary polynomial, we expand the initial state in Hagedorn's basis [1-3]. In harmonic systems, the coefficients of Hagedorn functions stay constant, and one only needs to evolve the guiding Gaussian's parameters and evaluate the autocorrelation function of Hagedorn wavepackets using an exact recursive expression [4]. To validate the method, we compare its results with exact quantum benchmarks for displaced, distorted, and Duschinsky-rotated harmonic models and for different polynomial dependences of the transition dipole moment. In *ab initio* applications, the bottleneck is the evaluation of the electronic structure required for the propagation of the guiding Gaussian. Therefore, the proposed method can evaluate corrections to the Condon and Herzberg-Teller spectra at a negligible additional cost, similarly to how Hagedorn wavepacket dynamics has been used to evaluate single-vibronic level fluorescence spectra from excited levels [5,6].

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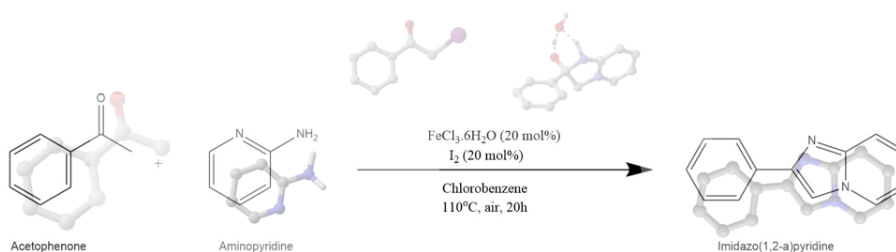
Deciphering the Mechanism Behind the Fe/I₂ Catalyzed Ortoleva–King Type Reaction: A DFT Study

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Transition metal-catalyzed condensation reactions represent an emerging frontier in pharmacological synthesis, particularly for constructing heterocycles of medicinal relevance such as Imidazo[1,2- α] pyridines. These scaffolds are valued for their versatile biological and therapeutic applications. While acid-catalyzed protocols have traditionally dominated this space, the adoption of first-row transition metals as cost-effective, non-toxic alternatives has gained prominence. In this context, the Fe/I₂-catalyzed synthesis of Imidazo[1,2- α] pyridines were selected as a topic of mechanistic interest. Although experimental investigations into these reactions are actively progressing, their mechanistic pathways remain largely unexplored. To address this gap, we conducted a comprehensive theoretical study of the iron/iodine-catalyzed Ortoleva–King type reaction using density functional theory. The reaction employs chlorobenzene as solvent and FeCl₃·6H₂O as a co-catalyst. All calculations were performed using the unrestricted M06X functional with the def2-SVP basis set in the Gaussian 09 software package, providing a robust computational framework.

Catalytic species were characterized, and the full energy profile of the reaction pathway was mapped. The roles of reactants, intermediates, and products were elucidated, offering mechanistic insight into each stage of the transformation. A detailed analysis on the substituent effects on the activation barrier and rate of reaction was calculated. This work presents a detailed theoretical framework for the iron–iodine catalyzed synthesis of imidazopyridines via the Ortoleva–King protocol, contributing to the rational design of transition metal-mediated heterocycle synthesis.



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RXNMapperv2: updated validation and evaluation on expanded chemical space

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Atom-to-atom mapping (AAM) assigns reactant atoms to product atoms and underlies reaction classification, template extraction, and synthesis planning. RXNMapper derives AAM from the attention of an ALBERT model trained by masked language modeling on unmapped reaction SMILES. However, its original model selection relied on USPTO-50K, a validation set later shown to contain erroneous mappings. Here we revisit RXNMapper using a curated validation set of 4'533 reactions from the dataset Pistachio. We retrained ALBERT-based RXNMapper models on USPTO-full and Pistachio and selected the best head, layer, and checkpoint on this new validation set. We also developed an evaluation framework that removes ambiguous reference reactions and compares predictions by reaction graph isomorphism rather than direct string matching, avoiding false negatives from inconsistent formats and symmetry-equivalent mappings. Across the golden dataset, Pistachio, and an internal AstraZeneca medicinal chemistry benchmark, the updated models outperform the original RXNMapper and LocalMapper, while rearrangements remain persistent challenges.

Flow Matching for Ligated Nanoclusters via Approximated Optimal Transport

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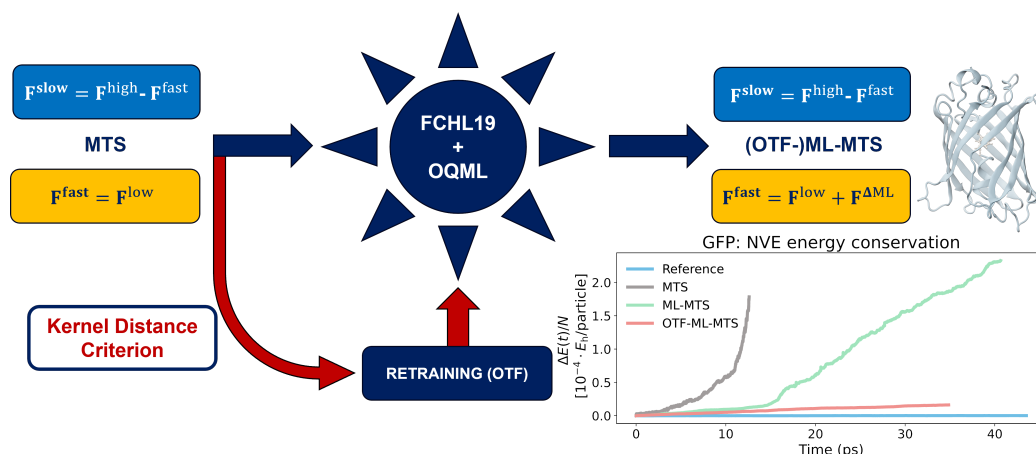
Ligand-protected metal nanoclusters occupy a unique regime between molecules and extended solids, with applications in catalysis, photoluminescence, and bioimaging. Here, neither molecular nor periodic methods for structure prediction apply. Conventional molecular representations cannot encode the metal core, and no existing generative method captures the steric effects, coordination preferences, and non-local interactions that govern ligand arrangement.

