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Chemistry Hacks: Tweaking Air Composition to Tackle Respiratory Virus Transmission

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In recent years the world has come to realize that airborne viruses are a force to be reckoned with. Non-pharmaceutical interventions, such as ventilation, moderate virus transmission by physically removing viruses from air. Alternatively, transmission may be reduced by inactivating viruses in air. This latter approach, however, is hampered by an incomplete understanding of the parameters that modulate airborne virus infectivity. In this presentation I will illustrate how we can use our knowledge of chemistry, virology and aerosol science to reduce the airborne infectious viral load and thereby mitigate airborne virus spread.

During transmission, infected hosts exhale viruses embedded in droplets of respiratory fluid of varying size. These viruses must pass through the environment before encountering and infecting a new host. Whether suspended in the air or lingering on surfaces, this environmental passage exposes viruses to a multitude of stressors that challenge their infectivity. We have combined experimental and biophysical modelling approaches to investigate the main environmental drivers of respiratory virus inactivation during airborne transmission. We focus on influenza virus, which has caused major pandemics in the past, and will likely continue to do so in the future. We demonstrate that droplets exhaled in indoor air will acidify to $pH < 4$ [1], a pH that causes influenza virus to lose its ability to infect host cells [2]. This process, however, is only efficient in very small droplets of few µm in size. In larger droplets, where acidification is slow, inactivation is instead governed by supersaturated salt concentrations that establish in droplets due to water evaporation and that compromise the integrity of the viral capsid [3]. Based on these insights we suggest simple strategies to manipulate the indoor air environment to maximize the virus' exposure to environmental stressors, such that the infectious viral load is reduced before a new host is reached.

Our work demonstrates the pivotal role of an interdisciplinary approach in comprehending airborne virus transmission and managing future pandemics.

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Effect of surfactants on inactivation of Bacillus subtilis spores by chlorine

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In low- and middle-income countries where healthcare facilities and schools are not connected to functional water supply systems, stand-alone handwashing systems provide a solution to safely recycle and reuse handwashing water. These handwashing systems use a two-step treatment, ultrafiltration followed by chlorine disinfection. Surfactants introduced into handwashing water from the use of soaps can interfere with the chlorine disinfection process. We investigated the synergistic effect between surfactants and chlorine on the inactivation kinetics of *Bacillus subtilis* spores using two surfactants, cocamidopropyl betaine (CAPB) and cetyltrimethylammonium chloride (CTMA). Compared to chlorine disinfection, the concurrent presence of chlorine and surfactants resulted in a moderate reduction in the lag-phases in spore inactivation but did not lead to an increase in the second-order inactivation rate constants. In contrast, when the spores were pre-exposed to either CAPB or CTMA, the lag-phases decreased by about 45% or 51% and the second-order inactivation rate constants during post-chlorination increased by factors of 1.7 or 3.2, respectively, compared to the concurrent application. The observed synergistic effect suggests that surfactants could potentially enhance the permeability of the coat which is the outmost layer of *B. subtilis* spores and a primary barrier for chemical disinfectants. A group of *B. subtilis* spores with a sequential treatment of surfactant and post-chlorination, showed a significant decrease in surface stiffness before chlorination, indicating alterations in the coat by surfactants. Furthermore, CTMA was found to inactivate *B. subtilis* spores but through mechanisms different from chlorine. Chlorine primarily inactivated *B. subtilis* spores before damaging the inner membrane of spores which plays a crucial role in protecting genetic materials stored in the core of spores. In comparison, CTMA damaged 22% of the inner membrane while the inactivation efficiency was 99%. A synergistic effect in damaging the inner membrane was observed when applying CTMA and chlorine simultaneously instead of sequentially.

In search of alternative herbicides to treat Swiss railway tracks

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Weeds can have detrimental effects on the railway infrastructure. This mainly through the accumulation of humus, which can increase water retention and may damage both sleepers and rails, as well as the overall stability of the ground. Ultimately, these factors can result in track deformation, which directly influences the speed at which trains are able to travel.

In Switzerland, herbicides are predominantly utilized for weed control, although alternative methods such as mechanical and thermal techniques are also employed. Currently, glyphosate is the only herbicide used to remove weeds from railway tracks, which has proven to be relatively effective. However, uncertainties concerning the renewal of authorisations of the substance in Europe have prompted railway companies to explore alternative herbicides that may replace glyphosate. Due to the inherent permeability of railway tracks and therefore increased net infiltration, it is important to choose herbicides with a low risk of leaching to groundwater. The characteristics of a suitable herbicide include thus a high sorption in the soil and/or rapid degradation (also for metabolites), as well as low application rates.

In order to help decision-makers to make informed decisions, we constructed ten lysimeters with railway materials from three locations, allowing us to study the leaching behaviour of herbicides in close-to-real conditions. Using liquid chromatography–mass spectrometry, we investigate the leaching potential of 12 alternative herbicides and their main metabolites. The selected group of alternative herbicides includes six auxin-mimics, three acetolactate synthase inhibitors, as well as three pigment-synthesis inhibitors.

One a year after the first application of the substances in May 2023, we observe that leaching is influenced by both the lysimeter soil properties and the herbicides used. While some of the herbicides have already reached their maximum concentrations under all soil conditions, some have not been detected yet. These undetected herbicides may have degraded completely or may still elute later. The project will continue for at least 2 years (from the time of the first application) and will allow us to conclude on the leaching potential of the applied substances and their metabolites under realistic conditions. Moreover, the project will allow a direct comparison of all applied substances under identical weather conditions in 3 different soil types.

Mining Actinomycetes' Metabolomes and Genomes for Anti-*Phytophthora infestans* Compounds

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Actinomycetes are well-known for their capacity to produce a wide array of specialized metabolites exhibiting diverse bioactivities. In a previous work, we examined a collection of 175 actinomycetes strains isolated from various Sudanese soils for their inhibitory activity against *P. infestans*, the causal agent of late blight disease in potato and tomato. A significant proportion of these strains demonstrated considerable inhibition or alteration of *P. infestans* mycelial growth. Considering the diverse inhibitory effects and morphological alterations induced by the strains, we aimed to identify the active metabolites responsible for these effects through a comparative metabolomic approach. To achieve this, we selected 63 strains displaying varying degrees of antagonistic activity against *P. infestans* and extracted their metabolites using ethyl acetate. Subsequent analysis via liquid chromatography coupled with mass spectrometry and spectral network analysis of our extracts revealed several compounds potentially active against *P. infestans*. These compounds, which were detected in active extracts but absent in inactive ones, included borrelidin, albonoursin, oxopropaline G, lansai A/C, actinomycin D, annimycin, antibiotic A 83586C, louisianin D, antimycin, collinomycin, among others. Furthermore, our analysis suggested that actinomycete surfactins, angucyclines, phenazines, and other compounds may be responsible for altering *P. infestans* morphology. The annotation of some of these compounds was validated by comparing them to purchased standards or by detecting the relevant biosynthetic gene clusters in the strains' genomes via antiSMASH analysis. This study provides a list of candidate compounds with potential as inhibitory agents against *P. infestans* and hints at broader applications against other plant pathogens.

Organic micropollutants in combined sewer overflows challenge sustainable water management

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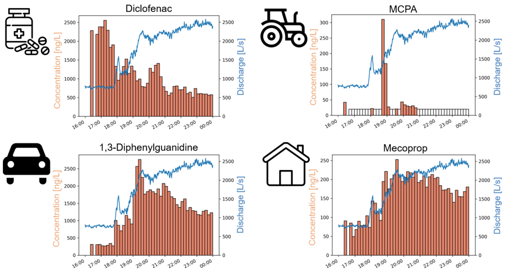
During heavy rainfalls, the capacity of sewer systems and wastewater treatment plants (WWTPs) is exceeded, resulting in the discharge of untreated combined sewage – comprising both raw wastewater and stormwater runoff – into open water bodies through combined sewer overflows (CSOs). CSOs are an important pathway of organic micropollutants (MPs) from urban areas into open water bodies posing risks to aquatic ecosystems and human health [1]. They can carry a wide spectrum of organic MPs, including pharmaceuticals, artificial sweeteners, and indoor biocides introduced through raw wastewater as well as plant protection products, biocides, and tire wear leachates in stormwater runoff. While WWTPs are increasingly upgraded to remove these organic MPs, there is no treatment in CSOs. The vast number of CSOs, 42'000 inlets (stormwater outlets + CSOs) in Switzerland alone, makes treatment efforts difficult. Moreover, the frequency and duration of CSO events are expected to rise with climate change due to more frequent heavy rainfall events.

