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AI-Based Interventions Along the Molecular MRI Pipeline: The Quest for Speed, Specificity, and Histological Fidelity

Alterations of in vivo molecular properties, such as intracellular pH and protein/metabolite concentrations, are known to underlie a variety of neurological diseases and manifest long before any anatomical or structural changes occur. While non-invasive imaging of such processes is a pivotal tool for achieving early diagnosis, the currently employed clinical in-vivo molecular imaging techniques proved to be slow, nonspecific, or require the use of radioactive or metal-based contrast agents. This talk will present a rapid and quantitative molecular MRI strategy integrating biophysical models with AI-based interventions. Potential implications for preclinical understanding of molecular mechanisms and preliminary clinical results for cancer characterization and treatment monitoring will be presented and discussed.

Solid-State NMR Investigations of Silica Biomineralization in Diatoms

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Biosilica, e.g., from diatoms is an organic/inorganic hybrid material with outstanding properties. Its formation as well as molecular and supramolecular architecture are not yet fully understood. A solid-state NMR approach combined with other analytical techniques like mass spectrometry, optical spectroscopy, as well as molecular dynamics (MD) simulations was applied to study the formation and structural organization of biosilica. Biosilica-associated long-chain polyamines (LCPAs) were characterized leading to a model for the supramolecular organization of intact biosilica. LCPAs are embedded into the silica as revealed by ^{1}H-^{13}C-{^{29}Si}-rotational echo double resonance (REDOR), ^{1}H-^{13}C-^{29}Si double cross polarization (DCP), and dynamic nuclear polarization (DNP) [1-3]. Functional groups in contact with silica were identified but accurate distance determination by REDOR is impossible for fully isotope-labeled biosilica with its complicated biomolecular composition. Distances and spin system geometries can be determined by using well defined synthetic model systems employing selective isotope labeling. As an example, *in vitro* prepared nanocomposites containing silica and selectively [^{13}C, ^{15}N]-labeled polyamines of similar structure as found in diatoms are available meanwhile. Precise REDOR data with maximum REDOR fractions exceeding 90 % are then measurable [4]. These experiments in combination with extended MD simulations provide reliable distance and spin system information beyond the simple 2-spin-approximation.

Finally, we have studied the incorporation of foreign elements like Al [5] and Fe into the biosilica. Surprisingly high concentrations of Al can be incorporated into the silica phase. ^{27}Al MAS NMR including multiple quantum experiments in combination with optical spectroscopy show that aluminium is dispersed into the silica phase thus forming a non-crystalline aluminisilicate. In contrast, iron forms iron oxide nanoparticles which are attached to the biosilica as could be shown by EPR spectroscopy.

In summary, the performed analytical studies provide insight into the structure and composition of diatom biosilica as well as into the supramolecular architecture of this amazing material.

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Moti Freiman, Technion

MBSS-T1: Model-Based Self-Supervised Motion Correction for Robust Cardiac T1 Mapping

Cardiac T1 mapping is a valuable quantitative MRI technique for diagnosing diffuse myocardial diseases. Traditional methods, relying on breath-hold sequences and echo triggering, face challenges with patient compliance, limiting their effectiveness. Image registration can enable motion-robust cardiac T1 mapping, but inherent intensity differences between time points pose a challenge. We introduce MBSS-T1, a self-supervised deep-learning model for motion correction in cardiac T1 mapping, constrained by physical and anatomical principles. The physical constraints ensure expected signal decay behavior, while the anatomical constraints maintain realistic deformations. The unique combination of these constraints ensures accurate cardiac T1 mapping along the longitudinal relaxation axis. MBSS-T1 outperformed baseline deep-learning-based image registration approaches in a 5-fold experiment on a public dataset of 210 patients (STONE sequence) and an internal dataset of 19 patients (MOLLI sequence). MBSS-T1 excelled in model fitting quality (R^2: 0.975 vs. 0.941, 0.946), anatomical alignment (Dice score: 0.89 vs. 0.84, 0.88), and expert visual quality assessment for the presence of visible motion artifacts (4.33 vs. 3.38, 3.66). MBSS-T1 has the potential to enable motion-robust T1 mapping for a broader range of patients, overcoming challenges such as suboptimal compliance, and allowing for free-breathing cardiac T1 mapping without requiring large training datasets.