We introduce LigNano Flow, a flow matching framework for generating full 3D structures of ligand-stabilized metal nanoclusters, trained on a newly generated database of over 3 million phosphine-ligated nanoclusters. This database includes g-xTB-calculated bandgaps and d-band centers to enable generative models to target specific electronic properties. LigNano Flow produces chemically reasonable 3D cluster geometries, with energies relatively close to MACE-MP ground truth.

This framework opens a path toward property-driven nanocluster design, where targeting descriptors such as the d-band center and bandgap can directly accelerate the rational engineering of nanocluster catalysts and luminescent nanoclusters.

***On-the-fly* Machine Learning-Enhanced Multiple Time-Step Propagation for QM/MM Dynamics**T. Kläy¹, F. L. Mouvet¹, U. Rothlisberger^{1*}¹LCBC, SB ISIC EPFL, CH-1015 Lausanne, Switzerland

Computer simulations of chemical systems deal with the fine balance between computational cost and accuracy. While Quantum Mechanics (QM) can study reactive events such as bond forming and bond breaking, it is usually limited to a few hundred atoms and a simulation time of tens of picoseconds per system. Molecular Mechanics (MM) on the other hand makes use of several approximations, so that the simulation of, for example, proteins or other biological compounds is possible for up to a few microseconds. To be able to simulate larger systems and/or for longer simulation times with high accuracy, different techniques have been proposed. In a first class of approaches, a separation between the fast and slow degrees of freedom, referred to as Multiple Time-Step integration, can save time if the slow-moving components correspond to the computationally expensive part of the forces. Additionally, Machine Learning (ML) enhancement, such as the Operator Quantum Machine Learning regressor (OQML) approach combined with e.g. the FCHL19 representation,^[1] can be used to infer the results that one would obtain at the QM level. Coupled with an adaptive/on-the-fly scheme that adjusts the ML model during the simulation, a significant decrease in required resources and time can be achieved while maintaining a high accuracy.^[2] Lastly, multiscale techniques such as the combination of QM and MM levels can be powerful by treating different regions of the simulated system with different methods and by carefully accounting for the interactions between the partitions.



The objective of my research is to further develop a method that combines all the above-mentioned techniques and apply it to various systems of interest. This recently developed technique termed "on-the-fly Machine Learning-Enhanced Multiple Time-Step QM/MM Dynamics (OTF-ML-MTS QM/MM)" has been validated on two test case systems, namely the green fluorescent protein (GFP), previously used to showcase the performance of the QM/MM interface MiMiC^[3], and an S_N2 bromo/chloromethane reaction in solution as a representative reactive event. For both systems, OTF-ML-MTS QM/MM shows speedups above one order of magnitude while retaining the same level of accuracy as QM/MM dynamics alone. These promising results open the door to many possible applications and ways to improve the methodology.

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[2] François Mouvet, Nicholas J. Browning, Pablo Baudin, Elisa Liberatore, Ursula Rothlisberger, *J. Chem. Phys.*, 2025, 163, 184115.

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Multiscale Modeling of Complex Biomolecular Systems: From Classical Force Fields to Polarizable QM/MMA. Levy¹, U. Rothlisberger¹¹Laboratory of Computational Chemistry and Biochemistry, Institute of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

Accurately describing molecular interactions is central to the multiscale modeling of biomolecular systems, and becomes particularly challenging in metal-containing systems, whether natively, as in metalloproteins, or exogenously, as in transition-metal-based drugs. Classical fixed-charge force fields offer a computationally efficient starting point, but present inherent limitations in capturing the anisotropic and dynamic charge distributions that govern coordination geometry and binding selectivity in such systems. The hybrid quantum mechanics/molecular mechanics (QM/MM) approach resolves many of these limitations [1] by treating the chemically active region at the quantum mechanical level while describing the environment with a classical force field, with embedding schemes ranging from the commonly used electrostatic embedding to the more sophisticated and computationally demanding polarizable alternatives.

In this contribution, I will present work at the interface of method development and applications in multiscale simulations, with a focus on the MiMiC framework. [2] Through two complementary case studies, i.e., the binding of a cyclic peptide ligand to the metal site of an integrin protein, and the interaction of transition-metal-based anticancer compounds with histone proteins in nucleosome core particles, I will illustrate the insights accessible at different levels of theory and the limitations that motivate moving beyond a force field description. In the integrin case, QM/MM helped elucidate the coordination modes observed in classical simulations, while for transition-metal-based compounds in nucleosome core particles, it was used to rationalize the binding preferences observed experimentally. [3]

Yet, even electrostatic-embedding QM/MM can be insufficient when environmental polarization plays a significant role. To address this, I will present ongoing work in MiMiC on the implementation of a fully polarizable QM/MM embedding scheme, coupling plane-wave Kohn–Sham DFT with the AMOEBA polarizable force field [4]. By enabling mutual polarization between the QM and MM subsystems, this approach goes beyond conventional electrostatic embedding and opens the door to a more accurate description of complex biomolecular environments.