Previous studies on organic MPs in CSOs often focused on a limited set of substances and primarily reported event mean concentrations [2]. We have collected an extensive dataset encompassing a wide range of organic MPs (65 substances) from various sources (indoor, road, pesticides) and at high temporal resolution (10 minutes) in two catchments. This dataset allows us to better understand the sources and dynamics of these pollutants, crucial for more realistic risk assessments and ultimately supporting the design of effective mitigation measures. Additionally, we conducted a nontarget analysis to expand the range of substances and linked the time series to specific sources, providing a more comprehensive view of the pollutants present in CSOs.



Our observations reveal a wide range of different dynamics, where substances from indoor in the large catchment and tire wear leachates in both catchments show source-specific patterns. Indoor substances in the small catchment and pesticides in both catchments show strong and random fluctuations. Furthermore, the source allocation of nontarget time series reveals several thousand indoor substances and a few hundred substances from the storm runoff not included in our initial target list. Thus, the huge number of present organic MPs and their vast variety of dynamics make the formulation of effective mitigation strategies, as for example first flush retention, challenging.

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Preserving the Biotransformation Potential of Activated Sludge in Time: Towards Reproducible Incubation Experiments for Persistence Assessment

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Micropollutants pose a growing environmental concern due to their widespread presence, (pseudo-)persistence, and potential ecotoxicological effects[1,2,3]. Environmental persistence, as one potential key hazard, is typically assessed using OECD-type simulation studies for environmental compartments such as water, soil and sediments. Biotransformation assays conducted in activated sludge from wastewater treatment plants offer various benefits over soil and sediments, as activated sludge is easily handled and readily available. Additionally, the high microbial density and comparably high bioavailability of the chemicals enables a short experimental duration of 72 hours. Most importantly, however, rate constants determined in activated sludge experiments have been shown to be reasonably predictive of soil half-lives[4]. These points suggest that conducting biotransformation experiments with activated sludge could serve as a valuable foundation for developing high-throughput persistence tests used for screening purposes, e.g., in a benign-by-design framework. One challenge in using such screening tests in activated sludge though is their potentially limited reproducibility due to inocula diversity[5,6]. In this study, we developed protocols for the preservation of activated sludge microbial communities using lyophilization or cryopreservation. Their performance in preserving the biotransformation potential of the activated sludge was evaluated on forty representative micropollutants in 72-hours, lab-scale batch assays, with fresh activated sludge as reference. Lyophilization was the least representative preservation method, with over 85 % of micropollutants showing significantly slower or faster biotransformation compared to fresh activated sludge. Cryopreservation using either DMSO or glycerol was more effective with only about 40 % of micropollutants exhibiting significantly different biotransformation kinetics compared to the fresh activated sludge. We also explored the impact of storage time (two weeks vs. four month) as well as the effect of using artificial supernatant instead of preserved native supernatant. We examined shifts in community composition based on amplicon sequencing data. Our results indicate that cryopreservation can effectively preserve the biotransformation potential of activated sludge, improving long-term reproducibility in persistence assessments. This enhances reliability for regulatory hazard assessments and biotransformation screening in the design of novel chemicals.

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Environmental chemistry for a sustainable future

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The future trajectory of the chemical industry is intricately linked to its environmental responsibility and efforts to fight global warming. The chemicals industry has a vital role to play in the global to reach net zero targets by lowering its emissions and assisting other industries in doing the same. Within this context, companies such as Casale are actively exploring novel eco-friendly technologies for the transition to a more sustainable future, ensuring that economic development and environmental preservation go hand in hand.

As part of its commitment to addressing ecological challenges, Casale prioritizes sustainable approaches in plant design. This includes the incorporation of green and blue technologies aimed at minimizing environmental impact and advancing towards a more sustainable future. Casale has notably developed an innovative green ammonia process and accompanying tools aimed at reducing the levelized cost of green ammonia production.

Casale is dedicated to researching and developing innovative approaches to new processes, products, and applications to reduce greenhouse gases emissions and promote food security. In this contribution two examples of Casale'e commitment to environmental sustainability will be presented: 1) smart fertilizers and 2) the technology for NO_x and N_2O abatement for stationary applications.

1.) Innovative urea based slow-realease feritilizers can contribute to improve agriculture sustainability as they lead to higher agronomic yields and nitrogen efficiency, thus supporting sustainable food production and soil health. Smart fertilizers can control the release and availability of nutrients to fit at the best the plant demand over time, allowing lower nitrogen losses and minor environmental impact. Nowadays, smart feritilizers are paramount for soil preservation and for resources utilization.

2.) In nitric acid plants, the tail gases contains of NO_x and N_2O, a catalytic abatement system is required as NO_x are poisonous and N_2O is more than 300 times more polluting than carbon dioxide. Casale developed a technology to treat tail gases that achieves greater than 99% N_2O abatement with NO_x abatement. Fe-FER catalyst, a proprietary catalyst of CASALE and ALSYS, is used in nitric acid plants; field and laboratory results have shown that Fe-FER might allow customers to benefit from higher catalytic activity and greater stability than the current commercial solution. Research and development on both process and catalyst front are paramount to create synergy andachieve amore efficient process to minimize abatement costs. This advancements not only mitigates harmful emissions but also enhances the overall efficiency and environmental compatibility of industrial processes.

Through these initiatives, Casale exemplifies how the chemical industry can drive progress towards a more sustainable and resilient future.

Biochars from chlorine-rich feedstock are low in polychlorinated dibenzo-*p*-dioxins, -furans and -biphenyls

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Chlorinated aromatic pollutants like polychlorinated dibenzo-*p*-dioxins, -furans (PCDD/Fs) and -biphenyls (PCBs) are omnipresent in the environment due to historic production, use, and (unintended) release. Nowadays, their emission and maximum concentration in environmental compartments is strictly regulated. During biochar production, PCDD/Fs and PCBs may be formed and retained on the solid pyrolysis product. Industrial biochars certified, e.g., under the European Biochar Certificate (EBC), exhibit concentrations that are always well below threshold values for soil application and even animal feed. However, this is not sufficiently tested for chlorine-rich organic material such as marine biomass or polyvinyl chloride (PVC)-contaminated feedstock. To investigate PCDD/F and PCB contamination in biochars produced from chlorine-rich biomass, we analyzed biochars pyrolyzed at different temperatures from different feedstocks with comparatively high chlorine contents in the range from 0.2 to 3.8% (w/w, seaweed, two types of saltwater algae, tobacco stalks, and PVC-contaminated feedstock). All of the biochars produced showed PCDD/F and PCB contents well below the applicable threshold values given by the EBC (<20 ng TEQ kg^{-1} for PCDD/F and $<2x10^5$ ng TEQ kg^{-1} for PCB). No consistent correlation between biomass chlorine contents and contents of PCDD/Fs and PCBs were found (both mass based and toxicity adjusted concentrations), however, the lowest chlorine content in the feedstock led to the lowest PCDD/F+PCB content (7×10^{-3} ng TEQ kg^{-1}) and the second highest chlorine content led to the highest contamination of the respective biochar (11.2 ng TEQ kg^{-1}). Further, higher chlorine contents in the biomass led to a more diverse PCDD/F congener pattern in the biochars. Pyrolysis of PVC-amended feedstocks resulted in consistently higher contamination with PCDD/F and PCB in the biochars compared to the other biomasses, potentially due to differences in chlorine speciation in the feedstocks, i.e., chlorine in PVC is already covalently bound to an organic carbon backbone. A high contamination in PCDD/F and PCB in the feedstocks was shown to mainly be a result of insufficient separation of pyrolysis gas and biochar in the reactor due to deficient heating of the solids at the biochar separation stage. Our results indicate that biochars produced from chlorine-rich biomasses with standard biochar production process control are conform with European certification guidelines for PCDD/F and PCB contamination. The results open the opportunity to exploit and valorize so far non used marine or chlorine-contaminated biomass potentials for/as biochar materials and carbon sequestration.

