

Bioengineering and Biomedicine

From bedside to clinical trials and company creation, how one patient's journey in improving the outcomes of their disease has just begun

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Cystic Fibrosis is a genetic disease that affects multiple organ systems. The severity of the disease is due to the genetic mutations a patient may carry. In my case, a rare mutation, diagnosis came later in life with the advent of widespread genetic sequencing. This disease has affected my reproductive health, ability for physical activity and general happiness. I have benefitted from advances in reproductive health as well as the recent approval of Vertex's Trikafta which was not indicated for my genetic mutation which has changed my life. As a successful investor, I am now privileged to help create biotechnology companies that I hope will directly impact my health outcomes for other patients. I am participating in a clinical trial for the latest therapeutic in development for CF. I will describe how I have benefited from scientific advancements, actively participate in therapeutic trials and aim to be involved in creating the next class of diagnostics and medicines.

Cytidine deaminases APOBEC3C and APOBEC3D promote DNA replication stress resistance in pancreatic cancer

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Pancreatic cancer is among the most refractory cancers and a leading cause of cancer death. A first line of treatment for advanced or metastatic pancreatic cancer is the DNA replication stress-inducing agent gemcitabine (2',2'-difluorodeoxycytidine), often used in combination with the microtubule stabilizing agent paclitaxel. Although gemcitabine has been the standard of care for pancreatic cancer for greater than two decades, most tumours exhibit intrinsic or acquired resistance to gemcitabine regimens. It is largely unknown how pancreatic cancer cells respond to the DNA replication stress produced by gemcitabine and why different pancreatic cancer cells display differential responses to the same treatment.

To address these knowledge gaps, we performed genome-wide CRISPR-Cas9 screens on pancreatic cancer cells with different genetic backgrounds and gemcitabine sensitivities. Our screens recalled known vulnerabilities to gemcitabine, in addition to novel shared and genotype-specific vulnerabilities. Of particular interest, we found that knockout of two cytidine deaminases, *APOBEC3C* and *APOBEC3D*, hypersensitized pancreatic cancer cells to gemcitabine. *A3C* and *A3D* encode members of the APOBEC3 family of cytidine deaminases involved in the restriction of viruses and endogenous retroelements by DNA and mRNA editing. We show that *A3C* and *A3D* expression is strongly induced by gemcitabine treatment and that *A3C* and *A3D* promote gemcitabine resistance in pancreatic cancer cells by deamination of deoxycytidines in ssDNA to promote replication fork re-start.

Our work provides the first comprehensive genetic network of targets that contribute to the sensitivity and resistance to gemcitabine and defines a novel role for *A3C* and *A3D* in maintaining genome stability, advancing our molecular understanding of the DNA replication stress response in pancreatic cancer.

The Emerging Roles of Live-Cell Assays and Artificial Intelligence in Cancer Drug Development and Precision Therapy

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During my talk I'll present our recent unpublished data showing the integration of Cyclica's artificial intelligence-driven computational tools with two high-throughput, live-cell drug discovery technologies recently developed in my lab - Mammalian Membrane Two-Hybrid Drug Screening (MaMTH-DS) and Split Intein Mediated Protein Ligation (SIMPL). By progressively screening a cohort of currently 'undruggable' protein targets such as EGFR-triple mutant and KRAS, we obtained valuable prospective validation of our integrated platform and rapidly discovered actionable compounds, establishing a robust pipeline against challenging disease targets associated with untreatable cancers.

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Sigma-1 receptor – a role in neuronal signaling and neurodegeneration

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The sigma 1 receptor (S1R) is a 223 amino acid-long transmembrane endoplasmic reticulum (ER) protein. Agonists of S1R demonstrated neuroprotective effects in variety of preclinical models and there are several on-going clinical trials of S1R agonists in neurodegenerative disorders. However, signaling functions of S1R are poorly understood. In our recent studies we tested the hypothesis that biological activity of S1R in cells can be explained by its ability to interact with cholesterol. By performing experiments in reduced reconstitution systems, we demonstrate direct effects of cholesterol on S1R clustering. We identify a novel cholesterol-binding motif in the transmembrane region of human S1R. Mutations of this motif impair association of recombinant S1R with cholesterol beads, affect S1R clustering in vitro and disrupt S1R subcellular localization. Further, we found that S1R agonists cause disruption of S1R clusters. Based on these results we propose that S1R-cholesterol interactions enable the formation of cholesterol-enriched microdomains in the ER membrane. We further propose that S1R agonists enable the disassembly of these cholesterol-enriched microdomains and the release of accumulated proteins such as ion channels, signaling receptors, and trophic factors from the ER. We also propose that these cholesterol-enriched microdomains form the basis for formation of membrane contact sites between ER and other subcellular organelles such as mitochondria and plasma membrane

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Mitochondrial Contributions To Cancer: Causes, Consequences, & Coincidence

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Mitochondria created an evolutionary advantage for eukaryote and metazoan organization, and their impact on cell biology extends from anabolic and catabolic metabolism to determining the final moments of cell survival by engaging apoptosis. Throughout the last decade, interest in studying how mitochondria influence cancer cell biology led our laboratory to identify mechanisms linking oncogenic signaling (i.e., BRAF^{V600E} / NRAS^{G12V}) to multiple mitochondria-centric processes within malignant cells including altered mitochondrial dynamics, oxidative phosphorylation, and chemosensitivity. More recently, we focused on exploring how oncogenes intersect upon mitochondrial biology prior to transformation – which will likely provide molecular details into pre-malignant cell biology and early stages of disease. We commonly position our studies in the context of melanoma as we have extensive experience with primary human melanocytes, integrated cohorts of patient RNA-seq datasets and tissues, and multiple in vitro and in vivo models of early and late disease. At present, we are investigating the implications of chronic mitochondrial division in oncogene-induced senescence, the mitochondrial unfolded protein response, and the immunobiology of melanoma in situ. Our discussion will provide new molecular insights into how mitochondrial biology impacts on the cell biology of melanoma, and informs the immune landscape of primary tumors.

Characterization and improvement of a nicotine degrading flavoenzyme

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Nicotine dependence is currently responsible for one in seven deaths worldwide, but methods of escaping this global addiction have limited efficacy. The flavoenzyme nicotine oxidoreductase (NicA2) has shown promise as an injectable treatment for nicotine addiction in rat studies.¹ It works by removing nicotine from the bloodstream before it reaches the brain. Unfortunately, this enzyme re-oxidizes very poorly with O₂, severely limiting nicotine turnover.² *In vitro*, NicA2 has a k_{cat} of only 0.006 s⁻¹.³ This necessitates the injection of clinically unrealistic amounts of enzyme in order to have the desired therapeutic effect. Using a genetic selection, we isolated variant forms of NicA2 that increase the O₂-dependent activity of NicA2 more than 100-fold. The mutations in these variants map to five hotspot locations that surround the active site. We evaluate the pharmacokinetic properties of increased activity variants in a rat model. Characterization of the resulting increased activity variants has allowed us to gain insight about how oxygen utilization can emerge in evolution, while also providing more clinically viable forms of NicA2.

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IzoView: The Advantages of Contrast Enhanced Cone-Beam Breast Computed Tomography for 3-Dimensional Imaging of the Breast for Diagnostic Imaging

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Mammography and ultrasound remain the principal tools for diagnostic breast imaging. Compression of the 3D structure of the breast is necessary for 2D mammography imaging. Over the past decade, mammography systems have in general been augmented with tomosynthesis, which uses a small number of mammographic projections covering an angular range of 15-50° (depending on vendor), and these data are reconstructed to produce pseudo-tomographic images (~2.5D). Mammography as well as tomosynthesis suffer from a significant loss of sensitivity in women with high breast density, because overlapping tissues can obscure the detection of a tumor, if present. The aggressive compression required for these modalities can also lead to breast implant rupture. Izotropic is building a dedicated cone-beam breast computed tomography (bCT) system, based on four successive prototypes from the laboratory of Dr. J.M. Boone¹⁻³. This system will be the first x-ray device that is completely self-shielded for breast imaging. The bCT system acquires ~500 images in 10 seconds, which are reconstructed into a high-resolution volume data set – a true 3D depiction of the breast. Breast CT overcomes the challenges of visualizing overlapping structures, eliminates the need for breast compression, and with the injection of contrast agent can demonstrate both physiologic function as well as breast anatomy. Informed by previous studies at UC Davis, we will demonstrate in the Izotropic system that the ability to precisely visualize breast tissue in 3 dimensions with contrast enhancement is superior to the current standard-of-care breast diagnostic examination. This approach will largely mimic the sensitivity of breast MRI at a fraction of the cost, and with much better spatial resolution. This new platform will enable robotic guided biopsies, allow better visualization of implants, and provide tumour classification based on morphology and physiologic enhancement patterns. Additionally, it will permit local staging and provide information on treatment response in the neoadjuvant setting.

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Reversible protein aggregation regulates cell growth in response to environmental stress conditions

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Protein aggregation has historically been viewed as an irreversible, deleterious process responsible for several pathologies, including neurodegenerative diseases. However, recent evidence in yeast suggests that aggregation of an increasing number of proteins is a reversible, highly-regulated physiological mechanism used by cells to adapt to several stress conditions. Indeed, our recent work identified reversible aggregation of Cdc19, the major isoform of yeast pyruvate kinase, as a critical factor contributing to the adaptation of cells to carbon starvation. Available suggest that its reversible aggregation protects Cdc19 from unscheduled degradation to allow efficient re-initiation of growth after stress release. However, the molecular structure and cellular mechanisms regulating assembly and disassembly of reversible aggregates remain poorly understood. Moreover, it remains to be determined whether reversible aggregation is conserved in mammalian cells, and whether reversible aggregates serve as precursors for toxic, irreversible amyloids. We have used a combination of genetic, biochemical and mass spectrometry-based approaches to tackle these questions, and recent progress on these efforts will be presented.

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Conformational models of APP processing by gamma secretase based on analysis of pathogenic mutations

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Proteolytic processing of amyloid precursor protein (APP) by β and γ secretases leads to generation of A β 40 (non-amyloidogenic) and A β 42 (amyloidogenic) peptides. Presenilin-1 (PS1) or presenilin-2 (PS2) play a role of catalytic subunit of γ -secretase. Multiple familial AD (FAD) mutations in APP, PS1, or PS2 result in increased A β 42:A β 40 ratio and accumulation of toxic A β 42 oligomers and plaques in patient brains. In this study we performed molecular modeling of APP complex with γ -secretase and analyzed potential effects of FAD mutations in APP and PS1. Based on structural analysis of known γ -secretase structures we proposed that APP can form a complex with γ -secretase in 2 potential conformations – M1 and M2. In conformation M1 transmembrane domain of APP forms a contact with perimembrane domain that follows the transmembrane domain 6 (TM6) in PS1 structure. In conformation M2 transmembrane domain of APP forms a contact with transmembrane domain 7 (TM7) in PS1 structure. By analyzing effects of PS1-FAD mutations on local protein disorder index, we discovered that these mutations increase conformational flexibility of M2 and reduce conformational flexibility of M1. Based on these results we proposed that M2 conformation, but not M1 conformation, of γ secretase complex with APP leads to amyloidogenic (A β 42-generating) processing of APP. Our results also suggest that specific inhibitors of A β 42 production could be potentially developed by selectively targeting M2 conformation of γ secretase complex with APP.

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Integrative analysis of lung cancer identifies distinct proteotypes associated with altered metabolism and patient outcomes

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer deaths worldwide. Only a fraction of NSCLC harbor actionable driver mutations and there is an urgent need for patient-derived model systems that will enable the development of new targeted therapies. NSCLC and other cancers display profound proteome remodeling compared to normal tissue that is not predicted by DNA or RNA analyses. Here, we generate 137 NSCLC patient-derived xenografts (PDXs) that recapitulate the histology and molecular features of primary NSCLC. Proteome analysis of the PDX models reveals 3 adenocarcinoma and 2 squamous cell carcinoma proteotypes that are associated with different patient outcomes, protein-phosphotyrosine profiles, signatures of activated pathways and candidate targets, and in adenocarcinoma, stromal immune features [1]. Altered iron regulation is identified as a key determinant of NSCLC aggressiveness associated with patient outcome [2]. These findings portend proteome-based NSCLC classification and treatment and support the PDX resource as a viable model for the development of new targeted therapies.

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Machine Learning for Understanding Molecular Complexity in Precision Medicine

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Abstract:

We are faced with a flood of molecular and clinical data. We are measuring interactions between various bio-molecules in and around a cell that form large, complex systems. Patient omics datasets are also increasingly becoming available. These systems-level network data provide heterogeneous, but complementary information about cells, tissues and diseases. The challenge is how to mine them collectively to answer fundamental biological and medical questions. This is nontrivial, because of computational intractability of many underlying problems on networks (also called *graphs*), necessitating the development of approximate algorithms (heuristic methods) for finding approximate solutions.

We develop artificial intelligence (AI) methods for extracting new biomedical knowledge from the wiring patterns of systems-level, heterogeneous biomedical networks. Our *graphlet*-based and other methods uncover the patterns in molecular networks and in the multi-scale organization of these networks indicative of biological function, translating the information hidden in the network topology into domain-specific knowledge. We also introduce a versatile data fusion (integration) machine learning (ML) framework to address key challenges in precision medicine from the wiring patterns of biomedical network data: better stratification of patients, prediction of driver genes in cancer, and re-purposing of approved drugs to particular patients and patient groups, including Covid-19 patients. Our new methods stem from novel network science algorithms coupled with graph-regularized non-negative matrix tri-factorization (NMTF), a machine learning technique for dimensionality reduction, inference and co-clustering of heterogeneous datasets. We utilize our new framework to develop methodologies for performing other related tasks, including disease re-classification from modern, heterogeneous molecular omic data, inferring new Gene Ontology relationships, aligning multiple molecular networks, and uncovering new cancer mechanisms.

Systems Biologics: Large-Scale Engineering of Modulators of Protein Networks

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In recent years, genomics technologies have revolutionized basic research and are also having a significant impact on understanding, predicting and diagnosing disease. Over the same period, the biologics revolution, led by therapeutic antibodies, has greatly expanded our ability to target proteins that drive cancer and other diseases. To date, however, the academic genomics revolution and the industrial biologics revolution have not been combined, so that the vast amounts of data generated by genomics technology have not been effectively translated to drug development, which remains a slow, case-by-case process. We have developed an approach that we call “systems biologics”, which combines large-scale systems biology with the development of new antibody drugs. The efficient pipeline extends from basic research through translational science, and it constitutes a new model for research and drug development. Through this model, cutting-edge systems biology basic research can be seamlessly translated into systems biologics: novel, multi-functional drugs and diagnostics that take advantage of the complexities of human biology revealed by genomics data.

Systems Biologies in Network Biology

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The interplay of environment and genome on the traits of an organism are reflected in how variations in either act on the biochemical networks that underlie all cellular processes. Current evidence suggests that predicting how environmental or genome variation affect specific cellular processes is most accurately determined by their effects on biochemical networks of the cell. It is impossible to measure, let alone predict, how entire molecular networks function, but we can choose useful surrogates of the network to act as reporters, such as protein interaction networks (PINs). We have developed general strategies to measure spatiotemporal dynamics of PINs in living cells, using Protein-fragment Complementation Assays (PCA) to measure PINs at whole proteome scales (Tarassov et al., 2008) and for smaller subsets of interactions, response to environmental perturbations and to map novel biochemical pathways and predict genes associated with human diseases (Macdonald et al., 2006; Messier et al., 2013; Stynen et al., 2018). I will present a simple and global strategy to map out gene functions and target pathways of drugs, toxins, or protein biologics based on “homomer dynamics” protein-fragment complementation assays (hdPCA), a method that captures the integrated fate of a gene following a genetic or environmental perturbation, from transcription to protein to post-translational modification (Stynen et al., 2018). I will then present recent developments of methods to measure and manipulate proteins, their abundances, and both abundance and protein-protein interaction stoichiometries, at a proteome-wide level and in any cell lines. These are allowing us to decipher mechanisms of action of biologics, and drugs and gene variations, on biochemical processes. They are also revealing details about the thermodynamics of PINs, providing insights into passive and active origins of energy and information propagation in living cells.

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Pulse labeling reveals the tail end of protein folding in the cell

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Over two million proteins are synthesized every minute in a rapidly dividing human cell. Some of these proteins will spontaneously reach their native state even while being translated and within a few milliseconds, whereas other proteins will only do so with the help of chaperone proteins and on a longer time span. Failure to correctly fold can result in an inactive protein and is associated with numerous neurodegenerative diseases, in which protein misfolding and aggregation is observed. To broaden our understanding on how protein folding is regimented at the cellular level, we probed which newly translated proteins are more thermo-sensitive and aggregate upon heat stress. These newly synthesized thermo-sensitive proteins correspond to a subset of abundant, short, and highly structured proteins. Notably, these proteins display a tendency to form β -sheet secondary structures and are enriched for chaperone binding motifs, suggesting a higher demand from chaperone-assisted folding. Importantly, these proteins are only thermos-sensitive following synthesis and not once “matured”. One possibility is that there is a tradeoff, where more time is needed for a subset of proteins to fold and mature into a conformation that is then more stable upon stress.

Using Deep Learning to Reveal Polypharmacology for Small Molecule Discovery

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Artificial Intelligence (AI) holds promise in ushering in a new era of drug discovery. MatchMaker™ is a deep learning approach trained on drug target interaction (DTI) data mapped to protein structures to predict binding complementarity of small molecules to proteins. MatchMaker routinely screens chemical spaces on the order of 10^9 molecules across the structurally characterized proteome – supplemented by AlphaFold structures – to provide a unique glimpse into the polypharmacology of evaluated molecules. Applying MatchMaker to known active small molecules reveals their putative interactions with proteins that may be pivotal for its biological activity. Revealing potential protein binders is particularly useful in cell-based or phenotypic-based experiments where the mechanism of action is unknown. Exemplifying this application is our work with EMI1¹, a molecule initially discovered using MaMTH-DS (mammalian membrane two-hybrid drug screening) that was found to block activation of EGFR triple mutant independent of kinase activity. Using EMI1's predicted polypharmacology as a guide, additional small molecules were generated to phenocopy the activity of EMI1. A small molecule hit was found that served as the basis for a series of compounds that, like EMI1, were able to block EGFR triple mutant activation in cell-based assays.

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A TLR-to-STING-to-UPR pathway modulated by Parkinson's disease-related proteins regulates the transition between innate to adaptive immunity

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While the contribution of inflammation in the pathological process leading to Parkinson's disease (PD) is firmly established, a growing body of evidence also supports a role for the adaptive arm of the immune system in the disease. We have shown that the PD-proteins PINK1 and Parkin regulate the presentation of mitochondrial antigens on MHC I molecules during inflammation, a process referred to as MitAP (**Mitochondrial Antigen Presentation**). We proposed that the over-activation of the MitAP pathway, in the absence of PINK1 for example, is part of an autoimmune response enabling the recognition and attack of dopaminergic neurons by cytotoxic T cells. The emerging concept that PD-proteins regulate, in part, both inflammation and antigen presentation led us to investigate the role these proteins may be playing in the transition from innate to adaptive immunity during stress. Our data indicate that this transition is triggered by multiple stress sensors along a TLR4-to-STING-to-UPR pathway. Remarkably, PD-proteins, including LRRK2, actively regulate this process, highlighting their role in the control of a balanced immune response during stress. Understanding the role played by the immune system in PD will lead to the development of novel immune-based therapeutic approaches.

Pathophysiology and Novel Therapies for Uremic Cardiomyopathy

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Chronic kidney disease (CKD) has reached epidemic proportions globally. The presence of CKD greatly elevates the risk of death and by far the most common cause of death is cardiac disease consisting clinically of heart failure and dysrhythmias and pathologically of cardiac hypertrophy and fibrosis. The cardiomyopathy in CKD can be affected by the traditional Framingham cardiovascular risk factors. However, the collective metabolic derangements in CKD, termed uremia, beget uremic cardiomyopathy which is a multifactorial disorder of the myocardium. The underlying metabolic causes of uremic cardiomyopathy is diverse and we have focused on three pathobiologic intermediates- Klotho deficiency, excess fibroblast growth factor (FGF)-23, and phosphotoxicity. Klotho deficiency results from the inability of the failing kidney to synthesize and supply the body with Klotho. The reason for the massive increase in FGF23 production from bone cells in CKD is unclear. Phosphotoxicity results from the inadequate renal phosphate excretion in CKD. We provide associative and interventional rodent data the each of the above three condition can individually and synergistically cause uremic cardiomyopathy. At this juncture, the preclinical data needs to be translated into human studies. Although Klotho therapy, FGF23 blockade, and phosphate control do not represent the totality of interruption of the pathobiology of uremic cardiomyopathy, but constitute three major pillars of reducing mortality in CKD.

Modeling the role of the gut in Parkinson's Disease

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Parkinson's disease is a neurodegenerative disorder associated with the progressive loss of dopaminergic neurons in specific regions of the brain. While the mechanisms leading to neuron cell death in Parkinson's disease are still poorly understood, host genetics and environmental factors are viewed as playing a key role. The gut-brain axis has long been suspected to play a role in this complex disease, with a growing body of evidence now supporting the notion that intestinal inflammation is an important driver of Parkinson's Disease development. We have recently developed a new mouse model to examine the link between these pathologies. Although mutations in the gene *PINK1* in humans are associated with a high risk of developing Parkinson's Disease, *Pink1* knockout mice are generally healthy and display no Parkinson's-like symptoms. We previously showed that intestinal infection with the Gram-negative intestinal pathogen *Citrobacter rodentium* in *Pink1* knockout mice leads to the emergence of motor symptoms that can be reversed by treatment with L-DOPA. Here we show, using single cell RNA sequencing, that loss of *Pink1* has profound impacts on the early response to intestinal infection. These findings provide a window to better understand how dysregulation of inflammatory events in the gut can trigger the development of Parkinson's Disease in genetically susceptible individuals.

Nanopores and Nanofluidics

APPLICATIONS OF SOLID-STATE NANOPORES TO TRANSLATIONAL HYALURONAN ANALYSIS

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Hyaluronan (or hyaluronic acid, HA) is a biological sugar that is found ubiquitously in mammalian tissues and biofluids. Both the abundance of HA *in vivo* and its varying size (molecular weight) can have important impacts on the critical roles the molecule has in human health and disease. However, current technologies have significant weaknesses in quantitation, resolution, and/or sensitivity that have limited the role of HA in translational diagnostics. To address this gap, our lab has established solid-state nanopores as a platform for robust HA analysis [1]. In this talk, I will discuss the effects of several key experimental conditions on measurement efficacy [2] as well as our development of supporting protocols that enable quantitative isolation of HA from diverse biological matrices. I will then present on extensions of our work towards translational studies as well as a covalently modified HA (heavy chain HA) that has recently emerged as an important regulator of inflammation.

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NANOPORE TRANSPORT BEYOND DNA SEQUENCING

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Nanopore systems are ubiquitous in biology and engineering, with applications ranging from transmembrane transport to power generation and sensing. Modeling and simulations have been integral to the development of the field, providing microscopic interpretation of experimental measurements and exploring transport modalities and phenomena beyond experimental reach. In this lecture, I will describe recent work from our lab directed at increasing realism of nanopore transport simulations, addressing both accuracy of the method and the breadth of systems amenable to it. Specific topics to be covered may include protein sequencing and fingerprinting, DNA molecular motors, artificial water and ion channels, viral genome packaging and transport through the nuclear pore complex. The lecture will highlight recent advances in the methodology of multi-resolution simulations [1-3], which make computational description of to-scale nanopore systems possible.

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Nanofluidics in 1D: Ion diffusion and ion transport in small diameter carbon nanotube porins

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Nanofluidic systems control ion and water transport on a unprecedentedly small scale, which is important for applications ranging from biosensing to precision separations. Living systems, which move ions and small molecules across biological membranes using protein pores, often rely on finely controlled nanoscale confinement effects to achieve efficient and exquisitely selective transport. I will show that carbon nanotube porins—pore channels formed by ultra-short carbon nanotubes assembled in a lipid membrane—can exploit similar physical principles to transport water, protons, and ions with efficiency that rivals and sometimes exceeds that of biological channels [1-3]. I will discuss how molecular confinement, slip flow, and the nature of the pore walls influence the mechanisms of ion diffusion, ion selectivity, electrophoretic transport, and electroosmotic coupling in these nanopores. Overall, carbon nanotube porins represent simple, versatile, and highly controlled biomimetic membrane pores that provide an ideal test bed for development of the next generation of biomimetic channels and pores.

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Using Nanochannels and Nanopores for single-molecule separation and sensing

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SARS-CoV-2 outbreak of the coronavirus disease has underlined the acute need for extremely sensitive, accurate, fast, point-of-care mRNA and proteins quantification sensors. Here I will show how solid-state nanopores can be used to digitally count target mRNA molecules from both biological *and* clinical Covid-19 samples surpassing the accuracy of “gold-standard” RT-qPCR. Moving beyond nucleic acids, I will discuss our on-going efforts towards the use of sub-wavelength depth nanochannels for single protein molecule separation, characterization and quantification using a single particle tracking algorithm. Moreover, we develop unique *plasmonic nanopore* devices for single protein molecules identification based on partial labelling of only two or three amino acids. We show that SDS-denatured protein can be electrically threaded and translocated through sub-5 nm solid-state nanopores given rise to molecular-weight dependent translocation properties. This research opens up new directions ultimately leading towards single-cell proteomics of even rarely expressed proteins.