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[3] Andrea Levy et al., *bioRxiv preprint*, **2026**, doi:10.64898/2026.01.29.702545.

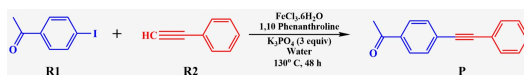
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A Computational Investigation into the Molecular Mechanism of Fe catalyzed Sonogashira Cross-Coupling Reaction

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The Sonogashira cross-coupling reaction is a cornerstone transformation in organic synthesis for constructing C(sp²)–C(sp) bonds, enabling the synthesis of structurally diverse aryl alkynes with broad applications in pharmaceuticals and materials science. These reactions traditionally rely on palladium-based catalysts. In pursuit of sustainable and cost-effective alternatives, iron has emerged as an attractive catalyst owing to its abundance, low toxicity and rich redox chemistry. Despite significant experimental advances in iron-catalyzed Sonogashira-type reactions, the underlying reaction mechanism remains poorly understood. In this study, Density Functional Theory (DFT) calculations were employed to investigate the mechanism of the Fe-catalyzed Sonogashira-type coupling between phenylacetylene and 4-iodoacetophenone in aqueous medium using an FeCl₃·6H₂O/1,10-phenanthroline catalytic system. The calculations were performed using the M06L functional with the def2-SVP basis set and SMD solvation model to elucidate the energetic profiles of intermediates, transition states and competing reaction pathways.



The computational results reveal that conventional radical pathways involving single-electron transfer and halogen atom transfer are energetically unfavorable. Instead, the reaction proceeds through a redox-neutral Fe(III) catalytic cycle in which the oxidation state of iron remains unchanged throughout the process. The active Fe(III)–phenanthroline species is generated via base-assisted activation of the terminal alkyne, followed by a concerted oxidative addition–reductive elimination step leading to C–C bond formation. The calculated activation barrier is consistent with the experimentally observed reaction conditions, while the highly exergonic product-forming step confirms the thermodynamic viability of the proposed mechanism. These insights not only highlight iron as a sustainable alternative to palladium but also provide a framework for optimizing ligand design, solvent choice and reaction conditions to expand the scope of iron-catalyzed cross-coupling reactions.

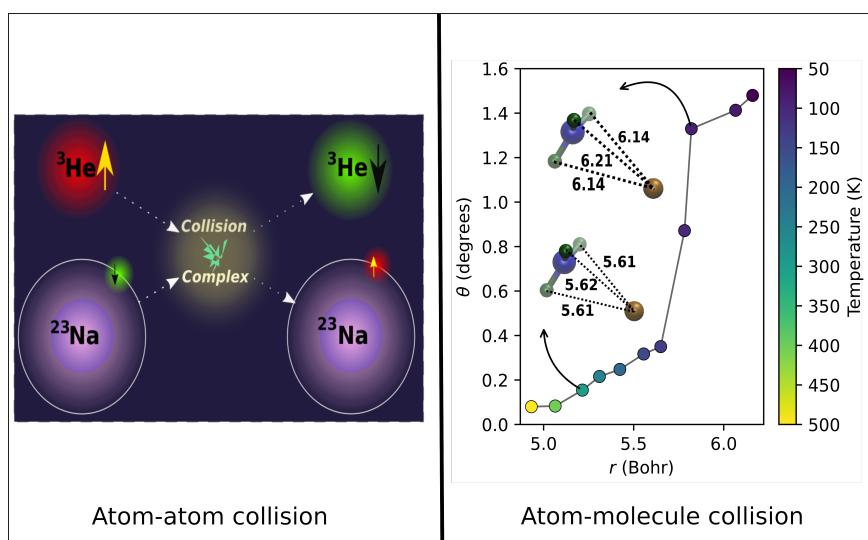
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Semiclassical Spin Exchange via Temperature-Dependent Transition States

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Spin-exchange collisions have been widely studied in recent years, and various quantum-mechanical scattering approaches have been developed to calculate the rates. However, these methods based on global knowledge of wave functions can be computationally demanding, are limited to small systems, and do not offer a mechanistic interpretation. Here, we present a semiclassical transition-state theory (SCTST) derived from first principles to describe the nonadiabatic transition between two states that differ only in their spins, where classical TST and Landau-Zener theory fail. We apply our theory to describe the spin-exchange collision between the nuclear spin of ^3He and the electronic spin of ^{23}Na . SCTST reveals that the reaction proceeds via temperature-dependent transition states, determined by an intricate compromise between minimizing the activation energy and maximizing the hyperfine coupling. It further demonstrates the importance of quantum delocalization effects prevalent in spin exchange even when tunneling is suppressed and successfully explains the observed weak temperature dependence of the rate. Finally, we showcase the power of SCTST by making predictions for the $^3\text{He} + \text{CH}_3$ spin-exchange collision in full dimensionality, where we find that the internal degrees of freedom induce symmetry-broken transition states