Differentiating Olefins and Phenols using the Stable Oxygen Isotope Composition of H_2O_2 Formed during Ozonation

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Characterization of dissolved organic matter (DOM) regarding oxidant reactive moieties is crucial to understand its role in consuming chemical oxidants and forming disinfection byproducts (DBPs). Particularly, distinguishing between olefinic and phenolic moieties has remained challenging as both consume ozone rapidly and form similar carbonyl-type DBPs. In this study, we applied a novel approach to differentiate olefinic and phenolic compounds by determining the stable oxygen isotope composition of H_2O_2, formed during their ozonation. The $\delta^{18}O$ values of H_2O_2 for 13 model compounds (6 olefins and 7 phenols) were tested at pH 3 and 7 with a newly developed method. This method involved H_2O_2 transformation by HOCl to O_2 and measurement of $^{18}O/^{16}O$ ratios in O_2 by gas chromatography-isotope ratio mass spectrometry. Different pH-dependencies were observed: for olefins, the signature values were either comparable ($\Delta\delta^{18}O(H_2O_2)$ at pH 7 - pH 3 = 0.4 – 1.2‰ for buten-3-ol and cinnamic acid) or increased at the higher pH ($\Delta\delta^{18}O$ = 2.0 – 9.0‰ for acrylic acid, methacrylic acid, sorbic acid, and dichloroethene). In contrast, phenols showed decreased values at pH 7 relative to pH 3 ($\Delta\delta^{18}O$ = -1.6 – -14 ‰), with a linear correlation between $\delta^{18}O$ and Hammet constants of substituents (*p*-nitro, *p*-chloro, *p*-methyl, *p* -methoxy, *p*-hydroxyl, and *m*-hydroxyl). The O isotope fractionation, arising from the stronger bonding with ^{18}O than ^{16}O, resulted in reduced $\delta^{18}O$ levels at pH 3 for olefins due to organic peroxide formation and at pH 7 for phenols due to a non-Criegee-type mechanism. The different pH-dependent behavior for olefins and phenols opens up the possibility of utilizing the O isotope signatures of H_2O_2 for elucidating precursor moieties in DOM.

Indirect aquatic photolysis of polyethylene glycol influences the biodegradability in soil and sediment: Linking kinetic simulations to experimental observations

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Water-soluble polymers (WSPs) and water-dispersible polymers (WDPs) are an integral component of agricultural formulations. These polymers serve to ensure the efficacy of active ingredients, such as pesticides and fertilizers. Despite their widespread use and application to agricultural fields, the environmental fate of these polymers remains poorly studied and understood. Yet, understanding the environmental fate of WSPs and WDPs is key for assessing their impacts on ecosystem health, guiding the development of environmentally benign alternatives, and informing regulatory decision makers on policies and potential regulation. Polyethylene glycols (PEGs) are the predominant polymer class used in agricultural spray formulations in Germany and Swizerland. Upon application, PEGs may undergo an initial phase of photodegradation in the field, either directly on plant leaves or in adjacent ditches and puddles. This initial stage is driven by elevated concentrations of nitrate or dissolved organic matter (DOM) and exposure to sunlight, leading to high steady-state hydroxyl radical concentrations. These radicals react with the PEGs, resulting in the cleavage of the polymer chains. This photochemically induced chain cleavage may significantly influence the subsequent biodegradability of the polymer chains in soil. Due to its high mobility, PEG may also migrate from the soil into groundwater and subsequently re-enter other surface water systems. In these settings, a second stage of photodegradation may occur, where similar photochemical processes continue to modify the PEG molecules, further affecting their biodegradation in sediment environments. In this study, we modeled the indirect environmental photolysis kinetics of PEG over a molecular weight range of 3 kDa to 12 kDa, evaluating photodegradation under varied steady-state hydroxyl radical concentrations. We observed a strong exponential decay in the number average molecular weight for all molecular weights simulated. Monte Carlo simulations complemented these findings, indicating substantial persistence of initial polymer chains despite extensive photodegradation and formation of low molecular weight fragments. Additionally, UV/H2O2 degradation experiments using 13C-labeled PEG validated the simulation results, showing consistent degradation patterns across tested time points and confirming the resilience of high molecular weight chains. High-resolution mass spectrometry combined with 13C-NMR could provide further insights into the photodegradation mechanisms and indicate the formation of oxidized chains as intermediates. Incubations with the photodegraded 13C-PEG in soil and sediment revealed contrasting mineralization dynamics. In soil, unaltered PEG mineralizes very slowly, with less than 1% converting to 13CO2 in 80 days. However, photodegradation prior to biodegradation can increase this mineralization extent to up to 35% conversion in 80 days. In sediment, however, we observed very fast mineralization, with conversions reaching up to 80% to 13CO2 in 80 days. These results highlight significant department-specific differences in the degradation and mineralization behavior of PEG, highlighting the influence of photodegradation on the environmental fate and potential persistence of PEGs.

Extracellular Electron Transfer in *Geobacter Sulfurreducens*

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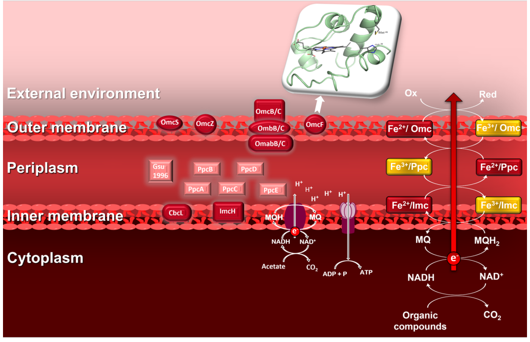
Geobacter sulfurreducens, renowned for its ability to reduce various metal ions through extracellular electron transfer (EET) mediated by cytochromes, remains a subject of intense investigation.[1][2] Previous kinetic studies indicated a constant respiration rate with inorganic salts,[1] prompting us to explore the potential of organic salts to enhance the electron transfer due to their different molecular interactions with the respiratory chain proteins compared to the other options of metal ion-cytochrome interactions.



Our investigation revealed that certain organic salts indeed exhibited higher respiration rates, aligning with our expectations. Some organic salts were identified as effective redox mediators between cytochromes and metal salts, resulting in a notable increase in the rate of metal salt reduction while reducing its associated toxicity.

This discovery not only expands our understanding of EET mechanisms in *G. sulfurreducens* but also presents a promising avenue for optimizing bacterial metal reduction processes through the strategic use of organic compounds as electron shuttles.

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Comparative Study of Chelating Agents in the Treatment of Heavy Metal Poisoning on Early Zebrafish Embryo Development

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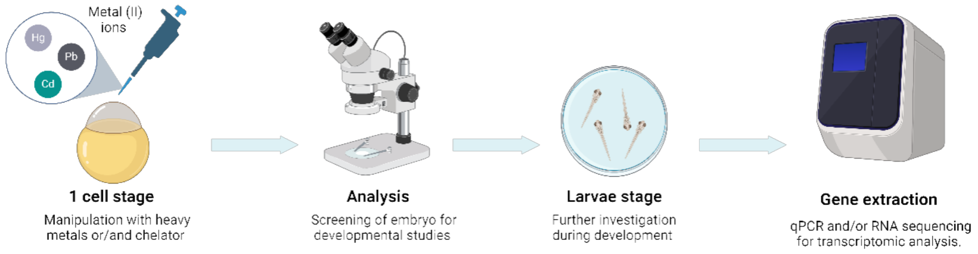
Heavy metals, such as mercury, lead, and cadmium, are known to be one of the most toxic and relevant species that concerns public health [1]. These metals have the tendency to access the central nervous system and accumulate in the kidney and liver, which in fact causes serious damage or fatality [2]. When higher concentrations are exceeded in the human body, the so-called chelation therapy is recommended, where traditional sulphur-based compounds such as alpha-lipoic acid (ALA), dimercaptosuccinic acid (DMSA), dimercatopropanesulfonic acid (DMPS), cysteine (L-CYS) and glutathione (L-GSH), are orally introduced in the body to chelate metal (II) [3]. Little is known for the most effective chelating agents to treat heavy metal poisoning. To investigate these compounds, we utilized the rapidly growing and experimentally traceable zebrafish, a model that has been widely used for toxicological studies. As first, we identified the lowest toxic concentration of the heavy metals for early-developing zebrafish embryo. As second, we compared different commercial and clinically approved chelating agents for efficient treatment. In our evaluation, the results suggest that (i) Pb can be tolerated at higher concentrations than Cd (II) (ii) DMSA, DMPS, cysteine and glutathione successfully rescue mercury-poisoned zebrafish embryo, while LA does not (iii) DMSA and DMPS rescue cadmium-poisoned zebrafish embryo, while LA, cysteine and glutathione do not (iv) qPCR analysis of genetic material extracted from the poisoned embryos revealed alterations in specific pathways, which can be reversed by chelation therapy.



