**Workshop: Non-equilibrium thermodynamics: from chemical reactions to machine learning (23-25 April 2025)**

**Abstracts**

**Prize Talks**

**Sarah Loos** (University of Cambridge) - Thermodynamics and optimal control of small-scale processes with memory

Stochastic thermodynamics is a powerful framework to describe the thermodynamic properties of fluctuating, small scale processes. A central assumption
is Markovianity, i.e. that one can single out a finite number of mesoscopic degrees of freedom coupled to a heat bath with no internal structure that remains in equilibrium at all times. However, realistic environments often have timescales comparable to those of the process under study, leading to memory effects and a temporarily nonequilibrium bath. This is the case, for example, with subcellular transport processes that typically take place in viscoelastic media. To go beyond this paradigm, we consider thermodynamic properties of systems described by generalized Langevin equations. We consider the canonical optimal control problem of moving a harmonic trap containing a Brownian particle over a fixed distance in a fixed time with minimum work input. We show that memory effects in the environment significantly alter the optimal
strategies. Surprisingly, the optimal solutions possess a universal time-reversal symmetry, which we show to be a universal and exclusive feature of the optimal solutions. The symmetry principle holds for a wide class of processes described by a linear generalized Langevin equation, irrespective of the memory kernel or noise properties [1,2]. To resolve the spatio-temporal correlations in the environment, we further explore a type of modelling where we combine a Langevin equation for the particle with a scalar fluctuating field theory for the medium [2].
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**Emanuele Penocchio** (Northwestern University) - Nonequilibrium thermodynamics of molecular ratchets

**Invited Speaker Talks**

**Elisabeth Agoritsas** (University of Geneva) - Out-of-equilibrium regimes from driven complex systems to machine-learning

Machine learning (ML) has become ubiquitous, and is nowadays an extremely active research field at the intersection of very diverse communities. Despite its remarkable success and versatility, a deeper theoretical understanding is needed as to why and when ML ‘works’ (or not). A very fruitful approach in ML theory is to study minimal statistical-physics models, starting from *equilibrium* settings where we have analytical tools and benchmarks at our disposal. ML models are not physical systems per se, but they genuinely are driven complex systems: training a ML model with a particular architecture amounts to evolve its parameters (e.g. its numerous interacting degrees of freedom) in a complex high-dimensional landscape. Statistical-physics tools can thus be used to study these systems, with the strong asset that the high-dimensional limit –relevant for ML applications– is also very convenient for analytical approaches. They have already provided key insights inspired from dense amorphous materials, e.g. on glassy physics and the jamming transition.

From this theoretical perspective, a natural question for a statistical physicist is *how to relate in general out-of-equilibrium regimes* of driven complex systems to ML algorithmic features in the training dynamics. In the first part of this talk, I will present a recent study illustrating how such out-of-equilibrium regimes can be exploited, in ML of generative models, for optimising the sampling procedure at each training step. We often know how to characterise these models in equilibrium settings, but out-of-equilibrium exact benchmarks are on the contrary scarce. In the second part of the talk, I will thus discuss a promising approach in this direction: how to formalise the analogy between driven complex systems (with structural disorder) and machine-learning algorithms, based on their common Langevin dynamics and the resulting dynamical mean-field theory (DMFT) one can build from it.

**Shuntaro Amano** (University of Strasbourg) - Synthesis and Analysis of Life-like Systems out of Equilibrium

Biology utilizes molecular machines for various nonequilibrium functions, such as intracellular transportation and energy conversion. These molecular machines operate by Brownian ratchets mechanisms, which rectify random thermal motion at the nanoscale to generate directional motion. Inspired by biology, chemists have strived to realize synthetic Brownian ratchets, because they are crucial for application of molecular machines in diverse fields such as active matter and soft robotics. However, the examples of synthetic Brownian ratchets are scarce, and their general design strategies have not been clearly understood. To overcome these limitations, we developed the first example of a synthetic autonomous molecular pump driven by chemical energy.1 Furthermore, we analyzed the mechanism of synthetic Brownian ratchets from thermodynamic2 and kinetic3 perspectives. These analyses elucidated how energy supplied to Brownian ratchets causes directional motion, and how the kinetics of each process contributes to directionality. We also realized a simple and general approach for developing chemically driven nonequilibrium systems, which is to repurpose a known catalytic cycle.4 Currently, we investigate application of Brownian ratchet mechanisms to various nonequilibrium processes such as endergonic synthesis5 and active transport across membrane.