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Beyond Just Reactions: The Strategic and Mechanistic Elements of AI-Driven Total Synthesis

X. N. Nguyen¹, D. P. Armstrong¹, O. Susany¹, M. Wehrbach¹, A. M. Bran^{1,2}, Z. Jončev^{1,2}

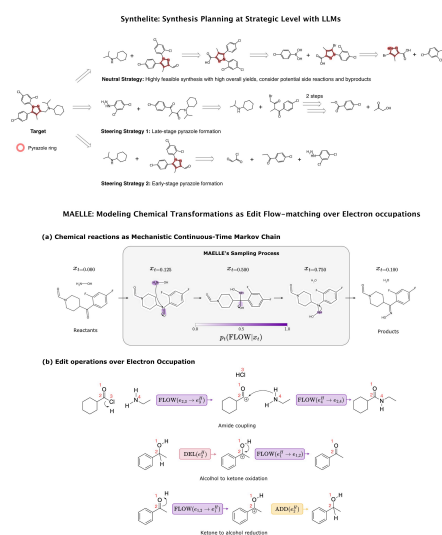
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The total synthesis of complex natural products remains the holy grail of computer-aided synthesis planning (CASP), yet no contemporary method can reliably tackle molecules at this level of complexity. We argue that progress requires advances on two fronts: strategic route planning at the macro level, and mechanistic reasoning at the micro level. In this talk, we present two recent works that target these complementary axes.

At the macro level, expert chemists rarely think one reaction at a time - they commit to an overall disconnection strategy before delving into individual steps. We introduce **Synthelite**, a framework that uses Large Language Models (LLMs) to plan multi-step retrosyntheses with a coherent strategy laid out from the outset, enabling exploration in the *strategy space* rather than the reaction space and naturally accommodating chemical feasibility and expert constraints through natural-language prompting. As a stress test on real-world complexity, we apply Synthelite to the Merck compound challenge 2026 and showcase how routes planned by Synthelite largely resemble those by human experts.

At the micro level, LLMs excel at high-level planning but stumble on the symbolic manipulation of molecules - precisely where chemists rely on arrow-pushing to reason their way through unfamiliar transformations. We introduce **MAELLE**, which models reactions as discrete flow matching over electron occupations on the molecular graph, learning mechanism-like trajectories without elementary-step supervision. MAELLE matches state-of-the-art accuracy on USPTO-480K, generalizes substantially better out-of-distribution, and recovers plausible side products as a natural consequence of generative sampling.

Together, Synthelite and MAELLE sketch a path toward CASP systems that plan like chemists at both scales.



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Modelling Quantum-Controlled Molecular Collisions of N_2^+ ions with He atoms

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The molecular ion N_2^+ plays a central role in both atmospheric and cold ion–neutral chemistry[1, 2]. In cold and ultracold environments, helium (He) acts as a buffer gas to cool N_2^+ via elastic and inelastic collisions, controlling both translational and internal quantum states. Our group has recently demonstrated full quantum-state preparation and non-destructive quantum-logic spectroscopy of single trapped N_2^+ ions [3]. These advances open the door to probing molecular ion–neutral collisions at the single-particle level with exceptional sensitivity and state resolution. Leveraging this new experimental capability, we investigate the state-dependent collisional dynamics of N_2^+ with He under precisely controlled conditions.

At low collision energies, only non-reactive scattering is expected in the N_2^+ –He system, although rotational state-changing collisions may occur. To characterize these processes, we computed the N_2^+ potential energy surface (PES) at the UCCSD(T)/aug-cc-pVQZ level using MOLPRO, and subsequently constructed a three-dimensional N_2^+ –He PES via Reproducing Kernel Hilbert Space (RKHS) [4] interpolation. The potential well depth of this system is approximately 180 cm^{-1} . All bound ro-vibrational levels of the complex were calculated, including detailed analyses of para- and ortho- N_2^+ states via wavefunction characterization.

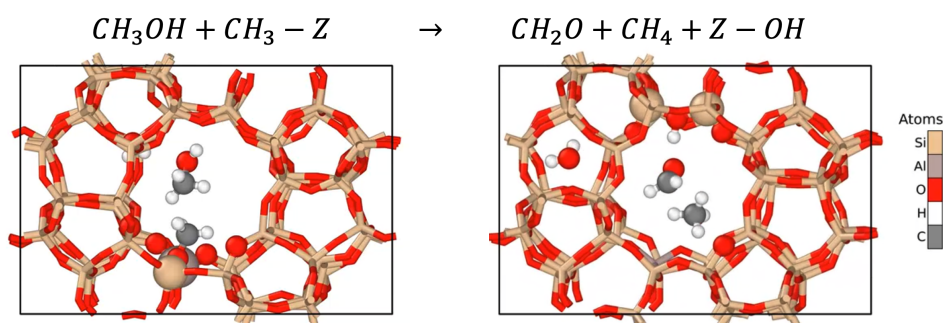
Quasi-classical trajectory (QCT) and full quantum dynamical (QD) calculations were performed to obtain final rotational (j) distributions for ortho- and para- N_2^+ , as well as the ratios of elastic to inelastic scattering events and the corresponding cross sections. In parallel, ongoing experiments are measuring the inelastic-to-elastic scattering ratio, providing key benchmarks for theoretical predictions.

Overall, this work provides a high-fidelity description of N_2^+ –He interactions and establishes a robust theoretical framework for understanding and ultimately controlling cold ion–neutral collisions, with implications quantum-controlled collision dynamics.