Lucio Frydman, Weizmann

Can NMR Spectroscopy be of Help for Preventing Deaths from Pancreatic Cancer?

Abstract – In Memory of Prof. Asher Schmidt, z"l

Pancreatic ductal adenocarcinoma (PDAC) is currently the 3rd most common cause of cancer-related mortality in both Israel and the US, and at its present rate it will become the deadliest of all cancers by the mid-2030s. This, despite the ≈10 years that it takes for PDAC to develop. The reasons for this are multiple, including: (1) There lack of efficient means to make an early PDAC detection before it metastasizes from the pancreas to other organs. (2) The absence – even when a tumor is suspected– of reliable ways to discriminate PDAC from confounding pancreatic complications like pancreatitis or pancreatic cysts. (3) The lack of preventive tools to reliable screen high-risk individuals, in this otherwise highly hereditary (e.g., among Ashkenazy Jews) disease. The latter point is particularly poignant, as much more widespread cancers like breast, prostate and melanoma, have been made much less lethal thanks to the success of preventing screening methods. The fact that medical imaging systematically fails PDAC patients is not because of lack of trying: CT, MRI, PET, and endoscopic ultrasound are all currently used for trying to detect PDAC –but in the present form, they are all found lacking. Over the last few years, we have been trying to address this problem using NMR spectroscopy; specifically, using metabolic reporters of the Warburg effect. This effect is a hallmark of cancer whereby tumors will, even in aerobic environments, generate ATP using a pathway that **consumes glucose and generates lactate** instead of relying on the more efficient TCA-cycle that concludes in water and CO_2. This has enabled us to image in vivo tumors that were only a few mm in diameter, thanks to the unambiguous lactate peak generated by the PDAC. While we are still waiting for the funds and for the permits needed to test our hypothesis on PDAC patients, I will describe why we believe that emerging high-field spectroscopic 2H NMR imaging methods being developed by us and others to target this oncometabolite, could provide the breakthrough needed –not just for the early diagnosis, but also for the recurring preventive screening of this hideous disease among wide population swaths.

^{19}F electron-nuclear double resonance as a tool for structural studies biological and chemical systems.

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Department of Chemical and Biological Physics, Weizmann Institute of Science

Measuring dipolar interactions between a spin label and a ^{19}F nucleus attached at strategically chosen positions in a protein or nucleic acid has recently emerged as an attractive approach to distance determination for structural biology applications.[1] This approach complements distance measurements between two spin labels, typically measured by electron-electron double resonance techniques, which have a low limit of around 1.5-2 nm. The electron-nuclear interactions can be accessed by the solid-state electron-nuclear double resonance (ENDOR) technique that allows measuring the NMR spectrum of the nuclei magnetically coupled to the unpaired electron. This technique can employ a variety of spin labels such as nitroxide, trityls, Gd(III), and Cu(II), and the choice of label depends on the problem at hand. The upper accessible range is around 1.5 nm. A comparison of the performance of these labels using the same spin and ^{19}F labeling positions on two model proteins will be presented. Next, we will focus on high spin, S=7/2 Gd(III) spin labels, which also allow in-cell measurements. In addition, we will show that using Gd(III), it is possible to extend the resolution of ENDOR spectra, thus extending the long-distance limits of this technique by almost a factor of two. This is achieved by exploiting the high electron spin of Gd(III) and performing measurements at high fields and low temperatures, such that the low-lying energy levels become highly populated. This is demonstrated on a model substance and Gd(III) and ^{19}F labeled proteins. Finally, we will show that this methodology is also very useful for studies of supramolecular host-guest systems. This will be illustrated on the binding modes of fluorinated benzylamine guests in cyclodextrin-based Gd(III) cavitands.