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TWO-DIMENSIONAL EMPTY SPACE AND ITS UNIQUE PROPERTIES

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I shall provide an overview of our recent work on atomic-scale cavities fabricated by van der Waals assembly of 2D crystals. These ultimately narrow cavities can be viewed as if an individual atomic plane is extracted from a bulk crystal leaving behind a 2D empty space, essentially an angstrom-scale gap connecting two edge dislocations. Gas, liquid, ion and proton transport has been studied using 2D cavities down to one atom in height, revealing interesting and sometimes counterintuitive properties.

The power of single-molecule approaches to biology

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Nanotechnology with its single-molecule techniques offers fantastic opportunities to contribute to biology. I will present some recent examples from my lab where nanotech single-molecule tools are used to unravel the biology of cells down to the single-molecule level as well as build nanoscale structures from the bottom up.

1. Nanopore-based sequential reading of peptides [1]

We recently demonstrated a nanopore-based single-molecule peptide reader capable of reliably detecting single amino-acid substitutions within individual peptides. A peptide is linked to a DNA molecule and sequentially pulled through a biological nanopore by a DNA helicase in single amino-acid steps. Stepping ion-current signals enable discrimination of single-amino-acid substitutions in single reads. Notably, we demonstrated the capability to ‘rewind’ peptide reads, obtaining indefinitely many independent reads of the same molecule, yielding an undetectably low error rate in single-amino-acid variant identification. These proof-of-concept experiments constitute a promising basis for the development of a single-molecule protein sequencer.

2. A DNA origami turbine powered by nanoscale flow [2]

We recently built an artificial nanoscale turbine. We demonstrate driven rotary motion of a DNA origami turbine which harnesses energy from a water/ion flow generated by a static chemical or electrical potential gradient in a solid-state nanopore. One type of origami nanoturbines consists of a 6-helix DNA bundle that adopts a chiral conformation upon phoretic docking onto the nanopore and subsequently displayed a sustained unidirectional rotary motion of up to 20 revolutions/s. Another type has designed turbine blades. These artificial nano-engines operate autonomously in physiological conditions, converting energy into useful mechanical work.

3. Real-time imaging of DNA loop extrusion by condensin and cohesin SMC complexes [3]

Structural Maintenance of Chromosomes (SMC) proteins like cohesin and condensin spatially organize chromosomes by extruding DNA into large loops. Using single-molecule assays, we provided unambiguous evidence for loop extrusion by directly visualizing the processive extension of DNA loops by SMCs in real-time. In recent extensions of this work, we showed that how this process occurs on supercoiled DNA, how SMCs also can exhibit phase condensation, and that SMC proteins can bypass huge roadblocks of bound proteins on DNA.

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Exploring new nanopore candidates from aerolysin like proteins

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Aerolysin-like proteins are a sub-family of β -pore forming toxins that are widely present in all kingdoms of life¹. Their structure and mechanism of pore formation have been a long-term interest which provides cues for the development of therapeutics in fighting disease. Recently, this family of proteins is also growing attention because of their biotechnological application as nanopore sensors for biological and synthetic molecules sensing and sequencing, especially for single-molecule proteomic analysis². However, in spite of the conserved structural fold, the sequence identity in this family is very low. This complicates their sequence alignment, hindering an understanding of their pore structure and properties, and therefore their further biotechnological applications. In an attempt to further understand the properties of aerolysin-like pores, we created models for the pore structure of three family members, *Clostridium perfringens* epsilon toxin (ETX), *Laetiporus sulphureus* lectin (LSL) and *Bacillus thuringiensis* parasporin-2. Their structures and sensing capabilities for ssDNA have been first assessed by *in silico* methods, and then ETX has been incorporated into a planar lipid membrane for nanopore experiments. Three types of ETX pores have been observed during single-channel recording experiments with only one type of them being able to translocate ssDNA, inducing a bigger depth of current blockade compared to aerolysin nanopore. Our findings open a new venue for improving and diversifying nanopore capabilities for molecular sensing.

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What Can We Do with Solid-State Nanopores beyond Translocation-Based Sensing and Transport Control?

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Research on solid state nanopores has attracted great attention over the last two decades because of their great potentials in mimicking protein channels in cell membranes. Although significant progress has been made, past research has mainly utilized solid nanopores for translocation-based single biomolecule/particle sensing and ion/molecule transport control. What can we do with solid-state nanopores beyond these two directions? This question can be answered from two different perspectives. On one hand, single nanopores are the basic constitute of nanoporous membranes. It is therefore possible to use single nanopores to study and understand complicated transport phenomena in nanoporous membranes, paving the way for developing nanoporous membranes with better performance. On the other hand, it is worth noting that most of the past nanopore research is focused on molecule/particle translocating through the nanopore. The opposite scenario, i.e. molecules/particles blocking the nanopore, has not been extensively studied. In this talk, I will present my group's recent efforts on exploring fundamentals and application of solid-state nanopore from these two new aspects.

First, I will present our work on exploring evaporation from single nanopores. We have developed a novel microscope-based optical measurement to measure evaporation rates down to 10 aL/s from single nanopores. I will show that the ultimate evaporation flux from ultrathin silicon nitride nanopores is not limited by liquid transport to the interface and vapor removal from the interface, but by the interfacial evaporation kinetics and shows a strong diameter dependence. I will also show that the kinetically-limited evaporation from graphene nanopores can be much larger than that from silicon nitride nanopores due to edge facilitated evaporation and minimum contaminant accumulation.

Secondly, I will introduce our latest work on studying nanoparticle-blocked nanopore systems. We have found that, when nanoparticles with sizes larger than the diameter of a nanopore are electrophoretically driven towards the nanopore, they can be either electrokinetically trapped near the nanopore or physically block the nanopore based on their surface charge polarity. These two types of nanoparticle blockage modes can respond to various electrical or mechanical stimuli and show stimuli-responsive transport. I will show how we utilize such nanoparticle-blockage-induced stimuli-responsive transport to develop new applications for nanoparticle characterization, nanopore gating as well as bio-sensing.

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NOISE-DRIVEN TRANSPORT IN A VISCOSITY GRADIENT

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Gradients of voltage, pressure, temperature, or salinity can transport objects in micro- and nanofluidic systems by well-known mechanisms. I will describe the discovery of an electrokinetic transport effect driven by a viscosity gradient: An imposed liquid viscosity gradient causes an ionic current to flow inside a glass nanofluidic channel [1]. Measurements of the current and numerical simulations reveal that the counterions in the electric double layers near the nanochannel surfaces drift in the direction of decreasing viscosity. The measurements are well described by a simple model in which the counterion drift speed equals the gradient of an ion's local diffusivity. Drift in a viscosity gradient, which we call “viscophoresis”, is a consequence of multiplicative (state-dependent) noise, where the magnitude of the thermal fluctuations experienced by a particle depends on its position. Viscophoresis is also observed in the motion of fluorescent nanoparticles, and I will briefly discuss biological settings where it may play an underappreciated role.

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ION PERMEATION IN NARROW CARBON NANOTUBES: PUTTING THE PUZZLE TOGETHER VIA COMBINED AB INITIO AND MEAN-FIELD MODELING

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Narrow carbon nanotubes (CNTs) are unique mimics of water channels in biological membranes, yet the physics behind their selectivity, especially, relative roles of water and ion interactions within CNT and with surrounding matrix, is still unclear. Here we report ab initio investigation of water and ion transfer from solution into CNTs of diameters 0.68 nm and wider 0.8 nm tubes, common in experimental studies. We first focus on the effect of the medium surrounding CNT, defined by its dielectric constant ϵ . The transfer energies computed for $1 < \epsilon < \infty$ permit a transparent breakdown of transfer energy to three main contributions: binding to CNT, intra-CNT hydration, and dielectric energy [1]. The dielectric energy is small for water but very significant for ions and scales linearly with $1/\epsilon$, reminiscent of the Born equation, with the slope of the order 100 kJ/mol for all ions and CNTs. It may easily turn ion transfer from preferential to strong exclusion, as observed for potassium. In contrast, chloride appear to be strongly excluded for all ϵ . Simulations also demonstrate that, while water arranges in a single file in (5,5) tubes, it is strongly distorted in (6,6) tubes, both for water without and with some (but not all) ions.

Subsequently, we incorporate thermodynamic quantities computed ab initio in a mean-field model, adding to the picture proton and hydroxide inherently present in water and a few other ions. We first consider transfer of free ions, to which ions pair formation is subsequently added as a proxy of ion-ion interactions [2]. Experimentally observed affinity of CNTs to hydroxide does not show up in computed quantities for single ions, yet it is revealed as an exceptionally favorable transfer of KOH pairs. Nevertheless, we conclude that free ions, coexisting with more abundant, but less mobile ion pairs control the ion transport. The model successfully explains most observed effects of salt and ion type, concentration and pH on conductivity, ion transport numbers, ion permeation, activation energies, and current rectification. The proposed approach may be extended to other sub-nanometer nanochannels, which may advance our understanding and help design novel desalination and osmotic materials and devices.

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Scanning Ion Conductance Microscopy and Spectroscopy

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Scanning ion conductance microscopy (SICM) has been around for decades [1], yet it has not received as much attention as other forms of scanning probe microscopy. Recently, this true non-contact technique has kindled renewed interest among biophysicists and biologists because it is ideally suited for label-free imaging of fragile cell surfaces where it achieves exquisite resolution down to the nanometer regime without distorting the cell membrane [2,3]. SICM uses a glass nanopipette as a scanning probe and measures the current through the glass nanopore as a proximity detection of the sample surface. The challenge to harness this technique for time resolved 3D nanocharacterization of living cells lies in the relatively slow imaging speed of SICM. In this presentation I will show how we apply what we have learned from high-speed AFM to the field of SICM. By reengineering the SICM microscope from the ground up, we were able to reduce the image acquisition time for SICM images from tens of minutes down to 0.5s while extending the imaging duration to days [4,5].

SICM, however, is much more versatile than just an imaging tool. I will also discuss our recent results using SICM as a single molecule characterization tool. We term this method scanning ion conductance spectroscopy (SICS). Using capillaries with exceptionally small nanopores [6], we are able to detect and manipulate single molecules in a repeatable and high throughput manner.

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Selective Permeation under Low-Dimensional Confinement

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In view of process intensification that membrane technology promises to bring in, it is crucial for membrane materials to attain great selectivity, enhanced permeation, and in-operando durability. To this end, understanding of transport phenomena at low dimensions could help renew our insight for membrane pore design. This talk presents selective transport phenomena across 0D-, 1D- and 2D-confined space that atomically thin orifices [1], nanotubes [2] and 2D material lamellae [3] provide respectively. As the pore dimension increases, permeation tends to decrease from ultimate permeation to fast transport to unimpeded diffusion, whereas selectivity can be engineered on its own. Hence, proper design of the pores and the membrane architecture can collaborate with process operation to further tailor the selectivity-permeance characteristic. Thus-obtained knowledge could lay the cornerstone of advancing membrane transport properties toward process intensification.

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MICROSCOPIC BIODETECTION ANALYSIS IN MoS₂ MULTI-LAYER NANOPORE TRANSISTORS

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We report on various resistive effects involved in the electronic detection of single biomolecules in a nanopore of a MoS₂ nanoribbon. Our approach based on all-atom molecular dynamics simulation coupled with Boltzmann transport formalism accounts for self-consistent interaction among ions, charge carriers around the pore rim and biomolecules, and provides a comprehensive picture of the effects of electrolyte concentration, pore size, nanoribbon geometry, but also the doping polarity of the nanoribbon on the electrical sensitivity of the nanopore in detecting biomolecules [1]. Furthermore, we show that vertically stacked monolayer MoS₂-hBN nanopore FETs in a multi-sensing electronic scheme exhibit improved sensing robustness and noise reduction in detecting biomolecules such as DNA and proteins. Our model indicates naturally occurring conformational motion quenching of the bio-molecule penetrating the multi-layer membrane. The synchronization of electronic sensing current signatures across the successive MoS₂ probes achieved by time-lagged cross-correlation (TLCC) enhances the signal-to-noise ratio notably in the lower frequency spectrum, enabling the identification of homopolymers [2].

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Single-Molecule Biophysics Using Protein Nanopores

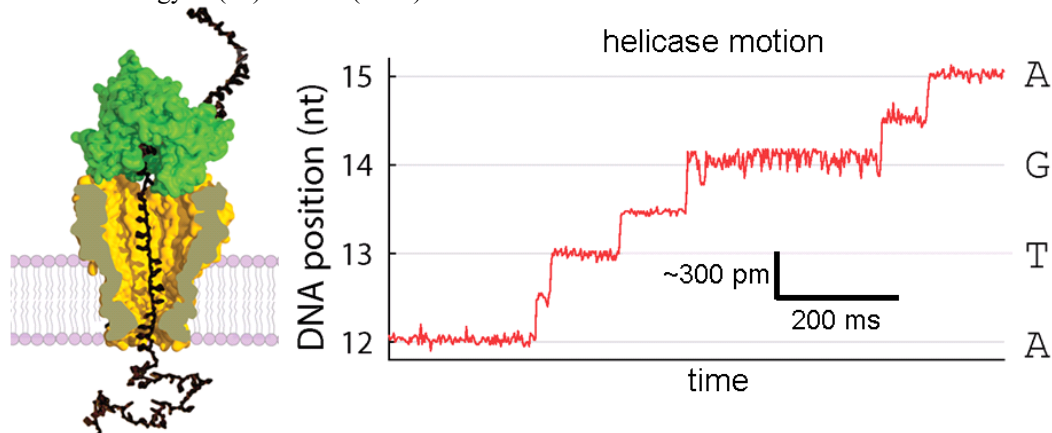
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My group has been at the nexus of developing nanopore sequencing¹ and establishing nanopores as a new tool for single-molecule biophysics². Much of our work is based on the engineered protein pore MspA. Here, I will show the stunning capabilities of using nanopores to observe enzyme mechanics in real-time as these enzymes move along DNA or RNA. We easily achieve ten times better position and time resolution than optical tweezers, while simultaneously measuring the exact nucleotide sequence in the enzyme. I will show hereto unseen detail in the motion of helicases, DNA and RNA polymerases, reverse transcriptases, etc. Besides establishing decisive kinetic enzyme models, we find (surprisingly) that the kinetics of most of these enzymes depends strongly on the template nucleic acid sequence. Of particular contemporary interest are the data we collected with the SARS-CoV-2 helicase nsp13.

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MEASURING BIOPOLYMERS AT THE SINGLE MOLECULE LIMIT: FROM SEQUENCING DNA TO IDENTIFYING PROTEINS WITH NANOMETER-SCALE PORES

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Biological nanometer-scale protein pores are the major basis of nerve and muscle activity and macromolecular transport across cell membranes. With the ultimate goal of providing low-cost measurements for health care applications, we have been studying the physical properties of bio-nanopores [1,2] and adapting them for the detection, characterization, and identification of molecules in aqueous solution [3-5]. In the absence of the target molecules to be detected, an applied voltage drives ions through a nanopore embedded in an electrically insulating lipid bilayer membrane. When a single molecule enters the pore, its physical and chemical properties control the degree by which it reduces the nanopore's ionic current and the molecule's residence time in the pore. Our work led to two novel DNA sequencing methods [6-8], the ability to discriminate between individual polymers based on their size [9,10], a method to identify subtly different species of metallo-nanoparticles [11], a single-molecule implementation of Eigen's temperature-jump method [12], and a technique to detect proteins in aqueous solution [13,14].

In collaboration with Abdelghani Oukhaled (Cergy, Université Paris), we recently demonstrated that a bio-nanopore can discriminate between proteins of similar mass [15]. If this method, which is designed to replace the mass spectrometry part of the clinical protein discrimination workflow, is implemented in chip-based devices, it might prove useful at point-of-care facilities.

We will also discuss our preliminary results that compare experimentally measurable properties of bio-nanopores with predictions based on computer molecular dynamics simulations (a collaboration with Jan C. Behrends and Tobi Ensslen at Universität Freiburg).

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Ion transport through atomically thin crystals

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The basal plane of graphene is impermeable to all atoms and molecules - even for helium, the smallest - at ambient conditions [1]. Nevertheless, it is permeable protons at ambient conditions [2]. This talk will provide an overview of our investigation of permeation of protons and other small ions through new 2D materials [3-5], including the unexpectedly fast ion exchange properties of atomically thin clays and micas [6].

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Sculpting of 2D Materials: From Pores and Nanoporous Membranes to Sequencing and Water desalination

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Introducing atomic-scale holes in 2D materials changes their electrical and optical properties. When 2D materials are suspended, vacancies make the membranes permeable to ions and molecules in liquid or gas phases, allowing transport studies at atomic scales. Angstrom-size holes allow the passage of water molecules but block the larger hydrated salt ions and can effectively desalinate water. Raman peak shifts combined with TEM, provide a comprehensive approach to characterize the holes and transport through them. When molecules are driven through 2D nanopores in solution, they can perturb the ion current flow through the pore, from which molecule's physical and chemical properties can be inferred. DNA other biomolecules can be detected in this way. Thanks to advanced materials, device designs and custom electronics, the temporal and spatial resolution for their detection has been rapidly improving.

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Aerolysin pores for molecular sensing

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Evolution has found countless ways to transport material across cells and cellular compartments separated by membranes, producing channels and pores that enable a regulated passage of molecules in and out of cells. As in several other occasions, we have borrowed from the natural properties of these biological systems to push technology forward and have been able to hijack these nanoscale proteinaceous pores to learn about the physical and chemical features of molecules passing through them [1]. Today, a large repertoire of biological pores is exploited for molecular sensing with the aim of characterizing molecules relevant for the advancement of medicine and technology. Aerolysin, a bacterial pore-forming toxin that my lab has been studying for more than a decade, is a promising system in this context. After having revealed its structure and pore-forming mechanism using integrative structural biology methods [2,3], we characterised the conduction properties of this pore and understood its ability to sense molecular entities such as DNA and peptides [4,5]. Exploiting this fundamental knowledge we could then design and engineer mutant pores that showed enhanced single-molecule sensing properties for applications as diverse as the detection of protein post-translational modifications for disease diagnosis and the reading of informational polymers for future data storage solutions [6].

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Inching closer to translation: The evolution of nanopores from genomics to proteomics

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Nanopores have gained a lot of attention recently for their ability to sequence nucleic acids. Recently, however, a surge of interest in the use of nanopores for analyzing proteins has been witnessed. I will talk about two approaches that our lab has taken in order to characterize proteins. First, I will describe a method for full-length single-file protein translocation and discrimination using a biological pore. Second, I will describe a method for probing conformational states of a protein and its electrical unfolding. Time permitting, I will also discuss other ongoing nanopore-related projects currently pursued in my lab.

Monitoring Conformational Dynamics of Single Proteins with Plasmonic Double Nanoholes

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This talk will present our ongoing efforts to assess the potential of nanoplasmonic optical tweezers for interrogating the conformational dynamics of single unmodified proteins in aqueous solution. Specifically, we employ double nanohole (DNH) structures to trap single enzyme proteins [1,2] for minutes to hours. While the protein resides in the trap, we monitor changes in transmission through the DNH in response to exposing the protein to substrate, product, or inhibitor molecules. We show that experiments with trapped enzymes that are known to undergo significant conformational changes during their catalytic cycle, exhibit multiple transmission levels.[3] Increasing concentration of substrate molecules increases the frequency of transitions between these levels in a dose-dependent manner, while the presence of different inhibitors reduces the frequency of transitions by favoring specific transmission levels (Fig. 1). Step-fitting the transmission recordings makes it possible to follow the rate of transition between levels, revealing individual enzymatic cycles, single molecule turnover frequencies, as well as heretofore unknown enzymatic sub-cycles during catalysis.[3] The talk will conclude with an outlook of applying this approach to additional unmodified enzymes, motor proteins, and transporters as well as a discussion of its current limitations and possible improvements.

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Single-molecule probing by rectification in a nanogap

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Towards efficient single-molecule detection, here in this talk we propose simultaneous measurement of rectification and amplitude of tunneling current during electrical probing of molecule in a nanogap. Also, we propose application of nitrogen-terminated graphene/or CNT nanogaps, due to their inherent outstanding features. With DFT and Non-Equilibrium Green's Functions formalism, we show that tunneling current through various molecules including ssDNA, TATP or small organics placed in those nanogaps, exhibit unique rectification behavior under square pulses of alternating biases. The rectification arises by on-off switching of electronic transport through the molecule's HOMO or LUMO level, sustained by partial charging of the probed molecule, which is generated by asymmetric hybridization of the molecule's level with Bloch states from one of the electrodes. This effect is strongly influenced by interaction between the molecule and the nitrogen-induced dipole moment located at the N-C interface of the electrode ends, an effect that mimics local gating. For example, in gas phase we found that TATP is detectable (triacetone triperoxide is a potent and hard to detect explosive made from commonly available chemicals and is a terrorist's weapon of choice in the last two decades). In liquid phase, we found that effects of the environment (neighboring nucleotides, water molecules and counter ions) do not mask rectification of ssDNA during its translocation through the nanogap, offering the possibility for high-throughput and precise ssDNA sequencing by rectification.

Nanofluidics with ultrathin nanopores

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Nanopores in solid state membranes are a tool able to probe nanofluidic phenomena or can act as a single molecular sensor. They also have diverse applications in filtration, desalination, or osmotic power generation. Many of these applications involve chemical, or hydrostatic pressure differences which act on both the supporting membrane and analyte, and can influence the ion transport through the pore. Although all of these diverse applications are done in an aqueous environment, little is known about fluid flow and its coupling with ion transport properties.

I will demonstrate an approach using hydraulic pressure coupled with alternating current which is used to probe small differences in ion transport characteristics of ultrathin nanopores. Through hydraulic pressure differences between the sides of the membrane we are able to induce two separate phenomena. First, due to a low hydraulic resistance at the mouth of the ultrathin pore, advective ion transport dominates diffusive, causing nonlinear coupling of ion transport with the applied pressure. This coupling can be leveraged to increase nanopore properties like ion selectivity, and can produce strong pressure dependent effects even without external driving forces. Secondly, we demonstrate that blistering of the membrane under pressure induces enlargement of the pore diameter, and is a direct measure of the strain at the pore. This allows controlled application of in-situ strain on nanopores in 2D materials like MoS₂ or hBN, opening up pathways for probing ionic hydration layers and artificial mechanosensitive sensors.

Gating of Nanopores with Large Polarizable Ions and Organic Solvents

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Solid-state nanopores have become the basis for biological sensors as well as preparation of nanopores with transport properties inspired by functionality of biological channels. Not surprisingly, therefore, the majority of experiments with solid state nanopores have been performed in aqueous media. My talk will be divided into two parts. In the first part I will show how ion specific effects can be induced in nanopores lined with hydrophobic groups.¹ Synergistic experimental and modeling work has revealed that large polarizable ions such as iodide and bromide accumulate at the hydrophobic walls, leading to pore wetting when external electric field is applied. The same nanopores are closed for any transport in chloride salts. The second part of the talk will show tuning transport properties of nanopores by the choice of a solvent. We have discovered that nanopores that are negatively charged in aqueous media acquire effective positive surface charge when in contact with electrolyte solutions in aprotic solvents, propylene carbonate and acetonitrile.² The effective positive charge stems from the long-range, bilayer-like structure of the solvent, revealed by the Vibrational Sum Frequency Generation Spectroscopy. We hypothesize that the highly robust organization of the solvent at the interface dictates partition of anions and cations to the surface, and consequently the effective surface charge. Consequences of the positive surface charge for electrokinetic phenomena will be presented. Description of solid/liquid interfaces discussed in this talk necessitates considering ion specific effects and solvent structure that cannot be captured by the classical electrical double layer model.

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Stimuli-Responsive Coacervates as Universal Carriers for Intracellular Delivery of Macromolecular Therapeutics

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Abstract

Macromolecular therapeutics (peptides, proteins, mRNAs, plasmid DNAs, etc...) hold vast therapeutic potential across human disease states by providing opportunities to address targets that have proven refractory to traditional approaches. However, a critical impediment for the successful application of these modalities is their inability to cross cellular membranes, preventing access to intracellular targets. Current approaches to solve this key issue are based on nanoscale carriers to deliver the payloads, which however have several drawbacks including a tendency to get entrapped in endosomal compartments, poor biodistribution, and in some cases dose-limiting toxicity. Bypassing endosomal entrapment for direct cytosolic payload delivery is an attractive alternative approach but current methods suffer from their own pitfalls. For example, the carriers are typically limited to delivery of a particular therapeutic modality or to relatively low molecular weight (MW) cargos. Furthermore, many approaches involve laborious synthetic procedures and/or encapsulation processes using organic solvents that can decrease bioactivity of the therapeutic cargo.