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Atomistic modelling of formaldehyde formation in zeolites: intrinsic kinetics and the role of extra-framework aluminium Lewis acid sitesL. Pesce¹, D. Polino^{1*}¹University of Applied Sciences and Arts of Southern Switzerland

Formaldehyde (CH₂O) is increasingly recognized as a key intermediate in the early stages of the methanol-to-olefins (MtO) process,[1,2] where it may contribute to the formation of dienes, aromatics, and polyaromatic coke precursors. However, the elementary origin of CH₂O formation in zeolite catalysts remains debated,[1,3] because experimentally inferred apparent barriers can differ substantially from computed intrinsic barriers. In this work, we investigate CH₂O formation from methanol and dimethyl ether in acidic zeolites using atomistic simulations based on machine-learning-potential molecular dynamics and infrequent metadynamics. First-event-time statistics were used to extract intrinsic rate constants for CH₂O-forming events in H-ZSM-5 and H-SSZ-13. The simulations show near-Poisson reactive-event statistics and indicate that CH₂O formation is intrinsically highly activated in both MFI and CHA frameworks, with computed free-energy barriers at 743 K in the range of ca. 193–203 kJ mol⁻¹. These results support an interpretation in which the elementary CH₂O-forming step is much more activated than low apparent experimental barriers would suggest, while apparent kinetics are additionally affected by coverage, site density, and reaction-network effects.

CH₂O formation from methanol

Building on this validated kinetic workflow, the poster will present new simulations aimed at quantifying how extra-framework aluminium species modify CH₂O formation. In particular, we will compare Brønsted-acid-site-mediated pathways with pathways occurring in the presence of Lewis acid sites associated with extra-framework Al. These sites may alter methanol/DME adsorption, methoxy stabilization, hydride-transfer propensity, and the relative accessibility of concerted versus sequential CH₂O-forming mechanisms. By extending the atomistic models to extra-framework Al-containing zeolites, we aim to determine whether Lewis acidity can lower the intrinsic barrier, change the preferred reaction channel, or modify the apparent CH₂O-formation kinetics through altered reactant stabilization and local confinement. The resulting comparison between framework topology, acid-site type, and reactive environment will provide molecular-level insight into how aluminium speciation controls formaldehyde formation, hydrocarbon-pool initiation, and ultimately catalyst selectivity and deactivation in MtO chemistry.

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Assessing Chemical Product Design: From Autonomous Quantum Reaction Discovery to Cheminformatics Applications

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Autonomous explorations of quantum chemical reaction networks (CRNs) have emerged as a powerful strategy for modeling and predicting the reactivity of complex chemical systems.[1] With the rapid development of fast quantum chemistry (QC)-based methods such as extended tight-binding approaches (xTB) and machine-learning interatomic potentials (MLIPs), numerous applications have become possible, enabling the characterization of experimentally inaccessible chemical space. One such field is the prediction of reactions between ozone and the many functional groups present in natural organic matter and aquatic pollutants—important processes in oxidative (waste)water treatment—which can give rise to potentially toxic disinfection transformation by-products.[2] Because these reaction networks are too complex to be completely surveyed and evaluated experimentally, the development of a comprehensive description of the chemical processes involved through QC-based CRNs is of great practical relevance.

In our current work, we have addressed three specific objectives for QC-based CRNs of ozonation reactions: (i) identifying an appropriate computational approach for describing the complex reactivity of ozone, balancing high chemical accuracy with low-to-moderate computational cost so as not to compromise the breadth and depth of the reaction network explorations; (ii) generating comprehensive reaction networks of ozone with selected organic moieties and reproducing experimental findings, including reaction mechanism elucidation and microkinetic modeling;[3] and (iii) developing an interoperable software tool for visualizing CRNs as standalone HTML files and interfacing them with cheminformatics and machine-learning applications, including, for example, structural queries to public databases such as PubChem and the conversion of QC-derived structures into string-based chemical representations.[4] Our work demonstrates the significant potential of automated QC-CRN explorations to identify previously unknown reaction pathways and highlights the utility of these data in addressing current product design challenges in oxidative water chemistry.

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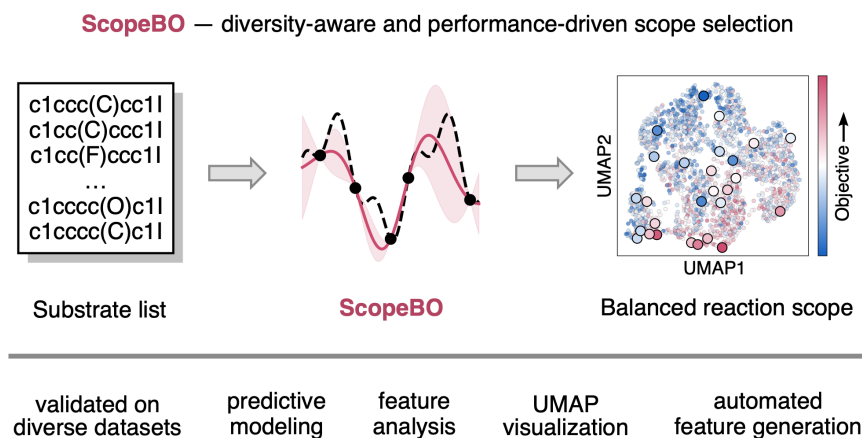
Machine Learning-Guided Scope Selection to Balance Performance and Substrate SimilarityS. Roediger¹, M. S. Sigman^{2*}, A. G. Doyle^{1*}