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**Ginestra Bianconi** (Queen Mary University of London) - Topology shapes dynamics of higher-order networks

Complex systems like the brain, climate, and next-generation artificial intelligence rely on higher-order interactions that extend beyond simple pairwise relationships. These many-body interactions are captured by higher-order networks By integrating algebraic topology with non-linear dynamics, theoretical physics and machine learning, this talk reveals the critical role of topology in shaping the dynamics of such systems. This talk highlights how topological signals, dynamical variables defined on nodes, edges, triangles, and other higher-order structures, drive phenomena such as topological synchronization, pattern formation, and triadic percolation. The surprising result that emerges from this research is that topological operators including the Topological Dirac operator, offer a common language for treating complexity, AI algorithms, and quantum physics. These findings not only advance the understanding of the underlying mechanisms in neuroscience and climate science but also pave the way for transformative machine learning algorithms inspired by theoretical physics.

**Francesco Cagnetta** (SISSA) - Towards a theory of deep learning for hierarchically compositional data

The theoretical understanding of deep learning methods requires us to consider the structure of the data that these methods are successful at learning. For instance, natural image- and text-like data display a hierarchically compositional structure that deep learning methods can capture due to their layered architecture. In this talk, I will present a strategy to model this structure based on probabilistic context-free grammars---tree-like generative models of text from theoretical linguistics. I will then describe how deep learning can leverage the hierarchical structure for learning with higher data efficiency than simpler, shallow machine-learning models. This analysis unveils a fundamental relationship between the data correlations, the latent hierarchical structure of the data and the size of the training set, leading to a prediction of learning curves that can be tested in experiments with deep convolutional networks and transformers. Finally, I will present empirical evidence demonstrating that the relationship between training set size and correlations extends beyond our synthetic datasets. In the context of self-supervised learning, this relationship predicts a scaling form for the behaviour of learning curves as a function of the length of the input sequences.

**Roberto Covino** (Goethe-University Frankfurt) – Using short out-of-equilibrium trajectories for learning free energy and rates of rare molecular events

Molecular dynamics is a powerful tool for studying the thermodynamics and kinetics of complex molecular events. However, these simulations can rarely sample the required time scales in practice. Transition path sampling overcomes this limitation by collecting unbiased trajectories and capturing the relevant events. Moreover, the integration of machine learning can boost the sampling while simultaneously learning the committor, a quantitative representation of the mechanism. Still, the resulting trajectories are by construction out-of-equilibrium, preventing the calculation of free energies and rates. I will present an algorithm to approximate the equilibrium path ensemble from machine-learning-guided path sampling data. At the same time, our algorithm provides efficient sampling, mechanism, free energy, and rates of rare molecular events at a moderate computational cost. I will showcase the applications of our method on protein folding and membrane protein assembly. I will also present our latest attempts to move towards a no-rejection algorithm and to overcome long correlations along the chain of sampled trajectories. Our algorithm is straightforward and data-efficient, opening the door to applications in many challenging molecular systems.

**Matteo Degiacomi** (University of Edinburgh) - Learning (from) protein dynamics

Determining the different conformational states of a protein and the transition paths between them is key to fully understanding the relationship between biomolecular structure and function. I will discuss how a machine learning models can learn a continuous conformational space representation from example structures produced by molecular dynamics simulations. I will then show how such representation, obtained via our software molearn, can be leveraged to predict putative protein transition states, or to generate conformations useful in the context of flexible protein-protein docking.

**Luigi del Debbio** (University of Edinburgh) -

**Fabian Thiemann** (IBM) - Force-free Molecular Dynamics for Efficient Long-Timescale Simulations

Molecular dynamics (MD) simulations are a cornerstone of scientific research, providing critical insights into material properties and molecular behavior. However, their high computational cost often restricts the accessible timescales and system sizes. While many data-driven approaches focus on accelerating the evaluation of accurate interatomic forces, they remain constrained by small integration time steps. In this work, we introduce a transferable and data-efficient framework based on autoregressive equivariant message-passing networks that directly update atomic positions and velocities, bypassing traditional numerical integration constraints. We validate our methodology across diverse systems—including small molecules, crystalline materials, and bulk liquids—demonstrating strong agreement with reference MD simulations for structural, dynamical, and energetic properties. Depending on the system, our models enable the usage of to 30× larger time steps compared to conventional MD simulations. By facilitating efficient and accurate large-scale simulations over extended timescales, our framework has the potential to accelerate materials discovery and reveal physical phenomena beyond the reach of traditional MD simulations.