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Heavy-atom tunnelling in singlet oxygen predicted with ab-initio instanton theory

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The reactive singlet state of the oxygen molecule decays nonradiatively in solution to its triplet state [1, 2]. The rate constant for this decay, which is a spin-crossover process (intersystem crossing) in the Marcus inverted regime, determines its lifetime and can in principle be calculated using Fermi's Golden Rule (FGR). However, it would require solutions to the nuclear Schrödinger equation and an exact treatment is thus computationally infeasible. Nonadiabatic instanton theory [3, 4] is a semiclassical approximation to FGR that captures multidimensional tunnelling and zeropoint energy effects by locating the optimal tunnelling path (reaction mechanism), called the instanton. This system is in the deep inverted regime and exhibits a completely new class of quantum tunnelling, which requires a new type of instanton theory. The tunnelling mechanism is found to comprise of an infinite ensemble of equally-likely paths [5]. Using this new theory combined with multireference electronic-structure calculations, we predict a rate constant with an enormous tunnelling effect— 27 orders of magnitude faster than the classical process—and which involves significant heavy-atom tunnelling contributions even at room temperature. The theory also correctly predicts the large experimentally-observed H2O/D2O kinetic isotope effect of approximately 20 and its temperature dependence.

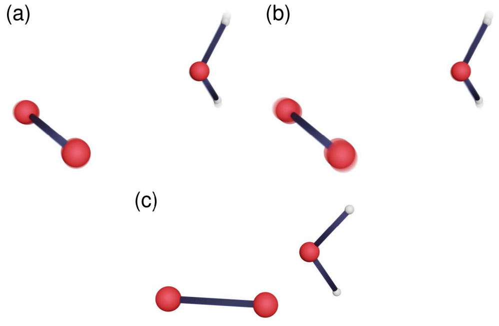

FIG. 1: The tunnelling mechanism for the decay of singlet oxygen in (a) water and (b) deuterated water, and (c) the geometry at the minimum-energy crossing point (MECP). The motion of the atoms involved in the tunnelling mechanism in (a) and (b) is depicted by a motion blur.

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Cooperative free energy: correlation, solvation, and conformation in protein-ligand-protein ternary complexation

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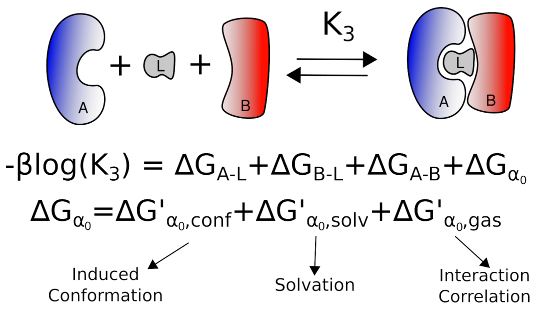
Cooperativity in the protein-ligand-protein ternary complex regulates the complexation efficiency and selectivity[1-2]. In terms of free energy, cooperativity can be decomposed into three three-body contributions. The gas-phase entropy part accounts for the correlation between the protein-ligand interactions, the solvation-free energy part accounts for the double-counted desolvation effect at the three-body interface, and the conformational free energy part accounts for the induced protein-protein interactions and the conformational penalty to bring the ligand, ligand-protein dimers, and protein-ligand-protein trimer to the stabilized conformational space. Under the theoretical framework, molecular dynamics simulations can be implemented to predict the cooperativity of the systems of interest. The study discusses the thermodynamics of the cooperative process, demonstrates *in silico* cooperative prediction, and is anticipated to facilitate the design of cooperative molecular glues.



$$\mathrm{A} + \mathrm{L} + \mathrm{B} \underset{}{\overset{K_3}{\rightleftarrows}} \mathrm{ALB}$$

$$-\beta\log(K_3) = \Delta G_{A\text{-}L}+\Delta G_{B\text{-}L}+\Delta G_{A\text{-}B}+\Delta G_{\alpha_0}$$

$$\Delta G_{\alpha_0}=\Delta G'_{\alpha_0,conf}+\Delta G'_{\alpha_0,solv}+\Delta G'_{\alpha_0,gas}$$

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Structure Determination of Single Crystal Quartz by Hirshfeld Atom Refinement

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Hirshfeld atom refinement [1,2] is an advanced technique that determines structural parameters from single-crystal X-ray diffraction data and aspherical atomic form factors calculated through *ab initio* quantum chemistry calculation and partitioning of electron density. Despite its success in molecular crystal systems, applying it to network compounds such as quartz has been challenging [3], because their unit cells have no stable free-standing configuration.

In this presentation, we introduce the development and application of a new periodic Hirshfeld atom refinement using the quartz system as the main example. This was achieved by combining the open-source quantum crystallography program *Tonto* with the commercially available package for periodic calculation *Crystal23* through the interface software *lamaGOET* [4]. A self-consistent model structure of quartz was obtained through an iterative process alternating between *Crystal23* for crystal electron density calculations and *Tonto* for electron density partitioning and least-squares fitting. This approach opens new avenues for exploring a wider range of crystal systems from the structural point of view.

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Predicting Off-targets from ChEMBL Data Using the Polypharmacology Browser

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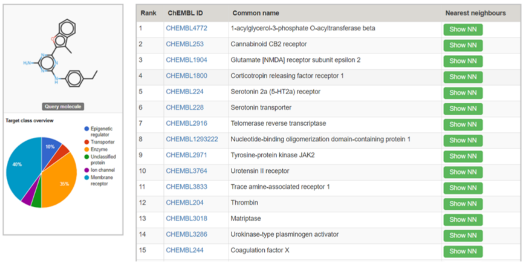
The public archive ChEMBL, which collects bioactive compounds and their associated targets from the literature, has been used by many groups to build models predicting the possible targets of small molecules to guide the experimental search for off-targets. In our group we have developed the polypharmacology browsers (PPB and PPB2), [1,2] which assign possible targets to a query molecule based on molecular fingerprint similarities to ChEMBL molecules, and provided critical insights in several practical case studies such as the identification of LPAATβ as the actual target of a putative kinase inhibitor (Figure). [3,4]



Rank	ChEMBL ID	Common name	Nearest neighbours
1	CHEMBL4772	1-acylglycerol-3-phosphate O-acyltransferase beta	Show NN
2	CHEMBL253	Cannabinoid CB2 receptor	Show NN
3	CHEMBL1904	Glutamate [NMDA] receptor subunit epsilon 2	Show NN
4	CHEMBL1800	Corticotropin releasing factor receptor 1	Show NN
5	CHEMBL224	Serotonin 2a (5-HT2a) receptor	Show NN
6	CHEMBL228	Serotonin transporter	Show NN
7	CHEMBL2916	Telomerase reverse transcriptase	Show NN
8	CHEMBL1293222	Nucleotide-binding oligomerization domain-containing protein 1	Show NN
9	CHEMBL2971	Tyrosine-protein kinase JAK2	Show NN
10	CHEMBL3764	Urotensin II receptor	Show NN
11	CHEMBL3833	Trace amine-associated receptor 1	Show NN
12	CHEMBL204	Thrombin	Show NN
13	CHEMBL3018	Matriptase	Show NN
14	CHEMBL3286	Urokinase-type plasminogen activator	Show NN
15	CHEMBL244	Coagulation factor X	Show NN

However, our PPB and PPB2 models associated only a single target per ChEMBL molecule. To better integrate the existing polypharmacology information available in ChEMBL, we are updating our PPB to handle multi-target information for ChEMBL molecules, using various machine learning models into account, and exploiting the latest version of the database featuring a total of 1.9 million molecule-target associations.