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The determination of a reaction substrate scope enables downstream users to decide whether the reaction in question is suitable for their envisioned application. The information content of the scope, as demonstrated by its performance and diversity, is crucial to inform the quality of this decision. However, scopes are so far only evaluated subjectively, leading to a well-documented selection bias towards high performing substrates at the cost of the scope diversity.[1]

Herein, we report a broadly applicable and easy to use machine learning algorithm, ScopeBO, for the selection of scopes that balances these two scope aspects.[2] We establish a scope score that for the first time allows to quantify scope quality. The hyperparameters of ScopeBO are optimized using this metric, and its performance is validated with several reaction datasets, demonstrating statistically significantly improved performance against that of alternative selection methods.

Through this quantitative optimization, ScopeBO provides an approach towards objective and standardized scope selection that maximizes the information content of the evaluated substrates.



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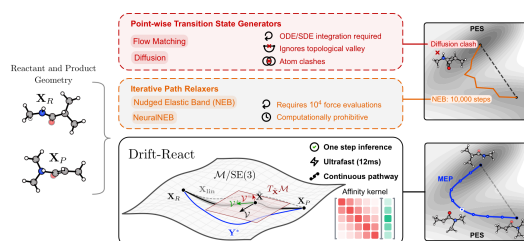
Drift-React: One-step Generation of Reaction Pathways via SE(3) Drifting Fields

R. Schlama^{1,2}, P. Schwaller^{1,2*}

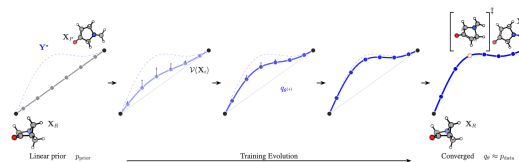
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Mapping reaction pathways is computationally expensive. Current generative models accelerate transition state (TS) prediction but rely on slow iterative inference and miss continuous trajectories. We introduce Drift-React, an SE(3)-equivariant framework predicting complete reaction pathways in a single forward pass. Using a Sinkhorn-weighted drifting field, Drift-React bypasses iterative force evaluations and ODE/SDE integration entirely. On Transition1x and Halo8, it generates physically consistent pathways and matches state-of-the-art TS accuracy with orders-of-magnitude acceleration, unlocking high-throughput reaction network exploration.

The computational exploration of complex chemical reaction networks is fundamentally limited by the cost of mapping minimum energy pathways (MEPs). While traditional *ab initio* chain-of-states methods like Nudged Elastic Band (NEB) are prohibitively expensive for large-scale screening, recent machine-learning alternatives often fall into two traps: they either predict isolated transition states, discarding crucial mechanistic context about intermediates, or they rely on slow, iterative integration loops. Drift-React introduces a paradigm shift in how we approach generative chemistry. By amortizing the iterative trajectory evolution entirely into the training phase via an SE(3)-equivariant drifting field, our framework generates the complete, physically contiguous reaction pathway in a single forward pass. This approach provides a direct, non-iterative bridge from reactants to products, offering chemists immediate structural insight into competing mechanisms and activation barriers.



Crucially, we demonstrate that single-step pathway generation does not require sacrificing physical or geometric fidelity. Across both standard organic reactions and complex halogenated chemistry, Drift-React achieves state-of-the-art geometric accuracy, returning sub-Ångström transition state alignments (TS-RMSD down to 0.107 Å) while rigorously avoiding unphysical atomic clashes. It accomplishes this in approximately 15 milliseconds per reaction. By jointly occupying the speed-optimal frontier for both point-wise TS prediction and continuous pathway generation, Drift-React offers a three-to-four orders of magnitude acceleration over classical and surrogate-force-field baselines. This breakthrough unlocks the ability to routinely and autonomously screen highly complex catalytic cycles and reaction networks at a fraction of the traditional computational cost.



A Framework for Predictive ML Modelling of Cross-Linked Polymers at Industrial Scale: Learning With Incomplete Chemical Representations

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¹DCL, D-CHAB, ETH Zurich, ²Huntsman Advanced Materials (Switzerland) GmbH

The development of novel thermoset materials is crucial to meet growing demand for aerospace, electronics and energy applications. However, development of novel polymers is often associated with a long and costly trial-and-error process. AI-assisted polymer design offers a promising alternative by providing a framework for a more efficient and data-driven methodology for the development of advanced materials [1].

Current thermoset predictive models are often targeted towards pure, simple, monodisperse substances [2]. In industrial settings, these assumptions are rarely applicable since researchers are confronted with heterogeneous chemical systems. Formulation mixtures and polydisperse substances are typically required to solve complex material science problems. In this work, we evaluate different strategies to build an epoxy amine predictive model which can support blends of chemical substances and non-well characterized substances (UVCB, polymers).

An emphasis is put on experimental data quality by having results from certified test methods and detailed product compositions. This focus reflects the centrality of sufficient data volume and quality to achieve discovery and design of functional polymers [3]. The key objective is to characterize epoxy-amine thermosets according to their thermomechanical properties (including glass transition temperature, tensile properties, flexural properties, and fracture toughness), using composition and processing data.