**Invited Talks**

**Graeme Ackland** (University of Edinburgh) - Solubility of methanol in water

Solubility of large objects in small objects is a challenge for statistical mechanics. One cannot easily enumerate all the configurations, and if atomic detail is important coarse graining is unlikely to be a good idea. Lattice-based solubilty models tend to be based on a concept that molecule either attract or repel one another - this is problematic for methanol-water, where the water as attracted to the OH end of the methanol, but not the CH3 end. One could use full atomistic simulations, but here we describe a simple lattice based model which addresses the issues: Simply, the methanol occupies two lattice sites, one end attracts the water and the other does not. The model has just one parameter, the ratio of temperature to the bonding. In two dimensions, it exhibits three phase boundaries—between a low-temperature phase comprising straight bilayers, intermediate phases exhibiting twisted bilayers and clustering, and a high-temperature phase, which is essentially gaslike. None of the observed phases correspond to the crystalization or phase separation expected of a simple mixture; instead, they correspond to loss of different types of entropy.

**Paweł Dąbrowski-Tumański** (Cardinal Wyszynski University in Warsaw) - Transformer model in understanding knot topology

The knot topology are naturally formed in many biopolymers, including DNA and proteins. However, with increasing chain length, the potential complexity (number of crossings) of the knot increases. As in current algorithms the computational time complexity rises exponentially with the number of crossings, the knot topology cannot be efficiently calculated for very complicated (usually very long) polymers. In this work, we tackle the problem of determining the knot topology by means of deep learning algorithms. In particular, compare using text transformer and graph transformer architectures, in either knot type determination, or knot simplification. As a result, we obtain much faster, and much more potent algorithm, than currently existing classical tools.

**Alexander Dack** (Imperial College London) - Recurrent neural chemical reaction networks that approximate arbitrary dynamics

Many important phenomena in chemistry and biology are realized via dynamical features such as multi-stability, oscillations, and chaos. Construction of novel chemical systems with such finely-tuned dynamics is a challenging problem central to the growing field of synthetic biology. In this paper, we address this problem by putting forward a molecular version of a recurrent artificial neural network, which we call a recurrent neural chemical reaction network (RNCRN). We prove that the RNCRN, with sufficiently many auxiliary chemical species and suitable fast reactions, can be systematically trained to achieve any dynamics. This approximation ability is shown to hold independent of the initial conditions for the auxiliary species, making the RNCRN more experimentally feasible. To demonstrate the results, we present a number of relatively simple RNCRNs trained to display a variety of biologically-important dynamical features.

See <https://arxiv.org/abs/2406.03456>

**Alessia Guadagnin Pattaro** (University of Trento) - Analysis of protein folding through the combination of transition path theory and informative low-resolution representations

The biologically active conformation of a protein is maintained by the interactions among those residues involved in native contacts, but in the course of the folding process amino acids can be involved in transient native as well as non-native interactions, which drive the molecule towards its folded state. Reconstructing how these interactions evolve is key to understanding the folding process; however, no technique is currently available to do so in a general and unsupervised manner.

We here present a method that highlights the most functionally relevant residues of a protein at each stage of its folding pathway. To do so, we jointly leverage two distinct techniques: transition path theory (TPT), to decompose the folding pathway in a sequence of steps according to the committor function; and the mapping entropy optimization workflow (MEOW), which highlights, at each step, the subset of residues that play the most relevant structural, energetic, and functional role.

We validate this method by applying it to a benchmark yet nontrivial case, namely miniprotein chignolin, showing that the combination of TPT and MEOW provides novel information on the molecule’s folding pathway that is nonetheless coherent with well-established results. This approach, which is of general applicability, complements existing analysis methods and paves the way to an increasingly detailed comprehension of protein folding.

**Eman Medani** (Heriot-Watt university) - Including the Effects of Speciation on the Estimation of the Viscosity of Amine/Water/CO2 Systems

Solvent-based chemical absorption is the most widely adopted carbon capture technology. Typically, CO2 is absorbed into an aqueous amine solution resulting in zwitterionic chemical reactions and the formation of carbamate (〖R'RNHCOO〗^-), bicarbonate (HCO\_3^-), and protonated amine (R'RNH\_2^+) species. Given the importance of the solvent viscosity, the ability to accurately predict the viscosity of aqueous amine/CO2 systems using computational tools, such as molecular dynamics (MD) simulation, would be very beneficial. Since classical MD force fields do not allow for chemical reactions, previous work has typically ignored chemical speciation; however, the viscosity of the system is strongly influenced by the presence of the reaction products. Although speciation can be determined experimentally, it is not feasible to perform such measurements for the vast quantity of amines that could be used in carbon capture processes. To address this issue, we employ the SAFT-γ Mie equation of state to implicitly model the chemical reactions and determine the reaction products present in the solution to be studied by MD simulation. The simulation results, when compared to experimental data, demonstrate that incorporation of chemical speciation enables the simulations to accurately capture the viscosity trends as a function of CO2 loading across the systems studied. These results highlight the importance of including the reaction products in simulations of aqueous amine systems in order to accurately predict transport properties and establishes a workflow for estimating the viscosity that can easily be extended to other reactive systems.