Keywords: Computer-aided drug design, Polypharmacology, Target prediction, Web-based tool, Cheminformatics

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Studying ion and water flow through aerolysin nanopores using molecular dynamic simulations

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Understanding the transport mechanisms of ions and water through nanopores is crucial for numerous applications in nanotechnology and biophysics. In this study, we utilize molecular dynamics (MD) simulations to investigate the flow of ions and water molecules through aerolysin nanopores. Aerolysin, a protein-based nanopore, along with its engineered mutant K238A, exhibits unique properties that make them promising candidates for biosensing and single-molecule sequencing technologies. Using MD simulations, we analyze the ion and water flow through aerolysin nanopores in different types of cation chloride solutions, including K^+, Li^+, and Gdm^+, and water molecules as they traverse the nanopore. We focus on key parameters such as ionic currents, conductivity, ion mobility, water flux, and possibility of interaction between cation with the pore, specifically their sticky characteristics. Our results reveal the influence of pore geometry, surface charge, and external electric fields on the flow behavior, providing insights into the fundamental mechanisms governing molecular transport in confined environments. This study enhances our understanding of nanopore-mediated transport processes and contributes to the development of advanced nanopore-based devices for diverse applications.

Accurate tunnelling splittings with second-order instantons

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In Ring-polymer instanton theory (RPI) [1], we expand around a minimum-action trajectory called the instanton to approximately evaluate path integrals. This approach can be used to calculate tunnelling splittings and since we require information from just one trajectory, the method scales favourably for large systems (see e. g. [2]).

To improve the accuracy of RPI, we have previously introduced first-order perturbative corrections (PC1) which account for anharmonicity around the tunnelling trajectory [3]. With RPI+PC1, we still only need one trajectory, but additionally require third and fourth derivatives along it. This already dramatically improves the accuracy of the method, e. g. from −11% to 2% in the case of malonaldehyde proton transfer depicted in Fig. 1. Recently, we have derived second-order perturbative corrections (PC2), which improve the accuracy even further. Together with resummation techniques, we hope to create an affordable yet accurate technique for describing quantum tunnelling.

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Performance of the new non-decomposable approximant for the non-additive kinetic potential for embedded radical

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The bi-functional $v_t^{nad}[\rho_A,\rho_B]$ (non-additive kinetic potential) is the key ingredient of multi-level simulation methods based on Frozen-Density Embedding Theory (FDET) (see [1]). The commonly used approximations for $v_t^{nad}[\rho_A,\rho_B]$ are decomposable and semi-local. In some cases, these result in an artificial incorrect redistribution of electron density between the embedded species and the environment. The recently developed new approximant (NDCS) [2] is based on first principles and eliminates this flow as shown for model non-covalently bound dimers consisting of closed-shell molecules, atoms, or ions [2,3]. In this work we test the NDCS approximant on cases where the embedded species is a model radical ($OH^\cdot$) in a complex with alkaline cations and other closed shell species. Such systems are prone to artificial spin leak onto the cation resulting from the use of approximation for $v_t^{nad}[\rho_A,\rho_B]$. The comparisons with the corresponding reference results obtained for the complex, show that the NDCS outperforms significantly other semi-local non-decomposable approximations in case of Li^+ and K^+ reducing the relative error in the complexation induced shits of the isotropic hyperfine tensor component from 9.5% to 4% in case of Li^+ and from 4.8% to 0.4% in case of K^+. For Na^+ even using the simplest approximation to $v_t^{nad}[\rho_A,\rho_B]$ (decomposable functional derived from the Thomas-Fermi kinetic energy functional), yields leads to very small relative error of 0.9% and NDCS increases it marginally to 1.2%. The results obtained using basis sets of various qualities (always including atomic functions centred on BOTH the radical AND the cation) confirm the numerical soundness of the above observation [4]. These results are consistant with the ones previously observed in closed shell systems [2,3].

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Data augmentation leads to near quantitative single-step round-trip accuracy in transformer-based retrosynthesis models

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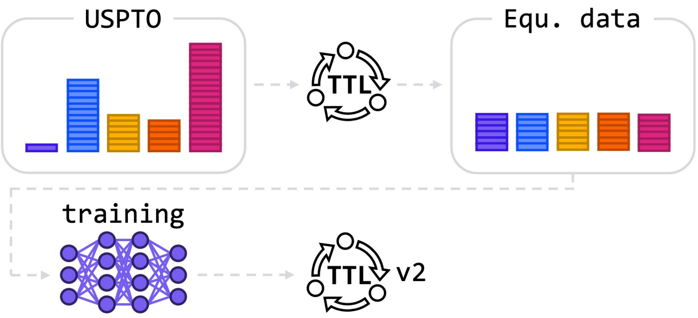
In computer-aided synthesis planning (CASP), one trains machine learning models with organic reactions from literature, and challenges them to predict possible retrosyntheses of unseen molecules[1]. Many models perform well for single-step retrosynthesis, however only for reaction types that are well represented in the training data. Here we used our recently reported triple transformer loop (TTL) retrosynthesis model[2] to perform data augmentation and obtain a balanced dataset where each reaction type is represented by a similar number of examples. By retraining the TTL using the balanced dataset, we obtained a model showing near-quantitative performance in single-step round-trip accuracy prediction. Our data augmentation approach might be generally useful to broaden the scope of retrosynthesis models



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Structure-based machine learning models to predict environmental biodegradation half-lives and their uncertainty

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Modelling the environmental persistence of chemicals is crucial to (i) develop new chemicals that are sustainable and safe by design, and (ii) to understand the environmental fate and hence exposure potential of existing micropollutants. Available biodegradation models fail to accurately predict the primary biodegradation half-lives (DT50s) of complex small molecules such as pharmaceuticals, pesticides, or industrial chemicals. This situation is mainly due to (i) the lack of abundant and standardized biodegradation data and (ii) to the high variability of experimental outcomes of biodegradation experiments.

In this work, we address these challenges by curating pesticide DT50s obtained from soil biodegradation experiments regarding their experimental variability, and by developing new Quantitative Structure-Biodegradation Relationships (QSBRs) to predict biodegradation half-lives for these structurally complex chemicals. The half-lives were obtained from the EAWAG-SOIL data package [1] on enviPath [2], resulting in a data set of 984 substances with at least one reported primary degradation half-life. For each substance, we applied a Bayesian inference technique to handle censored data points and to estimate the average DT50, its uncertainty, and its experimental variability across different studies [3]. QSBRs were constructed based on PaDEL descriptors, MACCS fingerprints, and enviPath's biotransformation rules, and machine learning models were trained using different regressors. While overall model performance was low (R2 < 0.4), Gaussian Process Regressors models not only predict a half-life value, but also assign a confidence metric to each prediction. We show that this confidence metric can be used to reliably distinguish accurate from inaccurate predictions, and to point towards classes of chemicals for which more experimental data is needed.

Our approach can be expanded to include more biodegradation data from other environmental compartments (e.g., activated sludge, water-sediment systems) in the future, with the objective to improve model performance, increase the coverage of the chemical space, and predict half-lives in other environments.

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Spin-flip TDDFT within the Sternheimer formalism

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In this work we present the state-of-the-art on low-scaling methods for spin-flip time dependent density functional theory (SF TDDFT) calculations. To this aim, the Sternheimer formalism[1] is employed to allow SF TDDFT calculations without the explicit need of unoccupied molecular orbitals, we name the resulting method SF TDDFPT. We implemented this method into the CP2K package (www.cp2k.org) to take advantage of its highly efficient methodologies, in particular, the Gaussian and plane-wave (GPW) method[2,3] and the auxiliary density matrix method (ADMM)[4]. The former is used to lower the computational scaling of the electron-electron repulsion and exchange-correlation contributions in the spin-flip kernel and the later is used for the calculation of the Fock exchange contribution with a reduced computational scaling. The resulting excitation energies are obtained within 0.3 eV with respect to highly accurate excitation energies[5], which is consistent with the reported accuracy of TDDFT[6,7].