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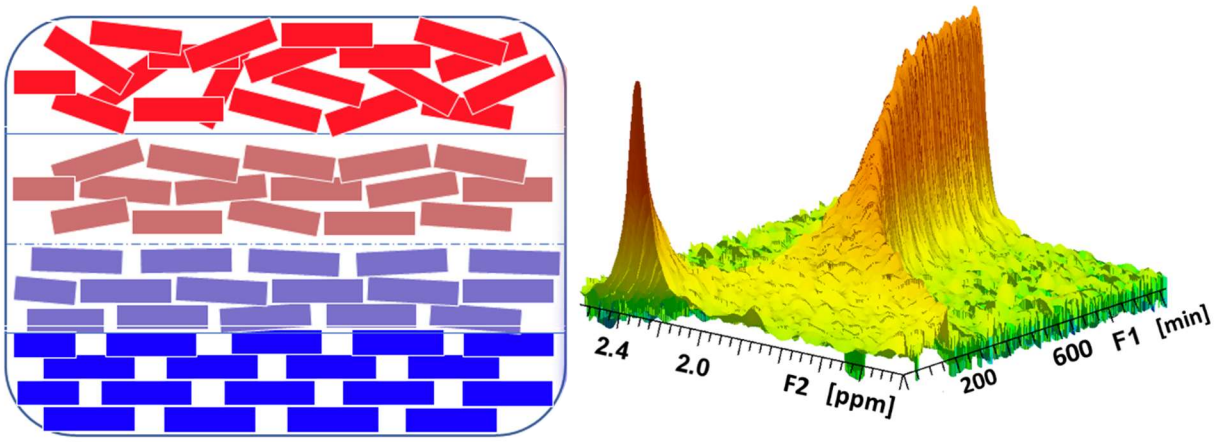
Regulation of mineral films on bone apatite crystals and early mineralization events by non-collagenous bone proteins

Sharon Barak, Lilian Cohen, Taly Iline-Vul, Irina Matlahov, Alexey Kulpanovich, Artyom Semionov, Meital Abaiev, Gil Goobes

It is now common knowledge that order and crystallinity are intimately coupled to disorder in the bio composite structure of bone conferring some of the tissue's essential mechanical properties. The mechanisms through which bone's inorganic material, apatite ($Ca_5(PO_4)_3OH$), crystallizes, a key step to bone proper function, are intensively scrutinized. At the same time, the formation of disordered mineral layers coating individual apatite crystals are enigmatic and still challenging to underpin. Over the last years, we have identified additional mineral layers with intermediate dis/order residing between the well-ordered apatite crystal and the amorphous coat layer. Characteristics of these nanometric interphases are under control of bone non-collagenous proteins such as osteocalcin, osteopontin, and others. Our use of spectrally filtered MAS NMR measurements to indicate the impact of these proteins on orientation of inorganic ions in the interphases and on the location of the different ions in them will be reviewed.

Osteocalcin and osteopontin also intervene and regulate events at the other end of mineral formation, at early stages of ion clustering that precedes nucleation of crystals and amorphous phases. Time resolved solution ^{31}P NMR results of apatite precursor ions during *in situ* mineralization in the NMR tube will be shown to indicate that.



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Chemical Upcycling of Polymers: Insights from NMR Methodology

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Despite growing public awareness, only about 15% of plastics are recycled, leaving a toxic trail in the environment and strongly impacting global health. One novel solution is to create a circular polymer–waste system, by chemically recycling plastic waste into reusable monomers, thus forming an efficient closed loop.[1]

Condensation polymers, namely polydiketoenamine (PDK) resins, are produced from triketone (TK) and amine monomers that condense spontaneously, producing water as the sole byproduct.[2] Protonation of PDK has been found to be the crucial first step of the degradation process. This can be tuned by changing the proton counter anion, leading to variation of the polymer water interactions and in turn, control of the depolymerization rate.[3]

Here I will present a new approach to gain atomic level insight into polymer degradation processes by using magnetic resonance techniques. I will show the application of multi-nuclear solid-state NMR to PDK samples at various deconstruction stages, providing molecular insight into bond activation, reaction selectivity and reactivity. Furthermore, in-situ pulsed-field gradient NMR is used as a monitoring tool for real time transformations of polymer decomposition.