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**Auro Varat Patnaik** (University of Edinburgh) - Zero-shot Adaptation of Drug Diffusion Model for Fragment Elaboration

Understanding how small molecules, or ligands, can bind to target proteins is crucial for drug design. Key potential intermolecular interactions can suggest new ligand growth vectors, and incorporating 3D structural information allows for efficient in-silico evaluation. One way to discover these interactions is through fragments bound to a target protein obtained from X-ray crystallography. Building on these fragments, fragment elaboration is a critical step in the design of complete molecules.

Diffusion models have emerged as a leading method for 3D molecular generationof drug-like molecules. [1–3] However, they do not inherently generate molecules that effectively elaborate fragment hits into complete drug-like structures. Frameworks like SILVR and MolSnapper use iterative guidance to generate molecules around a reference structure to address this issue. [4, 5] However, these methods exhibit diminished generation performance compared to the base model when reference information is incorporated.

We propose a framework, BRIDGE, that enhances the generation quality of the baseline diffusion model around a reference molecule. As a result, our protocol enables zero-shot adaptation for fragment elaboration, allowing for generation of targeted molecules. To demonstrate this, we retrospectively investigate the performance of BRIDGE for fragment linking, targetting the enzyme IMPDH. The computational experiments with BRIDGE successfully recovered known inhibitors that were experimentally tested with improved affinity by Trapero et al. [6] In addition, potential alternative structures with improved binding could be identified and would require validation through biophysical assays. We plan to apply and validate the tool in further fragment elaboration cases.

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**Poster Presentations**

**Shih-Huan Huang** (Department of Chemistry, University of Cambridge) - Explaining the main molecular mechanisms in neurodegenerative diseases: from a discrete model to a continuous theory

The molecular mechanisms underlying protein aggregation, which increases across the brain as neurodegenerative diseases like Alzheimer’s disease progress, remain poorly understood despite decades of research. The need for computational models is growing due to their ability to rapidly simulate real-world scenarios. Here, we propose a reductionist, minimal, cell-level model to describe aggregation patterns in diseased brains. The model incorporates two fundamental mechanisms driving aggregate formation: cell-autonomous triggers and cell-to-cell propagation. Given the fact the system follows Poisson statistics, analytical results for different length scale measures can be obtained. In addition, in the external-trigger-only case, the discrete model can be approximated by a continuous reaction-diffusion-like framework. Our model bridges the molecular level to the brain-region level and serves as a platform for parameter extraction and hypothesis testing.

**Marco Mattia** (University of Edinburgh) - Learning the role of dynamics of kinase activation loops

Proteins are flexible biopolymers essential to all biological processes, with their conformational ensemble dictating their biological function. Within a protein, intrinsically disordered regions (IDRs) are especially flexible, which enables them to participate in a wide range of cellular interactions. Kinases are a class of proteins often found overexpressed in cancer cells, making them a candidate for drug design. Several thousand kinases structures have been solved, revealing a conserved structure that includes an IDR called the “activation loop”. As kinases function is linked to their conformational switch between an inactive and an active state, our goal is to characterize how activation loop rearrangements may influence kinase activation.

While experimentally characterizing the whole conformational space of an IDR is challenging, insight into its dynamics can be obtained computationally, for instance, via molecular dynamics (MD) simulations [1]. Unfortunately, computational limitations to the timescales MD simulations can sample often prevent a full characterization of IDRs conformational spaces. An alternative sampling avenue is to exploit generative machine learning (ML) models, which can be used to predict unseen data from a limited set of examples. In this context, the molearn framework [3,4], has been designed to train generative models with protein conformational spaces. In this study we focus on a specific kinase, B-Raf. We exploit the wealth of experimental structural data on kinases to model an ensemble of B-Raf activation loops. Training molearn with this dataset enables us to identify two dominant loop arrangements, that we are now correlating with structural features on B-Raf known to be characteristic of its open and close state.