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Reaction prediction in the low-data regime with transition state descriptors

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Abstract: Despite advancements in chemical reactivity prediction with machine learning (ML), the accuracy is limited by the small size of the datasets. Including knowledge from transition states (TS) to predict reactivity has been shown to lead to better results in the low data range [1–5]. To obtain the TS structures, density function theory (DFT) is the state-of-the-art method, but it presents a significant failure rate [1,3,6] and its high computational cost makes it challenging to integrate into ML pipelines. The SEAM method, derived from the empirical valence bond theory (EVB), offers a faster alternative for TS generation by approximating the TS as the intersection between the non-interacting force fields of the ground states of a reaction.

We developed the polanyi Python package to generate TS structures starting from the ground states coordinates. Polanyi implements the SEAM method based on the GFN-FF [7] force field via an interface to the xTB program [8]. We apply polanyi to the nucleophilic aromatic substitution (SNAr) [1] and the palladium-catalysed oxidative addition [9] reactions and compare it against higher-level computations and experimental rate constants. We then calculate electronic and steric descriptors on these generated TS geometries and use them to predict the rate and selectivity of the studied reactions.

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Sampling strategies for expectation values within the Herman--Kluk approximation

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When computing quantum-mechanical observables, the curse of dimensionality limits the naive approach that uses the quantum-mechanical wavefunction. The semiclassical Herman--Kluk propagator provides a remarkable grid-free ansatz to evaluate the expectation values of these observables. In this paper, we investigate quadrature techniques for this high-dimensional and highly oscillatory propagator. In particular, we analyze Monte Carlo quadratures with three different initial sampling approaches. The first two, based on the Husimi density and its square root respectively, are independent of the observable while the third approach, which is new, incorporates the observable in the sampling to minimize the variance of the Monte Carlo integrand at initial time. We prove sufficient conditions for convergence of the Monte Carlo estimators and provide convergence error estimates. The analytical results are validated by numerical experiments in various dimensions on a harmonic oscillator and on a Henon-Heiles potential with an increasing degree of anharmonicity.

Multiscale simulations of hybrid halide-perovskite photovoltaic devices

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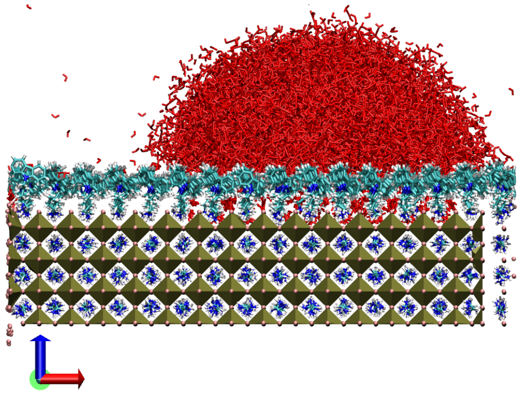
Hybrid halide perovskites rapidly captured the interest of the scientific community, in large part, due to their remarkable optical properties enabling high power conversion efficiencies their versatility and broad application spectrum including photovoltaics, light-emitting diodes, light detection, and energy storage. Most of this rapid progress is owed to changes in synthesis conditions, whose fundamental understanding at the atomic level is still elusive. In principle, computer simulation can elucidate the atomistic mechanisms underlying these phenomena. The efficient combination of multiscale simulation techniques spanning broad length/time scales can address formidable challenges related to having multiple atomic species, long relaxation times (high activation barriers), intricate system geometries, ir)reversible phase transitions, numerous metastable states and large system requirements to name a few approach to understanding structure-property relations entails the development, refinement and application of multiscale computational techniques acting synergistically to span electronic and atomistic levels of detail. Classical molecular dynamics simulations complemented by ab-initio molecular dynamics and density functional theory simulations are utilized to obtain an accurate description of the physics behind the mechanisms responsible for enhancing long-term stability and improving the efficiencies of PSCs, while also indicating possible new roadmaps for superior PSC devices.



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MiMiC Framework for Multiscale Simulations: Current Status and Recent Advancements

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Multiscale simulations represent an indispensable part of computational chemistry, as they provide important insights into chemical and biological phenomena occurring at different space and time scales. The most prominent example of these is the hybrid quantum mechanics/molecular mechanics (QM/MM) method, where the chemically active part of the system is treated at the QM level, while the rest is treated at the MM level, with classical force fields. In this context, we developed the MiMiC [1,2], a framework for multiscale simulations, designed to be extremely flexible and, at the same time, efficient. At the moment, MiMiC offers an efficient implementation of electrostatic embedding QM/MM, interfacing GROMACS and CPMD as MM and QM clients, respectively. A large effort is being put into extending available clients and, at the same time, the capabilities of the framework, in terms of supporting new features and different multiscale methods. In this contribution, I will give an overview of the current status of the MiMiC framework and provide insights into some future advancements in the development of which I am personally involved. In particular, these include the interface with new client codes, such as OpenMM and CP2K, and the introduction of new features in MiMiC itself, such as a generalised version of the D-RESP approach [3]. These additions will further extend the flexibility of the MiMiC framework, expanding its capabilities in multiscale simulations

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Nonadiabatic dynamics simulations in periodic condensed phase systems and challenges with hybrid-based ΔSCF

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Almost all nonadiabatic (NA) processes encountered in nature happen in the condensed phase. City smog is a direct consequence of various nitrogen oxides and hydroxides generated by solar light photodecomposition of various manmade pollutants, such as nitrophenols, in the atmospheric water droplets. In technological applications like CO_2 photocatalytic reduction, photocatalyst attachment to a solid surface can enhance its absorbance, increase its photostability, and utilize the surface as a direct sacrificial electrode, to name a few benefits. In silico modelling of NA processes of photoexcited systems in condensed phase represents a significant theoretical and computational challenge. In addition to the system size increase due to additional environment molecules that must be accounted for the number of electronic states and the potential nonradiative deactivation (NRD) pathways all increase. Two such photoexcited systems in a condensed phase environment were studied through NA molecular dynamics (MD) simulations with all atoms at the same time-dependent density functional(TDDFT) level of theory, incorporating periodic boundary conditions for the condensed phase description. NRD mechanisms of ortho- and para-nitrophenol initiated from the brightest π to π^* singlet excited electronic state were investigated with trajectory surface hopping NA MD simulations on a manifold including several (up to twelve in total) singlet and triplet excited electronic states, mutually coupled by the spin-orbit coupling elements computed at the TDDFT level of theory. By careful analysis between such NRD pathways obtained on isolated and in water-solvated nitrophenols, the cage effect exhibited by the surrounding water molecules on electronically excited nitrophenol reduces the number of inter-system crossings and facilitates its NRD deactivation from the first singlet excited electronic states. When the water solvent was modelled at a force field level as usually performed when applying the computationally cheaper molecular mechanics/quantum mechanics (QM/MM) approach, the NRD mechanisms resemble more those of the isolated system than when the whole solvent was treated at the same level of theory as the chromophore.[1] An ultrafast excitation transfer from a localized Re-photoreduction catalyst to a TiO_2 anatase (101) surface was simulated with Ehrenfest NA MD utilizing the real-time TDDFT propagation of the initially ΔSCF generated excited electronic state density. In a subfemtosecond time scale, the metal-to-ligand charge transfer excitation localized on the Re-photoreduction catalyst transfers through the ligand frame and its phosphate groups, anchoring it to the anatase (101) surface, to the anatase (101) surface and suddenly polarizes all its layers.[2] Finally, we investigated the origin of the ΔSCF singlet excited energy shift when the electronic state is constructed using fractional occupation numbers with a hybrid density functional. Additional terms, some identical to the self-interaction error culprit terms, arise from the Coulomb and the exact Hartree-Fock exchange terms obtained from nonidempotent density matrices incorporating fractional occupation numbers. Ways to alleviate them are investigated, as this issue seems ubiquitous to any DFT calculation employing fractional occupation numbers with hybrid density functionals.[3]

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Abraham solvation parameters model in the frame of graph convolutional neutral networks

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Abraham model solute descriptors model have been leveraged for 7000 contaminates extracted from UFZ-LSER database [1]. This database contains experimentally determined Linear Solvation Energy Relationship (LSER) descriptors, E (excess molar refraction), S (polarizability/dipolarity), A (solute hydrogen bond acidity), B and/or B0 (solute hydrogen bond basicity), and L (logarithmic gas-hexadecane partition coefficient). The database also stores the McGowan's molar volume V calculated for each compound from its molecular structure. These solute descriptors can be used, in combination with LSER equations or other types of polyparameter linear free energy relationships (pp-LFERs), to calculate partition coefficients for various systems.