In this talk, I will present a unifying delivery strategy of macromolecular therapeutics recently developed by our team that is cargo-agnostic, does not cross the cell membrane through classic endocytosis, and non-cytotoxic¹. This new method exploits Liquid-Liquid Phase Separation (LLPS) of engineered peptides^{2,3} self-assembling into therapeutic-carrying coacervate microdroplets that are capable to release their cargo in the cytosol. These peptide microdroplet carriers benefit from several unique advantages that set them apart from other approaches¹:

- (1) A remarkable wide range of therapeutics can be quickly recruited in the droplets, from short therapeutic anti-cancer stapled peptides to very large enzymes (430 kDa) to mRNAs;
- (2) The recruitment process is rapid and carried out under aqueous environments, thus preserving bioactivity of the therapeutics⁴. Furthermore, the recruitment efficiency is above 90% in all tested macromolecular therapeutics tested so far;
- (3) The coacervates readily cross the cellular membrane, bypassing classical endocytosis pathways to enter in the cytosol⁵;

(4) The side-chains of the peptides are conjugated with a redox-responsive moiety, which triggers disassembly of the droplets in the reducing environment of the cell, leading to efficient payload release;

(5) Finally, we have demonstrated that the bioactivity of the released therapeutics is retained in the cell and that mRNAs exhibit high transfection efficiency.

Together, this platform thus represents a general and robust strategy for the intracellular delivery of a range of macromolecular modalities with promising potential for the treatment of a spectrum of human diseases such as cancers, metabolic diseases, or genetic disorders. Furthermore, these peptide coacervates could also be used as novel carriers for next-generation mRNA-based therapeutics.

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RNA-DNA nanotechnology identifies native RNA with nanopore sensing

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Abstract body

DNA nanotechnology is transformative for experiments that require molecular control over the shape of nanometer-sized objects. In combination with nanopores DNA self-assembly allows for novel experiments that reveal the physics of ions, and polymers on the single molecule level.

Nanopore sensing, best known for DNA sequencing, translates the three-dimensional structure of molecules into ionic current signals. Designed DNA molecules enable multiplexed protein sensing with an all-electrical approach [1]. Here, I will discuss our recent developments to detect and localise structures as accurately as possible along DNA molecules approaching super-resolution microscopy [2]. Based on our high-resolution measurements, I will show how to use the fundamental understanding for the identification of miRNA, RNA viruses and their variants [3], and RNA isoforms without reverse transcription or amplification [4]. In the future, our technology will enable to identify and quantify RNA structural elements and offer a strategy for the mapping of RNA binding proteins.

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Is water just a substrate?

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Abstract

Water is the most important but also the most underestimated biological liquid. I will present the latest understanding of the structure and dynamics of water, based on state-of-the-art dielectric, terahertz, and infrared spectroscopic data. I will discuss the details of short sub-picosecond dynamics in water and will show its importance for understanding the aqueous biological and artificial systems. The particular reference will be given to aqueous solutions and the properties of water at nanoconfinement. The recent theoretical models will be discussed along with their application in electrochemical energy storage, nanofiltration, and biological systems.

Acknowledgment

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ELUCIDATING TRANSPORT DYNAMICS IN SOLID-STATE NANOPORES

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Many emerging applications in diverse areas such as proteomics, clinical diagnostics and molecular information storage make use of chimeric or nanostructured polymers and DNA nanotechnology (nanostructures self-assembled via specific base pairing of DNA) to fingerprint proteins, detect disease biomarkers, or encode digital information. Understanding the details of the process by which these polymers are captured and traverse solid-state nanopores however remains a challenging task due to the complex nature of the non-equilibrium translocation dynamics which occur on multiple timescales and that are dictated by forces over which experimental control is often limited. This unfortunately also makes verification of theoretical concepts difficult.

In this work, we present experimental solid-state nanopore data of linear DNA fragments and DNA nanostructures for a wide range of conditions to elucidate the dynamics of polymer capture and translocation and to highlight how the relevant forces and transport processes can change. More precisely, using asymmetric salt concentration conditions and DNA polymers patterned with 3 helix bundle (3HB) sub-structures, we report the scaling of various transport metrics on voltage and polymer length and use this data to corroborate the predictions of tension propagation theory and verify the impact of the electric field gradient on pre-stretching approaching polymers [1]. Furthermore, we present data relating the dependence of translocation time on pore size, in which longer translocation times for larger pores are counterintuitively observed, which we argue further support tension propagation theory. Finally, we show how statistics of folded translocations of linear and nanostructured DNA can give insights into polymer-pore interactions, and polymer conformations at the onset of translocation. In particular, we discuss how the passage of 3HB DNA nanostructures can be dictated by its defect density [2]. These results are used to inform several biosensing and digital data storage applications.

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TOOLS TO ACCELERATE SOLID-STATE NANOPORE RESEARCH

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Solid-state nanopores are promising sensors for electrical detection of a range of single copies of biological molecules. There are many potential applications, including sequencing, proteomics, clinical diagnostics, molecular information storage, and more. However, the pace of discovery and translation into practical applications has been hampered by the difficulty of fabricating precisely sized, low-noise, and stable solid-state nanopores, which in turn limits the rate of high-quality data generation. To address this challenge, we invented the controlled breakdown (CBD) nanopore fabrication method,[1] and developed a small benchtop tool and associated disposables which automates the CBD method. We made it freely available to the community,[2] and more recently are providing a turn-key solution through Northern Nanopore Instruments to further facilitate the dissemination of this technology.

Here we present advances toward the next generation of scientific tools and protocols to streamline and accelerate solid-state nanopore research. We present advances which enable parallel nanopore sensing at high bandwidth, including fully automated tools and workflows for rapid fabrication of many solid-state nanopores in parallel, utilizing multi-channel millifluidic flow cells and multi-membrane chips. Together these reduce experimental time and cost while increasing throughput. Furthermore, we present advanced, yet easy-to-use software tools to analyze time series of ionic current nanopore data. This tool simplifies data post-processing and automates most common nanopore analysis tasks without requiring any programming knowledge by the user, facilitating collaboration and reproducibility. Together, these tools are expected to democratize the use of solid-state nanopores and allow experts and non-experts alike to accelerate the pace of their research toward a host of applications including the fundamentals of ionic and polymer transport through nanofluidic channels, characterization of proteins, design of biomimetic nuclear pore complexes, and development of different bioassay schemes for diagnostic purposes.

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Prolonging the Nanopore Electro-Osmotic trap time for protein dynamics detection

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Protein dynamics detection is of great interest to a wide array of researchers in the life science [1]. The Nanopore Electro-Osmotic trap (NEOtrap) is an emerging single-molecule label-free technology for protein dynamics detection [2]. In the NEOtrap system, target proteins are trapped by the electroosmotic flow generated from the docking of a DNA origami sphere onto a nanopore. By analyzing ionic current traces during the trapping, which monitor volume and shape changes, various protein-specific features can be accessed, including unique morphological and dynamic information [3]. However, so far, large proteins could easily be trapped but the trapping time of small proteins was limited, e.g. by thermal fluctuations of the origami sphere, which sets a lower size limit of detection for this technology. In order to prolong the trapping time, we functionalized the surface of the DNA sphere with cholesterol molecules, which act as lipid anchors to lock the DNA sphere to on the lipid-coated surface of nanopore. The stabilized DNA sphere indeed significantly prolongs the trapping time of proteins by an order of magnitude, allowing to stably trap and monitor proteins with smaller molecular weights, down to at least 29 kDa (Carbonic Anhydrase). This stable docking likely is explained by elimination of a possible escape pathway between the nanopore and DNA sphere. We aim to clarify the trapping time and its relation to the size of nanopore and the orientation of the docked DNA sphere. The improvements presented here extend the detection ability of NEOtrap towards smaller proteins, which will promote the wider applications of NEOtrap in various biological and medical scenarios.

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Single-particle Methods for Quantitative Assessment of Geometrical Parameters of Small Viruses

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The geometrical structure of biological entities – including eukaryotic cells, bacteria, viruses, bacteriophage and macromolecules – are important to understand as their activity, function and heterogeneity[1–3] are critical for many future technologies, such as sustainable energy harvesting[4], DNA-based information storage[5], nanotechnology medicine[6] and imaging applications[7]. Therefore, precise, high-throughput methods of characterization have garnered significant interest to measure their geometrical features. For large structures, e.g. bacteria and large viruses, the task is manageable. For structures having dimensions below 100 nm, the precise measurements become complicated and new high-throughput methodology is needed. In this work, we explored and benchmarked two emerging single-particle methods, nanopore tomography (NT) and helium ion microscope (HIM) imaging, to measure bio-structures having dimension below 10 nm. Our model system is filamentous *fd* bacteriophage (*fd-wt*) and its modifications with different mechanical properties (*fd-Y21M*). It is a good model system – long filament makes it easy to find, but lateral dimension is hard to determine. NT methodology was established to detect viruses with current modelling. The results of NT and HIM are compared to our measurements of *fd* diameters with transmission electron microscopy (TEM) and atomic force microscopy (AFM), and also compared to an ensemble of methods in the literature, including transient electrical birefringence (TEB)[8], x-ray diffraction (XRD)[9], neutron scattering (NS)[10], nuclear magnetic resonance (NMR)[11]. The measured *fd* diameters of NT [6.85 ± 0.49 nm (*fd-wt*), 7.18 ± 0.48 nm (*fd-Y21M*)] and HIM [8.69 ± 0.55 nm (*fd-wt*), 6.38 ± 1.09 nm (*fd-Y21M*)] showed as good accuracy as that of TEM [7.21 ± 1.36 nm (*fd-wt*), 7.83 ± 0.86 nm (*fd-Y21M*)] and AFM [8.00 ± 0.39 nm (*fd-wt*), 10.23 ± 0.83 nm

(*fd-Y21M*)]. NT has very large throughput that 4568 individual virions were measured within 45 minutes operating time, but measurements rely on an accurate theoretical model to convert current blockade signals into geometric dimensions, which has to be well understood. NT could be used for fingerprinting viruses and pathogens by establishing a library of NT signals versus geometry. HIM has relatively high throughput and low operating time due to the greater depth of field than TEM and faster scanning speed than AFM, and simple sample preparation that does not require negative staining or gold coating. Given the continued importance of viruses, our work aims to develop the use of HIM and NT for fingerprinting and exploring heterogeneity of small viruses.

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ELUCIDATING TRANSPORT DYNAMICS IN SOLID-STATE NANOPORES

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Many emerging applications in diverse areas such as proteomics, clinical diagnostics and molecular information storage make use of chimeric or nanostructured polymers and DNA nanotechnology (nanostructures self-assembled via specific base pairing of DNA) to fingerprint proteins, detect disease biomarkers, or encode digital information. Understanding the details of the process by which these polymers are captured and traverse solid-state nanopores however remains a challenging task due to the complex nature of the non-equilibrium translocation dynamics which occur on multiple timescales and that are dictated by forces over which experimental control is often limited. This unfortunately also makes verification of theoretical concepts difficult.

In this work, we present experimental solid-state nanopore data of linear DNA fragments and DNA nanostructures for a wide range of conditions to elucidate the dynamics of polymer capture and translocation and to highlight how the relevant forces and transport processes can change. More precisely, using asymmetric salt concentration conditions and DNA polymers patterned with 3 helix bundle (3HB) sub-structures, we report the scaling of various transport metrics on voltage and polymer length and use this data to corroborate the predictions of tension propagation theory and verify the impact of the electric field gradient on pre-stretching approaching polymers [1]. Furthermore, we present data relating the dependence of translocation time on pore size, in which longer translocation times for larger pores are counterintuitively observed, which we argue further support tension propagation theory. Finally, we show how statistics of folded translocations of linear and nanostructured DNA can give insights into polymer-pore interactions, and polymer conformations at the onset of translocation. In particular, we discuss how the passage of 3HB DNA nanostructures can be dictated by its defect density [2]. These results are used to inform several biosensing and digital data storage applications.

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Liquid-activated quantum emission from native hBN defects for nanofluidic sensing

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Nanostructures made of two-dimensional (2D) materials have become the flagship of nanofluidic discoveries in recent years^{1,2}. By confining liquids down to a few atomic layers, anomalies in molecular transport^{3–5} and structure^{6,7} have been revealed. Currently, only indirect and ensemble averaged techniques have been able to operate in such extreme confinements, as even the smallest molecular fluorophores are too bulky to penetrate state-of-the-art single-digit nanofluidic systems⁸. This strong limitation calls for the development of novel optical approaches allowing for the direct molecular imaging of liquids confined at the nanoscale. Here, we show that native defects present at the surface of hexagonal boron nitride⁹ (hBN) - a widely used 2D material - can serve as probes for molecular sensing in liquid, without compromising the atomic smoothness of their host material. We first demonstrate that native surface defects are readily activated through interactions with organic solvents and confirm their quantum emission properties. Vibrational spectra of the emitters suggest that their activation occurs through the chemisorption of carbon-bearing liquid molecules onto native hBN defects. The correlated activation of neighboring defects reveals single-molecule dynamics at the interface, while defect emission spectra offer a direct readout of the local dielectric properties of the liquid medium. We then harvest these effects in atomically smooth slit-shaped van der Waals channels, revealing molecular dynamics and increasing dielectric order under nanometre-scale confinement. Liquid-activated native defects in pristine hBN bridge the gap between solid-state nanophotonics and nanofluidics and open up new avenues for nanoscale sensing and optofluidics.

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Nanopore-based single-molecule protein identification

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Proteins are the workhorses of living systems. Complete cataloging and accurate quantification of this physiologically important class of molecules are essential for proteome-scale elucidation of their functions, and the development of precise protein-based diagnosis and treatment of human diseases. However, a physical method for identification and counting of single protein molecules has remained elusive. Here, we describe a nanopore-based method for identification and digital counting of single protein molecules. The average human proteins contain many lysine residues and are relatively long. Our strategy is to use the pattern of lysine residues along the primary sequence of a protein as a fingerprint to identify the protein by pattern matching to a reference proteome database. The lysine patterns of single protein molecules are determined by measuring the current blockage of ionic current flow through a nanopore by the fully denatured linear polypeptides whose lysine residues that have been labeled with a chemical moiety. We investigated the feasibility of this method by developing an algorithm to calculate the probability of matching the simulated profiles to the references profiles of human proteome. We found that full-length proteins can be identified with >95% accuracy and up to 98% of protein fragments can be identified for fragments with 8 or more labeled lysine measurements in their signal profiles.

Activated carbon nanofluidics: from blue energy to ionic memory

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Nanofluidics is the study of fluids confined at the (sub)-nanoscale. From an experimental standpoint, a first and challenging step is to fabricate channels with such extreme dimensions. In that context 2D materials represent attractive building blocks to realize nanoconduits thanks to their versatility in geometry and surface properties. Here, we first display the fabrication of activated carbon nanochannels made by electron-beam induced etching and van der Waals assembly of bidimensional graphite crystals [1]. Using both voltage and pressure drop experiments, we then show that activated carbon exhibit a unique combination of high surface charge and small but non-negligible hydrodynamic slippage. Such favorable surface properties result in a strongly enhanced ionic transport and in particular osmotic currents coming from salinity gradients with single pore power densities exceeding hundreds of thousands of watts per meter-square. Finally, we show that activated carbon nanochannels can behave as ion-based memories with minute to hour long timescales [2]. This effect is related to the accumulation or depletion of ions caused by entrance effects and adsorption/desorption of ionic carriers on the channel walls. It directly echoes the building of memory in living organisms related to ionic accumulations at specific locations of neurons' membranes. Relying on this advanced response we implement an Hebbian learning algorithm using our nanofluidic channel. Our work paves the way to the development of neuromorphic nanofluidic machines and the study of ions as information carrier.

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Is water just a substrate?

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Abstract

Water is the most important but also the most underestimated biological liquid. I will present the latest understanding of the structure and dynamics of water, based on state-of-the-art dielectric, terahertz, and infrared spectroscopic data. I will discuss the details of short sub-picosecond dynamics in water and will show its importance for understanding the aqueous biological and artificial systems. The particular reference will be given to aqueous solutions and the properties of water at nanoconfinement. The recent theoretical models will be discussed along with their application in electrochemical energy storage, nanofiltration, and biological systems.

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Building DNA nanoturbines on nanopores

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Our societies have flourished because of macroscale machinery powered by engines and motors. And we are not alone in our reliance on active machines: all life itself depends on energy-consuming nanoscale machines, as work at the nanoscale is being done by millions of sophisticated molecular motors. However, until today, designing and building active energy-consuming machines at the nanoscale has remained challenging.

In this talk, I will be presenting our latest results on designing and building nanoscale DNA turbines: DNA nanostructures on nanopores that can autonomously convert transmembrane electrochemical potentials into rotary motion, similar to natural rotary motor proteins such as FoF1-ATP synthase and bacterial flagella motors. We have successfully designed and built two generations of such nanoturbines: a self-organized DNA active rotor, and a designed chiral-shaped DNA turbine. We observe sustained unidirectional the rotary motion of these nanoturbines at the single molecule level as we apply a voltage or salt gradient across the nanopore. These exciting results lay the groundwork, both theoretically and experimentally, for further studies and development of autonomous nanomachines that leverage autonomous, unidirectional rotational motion.

Simulations to complement experiments for quantitative assessment of geometrical parameters of filamentous *fd* bacteriophage

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An understanding of the morphology of viruses is critical to understanding their function in a physiological environment, and for modern, bio-inspired applications such as batteries and medicine, etc [1, 2]. Several imaging techniques have been used to study single particles. These include transmission electron microscopy (TEM), atomic force microscopy (AFM), and nuclear magnetic resonance (NMR) among many others. However, there is a need for a rapid and high-throughput method. Nanopore tomography (NT) is one such emerging single-particle technique with the ability to measure the geometrical features of individual viruses [3]. Here, this methodology is applied to measure the diameter of the wild and mutant types of *fd*, a long, filamentous bacteriophage translocating through a solid-state nanopore at high salt concentrations.

The diameter of the translocating virus is subject to the interpretation of current blockades reported from experiments through robust theoretical and simulation approaches. In principle, the diameter can be estimated from the conductance theory that defines the change in the current based on geometrical specifications of the pore and the virus. However, it neglects any surface charge dependence and variance in bulk conductivity and access resistance due to the presence of the virus. In such cases, carefully designed numerical simulations can be a valuable tool. Steady-state, continuum simulations are performed in COMSOL Multiphysics to estimate the phage diameter from experimentally reported changes in current due to the presence of the virus. The calculated diameters [6.85 ± 0.49 nm (*fd-wt*), 7.18 ± 0.48 nm (*fd-Y21M*)] match closely with the measured values using imaging techniques such as helium ion microscopy (HIM), AFM, and TEM. Furthermore, the robustness and sensitivity of these estimates to variations in surface charge densities of pore and virus as well as pore thickness are investigated.

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Second-harmonic imaging of passive ions transport through lipid membranes

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In biology, release of Ca^{2+} ions in the cytosol is essential to trigger or control many cell functions. Calcium signalling acutely depends on lipid membrane permeability to Ca^{2+} . For proper understanding of membrane permeability to Ca^{2+} , both membrane hydration and the structure of the hydrophobic core must be considered. In this work, we revisit the hypothesis that lipid membranes are impermeable to Ca^{2+} by second harmonic (SH) imaging the water structure at the interface of GUVs in contact with CaCl_2 solution. Varying the hydrophobic core of the bilayer membranes, different types of behavior are observed in the high throughput wide-field SH images. Ca^{2+} translocation is observed through mono-unsaturated (DOPC:DOPA) membranes and reduced upon adding cholesterol. Translocation occurs at different rates for different locations showing that a non-equilibrium membrane restructuring is needed. The complete inhibition of translocation is observed for branched (DPhPC:DPhPA) and poly-unsaturated (SLPC:SLPA) lipid membranes. The latter are found in cells such as neurons, whose function critically depends on impermeability of their membrane to Ca^{2+} . Translocated ions stay bound to the membrane which makes them invisible to conventional methods used to determine permeability. Our findings suggest that hydrophobic structure of lipids play a much more sophisticated regulating role than previously thought and that the membrane itself can play a role as a Ca^{2+} reservoir.

Manipulation of Interfacial hBN Emitters using Electrochemical Bias and AFM

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Point defects in the crystal lattice of 2D materials can significantly alter their optical, electrical, and quantum properties and the manipulation of these defects could allow the realization of nanoscale sensors and quantum information processing devices [1–3]. Hexagonal boron nitride (hBN) is a 2D material, as well as a wide-band gap semiconductor, meaning that it is generally transparent but defects in the lattice structure create intra-band gap energy levels and result in localized emission of visible light, known as colour centres [4]. Spectral single molecule localization microscopy (sSMLM) utilizes the blinking nature of these emitters to localize with nanometre resolution and determine emitter density, dynamics, intensity, and emission spectrum with a wide-field microscope [5]. While the nature of these defects is not well understood, they are significantly more active in carbon bearing liquids and scanning tunnelling microscopy (STM) has shown they exist with multiple charge states [6,7]. To investigate the interfacial dynamics of these charged sites in situ, we will employ an electrochemical cell adapted to our widefield spectral SMLM and confocal microscopes, applying an out-of-plane, and later in-plane, electrochemical bias. Various processes including plasma, focused ion beam, and atomic force microscopy have been employed to engineer defects beyond hBN's native population [8–10]. With an integrated AFM-sSMLM microscope we will also quantify and localize emitters while deterministically disrupting the crystal lattice by contact with a hard AFM cantilever.

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Nanopore-Based Scanning Probe Technology for Controlled-Translocation of DNA

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Uncontrolled dynamics of the translocation of the analyte is a key problem in solid state nanopore technology [1]. Here, we show the detection of complex topological variations in DNA by using a nanopore-based scanning probe approach. We use a glass nanopore as a scanning probe to translocate and map out molecules, tethered on a glass surface, at a constant velocity, independent of the applied bias, salt concentration and pH. Controlled-translocations with our approach increased the SNR two orders of magnitude (i.e. 100X) compared with free-translocations [2]. This improvement was achieved by decreasing the velocity of the scanning probe to achieve a constant motion and averaging multiple consecutive readings of the same molecule. We applied our method to molecular rulers, DNA gaps, Hairpins, DNA-dCas9 complexes with correlative fluorescence imaging. This method enabled high-throughput data acquisition above 100'000 readings per experiment and scanning rate of 4 readings/s. Our scanning probe approach is a promising platform for the development of diverse nanopore-based probes and redefining advanced solid-state and biological nanopore systems.

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Label-free Identification of Neurodegenerative Protein Inclusions Using Deep Learning

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Huntington's disease (HD) is a progressive neurodegenerative disease caused by a mutation in the Huntingtin (Htt) protein, which causes HD when its polyglutamine (polyQ) length is larger than 35 [1]. Mutant Htt has been observed to form intranuclear and cellular inclusions in HD post-mortem brain tissues [2]. The first exon of Htt (Httex1) is thought to be an important fragment to be studied, as it is a key component of intracellular protein inclusions and recapitulates the key features of HD human pathology [3]. Studies of Htt inclusions frequently use large fluorescent tags to visualize and monitor Htt expression. Despite these tags being extremely useful tools that have elucidated our current understanding of HD neuropathology, they also have their limitations, as fluorescently-tagged proteins have been shown to sometimes exhibit altered or destroyed structures and cellular functionalities [4]. It has been shown that labeling Httex1 with GFP induces a different structural organization, proteome composition and stiffness [5, 6]. It is therefore crucial to develop label-free techniques to study neurodegenerative protein inclusions to better recapitulate their true nature. In recent years, the concept of artificial staining has emerged, which uses deep learning to predict fluorescence signals from label-free signals [7, 8]. Here, we employ this concept to identify label-free Httex1 inclusions from quantitative phase images by training a convolutional neural network to do so. We have developed pixel-classification and pixel-regression models and validated them on different constructs of Httex1. Using such models, we can then analyze the properties of label-free inclusions – including their morphology, propensity and rate of aggregate growth. This proof-of-concept paves the way for similar techniques which can be of great aid in label-freely identifying other neurodegenerative inclusions.

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High-throughput nanopore fabrication and classification using FIB irradiation and automated pore edge analysis

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Large-area nanopore drilling is a major bottleneck in state-of-the-art nanoporous 2D membrane fabrication protocols. In addition, high-quality structural and statistical descriptions of as-fabricated porous membranes are key to predicting the corresponding membrane-wide permeation properties^{1,2}. In this work, we investigate Xe-ion focused ion beam as a tool for scalable, large-area nanopore fabrication on atomically thin, free-standing molybdenum disulphide. The presented irradiation protocol enables designing ultrathin membranes with tunable porosity and pore dimension, along with spatial uniformity across large-area substrates. Fabricated nanoporous membranes were characterized using scanning transmission electron microscopy imaging and the observed nanopore geometries were analyzed through a pore-edge detection script. We further demonstrated that the obtained structural and statistical data can be readily passed on to computational and analytical tools to predict the permeation properties at both individual pore and membrane-wide scales. As an example, membranes featuring angstrom-scale pores were investigated in terms of their emerging water and ion flow properties through extensive all-atom molecular dynamics simulations. We believe that the combination of experimental and analytical approaches presented here should yield accurate physics-based property estimates and thus potentially enable a true function-by-design approach to fabrication for applications such as osmotic power generation, desalination/filtration, as well as their strain-tunable versions.