Using this high-quality dataset, this study compares various chemical (including conventional cheminformatics and DFT-derived descriptors) and UVCB representations, formulation aggregation methods, and regression algorithms to identify a robust final modelling configuration and evaluate the benefits and trade-offs associated with each approach. The resulting models achieve R^2 values of around 0.9 for glass transition temperature and 0.7 for tensile properties. The broader goal is to establish a practical and experimentally focused recommendation to use machine learning modelling in thermosetting polymer research.

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Understanding the boundaries of universal machine learning potentials for organic photochemistryH. Seng¹, H. Zhang¹, K. Jorner^{1*}¹Institute for Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zürich

Universal machine-learning interatomic potentials (uMLIPs) offer near-DFT-quality energetics at a fraction of the computational cost. If trained to learn molecular energy as a function of structure, total charge and total spin, uMLIPs are potentially applicable to model processes relevant to triplet-driven organic photochemistry.

Their reliability beyond closed shell singlet states, however, remains unclear, particularly for open-shell singlet (OSS) states, where the DFT reference data, as for OMOL25¹, includes unrestricted, broken-symmetry DFT with potential for spin contamination.

We quantitatively benchmark charge- and spin-aware uMLIPs, including UMA-OMOL², MACE-OMOL³, MACE-POLAR-1⁴, OrbMol⁵, and AIMNet2-NSE⁶, against DFT reference energies for key photochemical quantities: triplet potential energy surfaces, triplet-state reaction energetics, vertical and adiabatic singlet–triplet gaps, and full reaction profiles on both singlet and triplet surfaces. For open-shell singlet pathways, we analyze closed-shell to open-shell transitions to determine where uMLIPs reproduce DFT behavior and where they fail.

While the reliability of triplet state energies varies across different uMLIPS, we identify several shared error modes linked to significant outliers. For energy predictions in OSS regimes, individual uMLIPs show unpredictable behavior, partially extrapolating either restricted or unrestricted DFT energies. We further explore the utility of spin populations, derived from AIMNet2-NSE and MACE-POLAR-1 models, to flag outlier energies and classify the behavior of OSS predictions.

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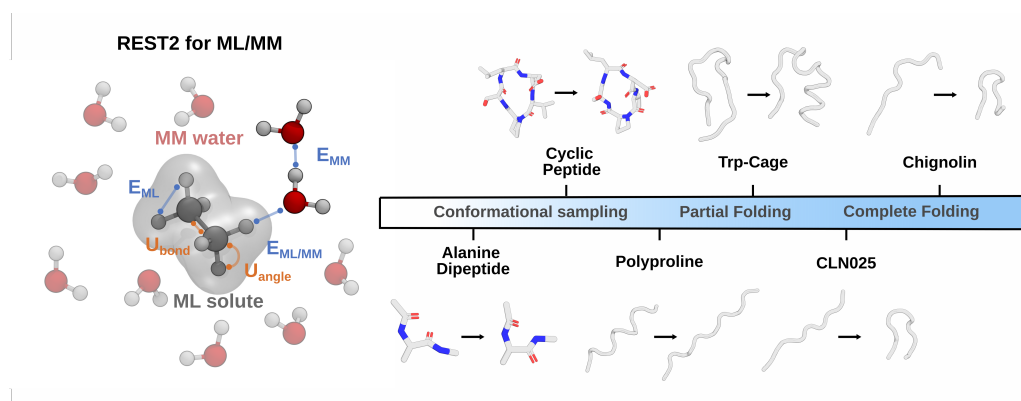
[6] Bhupalee Kalita et al. *chemrxiv-2025-kdg6n-v2* **2025**

Quantum-Accurate Enhanced Sampling and Mini-Protein Folding through Replica Exchange for Multiscale Neural Network Potentials

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Neural network potentials (NNPs) have emerged as efficient alternatives to computationally demanding quantum-mechanical (QM) methods, enabling simulations with near-quantum accuracy at significantly reduced cost. AMPv3-BMS25 (AMP-BMS) is an equivariant NNP designed for multiscale ML/MM simulations that accurately captures directional and long-range interactions^{1,2}. In classical molecular dynamics (MD), enhanced-sampling techniques are essential for overcoming large energy barriers and improving convergence. Among these, replica exchange with solute scaling (REST2) is particularly efficient, as it selectively scales solute interactions while maintaining a constant bath temperature, thereby reducing the number of required replicas³. Here, we introduce a REST2-like algorithm specifically tailored for multiscale ML/MM simulations. By exploiting the separability of the AMP-BMS Hamiltonian into solute-solute, solute-solvent, and solvent-solvent contributions, the method enables efficient and controlled scaling of interactions within the ML/MM framework. We validate the REST2-AMP approach on several peptide systems in explicit solvent, demonstrating improved conformational sampling and enhanced exploration of configurational space. Notably, we achieve successful folding of the mini-proteins chignolin and CLN025 from extended conformations without predefined reaction coordinates. Therefore, our approach enables access to biologically relevant timescales while maintaining near-DFT accuracy, providing a general framework for high-accuracy biomolecular simulations.



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Rooted fingerprints as a robust baseline for site-selectivity predictionG. Sulpizio^{1,2}, K. Jorner^{1,2}¹Institute of Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zurich, Zurich CH-8093, Switzerland, ²NCCR Catalysis, Switzerland

Site-selectivity prediction is central to modern reaction modeling, and machine learning approaches are increasingly proposed as fast and accurate alternatives to heavier and more reliable quantum mechanical methods such as density functional theory [1]. As more complex models enter the field, robust and standardized baselines are needed to assess whether added complexity translates into real performance gains. Reaction-based fingerprints such as difference fingerprints and DRFP [2] are the de facto baselines, but they require constructing full reaction SMILES from predefined templates and can degrade sharply on out-of-distribution data.