The ability to understand polymer deconstruction processes and reaction kinetics will provide much needed clarity to these systems and allow further control and guidance in the design and production of future circular materials.

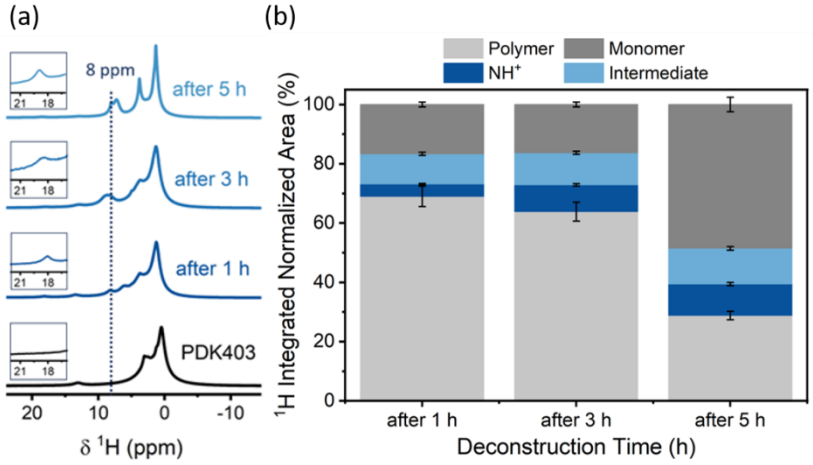

Figure 1. (a) ^{1}H Hahn echo measurements for recovered polymer after degradation times in 5M HBr. (b) Deconvolution, integration and separation into distinct groups, showing the heterogeneity of the polymer degradation process.

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High-field hyperpolarization of ^{13}C nuclei using NV centers in diamond

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The negatively charged nitrogen-vacancy (NV) center is a paramagnetic defect in diamonds, where a nitrogen substitutes for a carbon, and an adjacent carbon is absent. NV centers proved to be efficient dynamic nuclear polarization (DNP) agents[1], efficiently enhancing NMR signals by transferring their electron spin polarization to nuclei. They exhibit long coherence times at room temperature[2], and their electron spin and optical properties are coupled, allowing electronic hyperpolarization using light illumination[3]. While NV centers are mostly studied at low magnetic fields (≤ 0.3 T), we do so in NMR relevant fields (≥ 7 T), allowing to characterize their electron spin physics and dynamics under DNP-NMR characteristic conditions.

We present the first pulsed EPR data of NV centers at 14 T and employ the new Reverse ELectron electron DOuble Resonance (RELDOR) sequence to probe interactions within the NV-^{13}C system. While light illumination alone does not lead to the hyperpolarization of first-shell ^{13}C nuclei, we demonstrate how it can be done using a combination of light illumination and mm-wave irradiation. We further discuss the roles of light illumination and mm-wave irradiation in this process, and using ELDOR build-up curves we study its dynamics. This work lends itself to the investigation of NV-mediated DNP mechanisms, serving for the optimization of DNP enhancement.