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Dielectric properties of liquids confined in atomically thin nanochannels

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New advances in 2D heterostructure technology has allowed the controlled fabrication of arrays of nanochannels with thicknesses varying from a single atomic layer to tens of nanometers¹. Fumagalli et al² were able to measure the out-of-plane dielectric constant, ϵ_{\perp} , of water for the first time under strong confinement in these nanochannels by *in situ* dielectric characterization based atomic force microscopy (scanning dielectric microscopy)³. This was the first time that this fundamental property was directly measured in such extreme confinement, despite its huge impact on a myriad of phenomena, including van der Waals and electrostatic interactions between surfaces, ion solvation and transport, and the functioning of biomolecules. By building on that work, we are continuing the study of water confined in nanochannels of different materials such as graphene, hBN and mica and investigate their impact on water's dielectric properties. We are also studying the impact of confinement on the dielectric properties of electrolytic solutions and other solvents.

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On Durability and Stability of 2D Nanofluidic Devices for Long-term Single-Molecule Sensing

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Solid-state nanopores hold immense potential in various fields such as biosensing, osmotic power generation, and information storage. Atomically thin two-dimensional membranes such as MoS₂ can be beneficial for single-molecule nanopore-based sensing of biopolymers such as DNA. [1,2] Recent advances on 2D nanopores have mainly focused on the manufacturing and scalability of the MoS₂ nanopore devices. [3] However, there still remains a bottleneck to control the nanopore size of such atomically thin pores. Here, we evaluate major factors responsible for the instability of the monolayer MoS₂ nanopores. We identify chemical dissolution and detachment of monolayers from their underlying substrates as the major reasons for the instability of MoS₂ nanopores. Using an oxygen-free buffer environment and surface-modification of the substrate rendering them hydrophobic, improved the nanopore stability and increased their shelf-life. Understanding nanopore growth and stability can provide insights into controlling the pore size, shape, long-term measurements with high signal-to-noise ratio and engineering of durable nanopore devices.

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2D MoS₂ Nanopore Devices for Energy Harvesting

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Two-dimensional (2D) material MoS₂-based nanopore [1] has provided a superior platform for various applications from biosensing to energy harvesting. The atomic thickness of monolayer MoS₂ offers high temporal and spatial resolution for biosensing applications; meanwhile, atomic thickness also provides high osmotic conductance and thus high-power density when used for osmotic energy generation. Single MoS₂ nanopore power generator has been demonstrated [2] and theoretically extrapolating the single-pore value to a multi-pore system, a world-record high power density (up to 1 MW m⁻²) can be expected, but no experimental study on upscaling MoS₂ osmotic power generation has been done yet. Here, scaling potentiality of MoS₂ nanopore arrays for osmotic power generation is studied with 4 by 4 arrays and by precisely controlling the porosity on a “single-nanopore” level. By defining the pore size and the number of pores with the help of transmission electron microscope, the upscaling effect is observed as generated power increases when the pore amount is increased from single pore to multiple pores, meanwhile the pore area difference is maintained within ~1%. In addition, with the same number of pores, generated power increases with the pore size when it is below 10 nm. The inspiring outcomes from these studies suggest MoS₂ nanopores are promising candidates for developing renewable energy source with osmotic power.

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Towards Protein Fingerprinting Using Biological Nanopores

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Biological nanopores are successfully used for DNA sequencing today [1], a technological leap that took only 25 years from concept to commercialization[2]. The next significant advancement in the field is the sequencing of proteins, a far greater challenge than DNA sequencing due to several hurdles: Unlike DNA, proteins are not homogeneously charged, and instead of 4 bases, 20 amino acids have to be read out. Furthermore, the protein backbone is much more flexible than DNA, making the signal highly dependent on entropy which changes during translocation [3]. Thus, the signal contrast needs to be enhanced to achieve protein sequencing. To move towards a solution for these problems, we labeled the cysteines and lysines of proteins to fingerprint them in biological nanopores; our label is large, rendering it visible and providing negative charges, which aids translocation and unfolding. Reading only two amino acids is a step toward fingerprinting. Reading just two amino acids is far from sequencing but an important step, nonetheless.

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Using aptamer-functionalized interface nanopores for amino acid-specific peptide sensing

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In recent years nanopore (NP) technology has emerged as a powerful sequencing platform that enables differentiation of the four nucleobases in individual nucleic acids. Single-molecule protein sequencing has made progress over the last years [1], but is not achieved yet due to the daunting challenge of distinguishing not four, but 20 amino acids. One approach to overcome this challenge is to use engineered NPs that allow for amino acid-specific sensing and eventually put them in series.

In earlier works we showed that NPs can be integrated into hollow Atomic Force Microscope (AFM) cantilevers to *e.g.* sense inside cells [2] and that the same setup can be used to create interface nanopores between a soft polymeric substrate and the rigid AFM cantilever [3]. Here we extend this setup in order to allow for amino acid-specific peptide sensing. We harness DNA aptamers, single-stranded oligonucleotides specifically designed to recognize analytes of interest, to address nanopore selectivity while slowing translocation times through molecular interactions. We couple such selective recognition elements to a dynamic interface nanopore (INP) system that enables tuning of the nanopore size to nanoscale resolutions [3]. Adjustment of the dynamic pore by altering the force applied by a cantilever to a soft polymer interface enables optimized aptamer-specific stochastic sensing. As proof-of-concept, a recently isolated and validated DNA aptamer for phenylalanine (Phe) is integrated into the INP system [4]. Measuring translocations of peptides that do not contain Phe yields only short current spikes (Figure 1b) while peptides with same residue number, charge, and similar molecular weight yield specific, sequence-like signals. Correlation analysis seems to validate that current trace correlates to the sequence of the peptide of interest.

Our current attempts extend the interface nanopore system to manufacturing of serial nanopores and protein-tailored nanostructures, as well as improved data processing methodologies.

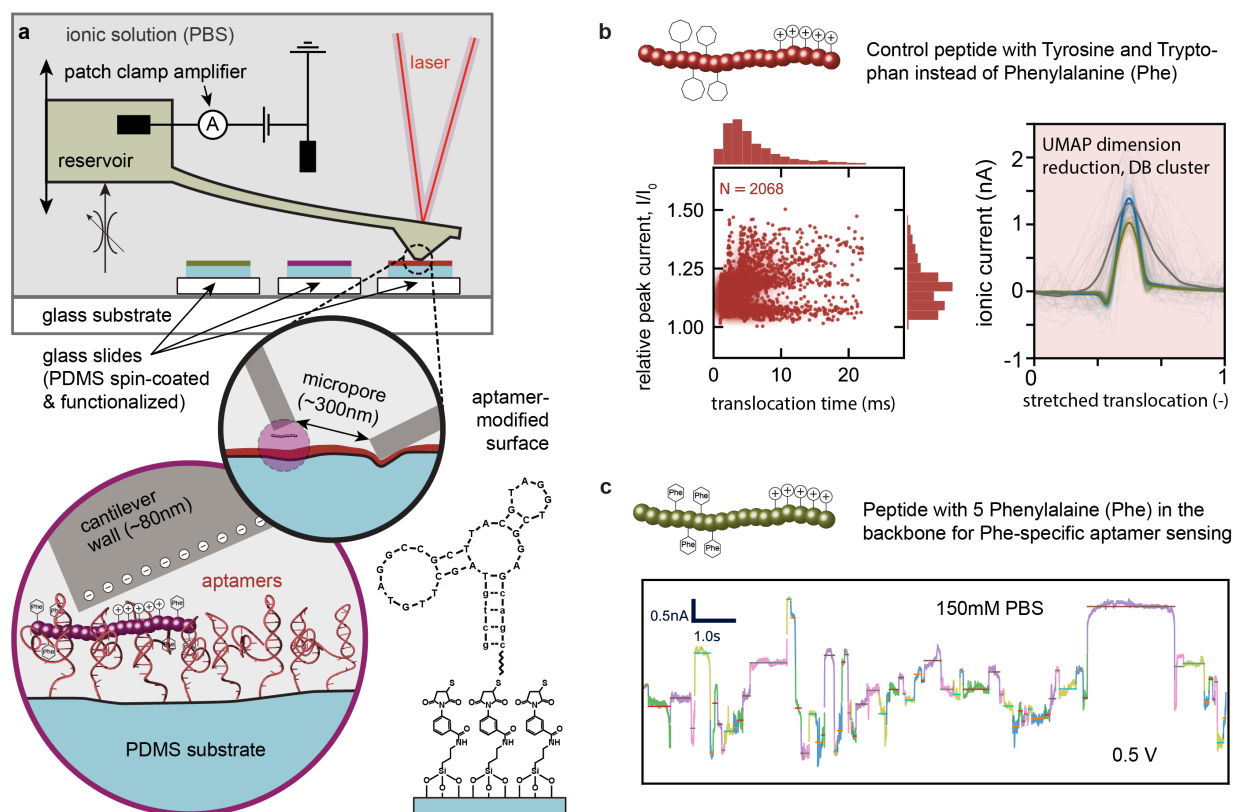


Figure 1: Translocations of specific and control peptide through force-controlled interface nanopore. **a**, Schematic of the force-controlled interface nanopore. **b**, translocation events of a control peptide that has 5 positive charges at one end and no phenylalanine (Phe) in the backbone. Left figure shows the translocation density plot. The right figure shows the mean shape of three different clusters of translocations that were identified using a UMAP dimension reduction with a subsequent density based (DB) clustering algorithm. **c**, time series current measurement of a PBS solution containing a specific peptide with 5 positive charges at one and 4 phenylalanine amino acids in the backbone for amino acid-specific aptamer sensing. The current trace shows color-coded current levels identified in the signal.

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Defect engineering of 2D material for biosensing applications

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2D materials offer huge potential as substrates to build devices for biosensing applications but are plagued by unwanted interactions such as binding/sticking. Controlling such interactions will be critical for the continued exploration of 2D materials in biosensing. We report ongoing work where we engineer and tune the surface interactions of hexagonal boron nitride (hBN) to direct the motion and diffusion of DNA. Using fluorescence microscopy techniques, we explore the nanoscopic interactions of DNA with different 2D materials [1]. We show that pristine hBN flakes exhibit the lowest surface interactions and DNA bind preferentially to the edges and regions of high defect density of the hBN flake. We tap into a recently reported Xenon Focused Ion Beam (FIB) technique to engineer edges and defects on hBN flakes. Our technique harnesses a Xenon-FIB to lightly irradiate the desired regions of the hBN flake followed by subsequent etching in water which allows for a much cleaner hBN surface [2]. We are able to enhance DNA binding and affinity at defined locations by inducing defects using FIB. By creating long tracks of defects, we induce diffusion along our created tracks, thereby allowing us to direct motion of the DNA molecules. We envision future devices where such engineered interactions are able to direct biomolecules to sensing regions (such as a nanopore) on 2D material based devices thereby increasing the rate of analyte capture and sensitivity of single molecule sensing devices.

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A promising nanopore technology to detect human viral infections

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Viruses are ubiquitous in the environment. While many impart no deleterious effects on their hosts, several are major pathogens. The risk for pathogenicity and the fact that many viruses can rapidly mutate highlights the need for suitable, rapid diagnostic measures. Currently, nucleic-acid detection and immunoassay methods are the most popular means for quickly identifying viral infection [1]. Despite these systems gaining attention after the spread of SARS-CoV-2, the analytical sensitivity of these assays is still arguable [2]. Moreover, the current gold standard RT-PCR, still has some limitations such as the need for an equipped lab and the long turnaround time for results [3]. Here, we propose a highly innovative system for the rapid detection of SARS-CoV-2 based on a nanopore technology combined with the resistive pulse sensing technique. In particular, the system consists of scalable, cost-effective nanopore chips and a portable high-precision current measuring instrument. Taking advantage of the SARS-CoV-2-Spike-ACE2 cryo-EM structure we have isolated a small (20 aa long) ACE2 peptide that we linked to gold nanoparticles of different sizes in order to make the virus detection specific for SARS-CoV-2. In our preliminary data, we show that our polyimide nanopores are suitable platforms to detect particles similar in size to SARS-CoV-2 whole virions. Also, we interchanged different types of nanoparticles like, commercial gold nanoparticles, self-made nanoparticles, and polystyrene nanoparticles suspended in different types of electrolyte solutions and concentrations. However, this approach still needs some tuning, especially for what concerns the reproducibility of the nanopore size and geometry as the translocation of the nanoparticles is inconsistent among the nanopores units. This system is a promising tool not only to develop novel diagnostics on SARS-Cov-2 but also to diagnose other human viral infections.

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Biophysics

How to split a droplet into two: the physics of cell division across evolution"

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The molecular machinery of life is largely created via self-organisation of individual molecules into functional larger-scaled assemblies. Such processes are multi-scale in nature and constantly driven far from thermodynamic equilibrium. Our group develops minimal physical models to investigate how macromolecular assemblies result in living machines, and how such processes can fail, leading to diseases.

Today I will present our research on computational modelling of active elastic filaments that dynamically reshape and divide cells across evolution. I will present the comparison of our simulation results to live cell data across the kingdoms of life. I will finish with our recent efforts in computationally evolving assemblies that perform a desired function. Beyond their biological context, our models can help guide the design of artificial structures that are able to mimic life at the nanoscale.

EPR investigations of skin allergens reacting through radical processes: from the molecule to tissue.

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By 2050, half of the world population will face an allergic disease according to the World Health Organization [1]. In Europe, allergic contact dermatitis (ACD) constitutes a serious occupational and environmental issue, with significant impact on the society as ca. 27% of the adult population experienced one or more allergies to chemicals commonly found in everyday products. Therefore, a comprehensive understanding on the mode of action of these skin sensitizers is a prerequisite to improve risk assessment. Although formal proof is still lacking, a significant part of chemical allergens is suspected to initiate the process leading to skin sensitization and ACD through mechanisms involving radical intermediates. This is indeed the case for hydroperoxides (R-OOHs) arising from the autooxidation of natural terpenes such as e.g., limonene [2], linalool [3] or ascaridole [4] widely used in the fragrance and cosmetics industries.

To unravel the radical based mechanisms that could trigger ACD we developed an Electron Paramagnetic Resonance (EPR) based methodology using spin trapping (EPR-ST) approach for the detection and identification of various kinds of radicals derived from the above discussed skin sensitizers [5]. The presented work is carried out “from the molecule to the tissue”: experiments were achieved in solution while parallel investigations were performed using reconstructed human epidermis (RHE) model. The benefits are to test chemicals under conditions close to human use and real-life sensitization exposures. RHE are very close in terms of histology and metabolic/enzymatic activity to real human epidermis and can be used as suitable biological tissue model and potential alternative to animal testing.

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New Frontiers in Brain-Interfacing Electronics: Mesh-Electrode Arrays

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Brain organoids are enabling the non-invasive study of human neural development and capturing phenotypes of disease. Cardiac organoids pave the way for regenerative medicine. Accessing the electrical activity of these electrogenic organoids is central to understanding the development and biological faithfulness of these novel tissue platforms.

Mesh electrode arrays are low footprint devices that are flexible and conformable. Owing to these features, organoids can integrate the device during its development in vitro which results in electrodes distributed all throughout and allow long-term recording of electrical activity.

Using lithography, we designed micron-thin polymer structures into a mesh which unfolds into a basket in aqueous solution, accommodating organoids in its center point. We have designed devices that are flexible by exploring rotational degrees of freedom of the design. Using this design, we can culture and record from organoids on these meshes for long time periods.

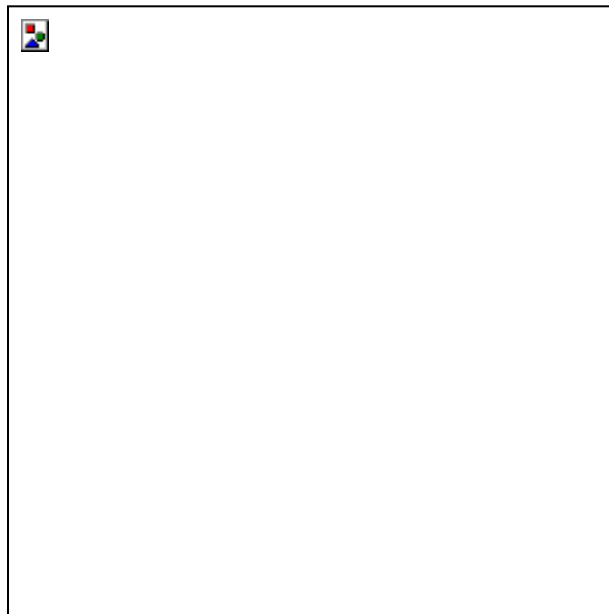


Figure 1 **Green** : stem-cell derived human brain organoid (3mm in widest diameter). **Red**: mesh-electrode array embedded in- and engulfed by the brain organoid. The mesh can withstand large deformations and rearrangements while still recording electrical signals from inside the brain tissue.

Trade-off between reducing mutational accumulation and increasing commitment to differentiation determines tissue organization

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Species-specific differences control cancer risk across orders of magnitude variation in body size and lifespan, e.g., by varying the copy numbers of tumor suppressor genes. It is unclear, however, how different tissues within an organism can control somatic evolution despite being subject to markedly different constraints, but sharing the same genome. Hierarchical differentiation, characteristic of self-renewing tissues, can restrain somatic evolution both by limiting divisional load, thereby reducing mutation accumulation, and by increasing cells' commitment to differentiation, which can “wash out” mutants. Here, we explore the organization of hierarchical tissues that have evolved to limit their lifetime incidence of cancer. Estimating the likelihood of cancer in the presence of mutations that enhance self-proliferation, we demonstrate that a trade-off exists between mutation accumulation and the strength of washing out. Our results explain differences in the organization of widely different hierarchical tissues, such as colon and blood [1].

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CONCEPTS GUIDING JOINT THEORETICAL AND EXPERIMENTAL APPROACHES FROM BIOIMAGING TO CATALYSIS

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Ligand protected gold and silver quantum nanoclusters are extensively used for bioimaging and therapeutic purposes. Due to tuneability of their size and functionalization theoretical design of new materials with desirable linear and nonlinear optical properties allow to construct concepts on which new bioimaging experiments can be realized.

We conducted the study developing the first NC based bioimaging system (Au₁₅SG₁₃) for protein carbonylation detection responsible for protein damages causing numerous diseases. This approach provides replacement of organic dyes due to increasing sensitivity of detection by functionalized ligated quantum clusters.¹

In order to design new catalyst the role of sub nanometer metallic clusters as well as their surrounding including support, metal-organic frame (MOF) as well as Zeolite will be presented on several examples. Determination of mechanism for efficient catalytic reactions is of crucial importance for building the concepts which offer basis for stimulating new experiments.

We illustrated on example of Cu tetramer and ZrO_x subunit the dual role of nanocluster as reactive center and interface. The energetically favorable reaction pathway during the activation and hydrogenation steps of CO₂ on route to its conversion to methane will be discussed.²

¹ Guillaume F. Combes, Hussein Fakhouri, Christophe Moulin, Marion Girod, Franck Bertorelle, Srestha Basu, Romain Ladouce, Martina Perić Bakulić, Željka Sanader Maršić, Isabelle Russier-Antoine, Pierre-François Brevet, Philippe Dugourd, Anita Krisko, Katarina Trajković, Miroslav Radman, Vlasta Bonačić-Koutecký & Rodolphe Antoine; *Functionalized Au₁₅ nanoclusters as luminescent probes for protein carbonylation detection*, May 14 2021., Communications Chemistry

² Avik Halder, Cristina Lenardi, Janis Timoshenko, Antonija Mravak, Bing Yang, Lakshmi K Kolipaka, Claudio Piazzoni, Sonke Seifert, Vlasta Bonačić-Koutecký, Anatoly I. Frenkel, Paolo Milani, Stefan Vajda; *CO₂ Methanation on Cu-Cluster Decorated Zirconia Supports with Different Morphology: A Combined Experimental In Situ GIXANES/GISAXS, ExSitu XPS and Theoretical DFT Study*, May 7 2021., ACS Catalysis

Theoretical and Computational Modeling of the Dissociation Force Distribution in Peptide-Lipid Membrane Interactions

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Peptide-lipid membrane interactions are essential for understanding various cellular processes and their mechanisms. High resolution AFM based dynamic force spectroscopy is most suitable to investigate peptide-lipid membrane interactions by measuring the dissociation (last-rupture) force distribution, $P(F)$, and the corresponding force dependent dissociation rate, $k(F)$. In general, the measured quantities, which differ considerably for different peptides, lipid-membranes, AFM tips (prepared under identical conditions), and retraction speeds of the AFM cantilever, cannot be described in terms of the standard theory, according to which peptide-lipid membrane dissociation occurs along a single pathway, corresponding to a diffusive escape process across a free energy barrier. In particular, the prominent retraction speed dependence of $k(F)$ is a clear indication that peptide-lipid membrane dissociation occurs stochastically along several dissociation pathways. Thereby, we have formulated a general theoretical approach for describing $P(F)$ and $k(F)$, by assuming that peptide dissociation from lipid membranes occurs, with certain probability, along a few dominant diffusive pathways [1, 2]. This new method was validated through a consistent interpretation of the experimental data [1-3]. Furthermore, we have found that for moderate retraction speeds at intermediate force values, $k(F)$ exhibits "catch-bond" behavior (i.e. decreasing dissociation rate with increasing force). According to the proposed model this behavior is due to the stochastic mixing of individual dissociation pathways which do not convert or cross during rupture. To our knowledge, such catch-bond mechanism has not been proposed and demonstrated before for a peptide-lipid interaction.

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TOPOGRAPHY, SPIKE DYNAMICS AND NANOMECHANICS OF INDIVIDUAL NATIVE SARS-COV-2 VIRIONS AND VARIANTS

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The development of advanced experimental methodologies, such as optical tweezers, scanning-probe and super-resolved optical microscopies, has led to the evolution of single-molecule biophysics, a field of science that allows direct access to the mechanistic detail of biomolecular structure and function [1]. The extension of single-molecule methods to the investigation of viruses permits unprecedented insights into their properties and behavior. Here we investigated the nanoscale biophysical properties of SARS-CoV-2, the virus responsible for the COVID-19 pandemic. This enveloped ssRNA virus displays a corona-shaped layer of spikes which play fundamental role in the infection process. By imaging and mechanically manipulating individual, native SARS-CoV-2 virions with atomic force microscopy, we show that their surface displays a dynamic brush owing to the flexibility and rapid motion of the spikes [2]. The virions are highly compliant and able to recover from drastic mechanical perturbations. Their global structure is remarkably temperature resistant, but the virion surface becomes progressively denuded of spikes upon thermal exposure. The dynamics and the mechanics of SARS-CoV-2 are likely to affect its stability and interactions. Variants of the virus possess increased infectivity, but the exact mechanisms behind this phenomenon are not fully understood. We imaged and mechanically manipulated individual, wild-type, alpha- and delta-variant SARS-CoV-2 virions. The variants appear to be significantly smaller in their radii than the wild type virus particles [3]. Considering that the surface and volume of the spherical virions scale with the second and third power of the radius, respectively, our results reveal an increased specific surface (surface/volume ratio) in the variant virus particles. Thus, while the infectivity of SARS-CoV-2 relies on the dynamics and the mechanics of the virus, it may be influenced by the specific surface as well.

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Stimuli-Responsive Coacervates as Universal Carriers for Intracellular Delivery of Macromolecular Therapeutics

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Abstract

Macromolecular therapeutics (peptides, proteins, mRNAs, plasmid DNAs, etc...) hold vast therapeutic potential across human disease states by providing opportunities to address targets that have proven refractory to traditional approaches. However, a critical impediment for the successful application of these modalities is their inability to cross cellular membranes, preventing access to intracellular targets. Current approaches to solve this key issue are based on nanoscale carriers to deliver the payloads, which however have several drawbacks including a tendency to get entrapped in endosomal compartments, poor biodistribution, and in some cases dose-limiting toxicity. Bypassing endosomal entrapment for direct cytosolic payload delivery is an attractive alternative approach but current methods suffer from their own pitfalls. For example, the carriers are typically limited to delivery of a particular therapeutic modality or to relatively low molecular weight (MW) cargos. Furthermore, many approaches involve laborious synthetic procedures and/or encapsulation processes using organic solvents that can decrease bioactivity of the therapeutic cargo.