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**Saabir Petker** (University of Edinburgh) - Understanding the Barocaloric Effect in Polymers with Molecular Dynamics

Current refrigeration processes consume over 20% of the global energy usage and emit high global warming potential gases. [1] This is unsustainable, so new refrigerants must be developed to avoid further global warming emissions and meet the growing demand. [2] Solid state refrigerants are a long-term solution, with the most promising being materials with a “massive” pressure-induced caloric effect: barocaloric effect (BCE). [3] The BCE is observed in polymers, and this work focusses on nitrile butadiene rubber (NBR). [4] Using polymers as refrigerants is an exciting avenue towards recycling and reusing otherwise-polluting refuse. [5] There is little experimental, and less computational, work on barocaloric polymers so the exact origins of their “giant” BCEs are unknown. [6] The BCE in polymers, specifically adiabatic temperature change, is affected by the glass transition temperature, above and below which we consider the polymer a rubber or glass respectively. We explore how copolymer ratio affects the BCE in NBR melts across their glass transition temperature domains using molecular dynamics simulations.

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**Harry Stroud** (CiTIUS, University of Santiago de Compostela, Spain) - A trajectory-based SMD approach for sampling complex reaction coordinates defined using iMD-VR

One of the major challenges when using molecular dynamics (MD) to simulate complex molecular systems is the sampling of rare events. Many enhanced sampling techniques involve choosing a specific reaction coordinate and/or set of collective variables (CVs) that accurately capture the desired behaviour. This can be difficult for complex molecular manipulations within large systems (e.g. drug docking in a protein-ligand system) due to their hyper-dimensionality. Interactive MD (iMD) enables researchers to investigate the behaviour of molecular systems by directly applying forces to the molecules, without the need to predefine either a reaction coordinate or a CV subspace. By performing iMD in virtual reality (iMD-VR) [1], researchers can interact with real-time molecular simulations in a 3-D environment, providing a natural interface that enables exploration of complex molecular behaviour on computationally feasible timescales. However, in iMD-VR it is often the case that the forces applied are so great that the system of interest is pulled far from equilibrium, making it difficult to directly extract quantitative information about the equilibrium or near-equilibrium behaviour of the system. To do so, researchers would have to (a) spend far longer in VR than is feasible in order to simulate the timescales necessary to keep the system close to equilibrium, and (b) apply forces in a controlled and consistent manner which would be difficult for a human to achieve. These issues can be addressed by taking the trajectories defined by researchers in iMD-VR and using them as reaction coordinates on which to perform steered MD (SMD) simulations. SMD involves applying forces to the molecular system along a pre-defined reaction coordinate to generate trajectories that are used to sample the nonequilibrium behaviour of the system. SMD has been used to efficiently recover equilibrium properties--such as the potential of mean force (PMF)--of molecular systems along specified reaction coordinates. For instance, Schulten et al. [2,3] used SMD simulations to obtain the PMF of the stretching of deca-alanine, and demonstrated that this can be accurately calculated using the second order cumulant expansion of Jarzynski’s equality [4] with data from as few as ten SMD simulations. Here, we present a trajectory-based version of SMD that uses a real-space trajectory to define the reaction coordinate along which to sample the behaviour of the system. This trajectory-based SMD approach can be used in a combined iMD-VR+SMD workflow, in which researchers can harness their chemical intuition to define and quantitatively investigate the nonequilibrium behaviour of molecular systems along specific reaction coordinates.

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**Till Welker** (University of Edinburgh) - Staying on Time: Precision and Cost of a Controlled Clock

The precision of an autonomous clock is associated with an entropic cost. In overdamped systems, the precision-cost tradeoff is bounded by the thermodynamic uncertainty relation (TUR). To avoid paying immense costs while staying accurate over an extended period, the clocks in our phones, radios, and computers adapt their dynamics according to a precise reference clock. We study two minimal model classes of controlled clocks. First, the two-state clock with one state running slower and one state running faster than the reference clock. At a rate R, the two-state clock reads out the reference clock and adjusts its state accordingly. Second, the reset clock. It resets at rate R to a distribution around the reference clock. While in both cases the clock hand progresses, the offset reaches an analytically solvable steady state, and the clock's error remains bounded. The combined cost of the controlled and reference clock obeys the TUR. However, the operator of the controlled clock only needs to pay a part of that cost, namely the driving of the controlled clock and the cost of control. By optimising both clocks, we show a tradeoff between the absolute error, the entropy production rate and the adjustment rate R