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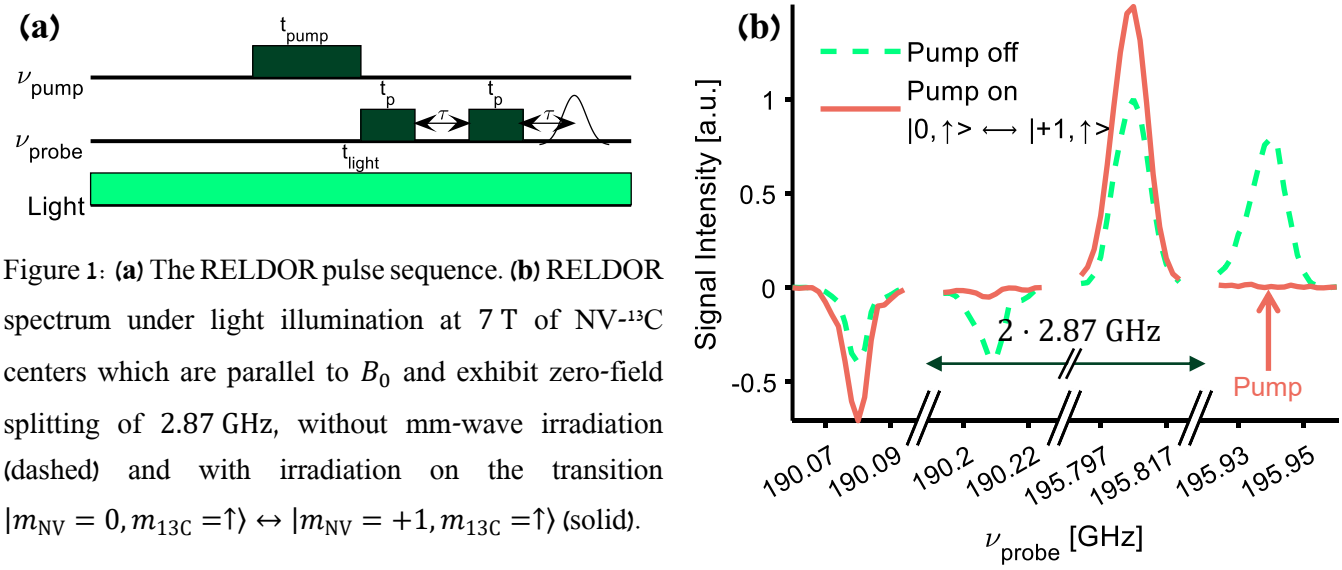

Figure 1: **(a)** The RELDOR pulse sequence. **(b)** RELDOR spectrum under light illumination at 7 T of NV-^{13}C centers which are parallel to B_0 and exhibit zero-field splitting of 2.87 GHz, without mm-wave irradiation (dashed) and with irradiation on the transition $|m_{NV} = 0, m_{13C} = \uparrow\rangle \leftrightarrow |m_{NV} = +1, m_{13C} = \uparrow\rangle$ (solid).

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The Composition and Structure of the SEI on Na-Ion Anodes Revealed by Exo- and Endogenous Dynamic Nuclear Polarization - NMR Spectroscopy

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The fast-growing need for large scale energy storage requires rechargeable batteries that are both high in energy density but low in cost. Na ion batteries (SIB) have sparked interest as they meet these two requirements, mainly because of the Na low redox potential and abundance in nature.

During cycling of SIBs, a nano-sized layer is formed between the electrolyte and the anode called the Solid Electrolyte Interphase (SEI), which greatly influences the capacity retention and functioning of the battery[1]. Although the importance of the SEI cannot be overstressed, research in this field is limited, especially with regards to anode materials for SIBs. Probing the SEI layer by tools such as XRD is not a viable option due to its nanoscale size and presence of disordered phases. One possible method to characterize the SEI is solid state Nuclear Magnetic Resonance (ssNMR), yet it is not sufficiently sensitive. In this project we developed an approach to characterize electrochemically formed SEI by enhancing its NMR signal with Dynamic Nuclear Polarization (DNP). We employ different sources of polarization to gain structural insight. The standard approach for MAS-DNP, which is based on exogenous organic radicals, allows us to gain insight into the outer layers of the SEI. To gain enhancement from the bulk of the material we use Metal Ion DNP (MIDNP), where the sample is doped during synthesis with paramagnetic centers. Endogenous DNP enables us to gain insight on the inner layers of the SEI[2][3].

I will present my work in developing this combined approach to DNP and, in particular, the MIDNP method to obtain signal enhancement from nuclei in different phases in the SEI formed on a Lithium Titanate anode. This includes characterization of the Mn(II) dopant through EPR and determination of its effect on nuclear relaxation. Most importantly, I will present the differential nature of these signal enhancements, discussing the dependence of the DNP process on the presence of spin diffusion and the distance from the paramagnetic centers. I will show how the combination of exogenous and endogenous DNP provides architectural insights into the formation and evolution of the SEI in multiple electrochemical systems, along with chemical understanding by means of ssNMR spectroscopy.

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