In this talk, I will present a unifying delivery strategy of macromolecular therapeutics recently developed by our team that is cargo-agnostic, does not cross the cell membrane through classic endocytosis, and non-cytotoxic¹. This new method exploits Liquid-Liquid Phase Separation (LLPS) of engineered peptides^{2,3} self-assembling into therapeutic-carrying coacervate microdroplets that are capable to release their cargo in the cytosol. These peptide microdroplet carriers benefit from several unique advantages that set them apart from other approaches¹:

- (1) A remarkable wide range of therapeutics can be quickly recruited in the droplets, from short therapeutic anti-cancer stapled peptides to very large enzymes (430 kDa) to mRNAs;
- (2) The recruitment process is rapid and carried out under aqueous environments, thus preserving bioactivity of the therapeutics⁴. Furthermore, the recruitment efficiency is above 90% in all tested macromolecular therapeutics tested so far;
- (3) The coacervates readily cross the cellular membrane, bypassing classical endocytosis pathways to enter in the cytosol⁵;

(4) The side-chains of the peptides are conjugated with a redox-responsive moiety, which triggers disassembly of the droplets in the reducing environment of the cell, leading to efficient payload release;

(5) Finally, we have demonstrated that the bioactivity of the released therapeutics is retained in the cell and that mRNAs exhibit high transfection efficiency.

Together, this platform thus represents a general and robust strategy for the intracellular delivery of a range of macromolecular modalities with promising potential for the treatment of a spectrum of human diseases such as cancers, metabolic diseases, or genetic disorders. Furthermore, these peptide coacervates could also be used as novel carriers for next-generation mRNA-based therapeutics.

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Scanning Nanopore Microscopy for Single-cell Profiling

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Nanopore-based sensors have become a prominent tool for analysis of nucleic acids and proteins. Here we introduce a type of nanopore sensor device which can be precisely positioned on demand using a force feedback [1]. The nanopore is integrated within a fluidic microchannel controlled with an atomic force microscope (FluidFM). The nanopore microscope allows sampling and sensing proteins secreted from single-cells, mapping the ion channels on the membranes and intracellular sensing and imaging. Using this tool, we have explored three different areas of application in molecular biology and physics: (1) localized confinement and detection of biomolecules, (2) extracellular recording from single cells to monitor the transmembrane activities (e.g. permeation of proteins/RNA/ions), (3) controlled localization of the nanopore chip into the cytoplasm and nucleus of the cell for intracellular sensing, injection and mapping, including the ionic current map obtained from the nanoscale organization of a nuclear membrane for the first time. We have also introduced a method for easy, fast, precise and on-demand formation of a nanopore in proximity of single-cells in order to monitor their activity [2]. By accurately positioning the nanopore in the proximity of single cells and continuously recording single molecule translations over several hours we obtained the secretome map of a single neuron cell.

The introduced method offers great potential for single-cell proteomics and genomic analysis; electrophysiology; injection and delivery. This will open new possibilities in many areas, ranging from drug discovery to monitoring cell-cell communications to studying mechanosensitive ion-channels.

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Molecular Scale Electronics: From Molecular Switches to Emulating Synaptic Behavior

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Molecular electronic devices are highly complementary to traditional electronic devices and may lead, in principle, to novel electronic functionalities that are very complicated to realize otherwise[1,2]. It has been notoriously difficult, however, to reversibly address molecular switches in solid-state tunnel junctions, but such switches are important to create molecular devices where multiple electronic functions are defined at the molecular length-scales or to develop dynamical systems needed for upcoming technologies, such as, neuromorphic computing.

After a brief introduction to the current status of molecular electronics, I will discuss our recent efforts to develop multi-functional molecular devices[3,4]. Recently, we developed a new type of an electrically driven molecular switch that can toggle between two different functionalities, that of a diode and memory.[5] This dual-functional switch resembles one diode–one resistor (1D–1R) resistive random access memory (RRAM) but defined within a single molecular layer. This molecular approach is very simple in design, greatly reduces the footprint of devices and the operating voltage (to just <1.0V). By coupling fast electron transport to slow proton addition steps (and associated dynamic covalent bond formation), we are able to create dynamic molecular switches that remember their past[6]. Here, the switching probabilities depend on the operation speed and history of the switches. These switches mimic synaptic plasticity and Pavlovian learning. These examples show that electric-field-driven molecular switches pave the way to complex molecular devices where multiple electronic functions are programmed within a single molecular layer.

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DIRECT, SINGLE-MOLECULE DETECTION OF PSEUDOURIDINE MODIFICATIONS IN THE HUMAN TRANSCRIPTOME

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Mammalian cells expend large amounts of energy into generating >100 different enzyme-mediated RNA chemical modifications that can change the base-pairing, RNA secondary and tertiary structures, or recruitment of RNA binding proteins among many functions. Pseudouridine modified mRNAs are more resistant to RNase-mediated degradation and have the potential to modulate immunogenicity and enhance translation in vivo. However, we have yet to understand the precise biological function of pseudouridine on mRNAs due to a lack of tools for their direct detection and quantification.

We have recently developed an algorithm for identifying pseudouridylated sites directly on mammalian mRNA transcripts using nanopore sequencing.[1] We achieve this by exploiting systematic base-calling errors that occur at pseudouridylated sites as a function of deviations in the current signals for k-mers as well as long, synthetic mRNA controls bearing pseudouridines. We have verified pseudouridylated sites that were identified previously by biochemical methods, creating an important list of “ground truth”, pseudouridylated sites, and have also uncovered previously unreported, pseudouridylated sites. We then use our algorithm to classify types of pseudouridine hyper-modification that may occur on mRNAs: Type 1 is mRNAs that have a high percentage of pseudouridine at a given site; type 2 is mRNAs that may have >1 pseudouridine on a single read.

Our pipeline enables the direct identification and quantification of the pseudouridine modification on native RNA molecules, without requiring RNA amplification, chemical reactions on RNA, enzyme-based replication, and DNA sequencing steps. Using our algorithm and pipeline we have discovered that 1. Many of the modified sites in the human transcriptome are conserved, and 2. Pseudouridine modifications are dynamically regulated in response to differentiation.

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Solid-State Physics

**Frontiers in science and
scientific policy**

Lifetime of transitions between Landau levels

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In a magnetic field, band electrons become confined to Landau levels. There is a clean link between the material's band structure, and the energy spectrum of these Landau levels. Since the early 1950s, excitations from one Landau level to another—Landau level spectroscopy—has been abundantly employed as an extremely sensitive probe of semimetal and semiconductor band structure. From it, we obtain band parameters: effective mass, or Fermi velocity, the band gap. However, we rarely consider the width of inter-Landau level transitions, a parameter that tells us about the lifetime of inter Landau level transitions. The purpose of this work is to explore how this lifetime depends on the magnetic field, for a number of topological materials. We employ new analysis strategies on highly detailed maps of Landau levels, obtained in extreme magnetic fields.

Exciton Manipulation and Transport in 2D Semiconductor Heterostructures

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The discovery of graphene marked the start of research in 2D electronic materials which was expanded in new directions with MoS₂ and other layered semiconducting materials. They have a wide range of interesting fundamental properties and potential applications. New opportunities are enabled by the band structure of transition metal dichalcogenides (TMDCs) in which we could harness the valley degree of freedom for valleytronics and next-generation photonics. Long-lived interlayer excitons in van der Waals heterostructures based on TMDCs have recently emerged as a promising platform for this, allowing control over exciton diffusion length, energy and polarization. I will show here how by using MoS₂/WSe₂ van der Waals heterostructures, we can realize excitonic transistors with switching action, confinement and control over diffusion length at room temperature in a reconfigurable potential landscape. On the other hand, the weak interlayer interaction and small lattice mismatch in MoSe₂/WSe₂ heterostructures results in brightening of forbidden optical transitions, allowing us to resolve two separate interlayer transitions with opposite helicities and meV-scale linewidths. These have opposite helicities under circularly polarized excitation, either preserving or reversing the polarization of incoming light. By using externally applied electrical fields, we can control their relative intensities and polarization by different regions in the moiré pattern, characterized by different local symmetries and optical selection rules. Our more advanced excitonic devices now also offer the way to manipulate the motion of valley (spin) polarized excitons.

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High- T_c superconductivity in strongly overdoped cuprates

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For over three decades, research on superconducting cuprates has been focused on the underdoped and optimally doped regions of the electronic phase diagram, where these materials display an unconventional normal state – or “strange metal” – properties. It is widely accepted that, in the overdoped region at $p > 0.27$ hole/Cu, where superconductivity disappears, the properties are conventional, i.e. Fermi-liquid like. In fact, until recently, this region has been little studied owing to the difficulty of overdoping the CuO_2 plane, so such conventional scenario for overdoped cuprates has never been verified experimentally in a systematic manner.

Here we present recent results that give evidence of high- T_c superconductivity in a number of cuprates, such as $\text{Cu}_{0.75}\text{Mo}_{0.25}\text{Sr}_2\text{YCu}_2\text{O}_{7.54}$ [1], $\text{Ba}_2\text{CuO}_{4-y}$ [2] and $\text{La}_{2-x}\text{Ca}_x\text{CuO}_4$ [3], where strong overdoping, $p > 0.4$ hole/Cu, is achieved using high-pressure oxygenation during synthesis. In order to investigate the superconducting properties in this unusual region of the phase diagram, we studied the local structure of the above compounds by means of Extended X-ray Absorption Fine Structure (EXAFS) spectroscopy. To our surprise, we found huge (~ 1 Å) dynamical distortions of the lattice at T_c that involve the apical oxygen [4,5], which suggests the existence of a lattice-driven change of the electronic structure in the superconducting state. The above unexpected results put into question the validity of the current phenomenological description of cuprates [6,7]. Specifically, we shall discuss the possibility of multi-orbital superconductivity [8] and the consequences of the nonadiabatic scenario suggested by our experiments on the description of the electron-lattice dynamics [5].

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Global band topology: Classification of Dirac points and nodal planes

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The concept of global band topology refers to the fact that a given topological band feature (e.g., a Weyl point) does not exist in isolation, but is part of a global network of band degeneracies, that extends through the entire Brillouin zone [1,2]. The composition of this topological network is strongly constrained by the symmetries of the lattice and the fermion doubling theorems [3]. For example, a single Weyl node at the Γ point of a chiral nonsymmorphic space group must necessarily be accompanied by topological nodal planes [1,2]. In this talk we apply this concept to classify (i) Dirac points in general 2D systems and (ii) nodal planes in 3D magnets.

First, we derive in an algorithmic fashion the principle building blocks, out of which all two-dimensional nodal systems are built [3]. This includes in particular, Dirac semimetals, nodal superconductors, as well as non-Hermitian systems with exceptional points. We discuss a number of physical examples of topological 2D materials, e.g., p2mm boron, to demonstrate the usefulness of our classification approach. Second, we enumerate all magnetic space groups whose symmetries enforce the existence of topological nodal planes [1]. Using database searches, several materials with nodal planes are identified, including ferromagnetic MnSi. We discuss experimental consequences of the nodal planes in the surface spectra and de Haas-van Alphen measurements of MnSi and CoSi [1,2].

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FROM NANOSCALE STRUCTURE TO NANOSCALE FUNCTION

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As we gain ever-greater control of materials on a very small scale, so a new world of possibilities opens to be studied for their scientific interest and harnessed for their technological benefits. Nanoscale structures must be understood in terms of the positions of individual atoms and electrons, and the behaviour of individual quantum states.

We can take a single molecule, attach two wires to it, and use it as the active element in a transistor with graphene electrodes.¹ We can use this as a testbed for quantum interference in single-electron transport, for example in porphyrin nanoribbons.²

In a similar but slightly larger device we can use a suspended carbon nanotube as a tiny guitar string,³ and thereby investigate how thermodynamics applies to a single object in which information could play a measurable entropic role.⁴ A vibrating membrane has enabled us to demonstrate the thermodynamic cost of timekeeping within an order of magnitude of the theoretical limit.⁵

A basic challenge in quantum computing is to tune and characterise qubits on an ever-expanding scale.⁶ We have developed machine learning methods for quantum technologies, which are able to learn how to do this more efficiently than even experienced humans.⁷

As scientists we have the responsibility and the privilege of advocating the responsible use of the progress to which we contribute. This calls for insight from science and wisdom from other disciplines to learn how together we can seek to promote human flourishing in times which seem to be increasingly subject to uncertainty.⁸

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² Z. Chen *et al.*, Charge transport through extended molecular wires with strongly correlated electrons. *Chemical Science* **12**, 11211-11129 (2021)

³ Y. Wen *et al.*, A coherent nanomechanical oscillator driven by single-electron tunnelling. *Nature Physics* **16**, 75-82 (2019)

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⁵ A.N. Pearson *et al.*, Measuring the thermodynamic cost of timekeeping. *Phys. Rev. X* **11**, 021029 (2021)

⁶ D.T. Lennon *et al.*, Efficiently measuring a quantum device using machine learning. *npj Quantum Information* **5**, 79 (2019)

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New exact theoretical methods for transport properties of quantum paraelectrics SrTiO₃, KTaO₃, and PbTe.

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Transport properties of quantum paraelectrics, including such famous perovskites as SrTiO₃, KTaO₃, and PbTe, were always treated basing on the assumption that the origin of anomalies of carrier movement in these compounds is the electron-phonon interaction. Historically, only linear coupling to the lattice vibrations was considered. However, recent studies [1,2] highlighted the fact that the temperature dependence of mobility cannot be explained in the framework of linear electron-phonon interaction paradigm and quadratic coupling to the lattice plays crucial role in explanation of transport anomalies in quantum paraelectrics.

Recent development of the Diagrammatic Monte Carlo (DMC) methods resulted in creation of the approximation-free machinery for theoretical description of the transport and optical properties of the models with linear electron-phonon interaction [3,4]. However, there was no exact approximation free approach to the treatment of the quadratic interaction.

We present two different novel approximation-free techniques valid for study of quadratic electron-phonon interaction. These DMC and path integral techniques pave the way to exact studies of the interplay between linear and quadratic couplings to lattice and theoretical interpretation of the puzzling transport and optical properties of quantum paraelectrics SrTiO₃, KTaO₃, and PbTe. We show our first data on the temperature dependence of the mobility in these cases.

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Exotic localization properties in one-dimensional quasiperiodic models

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Transport properties of quantum systems crucially depend on how ordered they are. Periodic order favours extended Bloch waves that generate metallic bands, whereas disorder is known to localize the motion of particles, especially in lower dimensions. In this context, quasiperiodic systems, which are neither periodic nor disordered, reveal exotic transport properties, self-similar wavefunctions, and critical phenomena. In this talk, I will present a theoretical study of localization in a particular one-dimensional quasiperiodic model, dubbed the interpolating Aubry-André-Fibonacci (IAAF) model [1]. This model interpolates between two paradigmatic quasiperiodic examples: the Aubry-André model, known for a metal-to-insulator transition at finite potential strength, and the Fibonacci model, which is always critical. In a single-particle case, contrary to what one would naively expect, we find that the IAAF model has a non-monotonous and non-uniform behaviour of the spectrum. More precisely, we discover that by controllably evolving an Aubry-André into a Fibonacci model, a cascade of localization-delocalization transitions take place before the spectrum becomes critical. In a many-body IAAF model [2], we find that the cascade of localization transitions found in the single-particle case is destroyed even for weak interactions between particles. Moreover, in the region of the parameter space where the single-particle spectrum contains a non-trivial mobility edge, we observe an anomalous effect with tuning the interaction strength; namely, weak interactions localize the system, whereas stronger interactions enhance ergodicity. Our findings offer a unique new insight into understanding the criticality of quasiperiodic chains as well as a controllable knob by which to engineer band-selective pass filters. Furthermore, our model serves as a rich playground for studying the interplay between many-body interactions and tunable potentials.

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Cellulose nanocrystals: from self-assembly to optical properties

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Cellulose is the most naturally abundant polymer on the planet and represents an ideal choice for sourcing materials. In its native form, it is usually found as part of plant cell walls arranged in highly crystalline microfibrils, which can be further processed to produce, after chemical treatment, stable suspensions of slender, splinter-like particles, termed ‘Cellulose Nanocrystals’. [1] These bio-sourced and highly polydisperse suspensions (with dimensions of *ca.* 200±100 nm in length and 15±10 nm in width) present fascinating properties: above a critical concentration, they form cholesteric colloidal liquid crystalline suspensions, with a pitch in the micron range. When these suspensions are left to dry in a shallow dish, they lead to the formation of a film displaying strong reflection of left-circularly polarised light of specific wavelength adjustable within the visible range. While the use of these particles is promising for a variety of applications in effect pigments industry, the optical properties of these films are impacted by many parameters that remain still unclear. In this talk, I will present our recent progress on the understanding of the mechanisms of their self-assembly and how to control them to produce a variety of optically interesting effects. [2–5]

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Quantum oscillations in $\text{Zr}_{1-x}\text{Hf}_x\text{SiS}$

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Dirac matter is a class of materials where the low-energy excitation spectrum can be described by the Dirac equation. They share a property of forming symmetry protected Dirac nodes (or lines) on valence and conductive bands crossings, with bands linear in close vicinity of nodes [1]. When magnetic field is applied to a system of free charged fermions, their energy states quantize into Landau levels. In a quantum oscillation experiment, the external magnetic field is varied, which causes Landau levels to pass over the Fermi surface. This in turn results in oscillations of the electronic density of states at the Fermi level, resulting in oscillations in various properties [2].

Using different angles of external field, we explored anisotropy of Dirac nodal line semimetal $\text{Zr}_{1-x}\text{Hf}_x\text{SiS}$. Material is solid solution of ZrSiS and HfSiS and we managed to grow quality single crystals that show quantum oscillations. Here we present Shubnikov-de Haas and de Haas-van Alphen oscillations for external field along [001] for several x in $\text{Zr}_{1-x}\text{Hf}_x\text{SiS}$. Knowing the frequency of recorded quantum oscillations, as well as direction of applied field, we were able to reconstruct parts of Fermi surface for ZrSiS and HfSiS .

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Confining Layered Conductors

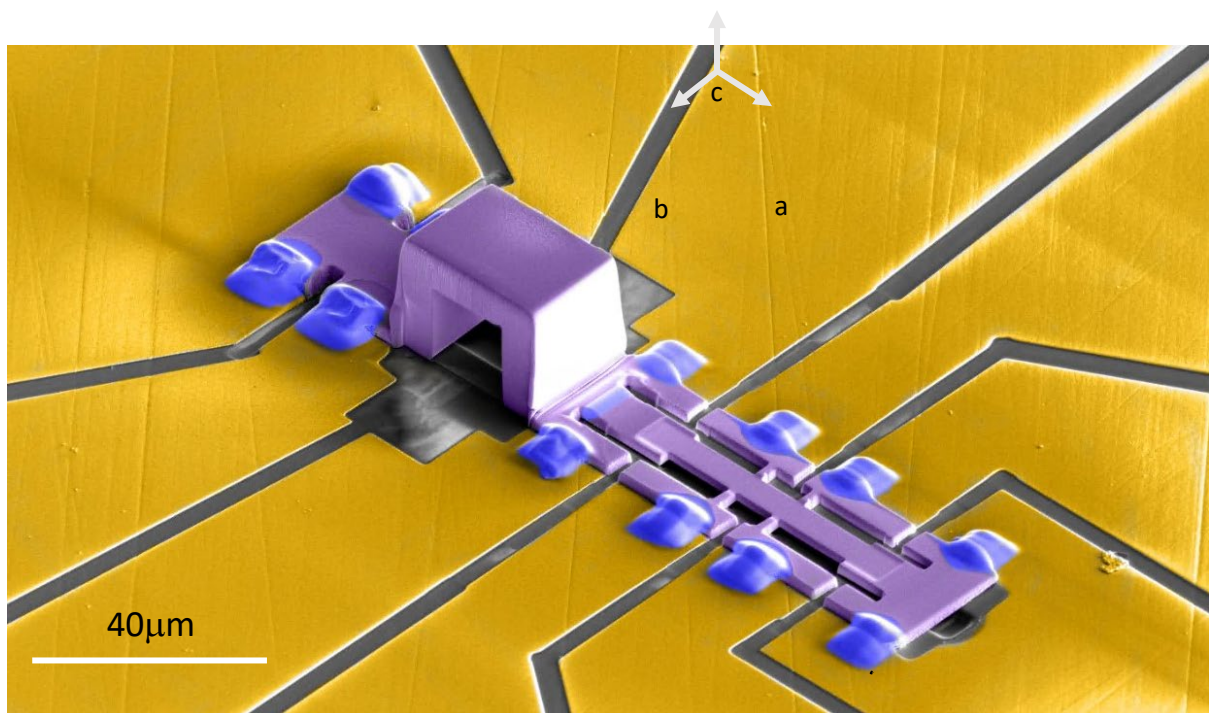
Carsten Putzke

Some of the most enigmatic correlated states in the field of quantum matter arise in lower dimensions such as quasi-2d and quasi-1d materials. The layered crystal structure in organic and high- T_c superconductors is an example of these materials, where a quasi-2D electronic structure gives rise to several unconventional electronic instabilities. The layered crystal structure allows exfoliation in some materials allowing to uncover transport properties such as the quantum Hall effect as well as enables spectroscopic probes in single layer and few layer systems.

It is the same crystallographic anisotropy that hinders the study of interlayer electrical transport and spectroscopic probes such as angle resolved photoemission spectroscopy (ARPES) of the states and Fermi surface warping relevant for interlayer conductivity. In this poster we will demonstrate the novel physical phenomena as well as experimental capabilities that focused ion beam micro-structuring enables. Confining the in-plane dimension of quasi-2D high purity metals of the Delafossites to length scales smaller than the electron mean free path gives rise to a novel realization of the particle-wave duality. In the ballistic regime the intra-layer resistivity becomes directionally dependent¹ which is absent in bulk single crystals. The same effect leads to the observation of 1D-modes in magnetic field, which propagate through the material like a light would through a grating, leading to constructive and destructive interference².

Beyond these exciting physical phenomena of finite size confined pillars, novel experimental possibilities will be presented which enable previously inaccessible insight into layered materials.

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Scanning electron microscope image of a 3D PdCoO₂ micro-structure enabling to study the interplay between inter- and intra-layer electrical transport.

SCANNING PROBE STUDIES OF CHARGE DENSITY WAVES - RECENT PROGRESS AND CHALLENGES.

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Charge density waves (CDWs) are the subject of renewed interest to understand their structure, their formation mechanism and their interplay with other quantum phases such as superconductivity and magnetism. Many models developed over the years often fail to fully describe specific experimental data sets, with embodiments of the classic Peierls Fermi surface nesting scenario being the exception rather than the rule. Scanning tunneling microscopy (STM) is a prime technique to investigate the CDW ground state, with a couple of pitfalls we will discuss based on recent high-resolution topographic STM images. Firstly, the correct identification of the CDW gap in tunneling conductance spectra is highly controversial, as evidenced by the large spread in gap amplitudes reported in the literature. Secondly, not all periodic charge modulations observed by STM are CDWs. We will present detailed analysis of the CDW modulation amplitudes and phases in real space [1], which offer unprecedented insight into the CDW gap in the band structure [2], including evidence for its multiband nature [3]. We find in particular that the CDW gap can open significantly below the Fermi level [2] and shift as a function of the local carrier concentration [4], providing an original insight into the competition between the CDW and superconducting ground states. We will also discuss possible orbital order and CDW chirality based on topographic STM images.

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TOPOLOGICAL SOLITONS IN CHIRAL QUANTUM MATTER

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Topological solitons and quantum mechanics have been intertwined for the past 60 years. Even before the term soliton had been coined, Abrikosov's theory predicted the formation of two-dimensional vortices in the phase field of superconductors, an exemplar exposition of macroscopic quantum coherence. Recent work shows that solitons are in fact a timely and promising platform for quantum operations. I will demonstrate the viability of using spin topology to influence a superconductor at selective length scales [1]. This includes adaptable recipes towards fluxonics and chiral superconductivity, as well as quantum processes such as non-perturbative, non-contact Majorana braiding. Time permitting, I will also introduce a new class of building blocks for realizing quantum logic elements [2]. Namely, nano-skyrmions in triangular magnets developing quantized helicity excitations with well-separated energy levels and distinct out-of-plane magnetizations.

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. Nanoscale self-organisation in Mott insulators: a pathway ^[L]_{SEP} to metastable metallicity ^[L]_{SEP}

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The interplay between electronic and lattice degrees of freedom in correlated materials often leads to spontaneous nanoscale architectures, which can favour and stabilize photoinduced emergent states with no counterpart at equilibrium. State-of-the-art light excitation protocols offer space-integrated information, which are insufficient to link and control the temporal and real-space dynamics of non-equilibrium states. We will present results [1] of time-resolved photoemission microscopy experiments on a VO_2 thin film, which at equilibrium undergoes a transition at $T \approx 140$ K from intrinsically nanotextured monoclinic insulator to homogeneous corundum metal. We demonstrate that the excitation with infrared light pulses turns the low- T insulating phase into a non-thermal metallic state that retains the monoclinic in-plane shear strain. Mean-field modelling shows that the topology of the monoclinic nanotexture is key for stabilizing the emergent photo-induced metal state. Engineering the nanotexture of insulating strained domains may thus constitute a new tool to control non-thermal phases in correlated materials.