In this work, we propose using rooted fingerprints as a more robust, simple, and template-free baseline that encodes only the local environment around each reactive atom. We evaluate various fingerprint variants on three site-selectivity datasets (bromination [3], thianthrenation [4], and borylation [5]) and benchmark them against difference fingerprints and DRFP, as well as the more complex RegioML [3] and T5Chem [5] models, under in-distribution, pooled, and out-of-distribution (unseen reaction class) splits. We find that while difference fingerprints and the more complex models match or outperform rooted fingerprints on in-distribution data, they largely underperform on out-of-distribution data. We attribute this performance gap to the nature of rooted fingerprints: they represent an atom in its immediate environment rather than a full reaction, making them less dependent on reaction-class-specific patterns. Rooted fingerprints could thus serve as a standardized baseline for assessing genuine model performance in site-selectivity prediction.

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Li-Promotion in Rh-based CO₂ Hydrogenation Catalysts to Ethanol

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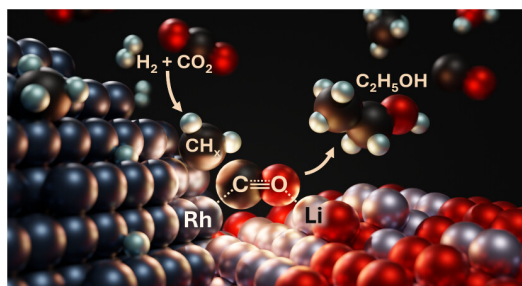
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The catalytic conversion of CO₂ into ethanol is a promising route toward sustainable carbon utilization. While conventional Rh@SiO₂ catalysts are highly selective toward methane, lithium promotion has been shown experimentally to decrease methanation and enhance ethanol formation. However, the origin of this promotional effect remains unclear. In this work, density functional theory (DFT) calculations combined with ab initio molecular dynamics and metadynamics simulations were used to investigate the electronic and catalytic properties of RhLi₂O interfaces. Simulations reveal that Li₂O partially wets the Rh nanoparticle surface, generating a high density of Rh–O–Li interfacial sites. These sites strongly stabilize CO and CO₂ adsorption and reproduce the characteristic low-frequency CO stretching band observed experimentally by in situ DRIFTS.

Projected density of states (PDOS) analyses show a significant modification of the electronic structure of adsorbed CO at the interface. In particular, the CO 2π* antibonding orbital shifts toward lower energies and becomes partially occupied through enhanced metal-to-CO π-backdonation. This increased activation weakens the C–O bond and promotes the electrophilic character of the adsorbed carbon atom.

Reaction-path calculations further demonstrate that these electronic effects directly impact catalytic reactivity. The activation barrier for CH_x + CO coupling decreases at the RhLi₂O interface, while methanation becomes less favorable.

These results establish a direct connection between local electronic structure, molecular activation, and catalytic selectivity, highlighting the Rh–CO–Li interfacial motif as a key descriptor governing ethanol formation in lithium-promoted Rh catalysts.



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[1] C. Hansen, N. Tavernier, M. Wiedmaier, P. M. Abdala, C. Müller, M. Iannuzzi, C. Copéret, *J. Am. Chem. Soc.*, **2026**, 148, 15, 16412–16421

From an AI-Generated NaV1.8 Inhibitor to Commercially Accessible Molecules: Bridging Generative Design and Ultra-Large Chemical Spaces

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The emergence of generative artificial intelligence has enabled the rapid creation of novel molecular concepts for challenging therapeutic targets. However, a major limitation of many AI-generated molecules remains their uncertain synthetic accessibility and the difficulty of translating virtual designs into compounds that can be experimentally tested. Bridging this gap between molecular generation and practical chemistry has become a critical challenge in modern computational drug discovery.

Here, we present a workflow that combines generative molecular design with Pharos3D, a pharmacophore- and shape-based virtual screening technology operating directly on ultra-large combinatorial spaces containing tens of trillions of commercially accessible molecules. As a representative case study, we investigated the voltage-gated sodium channel NaV1.8, a clinically validated target for the treatment of pain and the target of the recently approved drug Suzetrigine.

Starting from an AI-generated NaV1.8 inhibitor concept, a three-dimensional pharmacophore model was derived and used as a query for Pharos3D searches across multiple ultra-large supplier spaces. The search identified numerous commercially accessible compounds preserving the essential three-dimensional recognition pattern of the AI-designed molecule while simultaneously introducing structural diversity and improved synthetic feasibility. Candidate molecules were ranked using combined pharmacophore and shape similarity metrics and analyzed with respect to scaffold diversity and supplier availability.

The results demonstrate how generative AI and ultra-large chemical spaces can be combined into a practical discovery workflow. Rather than viewing AI-generated structures as final solutions, they can serve as three-dimensional design hypotheses that guide the identification of experimentally accessible novel chemical entities. This approach establishes an efficient route from virtual molecular concepts to purchasable compounds and highlights the growing synergy between artificial intelligence, structural biology, and large-scale computational chemistry in modern drug discovery.