As a molecular graph representation, we used a graph convolutional neural network architecture (GCN). Our approach showed that several important chemical and thermodynamic properties could be predicted using the applied approach, including partition coefficients, molar solubility ratios, gas-liquid chromatography and HPLC retention data, infinite dilution activity coefficients, molar enthalpies of solvation, molar vaporization and sublimation at 298 K, vapor pressures, and fusion coefficients.

The GCN can predict more accurately than previous methods over broader data sets and is independent of the descriptors selection space.

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Molecular dynamics simulation of aerolysin nanopore using high-resolution cryo-EM structure

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Nanopores have recently emerged as a powerful single molecule sensing tool. A diverse array of pore-forming toxins proteins are now utilized as nanopore sensors to characterize biomolecules, advancing both life sciences and medical applications[1-4]. Among these, aerolysin stands out as an excellent candidate due to its narrow and long lumen, which confers high sensitivity[5]. Despite its promising applications, the current resolution of the available aerolysin structure is 7.9 Å[6], comparable to the radius of its barrel (10-17 Å). This limitation hinders our understanding of the sensing principles of the aerolysin nanopore. In this study, based on two newly obtained high-resolution structures of aerolysin via cryo-EM (2.2 Å) in both amphibol and lipid nanodiscs, we use molecular dynamics simulations to analyze their structure profiles and ionic current flows at the atomic-level. Our results reveal a previously unidentified constriction within the pore's lumen, which has been underestimated in previous studies. Furthermore, the ionic current calculated from molecular dynamics trajectories with these structures align more closely with experimental data. These findings enhance our understanding of aerolysin nanopores' sensing principle and suggest potential advancements in their applications as molecular sensors.

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Reactivity prediction of highly flexible catalysts using conformationally enriched machine learning

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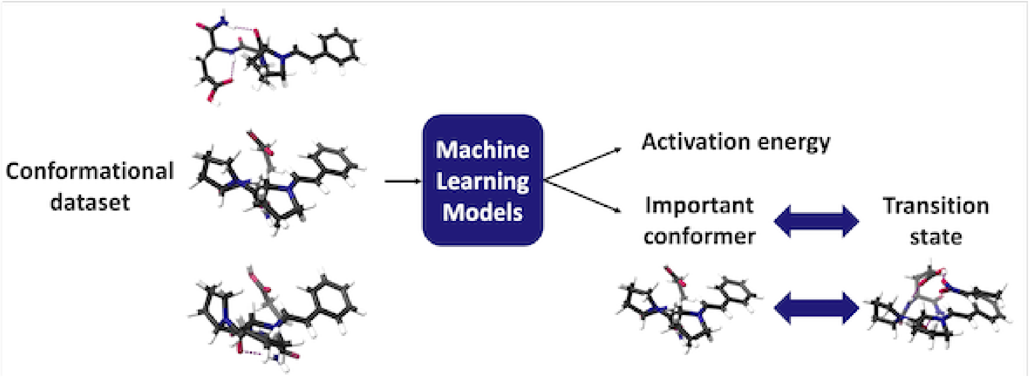
Recent years have seen a rise in the development of machine learning (ML) methods applied to chemical reactions, ranging from ML-guided reaction optimization to catalyst design [1,2]. Most applications consider molecules as SMILES line-notation, or through representations derived from their 2D- or lowest-energy 3D-structure. Thus, they neglect the conformational freedom of molecules, which has been identified as a crucial factor in numerous catalytic reactions [3,4]. Recent work has benchmarked the benefits of including conformational information into ML models for moderately flexible BINOL-phosphoric acid catalysts [5,6]. However, conformational ML remains unexplored for more flexible catalysts, where such models could identify reactive conformers, providing insight into the reaction mechanism.

This work introduces conformer-enriched machine learning for reactivity prediction of highly flexible tripeptide catalysts. We design and create a dataset for activation energy prediction of a peptide-catalysed addition of aldehydes to nitroolefins, considering both energetically and structurally representative catalyst conformers. Semi-empirical methods [7] are employed for the ultra-fast generation of multiple reactant, transition state and product conformers of over 1'000 reactions, thus providing a reactivity dataset with energetically relevant and structurally diverse conformers of all reaction species for further model development. The dataset is used to create a conformer-augmented molecular representation, considering conformational information for reactivity prediction of highly flexible molecules. Important conformers for the prediction are further extracted from the ML model and compared to reaction transition states to assess the capability of the model to identify reactive conformers.



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Cost-Informed Bayesian Reaction Optimization

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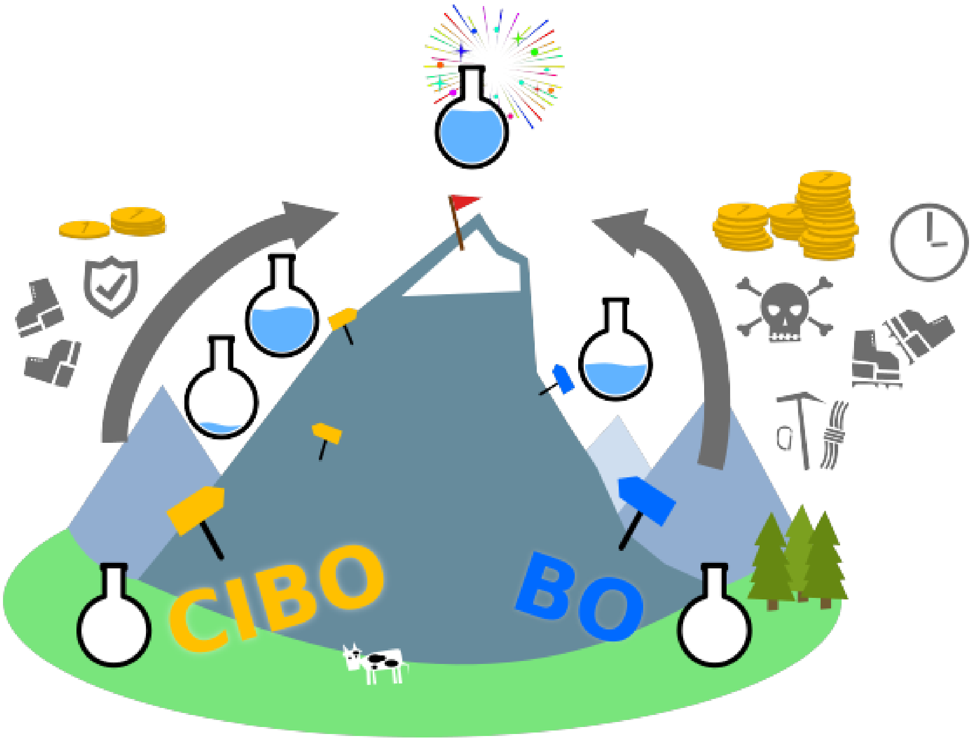
Bayesian optimization (BO) is an efficient method for solving complex optimization problems, including those in chemical research, where it is consequently gaining significant popularity. Although effective in guiding experimental design, BO does not account for experimentation costs: testing readily available reagents under different conditions might be more cost and time-effective than synthesizing or buying additional ones. To address this issue, we present cost-informed BO (CIBO), an approach tailored for the rational planning of chemical experimentation that prioritizes the most cost-effective experiments. Reagents are used only when their anticipated improvement in reaction performance sufficiently outweighs their costs. Our algorithm tracks the available reagents, including recently acquired ones, and dynamically updates their cost during the optimization. Using literature data of Pd-catalyzed reactions, we show that CIBO reduces the cost of reaction optimization by up to 90% compared to standard BO. Our approach is compatible with any type of cost, *e.g.*, the cost of buying equipment or compounds, waiting time, and environmental or security concerns. We believe CIBO supersedes BO in chemistry and envision applications in both traditional and self-driving laboratories for experiment planning.