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OPTICAL CONDUCTIVITY OF CUPRATES IN A NEW LIGHT

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Understanding the physical properties of unconventional superconductors as well as of other correlated materials presents a formidable challenge. Their unusual evolution with doping, frequency, and temperature, has frequently led to non-Fermi-liquid (non-FL) interpretations. Optical conductivity is a major challenge in this context. Here, the optical spectra of two archetypal cuprates, underdoped $\text{HgBa}_2\text{CuO}_{4+\delta}$ and optimally-doped $\text{Bi}_2\text{Sr}_2\text{CaCu}_2\text{O}_{8+\delta}$, are interpreted based on the standard Fermi liquid (FL) paradigm. At both dopings, perfect frequency-temperature FL scaling is found to be modified by the presence of a second, gapped electronic subsystem. This non-FL component emerges as a well-defined mid-infrared spectral feature after the FL contribution determined independently by transport is subtracted. The evolution of the mid infrared feature with temperature, frequency, and doping indicates a gapped rather than dissipative response. In contrast, the dissipative response is found to be relevant for pnictides and ruthenates. Such an unbiased FL/non-FL separation is extended across the cuprate phase diagram, capturing all the key features of the normal state and providing a natural explanation for, why the superfluid density is attenuated on the overdoped side. Thus, we obtain a unified interpretation of optical responses and transport measurements in all analyzed physical regimes and all analyzed compounds. Our work presents a major advance in the analysis and interpretation of the optical spectra of high-temperature superconducting cuprates and other correlated systems. The first unambiguous experimental determination of the non-conducting part of optical responses gives rise to an overall simplification of our understanding. For the cuprates, in particular, it proves that the conducting part is always an ordinary FL, while the non-Fermi liquid character is entirely due to the non-conducting part. This insight has been employed to understand the optical responses of superconducting pnictides as well as strontium ruthenate; the success of this approach represents a breakthrough in understanding entire classes of what are currently the most interesting functional materials.

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Studies of iron pnictide superconductors using XAS and XLD techniques

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Results of measurements on iron pnictide high-temperature superconductors using synchrotron radiation (Solaris and Elettra synchrotrons) and XAS (X-ray absorption spectroscopy) and XLD (X-ray linear dichroism) techniques will be discussed. XLD results on $L_{3,2}$ Fe edge on compounds from $\text{Eu}(\text{Fe}_{1-x}\text{Co}_x)_2\text{As}_2$ family indicate that there is an uneven occupation of Fe d_{xz} and d_{yz} orbitals, which is related to nematicity observed in these materials [1]. Additionally, comparison of XANES results (Fe and As edges) on compounds from so called 122 and 112 families, as a function of Ni and Co doping, will be presented.

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Magnetoconductivity of a metal with a closed Fermi surface reconstructed by a biaxial charge density wave

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We investigate quantum dynamics and kinetics of a 2D conductor with a closed Fermi surface reconstructed by a biaxial density wave, in which electrons move along a two-dimensional periodic net of semiclassical trajectories coupled by the magnetic breakdown tunneling under a strong magnetic field [1, 2]. We derive a quasiparticle dispersion law and magnetoconductivity tensor. The quasiparticle spectrum is found to be the alternating series of two-dimensional magnetic energy bands with gaps between them. The longitudinal magnetoconductivity shows giant oscillations with change of magnetic field, while the Hall coefficient changes sign and is absent in a wide range of the magnetic fields in between.[3] Preliminary estimations show that the suggested magnetoconductivity mechanism may be the origin of such behavior of the Hall coefficient versus magnetic field, as observed in experiments in materials with analogous topology of the Fermi surface, such as the high-T_c superconducting cuprates.

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The Ruđer Bošković Institute, Today and Tomorrow: Croatian Science and Beyond

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The Ruđer Bošković Institute (RBI) in Zagreb is the largest public research institute in Croatia. With a multidisciplinary focus, activities at the RBI span physics, chemistry, biology, marine and environmental research, molecular medicine, and informatics. Recent years have seen increasing success in securing competitive projects from both national and international funding agencies. This has been complemented with an increased effort for more direct relevance to society. The presentation will highlight selected past activities and outline future directions, all within the context of the ever changing domestic and foreign research landscapes.

Murunskite: A Bridge Between Cuprates and Pnictides

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Exploring novel materials as the candidates for unconventional superconductors can help to understand the mechanism of this exotic phenomenon but also lead to synthesis of compounds with important technological applications. The main compound of interest is murunskite ($\text{K}_2\text{FeCu}_3\text{S}_4$), a material isostructural to iron-based superconductors with iron and copper occupying the same crystal site. I will discuss the synthesis methods and measurements of structural, electronic and magnetic properties. [1] The current study shows that murunskite is a Mott insulator with sulfur orbitals partially open and electronically active, similar to oxygen orbitals in cuprates. Measurements indicate the conduction band is cuprate-like while the valence band is pnictide-like, positioning murunskite as an interpolation compound.

We have successfully modified murunskite structure by substitution and doping on all three crystallographic positions. Effects on the electronic and magnetic properties leading towards the metallization will be discussed.

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Cuprate Superconductivity: Perfect Match of Ionicity and Metallicity

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A recent comprehensive synthesis of observational and theoretical insights in cuprate superconductors is reviewed [1]. The evolution of the Fermi arcs and pseudogap with doping, and the concomitant evolution of superconductivity itself, are understood on an equal footing, within a simple picture of a Fermi liquid against an ionic background. The evolving background determines the relative proportion of the localized (ionic) and itinerant (Fermi liquid) components in the total charge. The transition from a low-density superconducting to a high-density non-superconducting Fermi liquid is related to the disappearance of the localized component at overdoping. It is understood microscopically as a transition from an ionic to a covalent Cu-O *d-p* bond. This transition is first-order, like an orbital transition, and does not entail a quantum critical point or any dissipative mechanism. A fast virtual local mechanism of Cooper pairing is proposed.

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Magnetotransport and supercurrents in HgTe-based topological nanowires

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Topological insulator (TI) nanowires in proximity to conventional superconductors have emerged as a tunable platform to realize topological superconductivity and Majorana zero modes [1]. The tuning is done using an axial magnetic flux ϕ which allows transforming the system from trivial at $\phi = 0$ to topologically nontrivial when half a magnetic flux quantum $\phi = \phi_0 / 2 = h / 2e$ threads the cross-section of the wire.

Our system of choice is wires made from strained HgTe layers, known to be a strong topological insulator. This material is characterized by high electron mobilities, enabling ballistic transport, and featuring pronounced quantum effects [2,3]. Besides magnetotransport properties, I focus on the properties of Josephson junctions engineered by placing superconducting Nb contacts across the wires, thus inducing superconductivity in the surface states of the HgTe wires. On the one hand, we investigate the evolution of the supercurrent in HgTe wire based JJs as a function of an axial magnetic field, on the other we probe the periodicity of the superconducting phase utilizing microwave irradiation and probing the Shapiro steps. From the suppression of odd Shapiro steps, we extract the 2π - and 4π -periodic portion of the supercurrent where the latter is a required signature for Majorana zero modes present. Suppressed odd Shapiro steps herald the existence of 4π -periodic supercurrents even at low magnetic fields, i.e., in the trivial regime, indicating that trivial mechanisms like Landau-Zener transitions are the origin. Our data suggest further that this 4π -periodic supercurrent of trivial origin can be suppressed by an in-plane magnetic field oriented perpendicular to the wire, but that at magnetic fields above $\phi_0 / 4$, topological 4π -periodic supercurrents take over [4].

Work done in cooperation with

Ralf Fischer, Wolfgang Himmeler, Johannes Ziegler, Jordi Picó-Cortés , Gloria Platero, Milena Grifoni, Dmitriy A. Kozlov, N. N. Mikhailov, Sergey A. Dvoretzky , Michael Barth, Jakob Fuchs, Cosimo Gorini, Klaus Richter, and Christoph Strunk,

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METASTABILITY - A LIFE FORCE IN QUANTUM MATERIALS

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Nonequilibrium processes are prevalent everywhere from life systems to cosmology. The study of nonequilibrium systems requires not only temporal, but also spatial and spectral resolution that is tailored to the system under study. Unfortunately achieving all these requirements is usually very difficult, and often impossible. Quantum systems offer an opportunity to study non-equilibrium processes and associated metastable states in detail all the way to the atomic level with a combination of state-of-the-art nonequilibrium time-resolved and microscopy techniques [1]. Here we will present an investigation of prototype charge ordered quantum materials in which emergent properties, and metastability in particular, are accessed through non-equilibrium routes [2–5]. Apart from advancing our understanding of nonequilibrium quantum matter, the emergent metastable systems also have a useful application for ultrafast, ultra-efficient cryomemory devices [6,7], addressing the energy consumption problem of future big data systems head on.

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Far-infrared *ab*-plane optical conductivity of $\text{La}_{2-x}\text{Ba}_x\text{CuO}_4$ single crystals

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Kramers-Kronig analysis of the *ab*-plane reflectance of ten $\text{La}_{2-x}\text{Ba}_x\text{CuO}_4$ single crystals, with x ranging from undoped to optimally doped, yields the optical conductivity $\sigma_1(\omega)$ at temperatures from 10–300 K. The influence of stripe order around $x = 0.125$ appears in the spectra below $T = 50$ K, observed both as a reduction in the free-carrier (normal state) and superfluid (superconducting state) density and by the appearance of a relatively narrow conductivity band near 25 meV. Away from this band, the low-frequency conductivity follows the Drude function, with a T -linear scattering rate, $\hbar/\tau = \alpha k_B T$. The prefactor α varies with x , exceeding the conjectured Planckian bound ($\alpha = 1$) on inelastic scattering by more than a factor of two near optimal doping.

*With Luyi Yan and Genda Gu

Transcutaneous electrical nerve stimulation via deep-red light transduced by implanted thin film photocapacitors

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Great demand exists for minimally-invasive neuromodulation technologies to enable next-generation bioelectronic medicine. We report on our developments of ultrathin (opto)electronic devices for neurostimulation. All of these devices rely on far red/near infrared irradiation in the tissue transparency window to actuate nanoscale organic semiconductor components. Our flagship technology is the organic electrolytic photocapacitor (OEPC) – a device that mimics biphasic current-pulse neurostimulation and thus transduces an optical signal into directly-evoked action potentials in neurons. These devices are not only wireless, but also 100-1000 times thinner than existing technologies. We will discuss examples of chronic implants capable of stimulating peripheral nerves, the cortical surface, as well as deeper brain structures. Light power can be safely and effectively transmitted to implants up to 15 mm below the skin surface, and effectively penetrates the scalp and skull. We believe that the combination of deep red light and ultrathin photovoltaic devices can account for a new paradigm in wireless bioelectronic medicine.

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High-Pressure Hydrides: Experimental Questions and some Theory

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Room-temperature superconductivity was reported in October, 2020, after 5 years of discovery of superconducting hydrides in the 200 - 250 K range. This talk will first critically review the experimental evidence for superconductivity. At the time of this writing, there are big resistivity drops, but no compelling measurements of the Meissner effect or flux trapping. We also provide a basic review of our current understanding of the electron-phonon interaction in relation to superconductivity. We revisit the age-old question (once thought settled) of whether or not the electron-phonon interaction can produce high-temperature superconductivity.

MAGNETO-OPTICAL DETECTION OF TOPOLOGICAL CONTRIBUTIONS TO THE ANOMALOUS HALL EFFECT

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Recently, the topology of the electronic band structure has attracted much attention in materials with broken time-reversal symmetry as these compounds may host non-trivial features such as Weyl fermions. One of the most profound manifestation of the non-trivial topology is the emergence of the anomalous Hall effect (AHE). When the spin degeneracy of the bands is lifted by the exchange splitting, their spin-orbit mixing leads to a finite Berry curvature, which, as a fictitious magnetic field, deflects electric currents. However, identifying the band structure features responsible for the AHE is difficult based on magnetotransport experiments alone, since the response is a sum of multiple bands as well as intrinsic and extrinsic contributions with sometimes identical dependence on the longitudinal conductivity.

Here, we demonstrate that the energy resolved measurement of the infrared Hall-effect via the detection of the magneto-optical Kerr-effect (MOKE) spectrum can provide the necessary information. We studied kagomé magnets such as Fe_3Sn_2 and $\text{Co}_3\text{Sn}_2\text{S}_2$, showing large AHE, which is attributed to Dirac and Weyl fermions. Using MOKE spectroscopy, we identified the inter-band excitations responsible for the intrinsic AHE. In Fe_3Sn_2 , we found that low-energy transitions, tracing "helical volumes" in momentum space reminiscent of the formerly predicted helical nodal lines, substantially contribute to the AHE, which is further increased by contributions from multiple higher-energy interband transitions [1]. Our study also reveals that local Coulomb interactions lead to band reconstructions near the Fermi level. Whereas in $\text{Co}_3\text{Sn}_2\text{S}_2$, we identified enhanced infrared Hall conductivity at the electronic excitation in the vicinity of a nodal-loop.

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Is there a Native Oxide for Intrinsic Magnetic Topological Insulator MnBi_2Te_4 Thin Films?

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Understanding the effects of interfacial modification on the functional properties of magnetic topological insulator thin films is crucial for developing novel technological applications from spintronics to quantum computing. Here, we report a large electronic and magnetic response that is induced in the intrinsic magnetic topological insulator MnBi_2Te_4 by controlling the propagation of surface oxidation [1]. We show that the formation of the surface oxide layer is confined to the top 1-2 unit cells but drives large changes in the overall magnetic response. Specifically, we observe a dramatic reversal of the sign of the anomalous Hall effect driven by finite thickness magnetism, which indicates that the film splits into distinct magnetic layers each with a unique electronic signature. These data reveal a delicate dependence of the overall magnetic and electronic response of MnBi_2Te_4 on the stoichiometry of the top layers. Our study suggests that perturbations resulting from surface oxidation may play a non-trivial role in the stabilization of the quantum anomalous Hall effect in this system and that understanding targeted modifications to the surface may open new routes for engineering novel topological and magnetic responses in this fascinating material.

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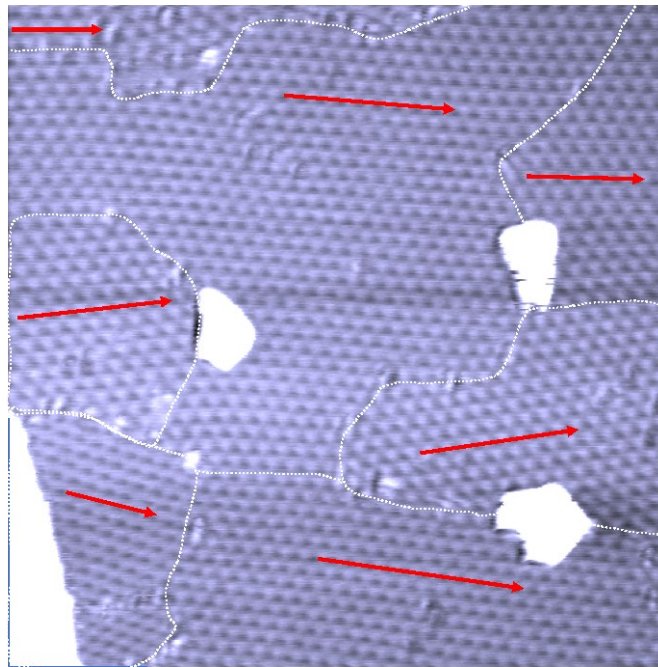
Transfer of Graphene under Ultra-High-Vacuum

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Current graphene transfer techniques most often require drop-coating of a supporting layer on top of graphene and immersion in an etching solution to remove the growth substrate, followed by removal of the supporting layer in another solution post-transfer, making them incompatible with ultra-high vacuum (UHV). We present a novel technique for graphene transfer fully compatible with UHV, based on the chemical etching of a Cu growth substrate, using teflon (PTFE) as a supporting layer combined with a wafer-bonding approach. We demonstrate successful transfer to both Ir(111) and Cu(100) crystals. The STM image shows UHV transferred graphene on Ir(111) after annealing to 1270 K (1000 Å x 1000 Å, $V_t = 0.3$ V, $I_t = 10$ nA, $T = 300$ K).



20 nm

SrCu₂(BO₃)₂ – a Deep Purple crystal

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The insulating quantum magnet SrCu₂(BO₃)₂ is a unique material realization of the theoretical Shastry-Sutherland model, which has become an arena for developing and testing quantum many body methods in 2D. Using extreme conditions of magnetic field and pressure to drive the system across quantum phase transitions, we report on the quantum phases and quantum excitations. I will summarize a couple of intriguing results: correlated decay of triplons [1]; existence of a plaquette singlet phase [2]; discovery of a critical point as the quantum equivalent of the vapour-liquid transition in water [3].

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STOCHASTIC RESONANCE SWITCHING IN A CORRELATED SPIN GLASS

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The interplay between spin-orbit interaction (SOI) and magnetic order is currently one of the most active research fields in condensed matter physics. Famous examples of this interplay are skyrmions and spin waves, but also the search for Majorana zero modes and magnetic topological insulators fit directly in this field and have gained much attention in recent years. The full spectrum of possibilities is unleashed in combination with breaking the symmetry of the system, either at interfaces or in the crystal structure itself. This makes multiferroic materials, where symmetry breaking in the form of ferroelectric order and magnetic order coexist, a promising playground to look for functional properties combining SOI and magnetism. Here we will show that starting from a ferroelectric system with strong spin orbit interaction and doping this with magnetic impurities is indeed a promising pathway to achieve magnetic order with tuneable dynamics. The switching mechanism in this correlated spin glass system will be explained based on stochastic resonance.

In α -GeTe the combination of the ferroelectric order and large SOI yields a switchable Rashba-type spin structure of the bulk states [1]. When doped with up to 20% Mn a magnetic order is induced while the ferroelectric order remains present, rendering it a multiferroic material [2]. Moreover, the strong magnetoelectric coupling in the system [1] ensures a coupling of the magnetisation and polarisation axes, resulting in the opening of a Zeeman gap in the Rashba split bands around the Brillouin zone centre [3]. This unique combination of properties creates a large bulk Rashba-Edelstein effect and allows for current driven magnetisation switching [4]. Here we will present X-ray magnetic circular dichroism (XMCD) and muon spin resonance (muSR) results supported by theory showing that the system orders in a correlated spin glass state with topological spin textures and spontaneously switches its magnetisation direction without changing any of the typical external parameters.

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Measuring and tailoring anisotropies in skyrmion and antiskyrmion hosts

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As known for long, in centrosymmetric crystals magnetic anisotropy plays a key role in the formation of magnetic bubbles, including topologically trivial and non-trivial ones. In contrast, in non-centrosymmetric crystals, where the Dzyaloshinskii-Moriya interaction is the key player in stabilizing magnetic skyrmions, systematic studies on the effect of anisotropy have been virtually non-existing. However, recent theoretical predictions and experimental observations show that the quantitative description of the (anti)skyrmion stability range, the formation of distinct high- and low-temperature skyrmion lattice phases and other emergent exotic mesoscale spin patterns all require the treatment of magnetic anisotropy on equal footing with the Dzyaloshinskii-Moriya interaction. Here we provide a short overview, from an experimental point of view, on the vital role of magnetic anisotropy in various skyrmion and antiskyrmion host materials, via the spectroscopic determination of relevant anisotropy terms in non-centrosymmetric cubic (O, T) and axial (C_{nv} , S_4) magnets as well as in centrosymmetric skyrmion hosts [1-6].

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New interpretation of a phonon dispersion relation in $\text{Nd}_{2-x}\text{Ce}_x\text{CuO}_4$

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The discovery of a high-temperature phonon anomaly in double-layer cuprate $\text{HgBa}_2\text{CaCu}_2\text{O}_{6+\delta}$ (Hg1212) [1], as well as the observation of dynamical charge correlations in its single-layer equivalent, $\text{HgBa}_2\text{CuO}_{4+\delta}$ (Hg1201) [2], raised a question concerning the character of the interplay between lattice dynamics and the CDW correlations, both static and dynamic. Interestingly, it was reported for a wide range of hole-doped cuprates [3,4] that the dispersion of acoustic phonon modes is modulated around the CDW order wave vector, q_{CDW} . However, it remains unclear whether the effect can also be observed at higher energies, for optical modes. To solve these issues, we performed studies of the phonon dispersion relation in electron-doped cuprate $\text{Nd}_{2-x}\text{Ce}_x\text{CuO}_4$ (NCCO), around the momentum transfer $q_{CDW} \approx 0.23$ which corresponds to the CDW wave vector. Our detailed temperature and doping-dependent inelastic X-ray scattering (IXS) studies resulted in a new interpretation of the bond-stretching mode dispersion and revealed broadening of this mode at the momentum where the two highest optical modes anticross. Our experimental results are complemented by density functional theory (DFT) calculations performed for an undoped compound.

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UNIVERSAL PROPERTIES OF FLUORESCENCE INTERMITTENCY IN NANOSCALE EMITTERS

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Virtually all known fluorophores exhibit mysterious episodes of emission intermittency. A remarkable feature of the phenomenon is a power-law distribution of on- and off-times observed in colloidal semiconductor quantum dots, nanorods, nanowires and some organic dyes. More recently, fluorescence intermittency has also been detected in a quasi-two dimensional material: reduced graphene oxide.

For nanoparticles, the resulting power law extends over an extraordinarily wide dynamic range: nine orders of magnitude in probability density and five to six orders of magnitude in time.

Exponents hover about the ubiquitous value of $-3/2$. Dark states routinely last for tens of seconds—practically forever on quantum mechanical timescales. Despite such infinite states of darkness, the dots miraculously recover and start emitting again. Although the underlying microscopic mechanism responsible for this phenomenon remains a mystery and many questions persist, I argue that substantial theoretical progress has been made. Within a single phenomenological framework[1] we succeeded to capture the universal behavior of a wide range of nanoscale emitters and, in some cases, to reveal microscopic scenarios that could lead to emission intermittency and optical $1/f$ noise in these systems.

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(ANTI-)SKYRMIONS IN CRYSTALS WITH S4 SYMMETRY

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Magnetic skyrmions are nowadays found in a variety of different material classes, ranging from single crystals to sputtered films. They often emerge on length scales much larger than the atomic lattice where they appear as vortex-like, rotationally symmetric whirls. Their anti-vortex-like partners, consequently dubbed anti-skyrmions, naturally break this rotational symmetry which leads to a plethora of new effects. However, only a limited number of antiskyrmion-hosting materials are known and, previously, they all belonged to the D2d symmetry class, even though crystals with S4 symmetry were predicted to also host antiskyrmions.[1]

In my talk, I will present our recent works on antiskyrmions in crystals with S4 symmetry. Combining experiments and theory, we studied antiskyrmions, skyrmions, and other textures in the S4-symmetric family of schreibersites (Fe,Ni)3P with heavy element doping.[2,3,4] The competition between the dominant demagnetization energy and small Dzyaloshinskii-Moriya interaction stabilizes both antiskyrmions and skyrmions in the transition region from the stripe phase to the field-aligned ferromagnet and, moreover, renders antiskyrmions square-shaped and skyrmions elliptical.[2] In general, antiskyrmions form in thicker samples and samples with larger uniaxial anisotropy where the bulk DMI can compete with dipolar interactions. Vice versa, skyrmions form in thinner samples where they profit from the strong dipolar interaction.[3] Moreover, I will show how the ellipticity of skyrmions in these systems can be used to estimate the magnitude of the DMI[4].

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Spin proximity effects in 2D materials

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Graphene has weak spin-orbit coupling and no magnetic order. But when placed in contact to a strong spin-orbit coupling material, such as a TMDC, or a ferromagnet, such as Cr₂Ge₂Te₆, Dirac electrons acquire strong spin-orbit or exchange coupling, respectively. Such proximity effects render graphene suitable for spintronic applications that require spin manipulation [1]. In addition, graphene with strong proximity spin interactions can host novel topological states [2]. Fascinating new phenomena appear when bilayer graphene gets encapsulated by a TMDC from one side, and a ferromagnet from another. The resulting, so called ex-so-tic structure [3], offers spin swap functionality: switching spin-orbit and exchange coupling on demand by gate. In this talk I will review the recent developments in the proximity phenomena in graphene, and present some recent theoretical results on the control of the proximity spin-orbit and exchange coupling by twisting the van der Waals layers. I will show that the signature proximity spin-orbit coupling in graphene---valley Zeeman coupling---can be efficiently tuned by the twist angle [4], and that proximity exchange coupling can be switched by the twist angle, and even morph from ferromagnetic to antiferromagnetic [5]. Support from DFG SPP1244, SFB 1277, and EU Graphene Flagship is acknowledged

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Nature and symmetry charge order in cuprate superconductors

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I will present recent synchrotron experiments on the problem of charge order in cuprate superconductors [1-5]. Improvements of energy resolution has led to a wave of new resonant inelastic x-ray scattering (RIXS) results on the cuprates. In particular, new grounds have been gained on the understanding of electron-phonon coupling and its role for charge ordering. Another string of experiments has explored the tunability of charge order in the presence of uniaxial pressure.

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Selected universal properties of high-temperature superconducting cuprates

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One of the fundamental problems of condensed matter physics is to explain the nature of electron states and microscopic pairing mechanism in the strongly correlated systems. Their specific characteristic is the circumstance that superconductivity appears in the systems, in which the reference state is either the Mott insulating state or that of magnetic metal, with specific exchange interaction surviving in the paired state. In our group we have constructed a unified theoretical model of these systems, which contains both the strong correlations and magnetic fluctuations. The model has been applied to the description of high-temperature superconducting cuprates [1,2,3], heavy fermions, and to the twisted graphene bilayer systems. The aim of our presentation is to summarize selected properties of those systems, that is: (i) to discuss evolution from the antiferromagnetic Mott insulator to high temperature superconductor and to provide its universal features in the latter case [1,3]; (ii) to describe the dynamic (paramagnons) and plasmon excitations across the phase diagram [4]. One should underline that pairing in all above systems is regarded as taking place in real space, what distinguishes them in a principal manner from the corresponding description in the BSC and Eliashberg theories. The theoretical results are compared with experiment in a quantitative manner.

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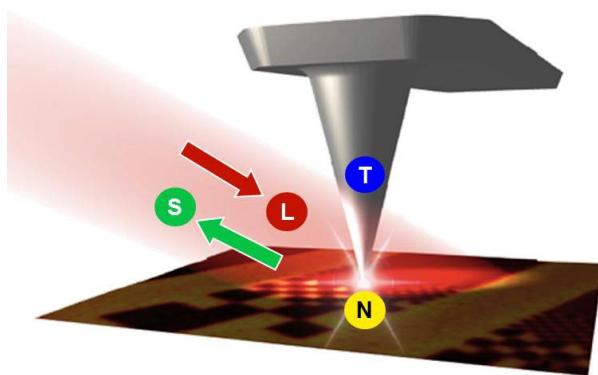
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NEAR-FIELD INFRARED MICROSCOPY ON CARBON NANOSTRUCTURES

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Scattering near-field optical microscopy (s-SNOM), based on the combination of atomic force microscopy and frequency-dependent light scattering, is an emerging method that combines high spatial resolution with high sensitivity even at long illuminating wavelengths. I will present results in the infrared frequency range obtained on various aspects of carbon nanostructures. The most obvious task, identifying individual molecules, is also the most difficult due to the weak scattering from molecular vibrations. Free (Drude) electrons in metallic carbon nanotubes [1] or encapsulated metal clusters [2] are more easily detected. The intense field under the tip can also be used to launch and detect the charge distribution inside nanotubes caused by interference of quasiparticles: plasmon-polaritons [3] or phonon-polaritons [4]. The interaction of phonon-polaritons with vibrational modes of molecules confined in the tubes [5] brings the capabilities of the method full circle, enabling to reach a detection threshold of a few hundred molecules and follow their chemical reactions by infrared spectroscopy.



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EuFe₂As₂-BASED COMPOUNDS INVESTIGATED BY ⁵⁷Fe AND ¹⁵¹Eu MÖSSBAUER SPECTROSCOPY

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The EuFe₂As₂-based compounds exhibiting 3*d* and/or 4*f* magnetic order were investigated with ⁵⁷Fe and ¹⁵¹Eu Mössbauer spectroscopy [1-3]. It was found that spin-density-wave order of the Fe itinerant moments is suppressed by the chemical doping and in many cases the superconductivity is achieved. The Eu localized moments usually order regardless of the dopant concentration *x*, but undergo spin reorientation with increasing *x* from the alignment parallel to the *a*-axis in the parent compound, toward the crystallographic *c*-axis. The change of the 4*f* spins ordering from antiferromagnetic to ferromagnetic occurs simultaneously with a disappearance of the 3*d* spins order. The Fe nuclei experience the transferred hyperfine magnetic field due to the Eu²⁺ ordering for sufficiently substituted compounds, while the transferred field is undetectable in EuFe₂As₂ and for compounds with a low substitution level. It seems that the 4*f* ferromagnetic component arising from a tilt of the Eu²⁺ moments to the crystallographic *c*-axis leads to the transferred magnetic field at the Fe atoms, even in the superconducting state.

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Sublattice extension of the Rashba nanowire model

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Interplay between superconductivity, spin orbit coupling and magnetic field can lead to realization of the topological phase. Majorana bound states (MBS) emerging at the ends of a one dimensional nanowire are one of its manifestations[1,2]. Signatures of these states have been observed, e.g. in superconductor-semiconductor hybrid nanostructures or adatom chains.

During this talk, We will present a few cases where the MBS can emerge outside of the usual topological regime, due to the impact of the sublattice on the topology of Oreg-Lutchyn model of Rashba nanowire. It is done by expanding the Rashba nanowire model with dimerized sublattice similar to SSH model[3] or with antiferromagnetic sublattice[4].

In the first case, the dimerization-induced topological superconductivity allows for forming of additional topological *branch*. We provide an analytical justification based on the symmetry and parity considerations and discuss feasible spectroscopic methods for its empirical observation.

In the second case, an additional topological *branch* emerges due to the antiferromagnetic order allowing Majorana bound states to exist close to half-filling, obviating the need for either doping or gating the nanowire to reach the low density regime.

Additionally, we show the emergence of the Majorana bound states in the absence of the external magnetic field, which is also a result of inherent antiferromagnetic order.

We will discuss results in context of topological phase diagrams showing the beneficial impact on the robustness of MBS. Furthermore, we will demonstrate how these topological phases could be probed experimentally within the non local transport measurements.

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Photoluminescence and optically detected magnetic resonance map of single-walled carbon nanotubes

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While the photoluminescence of semiconducting single-walled carbon nanotubes (SWCNTs) has only been observed first 20 years ago [1], these materials show high promises for applications of future technologies, such as light-harvesting, quantum computing, and optoelectronics. Thanks to this, they are being intensely studied ever since, with our group specializing in their investigation via optical spectroscopy by the usage of a self-developed spectrometer [2]. This device is equipped both with a tunable laser source as the excitation source and a spectrograph able to detect in the near-infrared range. Thanks to them, not only the photoluminescent (PL) spectrum of SWCNTs can be recorded, but their optically detected magnetic resonances (ODMR) as well. This can be performed for a range of exciting wavelengths, thus creating so-called PL and ODMR maps both at room temperature and at 77 K.

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The role of the electron-phonon interaction strength in shaping spectra of phonon-plasmon systems

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We provide a systematic analysis of phonon-plasmon coupled excitations in polar systems [1] through the complementary lens of electron energy loss spectroscopy (EELS) and phonon spectra [2]. The whole experimentally relevant parametric space, spanned by the adiabaticity parameter and the electron-phonon interaction (EPI) strength, is covered by referring to several real materials [3] that are of particular interest. Excitations' dispersions evolutions, damping, and various limiting behaviours are qualitatively and quantitatively discussed.

We find that the EPI strength plays a determining role in distributing spectral weights among coupled excitations, which opens the possibility of estimating its value directly from experimental EELS spectra, even in cases of very limited energy resolution.

The projection of the excitations onto the phonon degree of freedom reveals for strong couplings large phonon production contributions, which are of very different origins depending on the adiabaticity parameter. In particular, in the adiabatic regime the additional phonon spectral weight is a consequence of the phonon softening effects, while in the antiadiabatic regime it arises due to a cloud of phonons that accompanies plasma oscillations.

We also comment on phonon properties of phonon-plasmon coupled systems within the static screening and the static polarization approximation, where the former is being frequently used in studying the impact of non-adiabatic effects on phonon spectra in *ab initio* modelling [4-6].

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Green and rational synthesis of porous MOFs and their non-conventional forms via mechanochemistry

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Porous metal-organic frameworks (MOFs)[1] have become a highly researched area of modern materials science. MOFs are modular coordination materials whose structure and properties can be altered by a careful choice of metal nodes and suitable organic linkers. They are now widely studied for storage, separation, catalysis, sensing, light-harvesting, and other applications.[2] Microporous MOFs are now commercialized, but the standard synthetic procedures, involving an excess of organic solvents and harsh reaction conditions, still prevent their wider industrial application.

Here we present how mechanochemical reactions,[3], i.e. reactions between solid reactants induced by mechanical force, can be used for a rapid, sustainable, and controllable transformation of environmentally safe precursors into relevant microporous MOFs, such as MOF-74[4] or zirconium-based MOFs of UiO[5], NU-[6], and PCN-[7] families. It is particularly suitable for the preparation of their multi-metal or amorphous derivatives by using only a catalytic amount of green liquids, such as alcohols or water. Direct monitoring by powder X-ray diffraction [8] revealed that the mechanochemical formation of MOFs often proceeds through intermediate phases, most of which are inaccessible from solution procedures. It is possible to isolate and characterize these intermediates and use them for the controllable synthesis of non-conventional MOFs, such as various bimetallic MOF-74 materials,[9] with interesting magnetic properties and strong potential for new catalytic reactivity.

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The optical response of the quantum material family $\text{BaCoS}_2\text{-BaNiS}_2$

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BaCoS_2 and BaNiS_2 are the end members of a solid solution that shows a vast array of quantum properties. The Co material is a strongly correlated insulator with an antiferromagnetic transition, as well as a structural phase transition, around room temperature. At 28% Ni doping the solution undergoes an electronic metal-insulator phase transition to a Drude metal. The metallicity persists all the way to the pure Ni compound, where in addition to the Drude metal, we observe a strong contribution from bands with linear dispersion at the Fermi level. These will give origin to dispersive Dirac nodal lines. We performed optical conductivity measurements combined with ab-initio calculations to reverse engineer the role of each band in the physical response of these materials. We explained uncommon features in their optical response such as a linear dispersion of the optical conductivity [1] and the existence of an isosbestic line separating a spectral-weight transfer across Dirac nodal states [2].

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Mott Quantum Critical Points at finite doping

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We demonstrate that a finite-doping quantum critical point (QCP) naturally descends from the existence of a first-order Mott transition in the phase diagram of a strongly correlated material.

In a prototypical case of a first-order Mott transition the surface associated with the equation of state for the homogeneous system is "folded" so that in a range of parameters stable metallic and insulating phases exist and are connected by an unstable metallic branch.

Here we show that tuning the chemical potential the zero-temperature equation of state gradually unfolds. Under general conditions, we find that the Mott transition evolves into a first-order transition between two metals, associated to a phase separation region ending in the finite-doping QCP. This scenario is here demonstrated solving a simple multi-orbital Hubbard model relevant for the Iron-based superconductors, but its origin - the splitting of the atomic ground state multiplet by a small energy scale, here Hund's coupling - is much more general. A strong analogy with cuprate superconductors is traced. [1]

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Harmonic Nanoparticles: from Multiorder Nonlinear Mixing to Blood Flow Imaging at GHz Pixel Rate

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Whereas most of the reports on the nonlinear properties of micro- and nanostructures address the generation of distinct signals, such as second or third harmonic, we recently demonstrated that the novel generation of dual output lasers developed for microscopy can readily increase the accessible parameter space and enable the simultaneous excitation and detection of multiple emission orders such as several harmonics and signals stemming from various sum and difference frequency-mixing processes.[1] This rich response, which in our case features 10 distinct emissions and encompasses the whole spectral range from the deep ultraviolet to the short-wave infrared (SWIR), is demonstrated using various metal-oxide nanomaterials (harmonic nanoparticles, HNPs) while being characterized and simulated temporally and spectrally. Together with spectral flexibility, the quasi-instantaneous response of parametric signals by HNPs can be exploited to increase imaging speed attaining dwell times shorter than fluorophore lifetimes. In this context, we demonstrate the detection and in-flow imaging of cells labelled by HNPs within whole, unfiltered blood by high-speed SLIDE [2] microscopy at the disruptive speed of 16'000 images per second (1 GHz pixel rate). This novel approach is presented in the context of stem cells monitoring for regenerative medicine procedures.

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Quantum Manipulation of Graphene Edge States in Atomically-defined Nanoribbons

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Magnetic states in graphene nanostructures have undergone intense theoretical scrutiny, because their coherent manipulation would be a milestone for spintronic and quantum computing devices. In nanoribbons, experimental investigations are however hampered by lack of the required atomic control of the edges, and that the proposed graphene terminations are chemically unstable. Several questions remain thus unsolved: how can molecular spins be assembled into hybrid structures? What is the influence of the graphene environment on the spin? Can molecules be used to control coherent currents in graphene devices? Here we try to provide an answer to these questions, exploring spin-graphene interactions by using molecular magnetic materials.

Here we show our results using bottom-up shaping of graphene, first by graphene nanoribbons made via molecular routes. We observe the predicted delocalized magnetic edge states, and comparison with a non-graphitized reference material allows clear identification of fingerprint behaviours.[1] We quantify the spin-orbit coupling parameters, define the interaction patterns, and unravel the spin decoherence channels. We then show how such molecular structures can be included into molecular devices, producing ultra-clean nanoscale devices[2] where single spin levels can be investigated[3] and where magnetoresistive effects run are opposite to non-molecular devices.[4] Even without any optimization, the spin coherence time is in the μs range at room temperature, and we perform room temperature quantum inversion operations between spins [5,6,7].

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Atomic localization in many-particle reinterpretation of chemical bonding

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We analyze [1] two-particle binding factors of H_2 , LiH , and HeH^+ molecules/ions with the help of our original exact diagonalization *ab initio* (EDABI) approach [2]. The interelectronic correlations are considered rigorously within the second quantization scheme with a restricted basis of renormalized single-particle wave functions, i.e., with their size readjusted in the correlated state.

We determine the many-particle covalency and ionicity factors in terms of the microscopic single-particle and interaction parameters, which are also predetermined within our method. We discuss limitations of those basic characteristics and introduce the concept of partial atomicity (*Mottness*), corresponding to the Mott-Hubbard criterion concerning the localization threshold in those many-particle systems. This addition introduces atomic ingredient into the collective electron states and thus eliminates a spurious behavior of the covalency with the increasing interatomic distance, as well as provides a physical reinterpretation of the bonding.

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THIN FILMS OF SOLVATOMAGNETIC CN- BRIDGED COORDINATION POLYMERS: FROM MICRO TO NANOSCALE

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Molecular magnets exhibit many properties not found in conventional metallic magnetic materials, such as sensitivity to external stimuli e.g. light, pressure, temperature, magnetic field, or chemical modifications. A particularly interesting group of molecular magnets are solvatomagnetic compounds, in which magnetic properties are altered under the influence of the removal, introduction, or exchange of solvent molecules in the crystal lattice [1-2]. Porous magnets and magnetic sponges are potential chemosensitive switches and provide valuable insight into magneto-structural correlations.

In this report, two types of thin films of microporous CN-bridged hybrid organic-inorganic $\{[\text{Ni}^{\text{II}}(\text{cyclam})]_3[\text{M}^{\text{III}}(\text{CN})_6]_2 \cdot n\text{H}_2\text{O}\}_n$ ($\text{M} = \text{Cr}$ or Fe , cyclam = 1,4,7,11-tetraazacyclotetradecane) coordination networks will be presented. The films were obtained by using physical and chemical deposition techniques. In the first approach, the pre-formed nano-sized crystallites from water suspension were deposited on the PET/ITO substrate. As a result, films of 1-2 μm thickness composed of 40-200 nm size particles were obtained. As an alternative, the chemical sequential growth method was implemented, in which the coordination framework is anchored to the gold surface and built directly on the substrate from cationic and anionic building blocks. Finally, the films of reduced thickness (ca. 100 nm) and drastically improved morphology were obtained. Both types of thin films show solvatomagnetic behavior characteristics for bulk compounds and change magnetic characteristics, including the shape of the magnetic hysteresis, under different humidity conditions.

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Nodal-line driven anomalous susceptibility in ZrSiS

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We shall present our recent study on the nodal-line Dirac system ZrSiS and our unique approach to test the signature of the nodal-line physics by thermodynamic methods. By measuring magnetic susceptibility in ZrSiS, we found an intriguing step-like temperature-driven transition from dia- to paramagnetic behavior. We show that the anomalous behavior represents a real thermodynamic signature of the underlying nodal-line physics through the means of chemical pressure (isovalent substitution of Zr for Hf), quantum oscillations, and theoretical modelling. The anomalous part of the susceptibility is orbital by nature. It arises due to the vicinity of the Fermi level to a degeneracy point created by the crossing of two nodal lines. Furthermore, an unexpected Lifshitz topological transition at the degeneracy point is revealed by tuning the Fermi level. The present findings in ZrSiS give a new and attractive starting point for various nodal-line physics-related phenomena to be tested by thermodynamic methods in other related materials.

Interplay of various order parameters and disorder in iron chalcogenides

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Since the discovery of iron-based superconductors over a decade ago large efforts are directed towards uncovering the primary order parameter determining the properties of these materials. However, the abundance of various low-temperature phases observed experimentally suggests that there may be no single order parameter, instead, many degrees of freedom, including nematic, spin, charge, or orbital degrees of freedom, are strongly intertwined. In addition, these materials are prone to various forms of disorder, which influences the nature of the ground state.

In this talk, I will summarize several years of our studies of iron chalcogenide system, $\text{FeTe}_{1-x}\text{Se}_x$, in which the disorder is introduced intentionally by two different methods, substitution of transition metal element, Ni, into Fe-site, and by changing the crystallization rate during the crystal growth. This last method introduces either excess, or deficiency of the Fe, what affects both the crystal quality, and superconductivity, with the surprising result that the superconductivity is enhanced in crystals of inferior crystallographic properties [1]. Over the years, we have used various experimental probes to understand this behavior, including transport [2], photoemission [3], and, most recently, magnetization and angular magnetoresistance experiments. I will combine the results of these experiments and discuss how the interplay of nematicity, spin fluctuations, and disorder-induced doping affects ground state properties of this system.

The work done in collaboration with I. Zajcewa, K.M. Kosyl, A. Lynnyk, and D. J. Gawryluk. Supported by Polish NSC grant 2014/15/B/ST3/03889. The research was partially performed in the laboratory co-financed by the ERDF Project NanoFun POIG.02.02.00-00-025/09.

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Gate tunable supercurrent in the epitaxial superconducting shell in Ta/InAs nanowires

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Integrated circuits with superconducting building blocks would have several benefits, such as high speed and low power consumption. In recent years, surprisingly, gate control of the supercurrent in all-metallic transistors has been observed. This phenomenon can be used to fabricate gate controlled transistors from superconducting materials, analogous to the field effect transistors. The suppression of the supercurrent was investigated in several materials however there is no scientific consensus on the microscopical explanation [1-3]. In this work, we studied gate tunable supercurrents in Ta superconducting shells epitaxially grown on the top of InAs nanowires. The investigated device switches from superconducting state to normal state by applying $\sim \pm 5$ V on the gate, which is really promising for standard electronical applications. Magnetic field dependence and switching current distribution measurements suggest that the gating effect does not stem from a simple thermal heating. Moreover, electric field driven collapse of superconductivity is not consistent with our experimental findings, however out of equilibrium phonon generation in the substrate is more likely to be the origin of this effect in our device.

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Far-infrared and annealing studies of thermal donors in high-purity silicon

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We have measured the temperature-dependent infrared transmission of high-purity silicon samples having impurity concentrations of $\sim 10^{15}$ /cm³. Measurements were made in a frequency range from 10–10,000 cm⁻¹ at temperatures from 10–300 K. At 10 K, silicon is transparent in the far infrared (10–600 cm⁻¹) apart from narrow absorption lines caused by residual oxygen impurities known as thermal double donors (TDD). At higher temperatures, the electrons are ionized by the thermal energy in the crystal and become free electrons, causing a Drude-like response in the far infrared. There is also absorption caused by several vibrational modes of Si₂O in the far and mid infrared regions. The oxygen is introduced by the amorphous silica crucible during the Czochralski growth process and occurs as an uneven distribution of oxygen throughout the boule. Samples were annealed between 450-700 C in vacuum and a significant effect on the TDD oxygen but not on the vibrational oxygen concentration was observed. This leads us to believe that the thermal history of the boule plays an important role in determining the structure of the oxygen impurity.

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Tuning of charge density waves in correlated metals – New results and insights

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Transition metal compounds in which electrons from partially filled d-shells strongly interact with each other keep challenging the standard theory of solids as new, emergent exotic electronic orders are experimentally observed. Despite vastly different macroscopic properties, *e.g.* high temperature superconductivity (HTS), electronic nematicity or density waves to cite a few, the electronic phases encountered in these quantum materials can be almost degenerate and compete with each other within complex phase diagrams. The crystal lattice is more than a mere spectator. It can be used to tune the subtle interplay between charge, spin, orbital and lattice degrees of freedom that controls such competing electronic states and thereby to learn more about the microscopic mechanisms underpinning their stabilization.

I will show how the combination of pressure (hydrostatic or uniaxial) tuning and x-ray spectroscopy has been used in the course of the last decade to gain fresh insights on the properties of charge density waves (CDW) in high temperature superconducting cuprates [1-3].

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Spin chirality driven by thermal fluctuations in correlated paramagnets

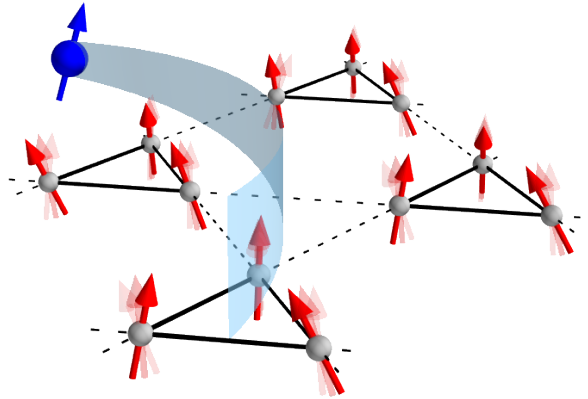
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Chirality is an ubiquitous concept in the natural sciences, distinguishing left- and right-handed objects or processes. In magnetic solids, the chirality of spin textures is derived from the twisting habit of neighboring atomic spins [1-3]. I will discuss dynamical processes, specifically thermal fluctuation processes, which are transient but generate a net chiral habit in a magnetic solid. Through their coupling to local magnetic moments, conduction electrons feel this chiral habit; hence, (thermo-) electric transport coefficients, which are time-averaged quantities, allow us to distinguish two scenarios:



- (1) Short-range spin correlations, where a small cluster of magnetic moments is sufficient to describe the physical properties of the thermally disordered solid [4,5] and
- (2) Longer-range correlations, such as dynamically nucleating and decaying topological defects [6].

I introduce toy model systems which realize Kagome and triangular lattices of magnetic moments, and discuss the role of lattice geometry in promoting these fluctuation phenomena [7]. Finally, I will show that the thermal Hall effect of magnetic insulators can also have a contribution related to thermal fluctuations of spin-chiral nature [8].

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Spin Centres in Crystals: Quantum Sensors and Quantum bits

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Spin centres in crystals are promising candidates for the creation of quantum sensing, computing, and communication technology [1].

Nitrogen-vacancy (NV) centres in diamond have risen to prominence as quantum sensors as they offer biocompatibility, bright photoluminescence, and long spin coherence at room temperature [2]. Developing these systems towards practical sensor devices is underway, but the collection of photoluminescence for optical readout remains too cumbersome and costly for many applications. Recently, it has been shown that their quantum state can also be read out electrically, which constitutes a large step towards compact, integrated devices. This method has been used to measure the state of a single electronic spin, and even to observe the spin state of a single atomic nucleus [3,4].

Communication between such spin centres can be used to build quantum networks and quantum computers. The optical transitions of NV centres are not ideally suited for this purpose, mainly because of their emission in the visible domain which leads to scattering losses and is not compatible with optical fiber networks [1]. Other spin centres are therefore under investigation which may be better suited for such applications, such as the vanadium centres in silicon carbide (SiC). This family of defects is of great interest because of their telecom-range optical transitions and their rich spin structure [5]. The presentation will cover progress on investigations of the optical and spin properties of vanadium in SiC, with a view towards spin polarization and control, integration into photonic structures such as high-finesse microcavities, and the creation of long-distance quantum networks [6–8]. A long spin relaxation lifetime is one of a set of advantageous features which make vanadium a strong contender for such applications [9].

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MAGNETO-OPTICS OF VAN DER WAALS ANTIFERROMAGNET FePS_3

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Research on magnetic materials currently constitutes a significant part of current activities in condensed-matter physics. Both experimental and theoretical studies are motivated by the scientific curiosity to uncover new phenomena, and also, triggered by the possible design of novel spintronic devices. Among current trends in the spintronic developments, there are many attempts to exploit antiferromagnetic materials (instead of ferromagnets), to work with 2D systems rather than with bulk crystals, as well as attempts to control the magnetic order in solids by means of light. These ideas have stimulated our magneto-optical studies of large-spin (Fe^{2+} , $S=2$) quasi-2D antiferromagnet FePS_3 . In this material, magnetic excitations (one-magnon gaps) have relatively large energies, and therefore, their interaction with light may be explored using techniques of THz and infrared magneto-spectroscopy.

In the present work, we report on THz/infrared magneto-spectroscopy and magneto-Raman studies of FePS_3 . Applying a magnetic field, we tune the one-magnon-gap excitation to coincide with the phonon modes. Hybrid magnon-phonon modes, the magnon polarons are unveiled with the demonstration of a pronounced avoided crossing between the otherwise bare magnon and phonon excitations. At higher photon energies, our data reveal a novel magnetic excitation. When a magnetic field is applied, it closely resembles semi-classical antiferromagnetic resonance in easy-axis antiferromagnets, nevertheless, the observed Zeeman splitting is four-times larger. We interpret this mode in terms of a longitudinal magnon excitation. This corresponds to a full reversal of a single iron spin in the magnetic lattice and thus carries a total angular momentum of $S_z = 4$. We argue that condensation of such longitudinal magnons may lead to new and exotic multipolar states.