Assessing the performance and accuracy of Delta Self-Consistent Field (ΔSCF) method within Restricted-Open Kohn–Sham formalism

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The simulation of photochemical processes requires efficient electronic structure methods to calculate the properties of excited electronic states (such as vertical excitation energies, oscillator strengths, nonadiabatic and spin-orbit couplings, etc). For the last couple of decades the method of choice has been the Linear-Response Time-Dependent Density Functional Theory (TDDFT). It is fast and reliable, but fails to describe certain phenomena such as long-range charge-transfer and multi-electron excitations. A computationally affordable alternative is the Δ Self-Consistent Field (ΔSCF) method. In principle it's a generalization of the SCF procedure, but instead of occupying the lowest-lying molecular orbitals according to the Aufbau principle, an electron is promoted to a higher molecular orbital to construct a specific excited state of a given electronic density.

A thorough investigation of the effectiveness of the ΔSCF method within the Restricted-Open Kohn–Sham formalism has been carried out. A modification of the Maximum Overlap Method to improve the convergence of the ΔSCF method while preserving the order of the molecular orbitals is presented. For benchmarking purposes a large-scale comparison with TDDFT has been conducted: both single- and multi-reference singlet and triplet excited states of various molecules have been reproduced using ΔSCF and compared to the reference states provided by TDDFT. A decent correlation between constructed excited states electron densities and other properties has been observed. It has also been found that the energy gap alone is not a reliable criterion to compare the calculated excited states. The similarity between the electron densities and the transition dipole moments of the molecules should be used along with the energy gaps. [1]

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Predicting Reaction Properties using SMILES/CGR

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Machine learning models have gained significant popularity for a wide variety of property predictions in chemistry, yet predicting reaction properties such as yield, activation energy, and kinetic rate constants remains a challenge. Currently, graph-based models seem to offer the highest accuracy and reliability, specifically models based on Condensed Graph of Reactions (CGR) [1]. Additionally, in recent years the field has seen the surge of large language models (LLMs) that have yielded alternative powerful methods for the task of predicting reaction properties mainly based on reaction SMILES [2]. In an effort to combine the advantages of the CGR representation with those of LLMs, we utilize the text representation of CGR (called SMILES/CGR [3]) to predict reaction properties using a BERT model. Preliminary results indicate that our model performs comparably to those based on reaction SMILES, although it is still outperformed by graph-based models.

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Striking the right balance of encoding electron correlation in the Hamiltonian and wavefunction ansatz

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Multi-configurational electronic structure theory delivers the most versatile approximations to many-electron wavefunctions, flexible enough to deal with all sorts of transformations, ranging from electronic excitations, to open-shell molecules and chemical reactions. Multi-configurational models are therefore essential to establish universally applicable, predictive ab initio methods for chemistry. Here, we present a discussion of explicit correlation approaches which address the nagging problem of dealing with static and dynamic electron correlation in multi-configurational approaches. We review the latest developments and then point to their key obstacles. Our discussion is supported by new data obtained with tensor network methods. We argue in favor of simple electrons-only correlator expressions that may allow one to define transcorrelated models, in which the correlator does not bear a dependence on molecular structure.

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Computational insights into organic halide perovskite solar devices

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Hybrid organic/inorganic halide perovskites solar cells (PSCs) have become a promising class of materials for solar cells. Researchers have recently developed numerous methods to reduce defects, suppress non-radiative recombination, and enhance device efficiency and stability. Among these, additive and interface engineering methods have attracted extensive attention and are particularly popular for high-efficiency and stable PSCs. However, fundamental knowledge of the underlying atomic-level processes leading to improved performance and lifespan is often lacking. We employ DFT calculations, classical and ab-initio molecular dynamics (MD) simulations, with the help of state-of-the-art, polarizable classical force-fields and machine-learned interatomic potentials, trained on ab-initio MD trajectories, to unveil the underlying mechanisms connected to the facilitated interfacial charge transfer and improved stability of various PSCs devices. In particular, we apply our methodology to assess the stabilizing nature, as well as the optoelectronic properties of recently proposed hydrophobic organic cations in the context of layered two-dimensional perovskite materials and inverted PSCs.

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Ligand-based 3D Pharmacophore Search for Drug Analogues in Ultra-Large Combinatorial Libraries

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In the field of drug discovery, "me-too" approaches are increasingly vital for identifying potential candidates for further development. Our study focuses on this aspect, evaluating both the performance and diversity of molecular analogues identified by an innovative pharmacophore search method in Ultra-Large Combinatorial Libraries (ULCLs). Our test set comprises eight recently approved first-in-class drugs.

We introduce the newly developed Pharos3D Method, which is a refinement of the Flexophore descriptor, a component of the open-source tools DataWarrior and OpenChemLib. Unlike classical ‘brute force’ approaches, Pharos3D enables the rapid screening of ULCLs within hours on computers with moderate hardware.

Here, we demonstrate that our new method identifies excellent fitting analogues for drugs. These analogues exhibit chemical diversity from the query molecule and can serve as a starting point for new medicinal chemistry programs aimed at addressing issues related to ADMET or intellectual property (IP).

3-Dimensional descriptors of molecular lipophilicity of macrocycles

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In the development of novel therapeutic compounds, understanding polarity and lipophilicity is crucial to predict biophysical properties such as solubility or membrane permeability. However, these properties depend on the molecular conformation, which is inherently dynamic and responds to the molecular environment. Especially for larger drug compounds such as macrocycles, strong adaptations to the polarity of the environment help increase the membrane permeability, an effect that has been termed chameleonicity. Thus, conformation-dependent polarity is important in the computational modeling of chameleonicity and related biophysical quantities. Molecular dynamics (MD) is a powerful method to compute conformational ensembles and allows for detailed analysis of chameleonicity.

Here, we present a 3D-based polarity descriptor, based on an ML-base implicit solvent model previously developed in our group as well as the solvent excluded surface area, and combine it with MD simulations to study lipophilicity and chameleonicity of small molecules and macrocycles. Our results demonstrate that MD-based ensembles can improve in-silico predictions of lipophilicity and give novel insights into chameleonicity.

Stochastic Sampling around Ring-Polymer Instanton

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Quantum tunneling plays a crucial role in various chemical processes. By identifying dominant tunneling paths without prior knowledge of the tunneling path, the semiclassical instanton theory with the ring-polymer implementation[1] represents a valuable theoretical approach to describe tunneling phenomena. However, due to its reliance on the steepest descent approximation, it is unable to capture anharmonic effects perpendicular to the tunneling path if higher-order corrections are not further considered[2].

To overcome this limitation, here we propose a novel numerically exact approach called the instanton Monte Carlo method. The basic idea lies in conducting Monte Carlo random sampling around the instanton path. Specifically, utilizing a ring-polymer implementation, we transform the real coordinate space around the instanton solution into a normal-mode coordinate space, rescaled by the eigenfrequencies, while maintaining affine isomorphism with the original coordinates. Within this new space, we conduct random sampling weighted by the imaginary-time action. Applying this approach to compute the tunneling splitting in the one- and two-dimensional double-well models, the sampling procedure exhibits remarkably high efficiency, requiring only a few configuration updates to eliminate the autocorrelation between adjacent samples.

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Microkinetic Molecular Volcano Plots for Enhanced Catalyst Selectivity and Activity Predictions

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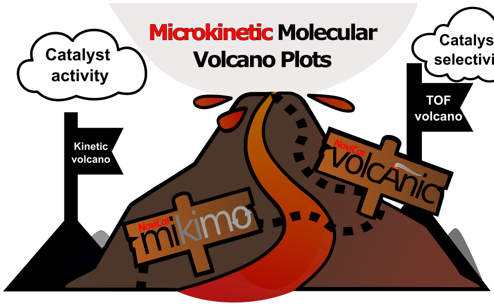
Volcano plots and 2D activity maps,[1] derived from linear free energy scaling relationships, are valuable tools for predicting and rationalizing catalytic properties. By exploiting Sabatier's principle, these tools enable rapid identification of optimal catalysts through visual representations that correlate catalytic performance with a key energetic descriptor representative of the catalytic cycle. This work combines the rapid screening ability of molecular volcano plots with microkinetic modeling to create the next-generation of *microkinetic volcano plots* that predict the concentration of the product(s) at a given reaction time. We also introduce *mikimo*,[3] a lightweight Python program that is seamlessly integrated with our previously released volcano plot/activity map builder, *volcanic*[2] which automates the construction of microkinetic molecular volcano plots and activity/selectivity maps.



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