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Size-dependent Electronic Properties of Strongly Confined Graphene Quantum Dots

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Laboratory for Advanced Materials (LAM) is a newly established research laboratory at the Faculty of Natural Sciences at Comenius University in Bratislava, Slovakia, supported by the European Commission under the Horizon 2020 program, the ERA Chair scheme. In the first part of my presentation, I will give a brief overview of the laboratory and the research areas the laboratory focuses on. In the second part of my talk, I will discuss in more detail our progress in one of the research areas, namely studies of strongly-confined graphene quantum dots (GQDs). I will present a new method for preparation of uniform ensembles of small (<2 nm) GQDs, using a systematic bottom-up step-wise synthesis. The new approach facilitates quantitative investigation of the effect of quantum confinement effect on the electronic structure of the GQDs using readily accessible ensemble level techniques. Using these techniques, we experimentally show how the bandgap, valence and conduction band offsets, exciton binding energies and densities of states systematically vary with the size in these strongly confined GQDs. The interpretation of the experimental results is supported by detailed DFT modelling. Experimental results indicate that the standard Dirac fermion model and tight-binding modelling approach do not adequately describe the electronic properties of GQDs in the strongly confined regime, which is attributed to stronger carrier-carrier interactions in the GQDs compared to the bulk graphene. Raman spectroscopy studies reveal that even the small GQDs show key D and G spectral features characteristic for periodic graphene structures and that the variation in the ratios of the corresponding band intensities (ID/IG) with the GQD size is in good agreement with previous studies of highly defected large area graphenes. This work was financially supported by the European Union's Horizon 2020 research and innovation programme under grant agreement No. 810701 and by the Los Alamos Laboratory Directed Research and Development (LDRD) Program.

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Dual character of the cuprate strange metal

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In this presentation, I will describe my group's recent studies of the (magneto)-transport properties of hole-doped cuprates across the strange metal regime in high magnetic fields up to 70 Tesla. By investigating three distinct families of hole-doped cuprates - $\text{Ti}_2\text{Ba}_2\text{CuO}_{6+\delta}$, $\text{La}_{2-x}\text{Sr}_x\text{CuO}_4$ and La/Pb-doped $\text{Bi}_2\text{Sr}_2\text{CuO}_{6+\delta}$ – a common picture begins to emerge of two charge sectors coexisting within the strange metal phase of overdoped cuprates, one harboring coherent Landau quasiparticles, the other incoherent 'Planckian' dissipators. Curiously, as the contribution from the latter grows with reduced doping, so too does the superconducting condensate. Finally, a link is established between the quadrature scaling of the magnetoresistance at high field strengths and the so-called separation of lifetimes seen at low-fields.

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DESIGNING SUPERCONDUCTIVITY IN NANOWIRES

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As the diameter of a superconducting nanowire approaches the coherence length, its superconducting state becomes increasingly sensitive to factors such as the disorder, texture, non-equilibrium effects and details of the interfaces with other materials. While this may present a difficulty for some applications, it also provides an opportunity for controlled manipulation of quantum states that is essential for creating tunable quantum devices. Full understanding and control of the physics at the interfaces is essential to understanding and control of the quantum state of a nanowire that may be dominated by such interfaces. I will describe a nanoprinting method for fabrication of ultranarrow nanowires with unprecedented control over their physical texture and will show how tunable interfaces with graphene and topological materials lead to unusual transport properties.

Exploring polar order in oxide heterostructures by optical second harmonic generation

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Oxide heterostructures hosting ferroelectric materials have emerged over the last decade as a promising platform for energy-efficient electronics. However, determining the polarization direction, magnitude and domain configuration, as key properties in applications, remains a challenge in ultrathin layers and multilayers. We seek to illuminate polar order arising in oxide heterostructures using a non-invasive nonlinear optical method – second harmonic generation (SHG). With this approach, we facilitate the integration of BaTiO₃-based superlattices on technologically relevant silicon by detecting the polarization state in the ferroelectric layer in dependence of its environment. We find that the out-of-plane polarization of BaTiO₃ is substantially enhanced in an asymmetric environment of tricolor superlattices in comparison to BaTiO₃ single films and standard bicolor superlattices [1]. We also contribute to understanding complex polar order arising in PbTiO₃|SrTiO₃ superlattices. Using SHG, we identify the phase coexistence of the multi-domain phase with in-plane ordering and the vortex phase [2]. We furthermore find interlayer coupling between ferroelectric layers leading to an antiparallel alignment of local polarization in neighboring layers. Our findings pave the way towards using non-invasive techniques for monitoring the evolution of polar order operando.

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Reversing the brain drain to promote scientific excellence in Eastern Europe

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Despite numerous measures on EU level to fight brain drain many intellectuals in Eastern European countries are still leaving to the West. The main problem is not that scientists and intellectuals are leaving to go abroad to work under better conditions — that is certainly beneficial for science as a whole. Rather, the problem occurs when they do not return.

For many years, EPFL has been participating in the so-called "Tenure Track Pilot Program" [1], which is administered by the Croatian Science Foundation and offers young talents the opportunity to build their careers as assistant professors at a Croatian academic institution. The program is based on the EPFL tenure track model and is adapted to local needs. Initial results and findings from the mid-term evaluation will be discussed in the presentation.

Recently, EPFL together with ETHZ helped creating a new institute called INSAIT on computer science and artificial intelligence as part of Sofia University in Bulgaria [2]. INSAIT's mission is to transform the world through excellence in science, research, and education by offering outstanding working conditions. The Bulgarian government supports INSAIT with 85 M€ over ten years. Key components, thoughts and hopes of INSAIT will be discussed during the presentation.

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ZEEMAN DRIVEN SUPERCONDUCTOR INSULATOR TRANSITION IN STRONGLY DISORDERED MoC FILM. STM AND TRANSPORT STUDIES IN TRANSVERSE MAGNETIC FIELD.

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Low temperature STM and transport studies on ultrathin polycrystalline MoC films provide evidence that, in contrast to the previously studied TiN, InO_x and NbN films, where the bosonic scenario of the superconductor-insulator transition is found upon increased disorder, unambiguous signs of the fermionic scenario are present [1].

In this presentation we study the transverse magnetic field induced superconductor-insulator transition in strongly disordered 3 nm thin MoC thin films, where the level of disorder approaches its critical value [2]. Surprisingly, the Zeeman paramagnetic effects dominate over orbital coupling on both sides of the transition. In superconducting state it is evidenced by a high upper critical magnetic field B_{c2} , by its square root dependence on temperature, as well as by the Zeeman splitting of the quasiparticle density of states (DOS) measured by scanning tunneling microscopy. At B_{c2} a logarithmic anomaly in DOS is observed. This anomaly is further enhanced in increasing magnetic field, which is explained by the Zeeman splitting of the Altshuler-Aronov DOS driving the system into a more insulating or resistive state.

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Numerical Modeling of an Optoelectronic Stimulation Device in Contact with a Single Neuron

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In this work we electrically characterise an organic optoelectronic stimulation device and construct a realistic equivalent circuit model that reproduces important device parameters such as the dependence of open circuit potential and short circuit current on illumination intensity. The device is based on two organic pigments, metal-free phthalocyanine (H₂PC) and N,N'-dimethyl perylenetetracarboxylic diimide (PTCDI) thermally deposited on the semi-transparent ITO back electrode. We use the constructed equivalent circuit to test the ability to stimulate a single CA3 pyramidal neuron cultured on top of the optoelectronic device. For that purpose, we developed a 3D FEM model of the CA3 pyramidal neuron along with realistic voltage-gated ion channels governed by Hodgkin–Huxley equations on the neuron membrane. We explore important parameters that determine the probability of successful stimulation including the distance from the device to the neuron and the illumination intensity.

Evolution of the Hall-coefficient, dc-resistivity and Fermi-surface in Cuprates

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Cuprates exhibit a number of unusual properties, including the highest superconducting transition temperatures at ambient pressures known today. Despite tremendous research efforts, there is no consensus regarding the understanding of these compounds, except in two limits: at zero doping (parent compounds) and in the highly overdoped regime. The parent compounds are charge-transfer insulators, while at high doping levels they behave as a Fermi liquid with $1 + p$ itinerant carriers.

Only recently it has been revealed that the itinerant charges preserve their Fermi-liquid nature across the phase diagram, without a change of the scattering rate and effective mass [1]. Consequently, the complexity of cuprates is due to a gradual (de)localization of exactly one hole per CuO_2 unit [1, 4]. Such an evolution implies the opening of a partial gap at the Fermi surface, not its reconstruction.

Here we show that the transport coefficients correspond to the ungapped parts of the Fermi surface, which are directly observed by photoemission spectroscopy. We use tight-binding parametrisations of measured ARPES spectra of $\text{HgBa}_2\text{CuO}_{4+\delta}$ [2, 6], $\text{Tl}_2\text{Ba}_2\text{CuO}_{6+\delta}$ [3, 5] and $\text{La}_{2-x}\text{Sr}_x\text{CuO}_4$ (LSCO) [7] to calculate the Hall-coefficient and dc-resistivity, where we consider only those parts of the Fermi surface which are not gapped. We find an excellent agreement between our model and measured values. This is particularly interesting in the case of LSCO which exhibits a complex evolution of the Fermi surface topology. Namely, LSCO undergoes a Lifshitz transition thereby strongly altering the Hall-response, an effect which is fully captured by our approach.

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Synthesis, structural, magnetic and optical properties of (Bi_{1-x}Ho_x)-ferrites

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Magnetoelectric multiferroics, due to simultaneous ferroelectric and ferromagnetic ordering, have attracted wide attention in recent years, offering a wide range of potential applications in data storage media, spintronics and multi-state memories [1]. One of the well-known materials exhibiting such properties is bismuth ferrite (BFO) BiFeO₃. Because of the technological progress in the direction of nanotechnologies our interest is to obtain this compound in a form of nanoparticles. Since those particles are thermodynamically stable only in a very narrow temperature interval, the main challenge is to obtain a high-quality, uniform, single-phase material. Here we report the hydrothermal synthesis of BFO and Bi_{1-x}Ho_xFeO₃ ultrafine nanopowders, with a diameter of ~ 300 nm with no tendency to agglomerate. The diffraction patterns show that all obtained particles belong to the *R3c* space group. Regularity of the particle's geometric shape was demonstrated by Scanning electron microscopy (SEM), while the high-resolution transmission electron microscopy (HRTEM) reveals an excellent crystallization with non-fragmented surfaces. Individual grain analysis confirmed the existence of an ultra-fine crystal structure, with an interplane distance of 0.297 nm (*d* = 0.297 nm), which corresponds to (012) crystal planes. Magnetometry revealed a magnetic phase transition at *T*_N = 220 K, from a paramagnetic to canted antiferromagnetic phase. Doping with Ho increased the value of magnetization showing that weak ferromagnetic moment grows with the introduced defects, originating from the non-compensated magnetic moments due to the distortions of both the spin-cycloid order and the super-exchange bridges. Both distortions promote the additional spin-canting and increase the magnetization. The optical properties of the material were examined by the spectroscopic ellipsometry method and the energy gap was found to be 2.71 eV. Using the structure prediction method, which is based on the bond valence calculations, 11 additional perovskite-related structure candidates in different space groups were obtained, including a novel tetragonal BiFeO₃ phase which has never been reported before. With this, we have demonstrated that the hydrothermal method has good potential in obtaining BFO, for achieving better properties for the multiferroic application and offers an overall conclusion that the local magnetic properties of nanoparticles mainly depend on the particle size and their diverse morphology due to the different preparation methods and annealing temperatures.

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DETECTION AND MANIPULATION OF ANTIFERROMAGNETIC ORDERS VIA THE MAGNETOELECTRIC EFFECT

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The concept of utilizing antiferromagnets (AFMs) in spintronic devices has attracted much attention recently. AFMs are appealing as the absence of net magnetization eliminates crosstalk between neighboring domains, the rich variety of antiferromagnetic orders offers new possibilities to encode information and their THz dynamics enables much faster manipulation compared to ferromagnets. However, the detection and manipulation of AFMs are notoriously difficult with the conventional methods that are based on the magnetization.

When the antiferromagnetic order breaks not only the time-reversal but also the spatial inversion symmetry, the magnetoelectric (ME) effect becomes allowed. This cross-coupling provides a new handle on the antiferromagnetic state. Moreover, in these compounds, the electric and magnetic dipoles are entangled at finite frequencies as well, thus, intriguing optical effects such as non-reciprocal light absorption and polarization rotation also emerge.

In this talk, we present our efforts to use these optical ME effects to detect antiferromagnetic orders. Using THz spectroscopy, we studied the antiferromagnetic resonances of LiCoPO_4 , an antiferromagnet with finite toroidal moment [1,2]. We found that some of the spin excitations are simultaneously electric and magnetic dipole active and show strong non-reciprocal light absorption. By cooling the sample in crossed electric and magnetic fields, we switched between the antiferromagnetic domains exhibiting different light absorption. In the easy-plane AFM, $\text{Ba}_2\text{CoGe}_2\text{O}_7$, we also detected strong non-reciprocal light absorption in the THz frequency range [3]. The soft antiferromagnetic structure of this compound allowed us to demonstrate the in situ electric field control of the antiferromagnetic state.

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Low-dimensional materials: from lab to industry

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Current and emerging trends in social media, virtual and augmented reality, autonomous vehicles, big data and artificial intelligence are driving inflections in the semiconductor industry, which requires materials enabled 3D NAND, innovations in transistors and interconnects for advanced node devices and sophisticated circuit patterning approaches that use materials engineering to shrink devices. For the continuous innovation of advanced materials, an integrated development of chemistry, process and equipment has become imperative. In this talk, we will discuss our recent efforts on the implementation of novel nanomaterials – including two dimensional (2D) ultrathin films, one dimensional (1D) nanowires/nanotubes, and zero dimensional (0D) nanocrystals – into real-world applications.

First, I will discuss recent initiatives within the Applied Materials-NUS Advanced Materials Corporate Lab that combines Applied Materials' leading expertise in materials engineering and semiconductor technologies with NUS' world-class and multi-disciplinary R&D capabilities that span applied chemistry, materials science and microelectronics process engineering. This collaboration focuses on R&D in advanced materials engineering with the intent to create innovations that can be quickly transferred into commercial applications and serves as a model of collaboration between industry and academia. Furthermore, we will discuss a new type of freestanding down-conversion color filters based on colloidal 1D quantum dots for the next generation of high-resolution displays. Finally, I will discuss our efforts to tailor nanomaterials on-demand and with the atomic precision using highly focused ion- and electron-beams.

Super exchange in artificial molecule coupled to a ferromagnet

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Exchange interaction is a key ingredient of strongly correlated electron systems. It plays important role in various fields of solid state physics like magnetic ordering, high temperature superconductivity or qubit operation. The magnetic ordering induced by exchange coupling depends on several parameters like the level position of atoms, their tunnel coupling to the neighbouring sites or coordination, which are fixed parameters in a crystal. Realizing artificial atoms and coupling them to ferromagnet opens a unique opportunity to modify these parameters and study the induced magnetic order on an individual atoms. In this contribution first we discuss the magnetic state of a single artificial atom coupled to a bulk ferromagnet: how the magnetic state of the atom can be measured and varied by parameters of the atom. Then we present our recent experimental results on an artificial molecule coupled to ferromagnet and show the presence of superexchange interaction. [1]

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Designing opto-bioelectronic interfaces: from *in-silico* to *in-vivo*

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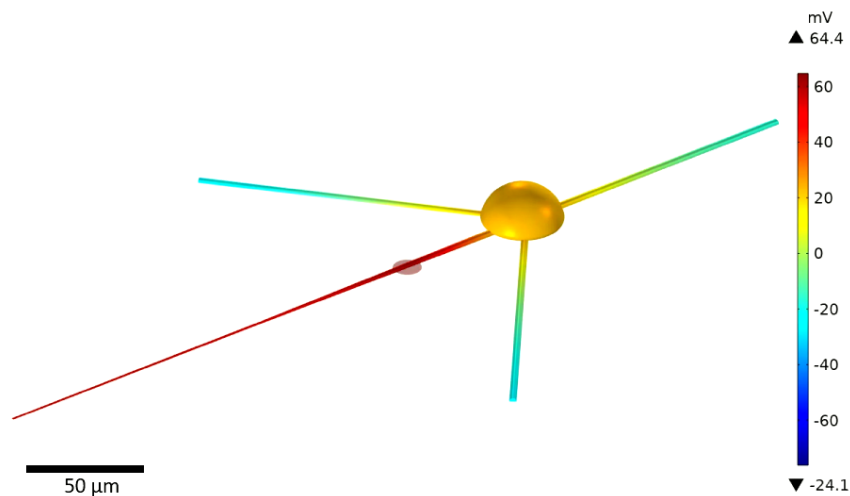
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Designing effective bioelectronic devices such as neurostimulators or recording interfaces requires a multi-disciplinary integrative approach involving experts from materials science, electrical- and bio-engineering and medical science due to the complex nature of the problem. To bridge the gaps in understanding between those fields, we propose using integrated realistic numerical models of the bioelectronic device and the biological system as a non-biased mediator and as an alternative to expensive and sometimes ethically dubious in-vivo experiments.

State of the art in computing power and software development currently enables the integration of numerical 3D models of the stimulation device and the stimulation target. Such models could speed up the device development and reduce the costs involved with the repetitive in-vivo experiments. We will show a numerical model of an opto-bioelectronic stimulation device coupled with Hodgkin-Huxley's numerical model of a single neuron to study the suitability of our devices for single-cell stimulation. Based on the model's results, we will show guidelines and requirements for the successful stimulation of single cells, especially relating to the electrode material and electrochemical parameters. We will show how our simulation toolset can be applied to a more general class of bioelectronic interfaces.



Na channel conductivity during the firing of the action potential along the axon of a model neuron stimulated by a model organic electrolytic photocapacitor.

The Role of Thermodynamic Confusion in Coarsening of Nanostructures

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The size distribution of particles, which is essential for many properties of nanomaterials, is equally important for the mechanical behavior of alloys whose yield and ultimate tensile strength are related to nanoscale precipitates. However, size distribution of particles formed by solid-state reactions is generally poorly controlled. This presentation will demonstrate an approach to forming highly monodisperse particle size distributions by simple solid-state reactions, involving the use of two-step heat treatment, whereby the core formed at high temperatures provides a template for growth of the shell at lower temperatures. If the core is allowed to grow to a sufficient size, the shell develops in a ‘size focusing’ regime, where smaller particles grow faster than larger ones. These results suggest new strategies for manipulating precipitate size distributions in similar systems through simple variations in chemical composition and thermal treatment. Formation of highly monodisperse particles can be perceived as a consequence of thermodynamic confusion of an alloy system and the delay of Gibbs-Thomson capillarity effect, contributing to high stability and resistance to coarsening of nanostructures. These phenomena have been studied by atomic resolution microscopy in tandem with first principal modeling and simulation applied to AlLiSc model system.

Charge order and the Fermi surface reconstruction in cuprate superconductors

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A major difficulty in understanding high- T_c systems is the complexity of the materials, the presence of strong electron-electron interactions, and their rich phase diagrams. We have employed synchrotron X-ray scattering to explore the electronic and structural degrees of freedom of complex materials, with the particular focus on the self-organized charge modulation, so called the charge density wave (CDW) order. Although its presence has been demonstrated within the CuO_2 plane of each family of cuprate superconductors [1], the extent of the CDW order as a function of doping, temperature, or magnetic field remains controversial.

I will present our results of the resonant X-ray scattering experiments in the model cuprate $\text{HgBa}_2\text{CuO}_{4+\delta}$ (Hg1201). While resonant X-ray scattering (RXS) allowed us to establish the doping-temperature range of the static CDW order in this compound [2,3], resonant inelastic X-ray scattering (RIXS) enabled the discovery of the short range CDW correlations at temperatures exceeding the onset of the static correlations observed by RXS. Such coexistence of static and dynamic CDW correlations is consistent with theoretical predictions [4]. The following electronic transport measurements in magnetic fields up to 70 T allowed us to investigate the reconstruction of the Fermi surface by the CDW order. We found, that at low temperatures, the moderately doped cuprates undergo a phase transition to a reconstructed state, when sufficiently strong magnetic field is applied. This transition is associated to the folding of the Fermi arcs into an electron pocket [5].

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MIXED COUPLED PLASMON MODES IN DIRAC ELECTRON SYSTEMS WITH DIFFERENT DIMENSIONALITIES

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We study the coupling between plasmon modes by the long-range Coulomb electron–electron interaction for a system consisting of a two-dimensional system of Dirac electrons embedded in three-dimensional Dirac semimetal for various separations of the subsystems [1]. The plasmon mode in the three-dimensional Dirac semimetal has the optic dispersion, while the plasmon mode in the two-dimensional system of Dirac electrons has the characteristic acoustic square-root dependence on the momentum. The mixing of the plasmon modes is achieved as the two-dimensional acoustic plasmon mode dispersion crosses the bulk plasmon mode. We find that the upper coupled plasmon mode increases from the bulk plasmon mode as the momentum increases and tends to the bare two-dimensional plasmon at large momenta, while at the same time the lower coupled plasmon mode increases linearly from zero as the momentum increases and approaches the bare bulk plasmon mode at large momenta. The coupled plasmon modes become more separated with decreasing the separation between two subsystems as the coupling increases due to the enhanced Coulomb interaction between electrons from different subsystems. We also demonstrate how the coupling affects the spectral weights of the obtained modes in two subsystems for different separations. In addition, we study the effects of the Dirac cones tilts on coupled plasmon modes in both subsystems [2]. We show that the tilts of Dirac cones anisotropically increase the coupled plasmon mode energies and renormalize their spectral weights. The anisotropic effects of the tilt are more significant for larger separations of the subsystems.

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Spin-Electric Coupling in Lead-Halide Perovskites

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Abstract body

Lead-halide perovskites enjoy a number of remarkable optoelectronic properties. To explain their origin, it is necessary to question how electromagnetic fields interact with these systems. We address this question here by studying two classical quantities: Faraday rotation and the complex refractive index in a paradigmatic perovskite $\text{CH}_3\text{NH}_3\text{PbBr}_3$ in a broad wavelength range. We find that the minimal coupling of electromagnetic fields to the $\mathbf{k} \cdot \mathbf{p}$ Hamiltonian is insufficient to describe the observed data even on the qualitative level. To amend this, we demonstrate that there exists a relevant atomic-level coupling between electromagnetic fields and the spin degree of freedom. This spin-electric coupling allows for quantitative description of a number of previous as well as present experimental data. In particular, we use it here to show that the Faraday effect in lead-halide perovskites is dominated by the Zeeman splitting of the energy levels, and has a substantial beyond-Becquerel contribution. Finally, we present general symmetry-based phenomenological arguments that in the low-energy limit our effective model includes all possible couplings to the electromagnetic field in the linear order.

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Spintronic Applications of Giant Rashba Effect in Bismuth Tellurohalides

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In the field of spintronics, efficient creation and manipulation of spin polarization without external magnetic fields is a key requirement for producing real-world devices, such as those based on spin-orbit torque (SOT), a potential technological successor of spin transfer torque.

Bismuth tellurohalides (BiTeX, where X is a halogen element), in addition to being layered semiconductors that can be used in 2D heterostructures, also exhibit giant bulk Rashba effect. The emerging spin texture allows for all-electric creation and manipulation of large spin polarization within the material by passing a bias current (the Rashba-Edelstein effect), a desirable feature for SOT applications. We experimentally demonstrate this in BiTeBr/graphene devices, using the graphene and conventional ferromagnetic contacts as nonlocal spin signal detectors.^[1] The spin polarized carriers injected into graphene using a bias current can be confirmed to originate inside the BiTeBr crystal. In another work, BiTeI is successfully isolated in monolayer form and its stability in ambient conditions is confirmed.^[2]

Tuning the carrier density in the material, by different growth techniques or by electrically gating few-layer devices, should enable significant enhancement of the achievable spin polarization. The inherent spin texture and electrically controllable polarization, without having to rely on proximity effects at the interface with another material, opens further avenues for applications in practical SOT-based devices.

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DC and optical signatures of the reconstructed Fermi surface for electrons with parabolic band

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We study the main intra-band and inter-band transport properties at zero temperature of free electron-like system undergoing a topological reconstruction of the Fermi surface for the two-dimensional and three-dimensional case. The calculated intra-band properties include the single-particle density of states, the total and the effective concentrations of electrons and the thermopower. As for the inter-band case, the real part of the conductivity has been calculated within the vanishing inter-band relaxation approximation as a function of the incident photon energy. Within this approach, it is shown that the optical conductivity has a nonvanishing component parallel to the reconstruction wave vector and the shape which depends on the value of the Fermi energy. Each dimensionality has its particular features in the transport quantities which are discussed and compared with those in the free electron scenario. Finally, we identify the signature of the topological reconstruction of the Fermi surface in the intra-band and inter-band transport functions.

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